NATIONAL PHARMACEUTICAL REGULATORY DIVISION
MINISTRY OF HEALTH, MALAYSIA

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)

Second Edition – September 2016, revised September 2017

Address:

Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor Darul Ehsan, Malaysia


+ 603-7883 5400


+ 603-7956 2924, 7956 7075


http://npra.moh.gov.my/

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GUIDELINE HISTORY

No.	Guideline	Description of Amendment	Effective date
1.	a) Guidelines for Application for Registration of Pharmaceutical Products, Third Edition b) *Permohonan Pendaftaran Keluaran Ubat Tradisional*, Second Edition	Initial Publication	a) October 1993 b) December 1998
2.	Drug Registration Guidance Document (DRGD)	Merging of 1(a) and 1(b)	* 2004
3.	Drug Registration Guidance Document (DRGD), First Edition - January 2013	Revision of DRGD November 2012	1st January 2013
4.	Drug Registration Guidance Document (DRGD), Second Edition – September 2016	Revision of DRGD, First Edition - January 2013	1st September 2016

This guidance document is issued by the Director of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984.

NPRA reserves the right to amend any part of the guidance document whichever it deems fit.

PREAMBLE

- This "**DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)"** will serve as the reference guide for the registration process including quality control, inspection & licensing and post-registration activities of medicinal products.

- This DRGD shall be read in conjunction with the current laws and regulations together with other relevant legislations, where applicable, governing pharmaceutical and natural products for human use in Malaysia, which include but not limited to the following:

    a) Sale of Drugs Act 1952;
    b) Control of Drugs and Cosmetics Regulations 1984;
    c) Dangerous Drugs Act 1952;
    d) Poisons Act 1952;
    e) Medicines (Advertisement & Sale) Act 1956;
    f) Patents Act 1983;
    g) Wildlife Conservation Act 2010 (Laws of Malaysia Act 716); and
    h) International Trade in Endangered Species Act 2008 (Act 686).

    The written laws shall take precedence over this guidance document in any event of discrepancy.

- The scope of this DRGD includes information relating to administrative requirements and procedures for:
    a) Submission of an application for the registration of medicinal products, which is based on the ASEAN Common Technical Dossier/ Requirements (ACTD/ ACTR), where applicable;
    b) Submission of an application for the licensing of manufacturers, importers and wholesalers;
    c) Submission for amendments to a registered medicinal product; and
    d) Post-registration activities.

- Applicants shall familiarize with the contents of this guidance document and the governing legislations before they submit applications for medicinal product registration.

- The Authority may request for information or specify conditions not described in this document that is deemed necessary to ensure the quality, safety and efficacy of the product.

- An on-going review of regulatory policies will continue taking into account the global regulatory environment, to allow for timely and pertinent changes.
  For more information, please refer to Circulars and Publications.

- Applicants are advised to refer to NPRA's website for the latest updates of the DRGD and other related guidelines. **Separate guidelines** are available for Cosmetics and Veterinary products.

- The Authority reserves the right to amend any part of the DRGD whenever it deems fit.

- Any enquiry on registration of products may be submitted to:

  Secretary,
  Drug Control Authority,
  National Pharmaceutical Regulatory Division,
  Ministry of Health Malaysia,
  Lot 36, Jalan Universiti,
  46200 Petaling Jaya, Selangor.

ABBREVIATIONS AND ACRONYMS

ACCSQ-PPWG	ASEAN Consultative Committee on Standards and Quality/ Pharmaceutical Product Working Group
ACTD	ASEAN Common Technical Dossier
ACTR	ASEAN Common Technical Requirement
AMV	Analytical Method Validation
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient (Interchangeable with drug substance or active substance).
ASEAN	Association of Southeast Asian Nations
ATC	Anatomical Therapeutic Chemical
BA	Bioavailability
BE	Bioequivalence
BET	Bacterial Endotoxins Test
BMF	Batch Manufacturing Formula
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
CCL	Centre for Compliance and Licensing
CDCR	Control of Drugs & Cosmetics Regulations 1984
CEO	Chief Executive Officer

CEP	Certificate of Suitability CEP is referring to Certificate of Suitability of European Pharmacopoeia monographs issued by the EDQM
CFC	Chlorofluorocarbons
CFS	Certificate of Free Sales
CI	Confidence Interval
CMC	Chemistry, Manufacturing And Controls
CoA	Certificate of Analysis
COH	Change of Product Registration Holder (Previously known as Change of Marketing Authorization Holder)
COMBO	Combination Pack
COS	Change of Manufacturing Site
CPP	Certificate of Pharmaceutical Product
CTX	Clinical Trial Exemption
CTIL	Clinical Trial Import Licence
DCA	Drug Control Authority
DE	Data Exclusivity
DMF	Drug Master File (interchangeable with Active Substance Master File)
DNA	Deoxyribonucleic acid
DRGD	Drug Registration Guidance Document
EDQM	European Directorate for the Quality of Medicine and Healthcare
ELC	Endotoxin Limit Concentration
EMA	European Medicines Agency
EP	European Pharmacopoeia

FDA	Food and Drug Administration
FDI	Food-Drug Interphase
FEO	For Export Only
FPQC	Finished Product Specification
FSQD	Food Safety and Quality Division
FTIR	Fourier Transform Infrared
g	gram
GABA	Gamma-Amino Butyric Acid
GC	Gas Chromatography
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HACCP	Hazard analysis and critical control points
HBsAg	Surface Antigen of the Hepatitis B Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HS	Health Supplement
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Names

IPQC	In-Process Quality Control
ISO	International Organization for Standardization
JAKIM	Malaysia Department of Islamic Development (*Jabatan Kemajuan Islam Malaysia*)
JP	Japanese Pharmacopoeia
L	Litre
LAL	Limulus Amebocyte Lysate
LOA	Letter of Authorization
LOC	Letter of Commitment
LOI	Letter of Intent
mAb	monoclonal antibody
MaV	Major Variation
max	maximum
MCB	Master Cell bank
MDDCI	Medical Device-Drug-Cosmetic Interphase
MiV-PA	Minor Variation Prior Approval
MiV-N	Minor Variation Notification
mL	milliLitre
MPN	Most-Probable Number
MSM	Methylsulphonylmethane
MVD	Maximum Valid Dilution

NAT	Nucleic Acid Testing
NCE	New Chemical Entity
NDP	New Drug Product
NMT	Not More Than
NPRA	National Pharmaceutical Regulatory Division
NRV	Nutrient Reference Value
OTC	Over-the-Counter
Ph. Eur.	European Pharmacopoeia
PI	Package Insert
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMF	Plasma Master File
POA	Protocol of Analysis
ppm	parts per million
PRH	Product Registration Holder (Previously known as Marketing Authorization Holder, MAH)
PSUR	Periodic Safety Update Report
PV	Process Validation
RiMUP	Consumer Medication Information Leaflet (RiMUP) (Previously known as Patient Information Leaflet or PIL)
RNA	Ribonucleic acid
RSD	Relative Standard Deviation
SIRIM	Standards and Industrial Research Institute of Malaysia

SPC	Summary of Product Characteristics
spp.	Species
Syn.	Synonym
TAMC	Total Aerobic Microbial Count
TGA	Therapeutic Goods Administration
TLC	Thin Layer Chromatography
TSE	Transmissible Spongiform Encephlopathies
TYMC	Total Yeasts and Moulds Count
USP	United State Pharmacopeia
USPI	US Package Insert
UV	Ultra-Violet
VVM	Vaccine Vial Monitor
WCB	Working Cell Bank
WHO	World Health Organisation

GLOSSARY

Bulk Product: A product that has completed all processing stages up to, but not including, final packaging.

Contract Manufacturer: Any person who manufactures any product on the order of another person to whom a manufacturer's licence has been issued under these Regulations (*as defined in Regulation 2, CDCR 1984*)

Finished Product: A product that has undergone all stages of production and quality control, including packaging in its final container and labelling.

Indigenous Medicine: As defined under Regulation 2, the CDCR 1984, indigenous medicine means a system of treatment and prevention of disease established through traditional use of naturally occurring substances.

Licensed Importer: A person to whom an import license has been issued under Regulation 12, CDCR 1984 (*as defined in Regulation 2, CDCR 1984*)

Licensed Manufacturer: A person to whom a manufacturer's licence has been issued under these Regulations, and includes a contract manufacturer (*as defined in Regulation 2, CDCR 1984*)

Licensed Wholesaler: A person to whom a wholesaler's licence has been issued Regulation 12, CDCR 1984 (*as defined in Regulation 2, CDCR 1984*)

Manufacturer: A person carrying out one or more of the steps specified in the definition of manufacture.

Manufacture, in relation to any product includes –

a) The making or assembling of the product;
b) The enclosing or packing of the product in any container in a form suitable for administration or application, and the labelling of the container and;
c) The carrying out of any process in the course of any of the foregoing activities.
(*as defined in Regulation 2, CDCR 1984*)

Medicinal Product: The term refers to 'product' as stated in Regulation 2, CDCR 1984 which is applicable to pharmaceutical and natural products

OTC: Refers to Generic product (Non-Scheduled Poison)

Product Owner: A person, company or entity who is the legal/ registered owner of the product formulation and/or process with whom the marketing authorization holder has a contract *(glossary used in ACTD and ACTR).*

Product Registration Holder: The company or corporate or legal entity in the field of pharmaceuticals whose name the marketing authorization has been granted. This party is responsible to all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorized holder must be subjected to legislation in the country that issued the marketing authorization, which normally means being physically located in that country *(glossary used in ACTD and ACTR)*.

Repacker: *Please refer *"Explanatory Notes for Repackers"* as below

The Authority: Refers to Drug Control Authority (DCA)

The System: Refers to QUEST system in website of NPRA

EXPLANATORY NOTES FOR REPACKERS

1. Introduction

This chapter is intended to provide guidance to those engaged in repackaging of finished products with the aim to provide information to any person/ establishments who removes finished products from their original container-closure system and repackages them into a different container-closure system for sale and/or for distribution.

2. Objectives

a) To provide uniform guidance and a means of assessing the operations of repackers/ relabelers as they relate to the provisions of the GMP and GDP requirements.

b) To identify the type of repacking activity and whether there is a need to comply with GMP and GDP requirements.

3. Definitions

Terms	Definitions
Manufacture	Manufacture, in relation to any product includes – a) The making or assembling of the product; b) The enclosing or packing of the product in any container in a form suitable for administration or application, and the labelling of the container and; c) The carrying out of any process in the course of any of the foregoing activities.
Packaging	All operations, including filling & labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.
Packaging Material	Any material employed in the packaging of a material or product or cosmetic, including any other packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.
Printed packaging material	Packaging material which is imprinted with text or numbers or a combination of both.
Labelling	The term 'labeling' designates all labels and other written, printed, or graphic matter upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. A shipping container, unless such container or the outside of the consumer package, is exempted from labelling requirements.
Labeller/ relabeller	A company that affixes the original label to a finished product (i.e labeller) or changes in any way the labelling on a product without affecting the product or its container (i.e. relabeller).
Packaging system	Composed of a container system with its closure. This system may include several layers of protection for the Pharmacopeia preparation along with any sealing devices, delivery devices, labelling and package inserts.

Terms	Definitions
Repacker	A company who removes a finished product from its final packaging and places the finished products into a different container which is labelled or to be labelled before the product is for sale and/or distribution for human use. Repacker may consist of primary and secondary repacker.
Primary repacker	A company who performs repacking activity that places the finished products into a primary/ immediate container which labelled or to be labelled before the product is for sale and/or distribution for human use.
Secondary repacker	A company who does the repacking activity relating to a) labelling of the product container; and/or b) packing the finished product which is already enclosed in its labelled primary container into a carton which is labelled or to be labelled. before the product is for sale and/or distribution for human use.

4. Examples of types of repacking activity

No.	Description of Repacking Activity	Require GMP/GDP Control	Product to be included in Manufacturing License List	Responsibility	Remarks (If any)
1.	Packing/ blistering of imported product (tablet/capsule/liquid/etc.) into a different container	√	√	Primary repacker	
2.	De-blistering of blister strips of tablets/capsules to repack into a new blister pack/container	√	√	Primary repacker	e.g. Blister packs de-blistered and repack into new blister pack due to market purposes, etc.
3.	To form a secondary packaging material (unit box) to pack blister strips, bottles, etc. into this packaging material	√	√	Secondary repacker	e.g. 5 strips in a unit box to be repack to 1 strip in a unit box
4.	To affix an immediate label to a container of product that contains information such as Product Name, Dosage Form, Name of Active Substance(s), Strength of Active Substance(s), Batch Number, Manufacturing Date, Expiry Date, Route of Administration, Storage Condition, etc.	√	√	Primary repacker/ Secondary repacker	Refer Appendix 9: Labelling Requirement for Immediate Labels
5.	To affix label of outer carton that contains information such as Product Name, Dosage Form, Name of Active Substance(s), Strength of Active Substance(s), Batch Number, Manufacturing Date, Expiry Date, Route of Administration, Storage Condition, etc.	√	√	Secondary repacker	Refer Appendix 9: Labelling Requirement for Unit Outer Carton

No.	Description of Repacking Activity	Require GMP/GDP Control	Product to be included in Manufacturing License List	Responsibility	Remarks (If any)
6.	To affix country specific label requirements for Malaysia a) Name & content of preservative(s) where present b) The words "Keep medicine out of reach of children" or words bearing similar meaning in both Bahasa Malaysia & English c) The words "Controlled Medicine/ Ubat Terkawal" (For scheduled poisons only) d) Security label (Hologram)	 √* √* √* √*	 X X X X	Importer/ Primary Repacker/ Secondary Repacker	The importer/ repacker shall maintain the relevant documents (e.g. hologram records, stock card)
7.	To insert new Package Insert/ to change original Package Insert into the inside of the secondary packaging product (unit box)	√	√	Secondary repacker	e.g. Remove Germany package insert from the product and replace with Malaysia specific Package Insert
8.	To attach/ tape Package Insert on the outside of the secondary packaging product (unit box)	√	√	Secondary repacker	
9.	To inkjet the Product Registration Number on the primary/secondary packaging material (unit box)	√	√	Primary/ Secondary repacker	
10.	To inkjet of the Manufacturing Date, Expiry Date and Batch Number on the primary/secondary packaging material (unit box)	√	√	Primary/ Secondary repacker	

No.	Description of Repacking Activity	Require GMP/GDP Control	Product to be included in Manufacturing License List	Responsibility	Remarks (If any)
11.	To affix specific labelling requirement of a product	√	√	Primary/ Secondary repacker	Refer Appendix 9: Labelling Requirements
12.	To inkjet/ affix label 'Sample Not For Sale'/ 'Physician's sample not for sale'/ 'Professional sample not for sale'/ etc. onto the secondary packaging material	√*	X	Secondary repacker/ Importer	
13.	To affix label 'Diimport/diedarkan oleh' onto the primary/ secondary packaging material	√*	X	Primary/ Secondary repacker/ importer	
14.	To affix 'Halal' label onto the primary/ secondary packaging material	√*	X	Primary/ Secondary repacker/ importer	
15.	To shrink wrap several boxes or bottles together	√*	X	Secondary repacker/ Importer	
16.	To repack finished products into tertiary packaging materials without any changes to the product	√*	X	Secondary repacker/ Importer	
17.	To repack several registered finished products as a convenient pack for promotional sale only without changing the product immediate and unit outer carton label	√*	X	Secondary repacker/ Importer	Refer 16.5 Application for a Convenient Pack
18.	To affix security seal onto the secondary/ tertiary packaging material	√*	X	Secondary repacker/ Importer	

5. Additional notes

5.1 √* denotes that the repacking activity has to be done in a Good Distribution Practise (GDP) controlled or licensed facility.

5.2 The repacking activities as listed in Para 4 is non-exhaustive. Product and license holders shall be responsible to ensure that the registered products are repacked in an appropriate manner and all relevant documents is maintained (batch packaging records/logbooks/inventory records/ procedures).

5.3 The conditions of the product must meet the storage requirements as stated in the Good Distribution Practice Guideline by National Pharmaceutical Regulatory Division (NPRA).

5.4 In deciding whether a particular bulk product is suitable for repacking, the repacker should take into consideration any available information from the manufacturer, published literature and any reference pharmacopoeia.

6. References

6.1 Drug Registration Guidance Document; First Edition; January 2013
6.2 Good Distribution Practice Guideline, 1st Edition; 2011
6.3 Control of Cosmetic Products
6.4 USP 31; Volume 1, 2008
6.5 Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics; May 1999
6.6 Irish Medicine Boards Guide to Parallel Imports; AUT-G0006-4.9
6.7 WHO GMP: Main Principles for Pharmaceutical Products.

Glossary for Homeopathic Products:

Active substance: Active substances are considered to be source materials processed by one or a sequence of homeopathic manufacturing procedures listed in pharmacopoeias in official use and other officially recognized documents (e.g. mother tinctures, dilutions or triturations).

Diluent: Substance used for the preparation of a stock/ starting material or the potentisation process and which may also represent the substance of the dosage form. Liquid diluents usually consist of purified water, aqueous solution, glycerol or ethanol of a suitable concentration or for which there is an appropriate monograph. The commonest solid diluent is usually lactose monohydrate.

Dilution: Dilution has two meanings in homeopathy:

- For a product, a dilution is a liquid homeopathic preparation which is potentised as described below (see the definition of potentisation). Individual dilutions are also called potencies;
- As a procedure, dilution means the de-concentration process of a liquid or a solid preparation. One part of each stage in the preparation of a homeopathic medicine from its stock or previous dilution (potency) by adding one part of a previous solid or liquid phase to a predetermined weight or volume of the diluent (see Potentisation below). Dilution occurs at all stages of production of the homeopathic medicines whether by addition of solid excipient in trituration or the addition of diluent in the liquid phase and succussion.

Dosage form: a dosage form in homeopathy complies with any relevant specifications for that dosage form for which an appropriate characterization exists in a pharmacopoeia in official use, or in other officially recognized documents. The most commonly encountered homeopathic dosage form, *the globule (pillule or pellet)*, is a solid spherule which consists of lactose, sucrose or any other suitable vehicle. Usually, preformed globules are impregnated with a dilution or directly by a mother tincture. The homeopathic dosage form *tablet* is a solid preparation which complies with any relevant characterization in the pharmacopoeia in official use (or in other officially recognized documents) for tablets. Homeopathic medicines in tablet form are either prepared by impregnation of preformed tablets or by compression of triturations with the vehicle. The most commonly used *liquid homeopathic medicines* are either alcoholic solutions or oral liquids.

Excipient: Substance needed for manufacturing a dosage form (used after potentisation) such as wheat starch and magnesium stearate for tablets. It may also represent the substance of the dosage form.

Homeopath: A qualified provider (practitioner) of homeopathic treatment.

Homeopathic medicines: Any medicine prepared in accordance with a homeopathic manufacturing procedure described by a pharmacopoeia in official use or other officially recognized documents. A homeopathic medicine may contain a number of homeopathic preparations.

Homeopathy: Classical homeopathy is a system of medicine using preparations of substances whose effects, when administered to healthy subjects, correspond to the manifestations of the disorder in the individual patients.

Mother tincture (also called tincture): The initial homeopathic preparation made from source material that can be further potentised (also called "liquid stock"), sometimes used as homeopathic medicines, is regarded as the most concentrated form of a finished homeopathic medicine. Mother tinctures are obtained classically by maceration or percolation (sometimes also by digestion, infusion, decoction or fermentation) techniques from source materials according to a procedure prescribed by a recognized homeopathic pharmacopoeia. Sometimes a mother tincture corresponds to the first decimal dilution, "1D" or "1X" (10-1), mostly when dry plant material is used as starting material.

Nosodes: Homeopathic medicines prepared from disease products from humans or animals; from pathogenic organisms or their metabolic products; or from decomposition products of animal organs.

Potency: The denominated degree of serial trituration or dilution and succession that is reached for each homeopathic medicine. The degrees of dilution or potencies are normally indicated by the letters D, DH or X for successive 1 to 10 (decimal) dilutions, the letters C, CH or K or CK for successive 1 to 100 (centesimal) dilutions while Q or LM denote successive 1 to 50 000 (Hahnemannian quinquagintamillesimal) dilutions. Dilution by 1 to 10 denotes 1 part processed with 9 parts of diluent (Hahnemannian decimal), dilution by 1 to 100, 1 part processed with 99 parts (Hahnemannian or Korsakovian centesimal), and so on. The number preceding the letters (e.g. D, C or LM) normally indicates the number of dilution steps employed (Table 1).

As a consequence of different views in various approaches in homeotherapy and because the notion of these terms may depend on the nature of the starting materials, the terms “high potency” and “low potency” cannot be defined unambiguously.

Potentisation (also called dinamization)**:** The combined process of serial dilution and succussion or trituration at each step in the manufacture of homeopathic medicines from stocks. (According to the tenet of homeopathy, potentisation represents the process by which the activity of a homeopathic medicine is developed.)

Table 1: Potency table

Dilution ratio	Common designation(s)	Examples
1:10[a]	X	1X, 2X, 3X, etc.
1:10[a]	D	D1, D2, D3, etc.
1:10[a]	DH	DH1, DH2, DH3, etc.
1:100[b]	C	1C, 2C, 3C, etc. C1, C2, C3, etc.
1:100[b]	CH	1CH, 2CH, 3CH, etc. CH1, CH2, CH3, etc.
1:100[b]	CK	1CK, 2CK, 3CK, etc. CK1, CK2, CK3, etc.
1:100[b]	K	1K, 2K, 3K, etc. K1, K2, K3, etc.
1:50 000[a]	LM	1LM, 2LM, 3LM, etc.
1:50 000[a]	Q	Q1, Q2, Q3, etc.

[a]For 1:10 and 1:50 000 dilution ratios only the Hahnemannian method of manufacture (multi-flask method) is used.

[b]For 1:100 dilution ratios a C potency is assumed to use the Hahnemannian method of manufacture (multi-flask method) and can also be denoted as CH. When the Korsakovian method of manufacture (single-flask method) is used, the potency is designated as CK or K.

Sarcodes: Homeopathic medicines made from healthy animal tissues or secretions. In Greek, sarcode means fleshly.

Source material (raw material, starting material, mother substance): Source material is the original raw material used for the production of homeopathic medicines. This material is obtained from natural sources, e.g. of botanical, zoological, microbiological, mineral, chemical, animal and human origin, or synthetic procedures. Source materials may undergo preliminary treatment in order to be further processed.

Stock: Substances or preparations made from the source materials (e.g. by maceration, succussion or trituration) used as starting points for the production of homeopathic medicines.

TABLE OF CONTENTS

SECTION A: GENERAL OVERVIEW

SECTION B: PRODUCT REGISTRATION PROCESS

SECTION C: QUALITY CONTROL

SECTION D: INSPECTION AND LICENSING

SECTION E: POST-REGISTRATION PROCESS

APPENDICES

SECTION A: GENERAL OVERVIEW

1. INTRODUCTION

The Control of Drugs and Cosmetics Regulations (CDCR) 1984 were promulgated under the Sale of Drugs Act 1952. The Authority (known as Drug Control Authority, DCA) established under these Regulations, is tasked with ensuring the quality, safety and efficacy of medicinal products through the registration, including quality control, inspection & licensing and post-registration activities. The National Pharmaceutical Regulatory Division (NPRA) acts as the secretariat to the Authority.

Under the CDCR 1984, Regulation 7(1): Except as otherwise provided in these Regulations, no person shall manufacture, sell, supply, import, possess or administer any product unless:

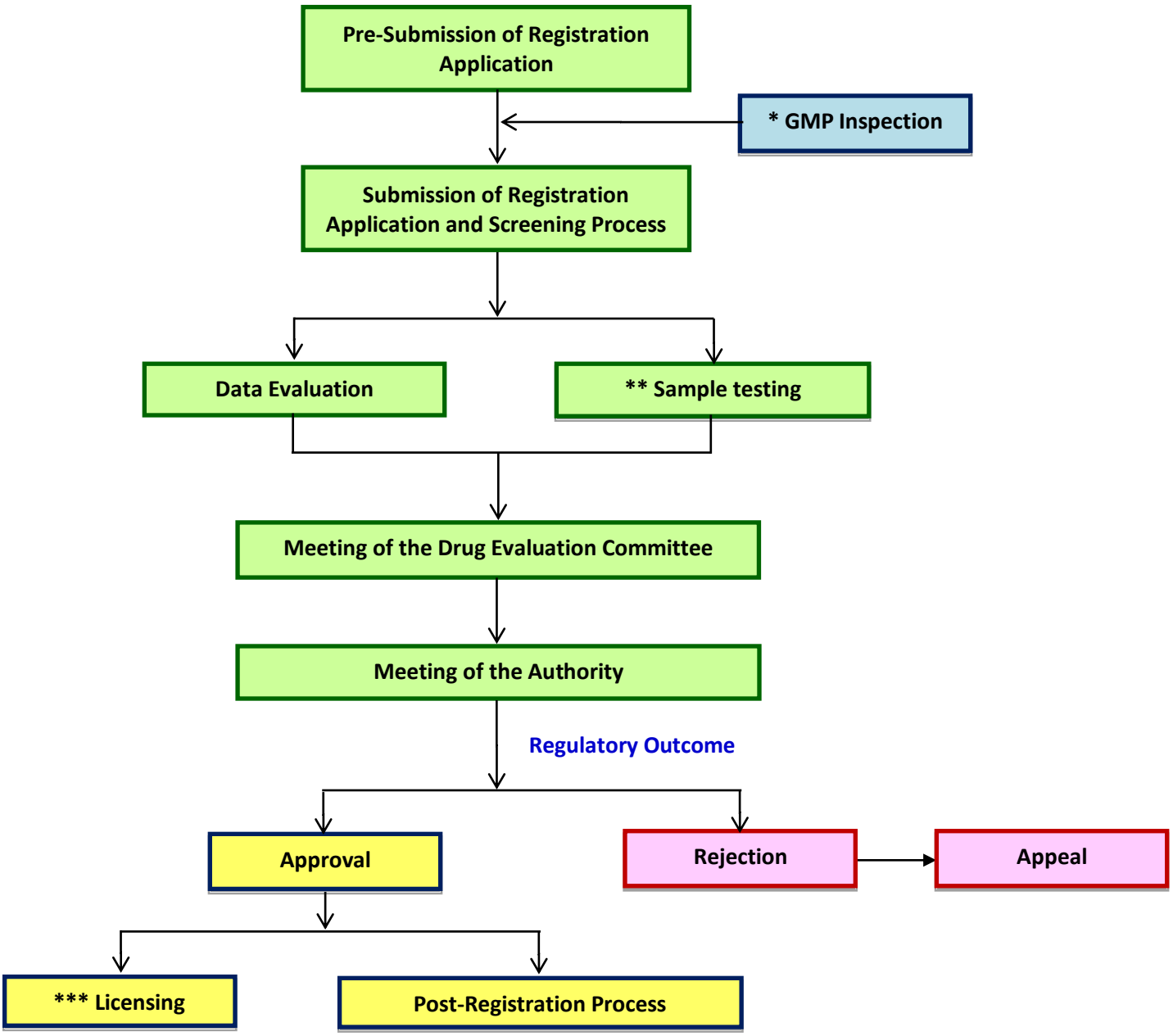
(a) the product is a registered product; and
(b) the person holds the appropriate licence required and issued under these Regulations.

The phases of implementation for product registration are as shown in **Figure 1** below:

Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
Registration Aug 1985 (Prescription Drugs)	Registration 1988 (OTC)	Registration Jan 1992 (Traditional Medicine)	Registration Feb 2002 (Cosmetics)	Registration Aug 2007 (Veterinary)	Regulatory control of Active Pharmaceutical Ingredient (API)**
Licensing May 1987	Licensing 1992	Licensing Manufacturer Importers Jan 1999	Licensing Jan 2004	Licensing 1 Jan 2012*	No licensing Requirements as registration of API is linked to products

*** 1st July 2012:**
All manufacturers shall be certified for GMP as directed by the Senior Director Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulation 1984;
Directive No. 1 Year 2012. Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB).
Reference: Circulars Bil (25) dlm BPFK/PPP/01/03 Jld 1 **and** Bil (96)dlm.BPFK/PPP/01/03 Jld. 2

Registration process includes quality control, inspection & licensing as well as post-registration process of medicinal products is illustrated in **Figure 2** below:



* Good Manufacturing Practice (GMP) Certification

** For natural products only

*** Application for Manufacturer, Import and/or Wholesale License

1.1 REGISTRATION OF PRODUCTS

Under the CDCR 1984, Regulation 2: **"*Product*"** means:

(a) a drug[1] in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose[2]; or

(b) a drug[1] to be used as an ingredient of a preparation for a medicinal purpose[2].

Under Sales of Drug Act 1952, Section 2:

[1] **"*drug*"** includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for a medicinal purpose.

[2] **"*medicinal purpose*"** means any of the following purposes:

(a) alleviating, treating , curing or preventing a disease or a pathological condition or symptoms of a disease;

(b) diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;

(c) contraception;

(d) inducing anaesthesia;

(e) maintaining, modifying, preventing, restoring, or interfering with, the normal operation of a physiological function;

(f) controlling body weight;

(g) general maintenance or promotion of health or wellbeing.

Note:
In this DRGD, the term "medicinal product" refers to the term "product" as stipulated in the Regulation 2, CDCR 1984.

1.1.1 REGISTRABLE PRODUCTS

Any product as defined in 1.1 shall be registered with the Authority.

The products include, but not limited to the following:

a) Pharmaceutical products containing scheduled poisons

b) Pharmaceutical products containing non-scheduled poisons
(For examples: Medicated plaster with medicine, antiseptic/ disinfectants for use on the human body, diagnostic agents for human use (in-vivo) and health supplement such as probiotics and chitosan)

c) Natural products
Includes herbal and traditional products

1.1.2 NON-REGISTRABLE PRODUCTS

i) Diagnostic agents and test kits for laboratory/ in-vitro use

Diagnostic agents/ test kits for laboratory use must be labeled **'FOR LABORATORY USE ONLY'**.

> ***Note:***
> *Products which are not labelled as such shall be deemed to be for human or animal use and need to be registered with the Authority.*

ii) Medical Devices

"***Medical device***" means any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article intended by the manufacturer to be used, alone or in combination, for human beings for the purpose of:

(i) diagnosis, prevention, monitoring, treatment or alleviation of disease;
(ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
(iii) investigation, replacement or modification, or support of the anatomy or of a physiological process;
(iv) support or sustaining life;
(v) control of conception;
(vi) disinfection of medical device; or
(vii) providing information for medical or diagnostic purpose by means of *in vitro* examination of specimens derived from the human body,

These products do not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its intended function by such means.

This includes but is not limited to the following:

- Non-medicated bandages, plaster
- Surgical dressings, wound care/ dressing materials containing hydrogel, collagen, calcium alginate
- Visco-elastic products for mechanical or physical protection of tissues during or after surgical procedures
- Instruments, apparatus, syringes, needles, sutures, catheters
- Disinfectants for equipments/ devices

- Lubricants for gloves, condoms and endoscopes
- Contact lens care products
- Copper IUDs
- Bone cement, tissue adhesives
- Dental fillings
- Blood bags containing anti-coagulants
- Non-medicated medical and contraceptive devices

For more information, please refer Medical Device Authority.

iii) Food

As defined under the Food Act 1983 and Food Regulations 1985, includes every article manufactured, sold or represented for use as food or drink for human consumption or which enters into or is used in the composition, preparation, and preservation, of any food or drink and includes confectionery, chewing substances and any ingredient of such food, drink, confectionery or chewing substances. This includes food for special dietary use for persons with a specific disease, disorder or medical condition, and food which contain quantities of added nutrients allowable under the Food Act 1983 and Regulations.

For more information, please refer Food Safety & Quality Division, Ministry of Health Malaysia.

iv) Sports Nutrition, such as body-building products containing protein/ whey/ soya bean

v) Raw herbs used in extemporaneous preparations, including those that are dried & cut into pieces, without dosage instructions and indications

vi) Insect repellants, insecticides, pesticides and parasiticides

Products containing pesticides as listed under First Schedule of Pesticide Act 1974 for external use only shall be controlled by the Pesticide Board.

For more information, please refer http://www.doa.gov.my

vii) Detergents/ disinfectants for domestic use

1.1.3 EXEMPTIONS FOR PRODUCTS USED IN CLINICAL TRIALS AND MANUFACTURING SAMPLES FOR REGISTRATION

a) Clinical Trial Import License (CTIL)

Products which are not registered with the Authority and are intended to be imported for the purpose of clinical trial shall have a Clinical Trial Import License.

This is in accordance to the Regulation 12(1)(c), CDCR 1984: "The Director of Pharmaceutical Services may, subject to the provisions of these Regulations, issue the following license subject to such conditions as he may impose, a clinical trial import license in Form 4 in the Schedule, authorizing the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product*".*

b) Clinical Trial Exemption (CTX) & Exemption for Manufacturing Sample for Registration

i) Products which are not registered with the Authority and are intended to be manufactured locally for the **purpose of clinical trial** shall require Clinical Trial Exemption (CTX) from the Director of Pharmaceutical Services; and

ii) Any person who wishes to manufacture any product solely for the **purpose of producing a sample for registration** should apply for an exemption for manufacture of sample. (Applies to **locally manufactured products only**).

This is in accordance to the Regulation 15(5), CDCR 1984: "Any person who wishes to manufacture any product solely for the purpose of producing samples for clinical trials, for registration or issuance of notification note under these Regulation may on application be exempted by the Director of Pharmaceutical Services from the provisions of regulation 7 (1) or regulation 18A".

For more information, please refer Regulation 15, CDCR 1984: Exemptions & Saving; and Guidelines on Clinical Trial.

1.2 CATEGORIES OF PRODUCT

Note:
Before submission of application for a product registration, applicants may submit for product classification if unsure of the product category.

Medicinal products for registration are classified under the following categories:

1.2.1 NEW DRUG PRODUCTS

New Drug Products (NDP) is defined as any pharmaceutical products that have not been previously registered in accordance with the provisions of the CDCR 1984.

An NDP may be classified according to the following categories:

a) New Chemical Entity (NCE)/ Radiopharmaceutical Substance

A new pharmaceutical product containing any of the following:

i. New Chemical Entity (NCE)
Defined as an active moiety that has not been registered in any pharmaceutical product.

ii. Radiopharmaceutical substance
Defined as a radionucleotide, ligand or the coupling mechanism to link the molecule and the radionucleotide that has not been registered in any pharmaceutical product.

b) New Combination Product

A new pharmaceutical product containing two or more drugs that are physically, chemically or otherwise combined or mixed and produced

as a single pharmaceutical product, in a combination that has not been registered in any other pharmaceutical product. This includes any of the following:

i. Combination of New Chemical Entities;
ii. Combination of registered chemical entity(s) AND New Chemical Entity(s);
iii. Combination of registered chemical entities;
iv. Combination of registered chemical entities in a new chemical forms;
v. Combination of registered chemical entity(s) in new chemical form(s) AND New Chemical Entity(s);
vi. Combination of registered chemical entity(s) in new chemical form(s) AND registered chemical entity(s).

c) Supplemental Product

A new pharmaceutical product containing a drug that has been previously registered as a pharmaceutical product but differing in properties with regards to safety and/or efficacy from the product that has been previously registered.

This includes any of the following:

i. Registered chemical entity in a new chemical form;
ii. Registered chemical entity in a new dosage form;
iii. Registered chemical entity in a new dosage strength with a change in dosing/ posology;
iv. Registered chemical entity for use by a new route of administration;
v. Registered chemical entity for new indication(s), dosage recommendation(s) and/or patient population(s).

1.2.2 BIOLOGICS

1. Definition:

The term 'biopharmaceutical' was coined in the 80's to define proteins that were made by recombinant DNA technology [which includes hybridoma technology for monoclonal antibody (mAb) production].

1.1 Biologic/ Biological product refers to a product whose active substance is made by or derived from a living organism (plant, human, animal or microorganism) and may be produced by biotechnology methods and other cutting-edge technologies. This product imitates natural biological substances in our bodies such as hormones, enzymes or antibodies.

1.2 Biological substance is defined as a substance that is produced by or extracted from a biological source and that needs, for its characterization and the determination of its **quality**, a combination of physicochemical-biological testing together with the production process and its controls.

1.3 Biopharmaceuticals/ Biologics/ Biological products can also be defined as:

"a protein (including antibodies) or nucleic acid-based pharmaceuticals used for therapeutic, which is produced by means other than direct extraction from a native (non-engineered) biological source". This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant/ genetically engineered and mAb-based products).

1.4 The term 'Biotechnology product' and 'Biological product' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view).

Note:
Today, biologics have become inextricably intertwined with biopharmaceuticals, to the point where they are synonymous. The general consensus is that the term 'Biologic' and 'Biopharmaceutical' are interchangeable.

Biologics include a wide range of products such as: vaccines, blood products, monoclonal antibodies (therapeutics), recombinant proteins (including but not limited to insulins, hormones, erythropoetins and other hematopoietic factors), cytokines (including but not limited to interferons, interleukins, colony-stimulating factors, tumour necrosis factors), cell and gene therapy products (CGTPs).

But does **not** include:

- Metabolites from microorganisms; e.g. antibiotics and some hormones;
- Macromolecules produced by chemical synthesis; e.g. peptides/ oligo-nucleotides produced by chemical synthesis;
- Whole blood or cellular blood components.

2. For detail on registration of Biologics products, please refer Appendix 3: Guideline on Registration of Biologics.

Note: *This document is not intended to apply on the control of genetically modified live organisms designed to be used directly in humans, e.g. live vaccines.*

3. Unlike small-molecule generic drugs, exact copies of biologics are impossible to produce because these are large and highly complex molecules produced in living cells. A 'biosimilar' medicinal product (a short designation for 'similar biological medicinal product') is considered as a new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, medicinal product. For details, please refer to Guideline on Registration for Biosimilars in Malaysia.

4. Cell and gene therapy products (CGTPs) is regulated as Biologic products. Unlike biotechnology products which are mostly purified proteins of cells, CGTPs contain living and functional cells. Therefore, CGTP is regulated under a separate framework. For details, please refer to: Guidance Document and Guidelines For Registration of Cell and Gene Therapy Products (CGTPs).
This document provides information for manufacturers, applicants, healthcare professionals and the general public on legal arrangements in Malaysia for the registration of CGTPs. The implementation of the guideline will be compulsory on **1 January 2021** as stated in the **Directive No. 6 Year 2017.** Ref: BPFK/PPP/07/25 (11) Jld.1**:** Direktif Untuk Menguatkuasakan Penggunaan

Guidance Document And Guideline For Registration Of Cell And Gene Therapy Products (CGTPS), December 2015 Dan *Good Tissue Practice Guideline, 2ND Edition, December 2015).*

1.2.3 GENERICS

A generic product is a product that is essentially similar to a currently registered product in Malaysia. However, the term generic is not applicable to Biologics.

Generics may be further classified into two groups:

1. **Scheduled Poison**
(Known as Controlled Medicine/ Controlled Poison)

Products containing poisons as listed in the First Schedule under Poisons Act 1952.

2. **Non-scheduled Poison**
(Known as Non-Poison or "Over-the-Counter", OTC)

Products containing active ingredients which are not listed in the First Schedule under Poisons Act 1952; and is excluding active ingredient which is categorized under health supplements or natural products or cosmetics.

1.2.4 HEALTH SUPPLEMENTS

A Health Supplement (HS) means any product that is used to supplement a diet and to maintain, enhance and improve the health function of human body. It is presented in small unit dosage forms (to be administered) such as capsules, tablets, powder, liquids and shall not include any sterile preparations (i.e. injectables, eyedrops). It may contain one or more, or the following combination:

i) Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics, and other bioactive substances;

ii) Substances derived from *natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolite;

iii) Synthetic sources of ingredients mentioned in (i) and (ii) may only be used where the safety of these has been proven.

For details, please refer to Appendix 4: Guidelines for Registration of Health Supplements

1.2.5 NATURAL PRODUCTS

a) Traditional medicine (as defined under the Control of Drugs and Cosmetics Regulations 1984):

Any product used in the practice of indigenous medicine, in which the drug consist solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof, in the unextracted or crude extract form, and a homeopathic medicine. It shall not include any sterile preparation, vaccines, any substance derived human parts, any isolated and characterized chemical substances.

b) Finished Herbal Product

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term “mixture herbal product” can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substance have been added, including synthetic compounds and/ isolated constituents from herbal materials, are not considered to be herbal.

c) Herbal Remedy

Any drug consisting of a substance or a mixture of substances produced by drying, crushing or comminuting, but without subjecting to any other process, a natural substance or substances of plant, animal or mineral origin, or any part of such substance or substances.

d) Homeopathic Medicine

Any pharmaceutical dosage form used in the homeopathic therapeutic system in which diseases are treated by the use of minute amounts as of such substances which are capable of producing in healthy persons symptoms similar to those of the disease being treated.

For details, please refer to Appendix 5: Guidelines for Registration of Natural Products

1.3 FOOD - DRUG INTERPHASE PRODUCTS

This guide serves to assist in determining if a product is to be regulated by the National Pharmaceutical Regulatory Division (NPRA) or by the Food Safety and Quality Division (FSQD) of the Ministry of Health Malaysia.

1.3.1 INTRODUCTION

Malaysians are now more health conscious and there is generally greater awareness of the importance of nutrition to overall well-being. In recent years, many consumers also rely on a variety of “dietary supplements” to improve their health. These diverse products are freely available through a myriad of outlets. A variety of products are available in the market, supposedly for the maintenance, prevention and even treatment of chronic diseases. These products may range from foods modified to have special properties or pure forms of vitamins and minerals to extract of various botanical or animal products.

It is important to monitor and regulate the marketing and sale of these products so as to protect the interest and health of the consumer. Some of these products are not clearly defined as “food” or “drugs” but are freely marketed. Such products include a variety of so-called health products and have been termed as “food-drug interphase (FDI) products”.

In order to better define and regulate the FDI products, both the NPRA and the FSQD, Ministry of Health Malaysia formed the Committee for the Classification of Food-Drug Interphase Products in 2000. The main Terms of Reference of the Committee is to assist both Divisions in classifying, in a consistent manner, an application from the industry which is not clearly defined either as a food or drug product. The Committee also serves as a platform in strengthening and updating the relevant regulations as well as to provide scientific input on these products.

1.3.2 DEFINITION OF FDI PRODUCTS

Generally FDI products are products for oral consumption containing a combination of food ingredients with active substances for oral consumption. Examples of food ingredients are fruit, vegetables, meat, poultry, milk, cocoa and cereal. Examples of active substances are vitamins, minerals, herbs, enzymes, probiotics, prebiotics, amino acids, peptides, coral calcium, and fatty acids

Such products as below are not categorized as FDI products due to its presentation and function:

A. Food based products that are not categorized as FDI products and regulated by FSQD include

1. Food based products **with or without** active ingredients (eg; herbs, vitamins, minerals, etc) as below:
    i) Instant drink products containing sugar and creamer (e.g. coffee, chocolate, soy, cereal).
    ii) Meat essence products (liquid) e.g. chicken essence, ostrich essence, duck essence, fish essence etc.
    iii) Ready to drink products (beverages) without dosing instruction in cheered pack/ canned / packet drinks.
    iv) Cordial products with recommended dilution ratio e.g. dates cordial, grape cordial.
    v) Vinegar products (liquid) e.g. apple vinegar, dates vinegar etc.
    vi) Honey products (liquid).

2. Energy drink products, isotonic drink products, sport nutrition products and special purpose food products.

3. Products in conventional food form e.g. biscuit, cake, confectionery, candy/sweet, gummy, noodle.

4. Products used for cooking and food preparation e.g. cooking oil (olive oil, coconut oil, sunflower oil), turmeric powder.

5. Herbs and spices in crude form.

B. Products that are not categorized as FDI products and regulated by NPRA include:

1. Products containing active ingredient(s) with or without excipient .

2. Products containing specific active ingredients which possess high pharmacological or therapeutic potencies. Examples of the ingredients are paracetamol, glucosamine, tranexamic acid, aspirin, substances listed in Poison Act 1952.

3. Products containing specific active ingredients which possess dose-related therapeutic potencies such as:
    - Plant sterols/ stanols and esters that are consumed ≥ 3.5g/day
    - Psyllium husk that are consumed ≥ 3.5g/day
    - Products containing senna ≥ 0.5g

4. Products in pharmaceutical dosage form such as soft gel, capsule or tablet (that is to be directly swallowed), sublingual, spray into the mouth, etc.

1.3.3 CLASSIFICATION FOR FDI PRODUCTS

The classification of FDI products are based on criteria, as outlined below:

a) Main criteria

i) Negative List For Food as listed *in Table 1: Negative List For Food*:

- FDI products containing ingredient(s) from Negative List for Food shall be regulated by NPRA.

ii) Medicinal/ health claim refer to the term "medicinal purpose" as stipulated in the Sales of Drug Act 1952, Section 2:

- FDI products not containing ingredient(s) from Negative List For Food and with medicinal/ health claim shall be regulated by NPRA

- FDI products not containing ingredient(s) from Negative List For Food and without medicinal/ health claim shall be regulated by FSQD.

Reference : Pekeliling Kriteria Baru Pengkelasan Produk (07 August 2014) Circular No. (19)dlm.BPFK/PPP/01/03 Jld.3

b) Other criteria

- When there is greater uncertainty regarding the safety of a FDI product, such shall be regulated by NPRA. This is to enable closer monitoring of such products, so as to safeguard the health of the consumer.

Table 1: Summary table of Classification of Food Drug Interphase Product

NO.	DRUG	NON-DRUG
i)	Contain Active ingredient and with medicinal/ health claim	Not containing Active ingredient from **Negative List For Food** and **NO** medicinal/ health claim
ii)	Contain Active ingredient listed in **Table 2: Negative List for Food with** medicinal/ health claim	
iii)	Contain Active ingredient listed in **Table 2: Negative List for Food without** medicinal/ health claim	
iv)	Formulated in pharmaceutical dosage form (eg. tablet, capsule, liquid,softgel, sublingual, etc)	
v)	When there is greater uncertainty regarding the safety of an FDI product, such shall be regulated by NPRA. This is to enable closer monitoring of such products, so as to safeguard the interest of the consumer.	

1.3.4 ADDITIONAL NOTES

1. Substances listed in the prohibited/ banned ingredient list of the Drug Registration Guidance Document (DRGD) and Schedule Poison shall not be permitted for use in any FDI products.

2. Products categorized as a natural product are not allowed to contain creamer.

3. Food products are not allowed to be packed in blister pack/ any other form of packaging which resembles the packing of drug product.

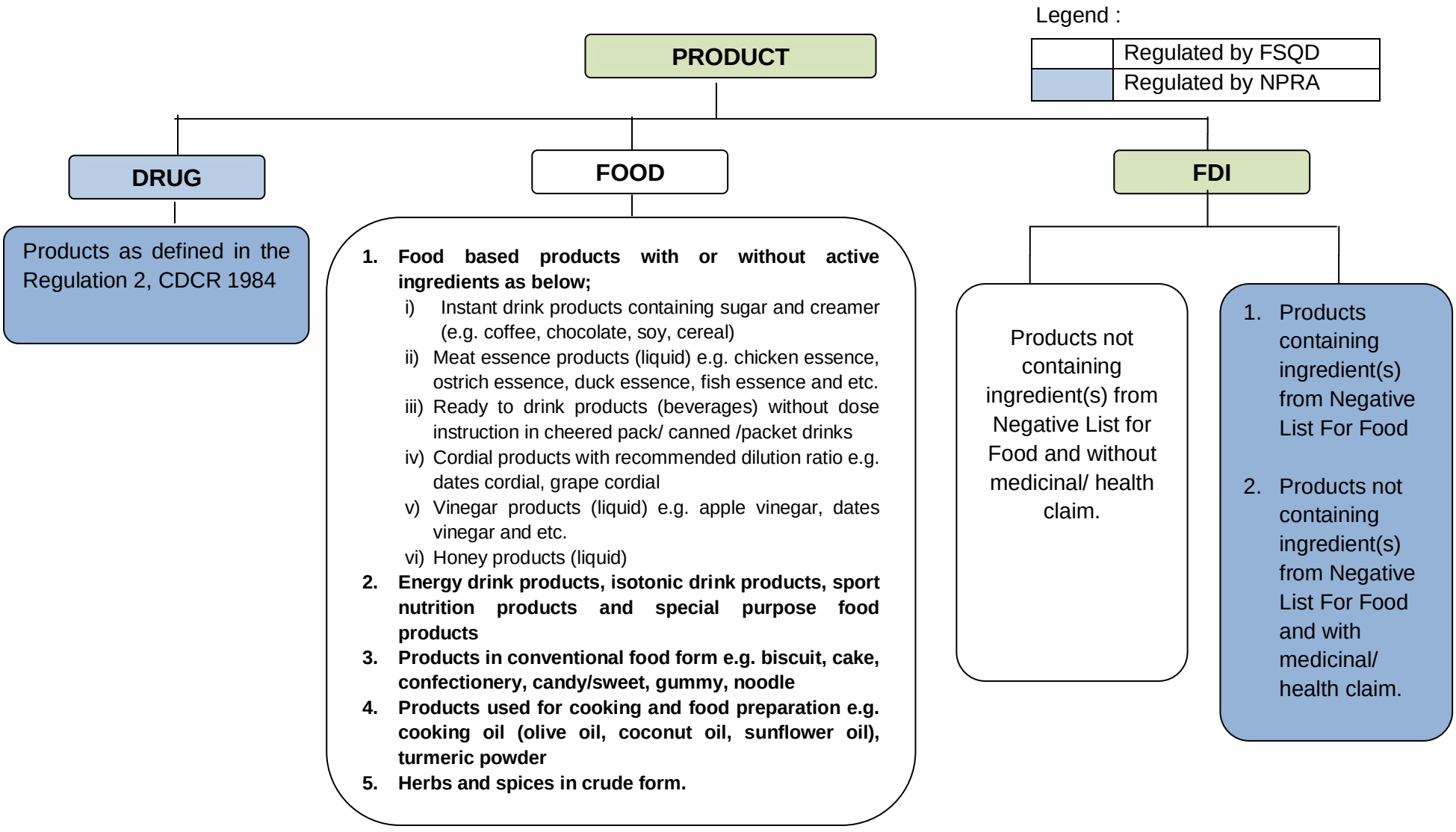
4. Any foods or combination of foods that are regulated by FSQD shall not be in pharmaceutical dosage form, such products are advised to reformulate into a non-pharmaceutical dosage form.

5. Food products shall not have name/ brand name with the word of ‘stem cell’.

6. Products containing only ingredient(s) such as roselle, jasmine, rose, chamomile, chrysanthemum flower, ginger (rhizome), vanilla(stem), mint leaf, lemon peel and cinnamon bark (with/without C*amelia sinensis*) will be regulated by FSQD.

7. Fruit ingredients that are not commonly consumed as food in Malaysia will be considered as active ingredient.

1.3.5 PICTORIAL GUIDE TO CLASSIFICATION OF FOOD-DRUG INTERPHASE PRODUCTS



1.3.6 NEGATIVE LIST FOR FOOD

Table 2: Negative List For Food

Ingredient	Common or Other Name
Stichopus spp.	Gamat
Gypsum Fibrosum	
Monascus purpureus	Red yeast rice
Natto extract	Fermented soy bean extract
Placenta	
Pearl	
Bile	
Glucosamine	
Hyaluronic acid	
Glutathione	
Gamma-amino Butyric Acid (GABA)	
Resveratrol	
Actaea racemosa	Black Cohosh, Cimicifuga racemosa
Artemisia Spp. (all species)	Wormwood, Mugwort
Azadirachta indica	Nimba, Neem
Brucea javanica, Brucea amarissima	Sumatrana amarissimus, Java brucea
Bufo gargarizans Cantor, Bufo melanostictus Schneider, Bufo vulgaris Lour	Toad, Samsu, kodok, kerok
Chelidonium majus	Celandine, Great Celandine, Nipplewort
Conium maculatum	Hemlock
Coptis chinensis, Coptis teeta	Chinese Goldthread
Croton tiglium L.	Croton
Datura spp. (all species)	Jimson weed, Devil's apple, Green Dragon, Zombie's Cucumber, Moon Weed, Trumpet Lily, Stinkweed
Digitalis spp.(all species)	
Dryobalanops lanceolata Burck	Borneo camphor, Kapur, Malay Camphor, Sumatra camphor
Fritillaria spp.	Fritillary Bulb
Gelsemium semperi virens	Palaung Thay
Hypericum perforatum	St. John's Wort
Juniperus sabina	Savin, Savine

Mahonia aquifolium, Mahonia repens, Mahonia nervosa	Mahonia Aquifolium: Oregon Grape, Mountain Grape, Barberry. Mahonia Repens: Creeping Barberry, Creeping Mahonia, Creeping Oregon-Grape
Melanorrhoea usitata Wall.	Vanish tree
Mucuna pruriens	Cowhage, Cowage
Mylabris phalerata, Mylabris cichorii	Blister beatle, Mylabris
Nerium indicum	Indian oleander, Exile Tree.
Nerium oleander	Indian oleander, Exile Tree.
Phellodendron amurense, Phellodendron chinense	Amur Cork tree
Plumbago indica	Rose-coloured leadwort
Plumbago zeylanica	White leadwort
Psilocybe cubensis	Boomers, Gold caps
Sanguinaria canadensis	Bloodroot, Indian Paint
Scilla sinensis	
Simmondsia Chinesis	**Jojoba**
Sophora tomentosa	Sea coast Laburnum, Silver Bush
Spigelia marilandica	**Worm grass, Pinkroot**
Strophanthus spp.(all species)	Kombe
Strychnos ignatii, Strychnos lucida, Strychnos roberans	**Nux-vomica**
Symphytum peregrinum	Comfrey

Note:

This list :

- is a compilation by the FDI committee.
- is not meant to be exhaustive and will be reviewed from time to time.

- shall be read in conjunction with the current laws and regulations together with other relevant legislations, where applicable, governing pharmaceutical and natural products for human use in Malaysia

Note:

Applicant shall verify on FDI product classification with NPRA in order to determine whether the product shall be registered with the Authority or otherwise.

Reference : Pengkelasan Produk Food-Drug Interphase (27 December 2012)
Circular : Bil.(97)dlm.BPFK/PPP/01/03 Jld. 2

1.4 MEDICAL DEVICE - DRUG - COSMETIC INTERPHASE PRODUCTS

1.4.1 INTRODUCTION

Medical Device-Drug-Cosmetic Interphase (MDDCI) Products are those products that are not clearly defined as a medical device or drug/cosmetic in accordance to the Medical Device Act 737, Control of Drugs and Cosmetics Regulations 1984 and Sale of Drugs Act 1952.

Registration of drug products/ notification of cosmetics that has been classified must follow the requirements that have been set forth as follows:

a) **Drugs & Cosmetics** – The registration/ notification regulated by the NPRA is in accordance with the requirements set forth in the Poisons Act 1952 and its Regulations, Sales of Drugs Act 1952 and the Control of Drugs and Cosmetics Regulations 1984;

b) **Medical Device** – The registration regulated by Medical Device Authority is in accordance with the requirements set forth in the Medical Devices Act 2012 (Act 737).

Combination products includes:
i) A product comprised of two or more regulated components, i.e., drug/device, biological/device, or drug/device/biological, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
ii) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products.

For Interphase Product and Combination Product (Device-Drug or Drug-Device), it will be regulated according to the classification that has been made and by the relevant agencies.

Please refer ;
(i) Directive No. 4 Year 2017, Ref. (9) dlm.BPFK/PPP/07/25 Jld. 1 : DIREKTIF KUATKUASA PEMAKAIAN *GUIDELINE FOR REGISTRATION OF DRUG-MEDICAL DEVICE AND MEDICAL DEVICE-DRUG COMBINATION PRODUCTS*
(ii) Guideline For Registration Of Drug-Medical Device and Medical Device-Drug Combination Products

1.4.2 CLASSIFICATION CRITERIA

The following may be used as criteria to assist in the classification of products:

a) The primary intended purpose of the product;
b) The primary mode of action/ the principal mechanism of action by which the claimed effect or purpose of the product is achieved;

- Drug is based on pharmacological, immunological or metabolic action in/on the body; but
- Medical device does not achieve its primary mode of action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its intended function by such means.;

c) Active ingredient, indication and pharmaceutical dosage form (these are the main criteria for classification of the drugs);
d) Classification of the products in reference countries.

For classification of MDDCI products and combination products as decided by the committee, please refer to **Table III**. It shall be used as guidance for classification only.

Applicant shall verify on MDDCI product classification with NPRA in order to determine whether the product shall be registered by the Authority or otherwise.

Table III: SUMMARY OF MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) PRODUCT CLASSIFICATION DECISION

NO	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN DIVISION
1.	**Aqueous Cream Product**	As an emollient cream with moisturizing properties to promote healing and relief to the symptoms of skin dryness, impaired barrier function, skin problems/ diseases.	**OTC DRUG**	**NPRA**

2.	**<u>Blood bag containing anticoagulant/ preservation agent</u>**	To collect and preserve blood and its components (for use with cytapheresis device only) **NOTE :** It is not for direct intravenous infusion.	**MEDICAL DEVICE**	**MDA**
3.	**<u>Catheter Lock/ Flush Solutions</u>** (eg. heparinised saline, sodium citrate solution)	As an anticoagulant for use as a catheter lock / flush solution for flushing off catheters and cannulas to maintain catheter/ cannula patency and to prevent coagulation of blood or infection in the cathether. **NOTE :** **-** It is not indicated for therapeutic use. - Contraindicated for direct systemic administration.	**MEDICAL DEVICE**	**MDA**
4.	**<u>Collagen Hemostatic Agents</u>** (fibrillar or soft, pliable pad/sponge or loose fibres)	A sterile, bioabsorbable device derived from animal collagen (e.g., bovine or porcine collagen) designed to produce a rapid haemostasis through platelet activation/aggregation (which initiates the haemostatic cascade leading to a fibrin clot) during a surgical procedure. It is applied directly to the wound where it remains to be absorbed by the body; it is not dedicated to a specific anatomy/application and does not contain an antimicrobial agent	**MEDICAL DEVICE**	**MDA**

5.	**<u>Dental Products</u>**			
	i. Fluoride dental preparations (eg. toothpaste, tooth powder, mouthwash, dental varnish)	a. To maintain oral hygiene.	**COSMETIC** (If concentration of fluoride ≤1500ppm)	**NPRA**
		b. To maintain oral hygiene and prevent oral diseases.	**DRUG** (If concentration of fluoride is >1500ppm)	**NPRA**
		c. A liquid substance used for the protection of pulpal tissue and to provide a marginal seal to newly placed amalgam restorations. A thin coating of this solution is applied over the tooth's surfaces before placement of restorations. It is used as a protective agent for the tooth against constituents of restorative materials. After application, this device cannot be reused.	MEDICAL DEVICE	MDA
		d. As a desensitizing agent for the treatment of hypersensitive teeth, for sealing the dentinal tubules for cavity preparations or on sensitive root surfaces or to line cavity preparations under amalgam restorations.	**MEDICAL DEVICE**	**MDA**

	ii. Root canal filling incorporating antibiotic	To seal the canal and disinfect the dentinal walls by diffusing through dentine. The antibiotic provides ancillary actions as bactericidal antibiotic and anti-inflammatory agent to assist in reducing pain and in maintaining a bacteria-free environment within the root canal.	**Device-Drug combination product regulated as MEDICAL DEVICE**	**MDA**
6.	**<u>Dialysis Products</u>**			
	i. Peritoneal dialysis dialysate	It is used for the exchange of solutes across the peritoneum of the patient (in this case, used as a semi-permeable membrane)	**DRUG**	**NPRA**
	ii. Haemofiltration solution	It is used for the exchange of solutes with blood through a system of extracorporeal filters.	**DRUG**	**NPRA**
	iii. Haemodialysis dialysate	It is used for the exchange of solutes with blood through a semi-permeable membrane in the dialyser of a haemodialysis system.	**MEDICAL DEVICE**	**MDA**
	iv. Haemodiafiltration solution	It is used as a replacement solution in haemodiafiltration. **NOTE** : Haemodiafiltration is the combination of haemodialysis and haemofiltration performed either simultaneously or sequentially.	**DRUG**	**NPRA**

7.	**<u>Drug-Eluting Beads</u>** (Produced from biocompatible polyvinyl alcohol hydrogel modified with sulphonate groups in phosphate buffered saline.)	It is an embolic agent which is intended to be loaded with a chemotherapy agent, eg. doxorubicin for the purpose of treatment of malignant hypervascularised tumour(s) by embolisation of vessels and occlusion of blood flow supplying malignant hypervascularised tumour(s) and as a secondary action, delivers/elutes a local, controlled, sustained dose of the chemotherapy agent directly to the tumour(s).	If the beads are sold separately from the drug, it will be classified as **MEDICAL DEVICE** If the beads and drug are packaged and sold together, it will be classified as **Drug-device combination product regulated as DRUG**	**MDA/NPRA**
8.	**<u>Drug-Eluting Stents (DES)</u>**	For use in angioplasty or coronary stenting procedures.	**Device-Drug combination product regulated as MEDICAL DEVICE**	**MDA**
9.	**<u>Drug - Delivery Products Regulated as Drug Products</u>** (eg. insulin prefilled pen/ syringes, asthma inhalers, intrauterine contraceptives whose primary purpose is to release progestogens)	To administer pharmacologically active substance	**Drug-device combination product regulated as DRUG** **NOTE:** The device component will be regulated on a case to case basis.	**NPRA**

10.	**<u>Enteral Feeding Kit</u>** (containing Iodine Pack drug)	A collection of sterile devices that includes tubing and other materials intended to administer nutrient liquids directly into the stomach, duodenum, or jejunum of a patient by means of gravity or an enteral pump.	**Device-Drug combination product regulated as MEDICAL DEVICE**	**MDA**
11.	**<u>Eye Products</u>**			
	i. Eye/ ocular lubricants, including artificial tears	A sterile substance used to provide supplemental lubrication/hydration/ moisturization to the eyes to treat/ alleviate symptoms of soreness, burning, irritation and discomfort caused by dry, tired, and/or strained eyes resulting from dry eye syndrome, ageing/ hormone changes (menopause), or environmental factors (e.g., pollution, dust, heat, smoke and air conditioning).	**MEDICAL DEVICE** (If it contains an active substance with pharmacological, immunological or metabolic primary mode of action, it will be classified as **DRUG**)	**MDA**
	ii. Aqueous/vitreous humour replacement medium	It is used to assist in performing ophthalmic surgery, e.g., to maintain the shape of the eyeball during the intervention, preserve tissue integrity, protect from surgical trauma, or to function as a tamponade during retinal reattachment.	**MEDICAL DEVICE**	**MDA**
	iii. Cold Sensation Eye Pillow	To reduce fatigue from work stress or lack of sleep.	**MEDICAL DEVICE**	**MDA**
12.	**<u>General Purpose</u>**	To isolate a site of surgical	**MEDICAL**	**MDA**

	Surgical or Barrier Drapes (A sterile protective covering made of natural or synthetic materials, or both.)	incision or a surgical field from contamination (e.g., microbial, substance) in various clinical settings (e.g., in an operating room or catheterization laboratory). The device may also be used to protect a patient from heat/flame during a surgical procedure. This is a reusable or single use device.	**DEVICE** (If it incorporates an ancillary pharmacologically active substance, it will be classified as **Device-Drug combination product regulated as MEDICAL DEVICE)**	
13.	**General-body orifice lubricant**	Lubricant intended to facilitate entry of a diagnostic or therapeutic device into a body orifice by reducing friction between the device and the body; Lubricant during catherisation, probing,endoscopy, changing fistula catheters,intubation,and prevention of iatrogenic injuries to the rectum and colon. E.g ancillary local anaesthetic: lidocaine	**MEDICAL DEVICE** (If it incorporates an ancillary pharmacologically active substance, it will be classified as **Device-Drug combination product regulated as MEDICAL DEVICE**	**MDA**
14.	**Heat Pad/ Cooling Pad**	To relief aches and pains.	**MEDICAL DEVICE**	**MDA**
15.	**In vivo diagnostic agents**	a. For diagnostic purposes, eg. : - X-ray / MRI contrast media - NMR enhancing agents - Opthalmic diagnostic agents,	**DRUG**	**NPRA**

		eg. staining agent such as fluorescent ophthalmic strips for diagnostic purposes - Carrier solutions to stabilize microbubbles for ultrasound imaging - Radiopharmaceuticals for diagnostic use eg ^{14}C- Urea Capsule for H pylori test		
		b. As Diagnostic Test Kit consist of drug and analyser	**DRUG-DEVICE combination product regulated as DRUG** **NOTE:** The device component will be regulated on a case to case basis.	**NPRA**
		c. As diagnostic analyser only (without drug)	**MEDICAL DEVICE**	**MDA**
16.	**<u>Irrigation solutions</u>**	For mechanical cleansing and rinsing including those used in the eye such as for cleansing of the eye, body tissues, body cavities, wounds or irrigation of a special tube called a catheter which is used to drain the bladder.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it will be classified as **DRUG**)	**MDA**
17.	**<u>Medical gases</u>**	a. To be used in anaesthesia and inhalation therapy, including their primary containers.	**DRUG**	**NPRA**

		b. For in-vivo diagnostic purposes including lung function tests.	**DRUG**	**NPRA**
18.	**<u>Medicinal Patch</u>**	To relieve fatigue, body aches, joint pains; To regulate hormone imbalance	**DRUG**	**NPRA**
19.	**<u>Nail Anti-fungal Products</u>** (eg. pen applicator containing acetic acid/ lactic acid)	Treatment of onychomycosis (fungal nail infection) by lowering the pH of the nail bed, thus creating a micro-environment that is hostile to fungal growth.	**MEDICAL DEVICE**	**MDA**
20.	**<u>Nasal inhaler</u>**	A hand-held device designed to administer substances directly into the nares of a patient, to serve as a barrier against external influences by formation of a moisturizing film on the nasal mucosa.	**MEDICAL DEVICE**	**MDA**
21.	**<u>Oral care products</u>**			
	Artificial Saliva / Saliva Substitute/ Replacement	Solutions used to mimic and replace/substitute normal saliva in the symptomatic treatment of dry mouth (xerostomia). Generally contain viscosity-increasing agents, such as mucins or cellulose derivatives such as carmellose as well as electrolytes, including fluoride. They seldom relieve symptoms for more than 1 or 2 hours and does not stimulate saliva production.	**MEDICAL DEVICE**	**MDA**

22.	**<u>Other topical antiseptics/ disinfectants</u>**			
	i. Swabs/ Wipes containing antiseptics/ disinfectants/ antimicrobial substances (eg. alcohol, chlorhexidine, iodine, cetrimide)	For use on human skin and intended to be used for a medical purpose, eg pre/post injection, wound cleaning etc.	**DRUG**	**NPRA**
	ii. Preparations (including swabs/ wipes) containing antiseptics/ disinfectants/ antimicrobial substances (eg. alcohol, chlorhexidine, iodine, cetrimide)	Intended for the disinfection of medical devices.	**MEDICAL DEVICE**	**MDA**
23.	**<u>Peeling/Exfoliator Products</u>** (eg. Products containing glycolic acid and salicylic acid)	To improve skin texture due to unaesthetic skin appearance caused by pigmentation, post acne scars, photo damage, etc. **NOTE :** The ingredient and intended use should comply with the Guidelines for Control of Cosmetic Products in Malaysia.	**COSMETIC**	**NPRA**
24.	**<u>Personal Care Products</u>**			
	i. Personal Intimate Hygiene	a. For female/ male intimate hygiene **NOTE** : The product should be rinsed off.	**COSMETIC**	**NPRA**

		b. For symptomatic relief of vaginal irritation/ infections by changing the vaginal pH.	**DRUG**	**NPRA**
	ii. Vaginal Douche	Vaginal douching is the process of intravaginal cleansing with a liquid solution for : - personal hygiene or aesthetic reasons - preventing or treating/managing vaginal infections - symptomatic relief of minor vaginal soreness, irritation, itching - cleansing and deodorizing after menstruation - washing out vaginal medication, if so instructed by the physician - deodorizing and washing out the accumulations of normal secretions - removing contraceptive creams and jellies - cleansing the vaginal vault after sexual relations **NOTE :** - Douching is not recommended during pregnancy - A douch is to be used as a cleanser and it should not be used as a contraceptive	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG**)	**MDA**

	iii. Hand sanitizer (eg. gel, foam, liquid)	For general hand hygiene without therapeutic claims.	**COSMETIC**	**NPRA**
	iv. Personal Intimate Lubricant	To use as a vaginal lubricant during the climaterium (pre-menopause, menopause, post-menopause) and to treat irritations in vaginal epithelium in cases of physiological decrease of lubrication and consequent increase in vaginal dryness.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG**)	**MDA**
25.	**<u>Skin Barrier Product</u>** (eg. lotion, emulsion, ointment, cream)	a. To form a physical barrier between the skin and the environment to seal out moisture in order to promote healing and relief to the symptoms of skin dryness, impaired barrier function, skin problems/ diseases.	**MEDICAL DEVICE** (If it contains a pharmacologically active substance, it may be classified as **DRUG**)	**MDA**
		b. Soothe and prevent diaper rash discomfort.	**DRUG**	**NPRA**
		c. To maintain/ improve normal skin condition without any therapeutic claims.	**COSMETIC**	**NPRA**

26.	**Soft tissue filler/ Dermal filler**	To correct cutaneous contour deformities of the skin (e.g., moderate to severe facial wrinkles and folds such as nasolabial folds, scars), particularly in cases of aging or degenerative lesions.	**MEDICAL DEVICE** (If it incorporates an ancillary local anaesthetic eg. lidocaine, it will be classified as a **Device-Drug combination product regulated as MEDICAL DEVICE)**	**MDA**
27.	**Synthetic fluid tissue reconstructive material**	As a submucosal implant in the urinary tract for urinary incontinence or vesicoureteral reflux. It may also be injected into the vocal cords to treat the effects of paralysis, atrophy, or scarring. After application, this device cannot be reused.	**MEDICAL DEVICE** (If it incorporates an ancillary pharmacologically active substance eg. local anaesthetic such as lidocaine, it will be classified as a **Device-Drug combination product regulated as MEDICAL DEVICE)**	
28.	**Synovial joint replacement fluid (Joint lubricant)**	To help cushion the joint, especially in cases of reduced endogenous synovial fluid viscosity from degenerative disease.	**MEDICAL DEVICE**	**MDA**
29.	**Wart Products**	a. Containing a caustic	**DRUG**	**NPRA**

	(eg. pen applicator containing a caustic agent, cyryogenic kit with refrigerant)	agent eg. trichloroacetic acid (TCA) that destroys warts by chemical coagulation of proteins.	**NOTE :** If a device component is present, it will be regulated on a case to case basis	
		b. Cryotherapy which destroys warts by freezing them using a very cold substance eg. liquid nitrogen or refrigerant made from dimethyl ether and propane.	**MEDICAL DEVICE**	**MDA**
30.	**<u>Wound care/ treatment products</u>**			
	i. Comprising a matrix (eg. dressing, gauze, swabstick, plaster, sponge)	a. To administer a medicinal substance to the wound eg. antimicrobial/ antiseptic agent for the purpose of controlling infection**.**	**DRUG**	**NPRA**
		b. To provide a protective layer/barrier to the wound and prevent microbial penetration and create healing environment. It may incorporate an ancillary medicinal substance eg. antimicrobial/ antiseptic agent.	**MEDICAL DEVICE**	**MDA**
	ii. Comprising a matrix, typically of living cells (fibroblasts) and/or structural	To facilitate the infiltration of native skin elements (e.g. fibroblasts, leukocytes, blood vessels) for skin regeneration.	**MEDICAL DEVICE**	**MDA**

		proteins			
	iii.	**Topical preparation for application to a skin wound** (e.g., abrasion, laceration, cut, ulcer)	To facilitate local haemostasis. It is available in various forms (e.g., gel, spray, powder, ointment, plaster/gauze pad) that can be applied directly to the wound where it forms a seal of transparent layer.	**MEDICAL DEVICE**	**MDA**
	iv.	**Deep cavity wounds dressing for application to a surgical wound**	To use as the wound covering material for deep body cavity to reduce the adhesion of surrounding tissues by applying to the surgical area	**MEDICAL DEVICE**	**MDA**
	v.	**Silver-containing topical preparations for application to a skin wound (eg. silver nitrate/ silver sulfadiazine/ colloidal silver gel, cream)**	To administer/ apply an antiseptic to wounds with mild to moderate exudates such as: - First and second degree burns - Traumatic wounds - Surgical wounds - Partial full thickness wounds - Grafted wounds and donor sites - Lacerations and abrasions	**DRUG**	**NPRA**
	vi.	**Intravascular catheter securement device containing antimicrobial/antiseptic agent (e.g. chlorohexidine gluconate, CHG)**	An intravascular catheter securement device is a device with an adhesive backing that is placed over a needle or catheter and is used to keep the hub of the needle or the catheter flat and securely anchored to the skin. The antimicrobial agent provides ancillary antimicrobial activity to reduce skin colonization and catheter colonization, supress regrowth of microorganism's, and	**DEVICE-DRUG combination product regulated as MEDICAL DEVICE**	**MDA**

		reduce catheter-related bloodstream infections (CRBSI) in patients with central venous or arterial catheters.		

Note:

- The above table is to be used as guidance for classification only.
- The registration/notification of products that have been classified must follow the requirements that have been set forth as follows:

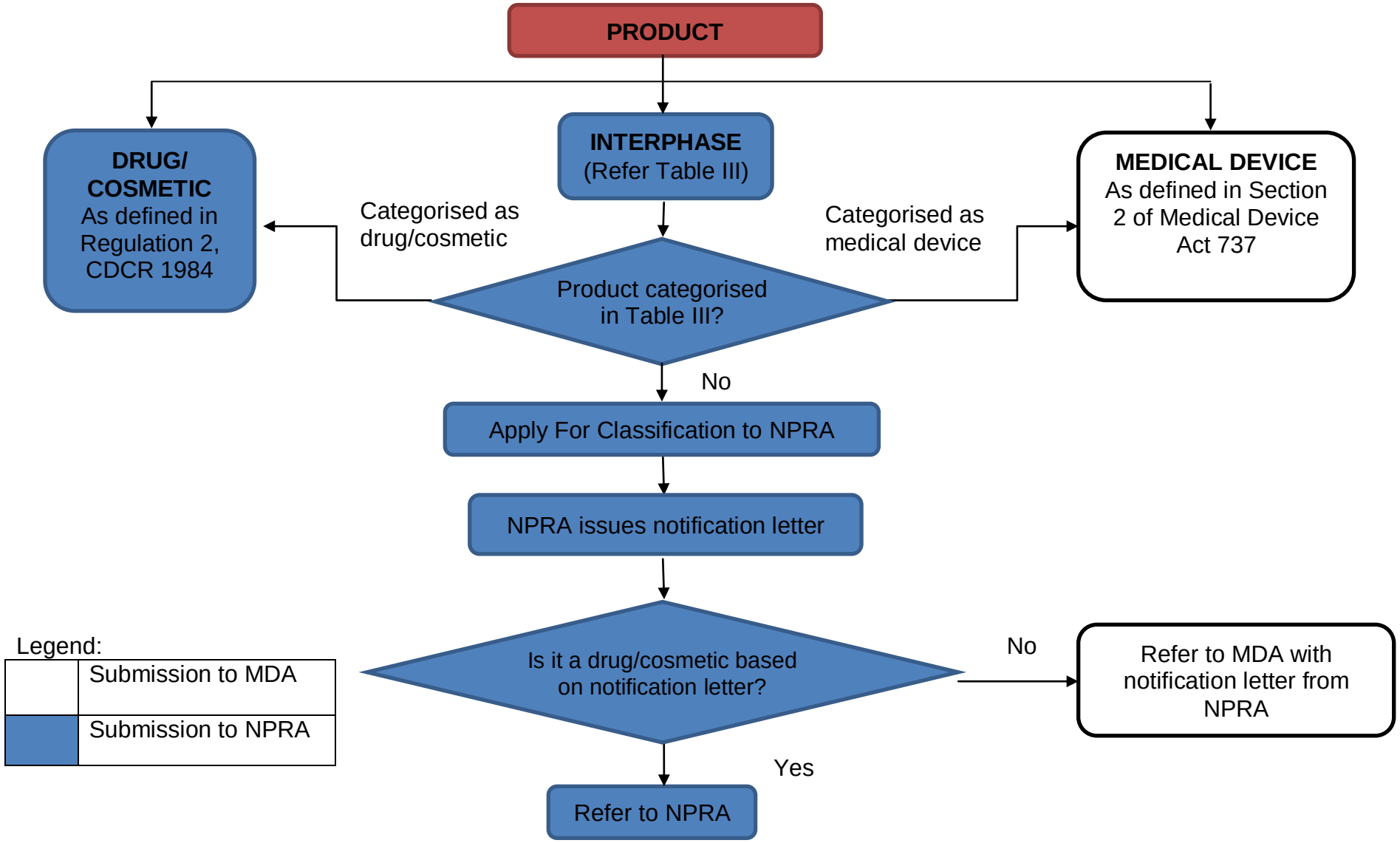
  i- **Drug & Cosmetic** – The registration/notification is in accordance with the requirements set forth in the Poisons Act 1952 and its Regulations, Sale of Drugs Act 1952 and the Control of Drugs and Cosmetics Regulations 1984.

  ii- **Medical Device** – The registration is in accordance with the requirements set forth in the Medical Devices Act 2012 (Act 737).

- **Medical Device** will be regulated by **MEDICAL DEVICE Authority.**
- **Drug & Cosmetic** will be regulated by the **NATIONAL PHARMACEUTICAL REGULATORY DIVISION, Ministry of Health Malaysia.**
- **Drug – Device Combination Product** will be regulated according to the classification that has been made and by the relevant agencies.

Reference: Pekeliling Mengenai Pengkelasan Semula Produk-produk Daripada Kategori Ubat (Drug) Kepada Kategori Peranti Perubatan (Medical Device) (09 December 2014). *Circular : Bil (21) dlm.BPFK/PPP/01/03 Jld. 3)*

GUIDANCE FOR THE CLASSIFICATION OF MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) PRODUCTS



2. DATA EXCLUSIVITY

Data exclusivity refers to protection of undisclosed, unpublished and non-public domain pharmaceutical test data, the origination of which involves a considerable effort, submitted as required to the Director of Pharmaceutical Services for the purpose of scientific assessment in consideration of the:

a) Quality, safety and efficacy of any new drug product containing a New Chemical Entity

b) Safety and efficacy for a second indication of a registered drug product as a condition for registration of any new drug product containing a New Chemical Entity; or approval for a Second Indication of a registered drug product.

For information pertaining to Register of Data Exclusivity Granted in Malaysia, please refer: Register of Data Exclusivity Granted in Malaysia (New Drug) and Register of Data Exclusivity Granted in Malaysia (Second Indication)

2.1 HOW TO APPLY

An application for Data Exclusivity (DE) can be made via a Letter of Intent (LOI) in conjunction with the:

a) Application for registration of a new drug product containing a New Chemical Entity; or
b) Application for a Second Indication of a registered drug product.

The LOI shall be addressed and submitted manually to the Director of NPRA.

The application must comply with all terms and conditions stated in the directive *Arahan Bagi Melaksanakan Data Eksklusiviti Di Malaysia, Bilangan 2 Year 2011.*

The following details are extracted from the Directive on Data Exclusivity (DE) issued by the Director of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984, Bil (11) dlm BPFK/PPP/01/03 Jld 1, 28 February 2011.

2.2 APPLICABILITY AND DATE OF COMING INTO FORCE

The directive is applicable to:

i) New drug product containing a new chemical entity; and
ii) Second indication of a registered drug product.

New drug product containing any new chemical entity means a product that contains an [1]**active moiety** that has not been registered in accordance with the provisions of the CDCR 1984.

[1]**An active moiety** is defined as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other non-covalent derivative (such as a complex, chelate or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Second indication for a registered drug product means a single or cluster of therapeutic indications applied subsequent to the first indication(s) approved at the point of registration of the product. The application for approval of the second indication contains reports of new clinical investigations other than bioavailability studies.

The directive shall come into force on **1st March 2011.**

2.3 GRANT OF DATA EXCLUSIVITY

Any person may apply for Data Exclusivity. Such application shall be made upon submission of documents to the Director of Pharmaceutical Services for the:

a) Registration of a new drug product containing a new chemical entity; or
b) Approval for second indication of a registered drug product.

An application for Data Exclusivity shall only be considered if the application in Malaysia for:

a) New drug product containing a new chemical entity is made within eighteen (18) months from the date the product is first registered or granted marketing authorization; AND

   Granted Data Exclusivity/ Test Data Protection in the country of origin or in any country, recognized and deem appropriate by the Director of Pharmaceutical Services.

b) Second indication of a registered drug product is made within twelve (12) months from the date the second indication is approved; AND
   Granted Data Exclusivity/ Test Data Protection in the country of origin or in any country, recognized and deemed appropriate by the Director of Pharmaceutical Services.

Before the Data Exclusivity is granted:

a) The applicant of a new drug product containing a new chemical entity shall provide to the Director of Pharmaceutical Services the undisclosed, unpublished and non-public domain pharmaceutical test data, the origination, of which involves a considerable effort; OR

b) The applicant for a second indication of a registered drug product shall provide to the Director of Pharmaceutical Services, the reports of new clinical investigations other than bioavailability studies, conducted in relation to the second indication and the origination of which has involved considerable effort.

The Director of Pharmaceutical Services shall decide on whether the application will be granted the Data Exclusivity. The period of the Data Exclusivity granted shall be made on a case to case basis.

The period of the Data Exclusivity **shall not** be more than:

a) Five (5) years for a new drug product containing a new chemical entity; and

b) Three (3) years for a second indication of a registered drug product. The period of Data Exclusivity is for the data concerning the second indication only.

Calculation of the period of Data Exclusivity:

a) For a new drug product containing a new chemical entity, the period of Data Exclusivity shall be calculated from the date the product is first registered or granted marketing authorization AND granted Data Exclusivity/ Test Data Protection in the country of origin or in any country recognized and deemed appropriate by the Director of Pharmaceutical Services.

b) For a second indication of a registered drug product, the period of Data Exclusivity shall be calculated from the date the second indication is first approved AND granted Data Exclusivity/ Test Data Protection in the country of origin or in any country recognized and deemed appropriate by the Director of Pharmaceutical Services.

2.4 CONSIDERATION OF OTHER APPLICATIONS UPON THE GRANT OF DATA EXCLUSIVITY

For a registered new drug product containing a new chemical entity, registration of any other drug product where the active moiety is in all respect the same as the active moiety in the registered drug product which has been granted Data Exclusivity in Malaysia can be considered if:

a) The applicant provides undisclosed, unpublished and non-public domain pharmaceutical test data, the origination of which involves a considerable effort to demonstrate the quality, safety and efficacy if the drug product submitted for registration; OR

b) The applicant has obtained consent in writing for right of reference or use of the test data from a person authorised by the owner of the registered new drug product containing a new chemical entity.

2.5 NON-APPLICATION OF DATA EXCLUSIVITY

Nothing in the Data Exclusivity shall:

a) Apply to situations where compulsory licences have been issued or the implementation of any other measures consistent with the need to protect public health and ensure access to medicines for all; or
b) Prevent the Government from taking any necessary action to protect public health, national security, non-commercial public use, national emergency, public health crisis or other extremely urgent circumstances declared by the Government.

2.6 APPEAL

Any person aggrieved by the decisions of the Director of Pharmaceutical Services may make a written appeal to the Minister within fourteen (14) days from the date the decision is made known to him and any decision of the Minister made on an appeal shall be final.

A person making an appeal may submit any supporting data or documents to the Director of Pharmaceutical Services not later than:

a) 120 days for application of new drug products containing any new chemical entity; or
b) 90 days for the application for second indication of a registered drug product.

3. APPLICATION FORMALITIES

3.1 WHO CAN APPLY FOR PRODUCT REGISTRATION

The applicant for product registration shall be known as the Product Registration Holder (PRH) and must be a locally incorporated company, corporate or legal entity, with permanent address and registered with Companies Commission of Malaysia (with the scope of business related to the health/ pharmaceutical product).

The name of the PRH, including product manufacturer shall not reflect the following:

a) Name of a government agency;
b) Name of a research/ institute of higher education;
c) A name that reflects the quality of pharmaceutical product
   e.g. "*Amalan Perkilangan Baik (APB)*", Good Manufacturing Practice (GMP);
d) Name of a disease;
e) Name of an organ.
   e.g. Heart, Brain, Kidney etc.

The PRH (if the company is not the product owner) should be authorized in writing by the product owner to be holder of the product registration and be responsible for all matters pertaining to quality, safety and efficacy of the product. This shall include updating any information relevant to the product/ application.

3.2 RESPONSIBILITY OF APPLICANT

a) To ensure that all transactions with NPRA shall be done by their appointed person(s);

b) Responsible for all information pertaining to quality, safety and efficacy in support of the product registration application; and shall inform the Authority in a timely manner any change in product information during course of evaluation;

   Under the CDCR 1984, Regulation 8(9): Any person who knowingly supplies any false or misleading information to the Authority with his application for the registration of a product commits an offence.

c) Responsible for all matters pertaining to quality, safety and efficacy of the registered product, including:

   i. Data updates on product quality, safety and efficacy or current Good Manufacturing Practice (cGMP) compliance of the manufacturers (and repackers, where applicable).

      Under the CDCR 1984, Regulation 8(5): Any change in any document, item, sample, particulars or information which shall be notified in writing by the applicant to the Authority within fourteen (14) days from the date of such change.

   ii. Any decision to withdraw the registration of the product with reasons.

d) To notify the Authority of any change in correspondence details, including the name, address, contact person, telephone number, fax number and email;

e) To notify the Authority immediately upon cessation of the applicant as the product registration holder;

3.3 HOW TO APPLY

For registration of products, only web-based online submissions via QUEST at http://npra.moh.gov.my/ shall be accepted.

To conduct transactions via QUEST system, the applicant must first register a membership for QUEST system with NPRA and purchase a USB Token that contains a User Digital Certificate, from MSC Trustgate.com Sdn. Bhd., which shall be installed to the applicant's computer.

For details, please refer to Frequently Asked Questions on QUEST System.

For charges regarding QUEST USB token, please refer to Appendix 1: Fees.

The applicant shall be responsible for any act of fraudulence or misuse pertaining to its authorized QUEST USB token(s).

The NPRA reserves the rights to approve or reject any application for the QUEST membership.

4. FEES

Under the CDCR 1984, Regulation 8(3): The Authority may charge any applicant such costs as it may incur for the purpose of carrying out any evaluation or investigation prior to the registration of any product.

Any payment made shall **NOT** be **REFUNDABLE** once the application has been submitted and payment confirmed.

Applications without the correct fees will not be processed.

4.1 FEES IMPOSED

Please refer to Appendix 1: Fees for fees imposed, which include:

a) Charges for USB Token of QUEST Membership;
b) Processing and Analysis Fee for Product Registration;
c) Charges for Application of Licence;
d) Charges for Amendments to Particulars of a Registered Product;
e) Fee for Certificates; and
f) Charges for Product Classification.

4.2 MODE OF PAYMENT

The processing fee and any other charges shall be paid in the form of bank draft/ banker's cheque/ money order/ postal order made payable to **"Biro Pengawalan Farmaseutikal Kebangsaan"**.

A separate bank draft/ banker's cheque/ money order/ postal order are required for each application.

5. TYPES OF APPLICATION

5.1 REGISTRATION OF PRODUCTS

5.1.1 APPLICATION FOR PRODUCT REGISTRATION FOR THE FOLLOWING CATEGORIES:

a) New Drug Products;
b) Biologics;
c) Generic;
d) Health supplements; and
e) Natural Products.

For details, please refer to Section A, 1.2 Categories of Product and Section B: Product Registration Process.

5.1.2 REGISTRATION OF COMBINATION PACK (COMBO PACK)

a) Refers to products which are packed together in combination for a therapeutic regimen such as for the treatment of *Helicobacter Pylori*, Hepatitis C, etc.).

   Note: *Products which are packed together in combination NOT FOR THERAPEUTIC REGIMEN but for convenience of the consumers (e.g. capsules of five health supplement products in a blister pack) will not be considered for registration as a combo pack.*

b) Shall be registered as a single product.

c) Must consist of registered products only**:**

   i. Where a combination pack consists of registered and unregistered products, the unregistered product needs to be registered first, prior to submission of the application;

   ii. Where a combination pack consists of registered products from different product owners/ PRH, letters of authorization which

include product name and product registration number from each product owner shall be submitted.

d) A product which is packed together with diluent(s)/ adjuvant(s) is NOT considered as a combination pack.

e) Labelling requirement specifically for combination pack is shown in **Table IV**:

No.	Outer Label	Immediate Label
1.	Name of combination pack	Individual name for each products OR name of combination pack
2.	Registration number for the combination pack	Individual registration number for each products OR registration number for combination pack
3.	Name and address of manufacturer and product registration holder	Name and address of manufacturer and product registration holder
4.	Batch number of the combination pack product	Individual batch number for each products
5.	Expiry date (according to the shortest expiry date from the individual products)	Individual expiry date for each products

Note:

These labeling requirements for a combo pack shall as well be subjected to other labelling requirements as stated in Appendix 9.1: Label (mock-up) for Immediate Container, Outer Carton and Proposed Package Insert)

5.1.3 REGISTRATION OF STARTER PACK/ PATIENT INITIATION PACK

a) Starter pack /patient initiation pack may consist of:

   i) Combination of products with different strengths which are packed together in one packaging such as blister or calendar pack.
   ii) Combination of more than one pre-filled pen containing different strengths of preparation in one packaging.
   iii) Must be registered under the same product owner and PRH.

b) Justified and proven specific dosing regimen demonstrated through clinical studies.

c) Each product must be differentiated in terms of its physical description, e.g. colour, shape/size etc. to avoid confusion during drug administration.

d) For products in calendar pack packaging type, additional beneficial criteria such as different strength of tablets arranged in order of the day available per week can be implemented to assist the patients.

e) Labelling requirement specifically for starter pack /patient initiation is shown in **Table V**:

No.	Outer Label	Immediate Label
1.	Statement of starter pack/patient initiation pack Individual name for each products	Individual name for each products
2.	Individual registration number for each products	Individual registration number for each products
3.	Name and address of manufacturer and product registration holder	Name and address of manufacturer and product registration holder
4.	Individual batch number for each products	Individual batch number for each products
5.	Manufacturing date	Manufacturing date

	(according to the earliest manufacturing date from the individual products)	(according to the earliest manufacturing date from the individual products)
6.	Expiry date (according to the shortest expiry date from the individual products)	Expiry date (according to the shortest expiry date from the individual products)
Note: *These labeling requirements for a starter pack/patient initiation pack shall as well be subjected to other labelling requirements as stated in Appendix 9.1: Label (mock-up) for Immediate Container, Outer Carton and Proposed Package Insert)*		

5.1.4 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)

a) Refers to locally manufactured products for export only which are not marketed locally with a different formulation (e.g. colour or strength of ingredients) or shape compared to a registered product;

b) For products containing ingredients/ formulations which are not allowed by the Authority for local use, applicant shall submit a confirmation in writing from the competent authority of the importing country that there is no objection to the importation and sale of the said ingredients/ formulations. Evidence of registration of the said formulation with the competent authority in importing country may be submitted as supporting data;

c) Upon application, a Certificate of Pharmaceutical Product (CPP) will be issued to the applicant for the registered FEO products;

d) For a registered product intended for exportation as well as to be sold in Malaysia:
   - New application for registration for export only will NOT be required if there is no change in the formulation and appearance of the registered product.
   - A CPP will be issued to the applicant for the registered product, together with an explanation/ declaration letter of any difference(s) to the importing country (e.g. a product exported with a different product name), upon application.

e) For a registered product, now intended to be for export only and no longer for sale in Malaysia:
   - Application for registration as a FEO product is required.
   - The existing registration number (i.e. MAL number) will remain the same but with the addition of the administrative code E (For Export Only)

f) Applications for registration of FEO products are processed based on abridged evaluation.

g) Applications shall be submitted by using an application form BPFK 438.1 (for Generic Medicines/ Health Supplements) and BPFK 438.1 (T) (for Traditional Products).

   Note: *The applicant must first register membership for QUEST system with NPRA and subsequently purchase a USB Token that contains a User Digital Certificate, from MSC Trustgate.com Sdn. Bhd. This is to enable the applicant to access the system for product updating once the application for registration is approved. For further detail, please refer Section A General Overview under 3.3 How To Apply.*

5.1.5 REGISTRATION OF ORPHAN PRODUCT

1. As defined in the Malaysian National Medicines Policy 2012 (DUNas) , an orphan product is:

   i. a medicine,vaccine or *in vivo* diagnostic agent that is intended to treat, prevent or diagnose a rare disease
   or
   ii. not commercially viable to supply to treat, prevent or diagnose another disease or condition.

2. For all categories of products namely **new chemical entities/new drugs**, **biologics and generics (including Non-Scheduled Poison product)**:

   i. Application for registration that being submitted to National Pharmaceutical Regulatory Division (NPRA) will only be accepted/ considered after the products have been designated as orphan products.
   ii. Application for registration must be submitted via online system and with appropriate processing fee.
   iii. Upon receipt of complete application, the application will be processed within ninety (90) working days.

iv. Once an orphan product is registered by the Drug Control Authority (DCA), registration number with the addition of special alphabet, MAL ---------- A**Y** / MAL ---------- X**Y** will be given to ease identification for the purpose of surveillance or monitoring.

v. If the product has been registered with some flexibilities in terms of registration requirements, surveillance activities and monitoring of quality, safety, and efficacy will be implemented within **six months** after the product is registered. Surveillance procedures and requirements are as follows:

   a) The product registration holder must report any adverse reactions involving orphan product to NPRA (please refer to the guideline for adverse drug reactions reporting on NPRA website)
   b) Periodic Safety Updates Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) must be submitted to NPRA for orphan products in the category of new chemical entities/new products and biologics every 6 months for the first 2 years and once a year for the following 3 years.
   c) Products will be sampled and tested to ensure that it complies to the established standards and specifications. Actions will be taken against products that do not comply to the established standards.

3. For orphan products in the category of **new chemical entities or new drugs**, other than the requirements as stated in para 2, the followings are also required:

   i. For new active ingredients, data on pre-clinical and clinical studies must be submitted to support the safety and efficacy of the product. In addition, the product must be registered in at least one reference country.
   ii. If the product / active ingredient has been established, published literature to support the safety and efficacy of the product is sufficient and pre-clinical or new clinical studies are not required. In addition, the product must be registered in at least one country.
   iii. The product can be manufactured in countries where the health authorities is not the participating authority in the Pharmaceutical Inspection Cooperation / Scheme (PIC/S) . However, the product registration is valid only for 2 years and the inspection of Good Manufacturing Practice (GMP) will be conducted by NPRA within that period of time.
   iv. Stability data and storage condition of the product is not limited to the requirements of Zone IVB provided that post-approval commitment will be

given and requirements to Zone IVB will be complied during the renewal of product registration.

v. If applicants are unable to submit the process validation report and analytical validation report, the product samples should be tested by NPRA **within 6 months** from the date the product is registered. However, applicants are still required to submit the protocol of analysis to be evaluated together with the registration application.

4. For orphan products in the category of **generics** in which the innovator with the same active ingredients and same dosage forms previously registered with DCA but its registration status has changed to expired/ terminated/ withdrawn, bioequivalence study reports is not required. This product can also be registered with the requirements pertaining to GMP, stability data, process validation and analytical validation report as allowed for the products of new chemical entities or new drugs as stated in para 3.

5. For orphan products in the category of **biologics**, requirements and conditions for registration as per para 2 can be considered. However, flexibilities or other conditions as per para 3 will only be considered on a case by case basis.

6. Requirements and other conditions that are not mentioned here such as labelling requirements etc. are in accordance with the existing policies as required in the Drug Registration Guidance Document (DRGD), related directives and circulars.

Summary of Procedures, Requirements and Conditions For Registration of Orphan Products by Product Categories

No.	Procedures/Requirements/Conditions For Registration	New Chemical Entity/New Drug Products	Biologic Products	Generic Products (Including Non-Scheduled Poison)
1.	Upon receipt of complete application, the application will be processed within ninety (90) working days (submitted via online system and with appropriate processing fee).	√	√	√

2.	Pre-clinical and clinical studies must be submitted to support the safety and efficacy of the product. The product must be registered in at least one reference country.	√	Case-by-case basis	Not applicable
3.	If the product / active ingredient has been established, published literature is sufficient to support the safety and efficacy of the product and pre-clinical or new clinical studies are not required. The product must be registered in at least one country.	√	Case-by-case basis	Not applicable
4.	The product can be manufactured in countries where the health authorities is not the participating authority in the Pharmaceutical Inspection Cooperation / Scheme (PIC/S). However, the product registration is valid only for 2 years and the inspection of Good Manufacturing Practice (GMP) will be conducted by NPRA within that period of time.	√	Case-by-case basis	√
5.	Stability data and storage condition of the product are not limited to the requirements of Zone IVB provided that post-approval commitment will be given and requirements to Zone IVB will be complied during the renewal of product registration	√	Case-by-case basis	√
6.	If applicants are unable to submit the process validation report and analytical validation report, the product samples should be tested by NPRA within 6 months from the date the product is registered. However, applicants are still required to submit the protocol of analysis to be evaluated together with the registration application.	√	Case-by-case basis	√

7.	Bioequivalence study reports are not required if the innovator product is no longer registered in Malaysia.	Not applicable	Not applicable	√
8.	Registration number with the addition of special alphabet , MAL ---------- AY / MAL ---------- XY	√	√	√
9.	Surveillance activities and monitoring of quality, safety, and efficacy will be implemented within six months after the product is registered.	√	√	√

5.2 AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

5.2.1 VARIATION

Variation refers to change of particulars of a registered product.

a) For pharmaceutical products, there are three (3) types of variation, which are Major Variation (MaV), Minor Variation Prior Approval (MiV-PA) and Minor Variation Notification (MiV-N). For details, please refer Malaysian Variation Guideline (MVG).

b) For health supplement and natural product, there are three (3) types of variation, which are Major Variation (MaV), Minor Variation Prior Approval (MiV-PA) and Minor Variation Notification (MiV-N). For details, please refer Malaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation)

c) For biologic products, please refer to the Malaysian Variation Guidelines for Biologics (MVGB) and Section E: 16.1.3 "Variation Application for Biologic Products.

No change of any particulars of a registered product (except for Minor Variation Notification) shall be made without prior approval from NPRA. The registration of a product shall be reviewed for suspension or cancellation if changes are made without prior approval of the Authority.

5.2.2 CHANGE IN MANUFACTURING SITE

Change of Manufacturing Site (COS) refers to change of manufacturing site for certain part or all of the manufacturing process of a product, but it does not cover changes related to a new site, where only:

a) batch release takes place OR

b) to a new packager (secondary packaging or labelling), as these changes are covered under applications for amendments to the particulars of a registered product (variation).

However, a change of manufacturing site for biologics shall require a new product application only if the change is extensive that will have an impact on the quality, safety and efficacy profile of the final product.

For details, please refer to Section E: 16.2 Change of Manufacturing Site.

5.2.3 CHANGE IN PRODUCT REGISTRATION HOLDER

It refers to a transfer of marketing authorization from the existing product registration holder (PRH) to another proposed new holder. This application allows the same registration number of the registered product to be maintained.

For details, please refer to Section E: 16.3 Change of Product Registration Holder.

5.2.4 NEW/ ADDITIONAL INDICATION

It is defined as an indication which was not initially approved for a registered pharmaceutical product. This shall include new therapeutic indication or indication for a new age group, such as usage in children and shall not include changing/ rephrasing of sentences.

There are two (2) types of evaluation process available for a new/ additional indication application, i.e. full evaluation process and verification process.

For details, please refer to Section E: 16.4 New/ Additional Indication.

5.2.5 APPLICATION FOR A CONVENIENT PACK

a) Refers to products which are packed together in a single packaging unit for convenience of the consumers, such as a Confinement Set or *Set Jamu Bersalin*.

b) Shall consist of registered products only.

c) The convenient pack is applicable for registered products in the categories of;

i) Health supplements.

ii) Natural products.

Or registered products from both categories (i) and (ii)

iii) Non-Scheduled Poison (OTC)

(Only between OTC products with Abridge Evaluation category)

d) Application for a convenient pack shall be made via the variation process.

For details, please refer to Section E: 16.1 Variation and Section E: 16.5 Application for a Convenient Pack.

5.3 RENEWAL OF PRODUCT REGISTRATION

The registration shall be valid for five (5) years or such a period as specified in the Authority database (unless sooner suspended or cancelled by the Authority);

The renewal of product registration should be submitted **within six (6) months prior to the expiry** of the validity period of a product registration, together with the appropriate fee.

Please refer also at Section E: 14 Maintenance of Registration.

5.4 CERTIFICATES

5.4.1 CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP)

A CPP which follows the format recommended by WHO shall be issued to locally manufactured products that are to be exported. For application of CPP, applicant shall fill in form BPFK 412.2: Permohonan Perakuan Keluaran Farmaseutikal.

A fee, as stated in Appendix 1: Fees, is payable on the issue of such certification.

Upon receipt of complete application, the certificate shall be issued within fifteen (15) working days.

5.4.2 GOOD MANUFACTURING PRACTICE (GMP) CERTIFICATE

According to the CDCR 1984, compliance to Good Manufacturing Practice (GMP) is prerequisite to application of a manufacturing license, as well as product registration/ cosmetic notification.

GMP is a standard which shall be followed by the manufacturers to ensure that the products manufactured are safe, efficacious and of quality.

Upon complete application, a GMP certificate will be issued and a fee, as stated in Appendix 1: Fees, is payable on the issue of such certification.

If a manufacturer who wishes to build a new manufacturing premise, the manufacturer may submit a proposed premise layout plan to the Centre for Compliance and Licensing, NPRA for evaluation.

For more information, please refer Section D: 13.4 GMP Certificate.

5.5 LICENSES

Note:
In addition to the relevant laws and regulations as stated in this DRGD, manufacturers are required to comply with the principles of Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP). Meanwhile, Importers and Wholesalers are required to comply with the principles of Good Distribution Practice (GDP).

According to the CDCR 1984, any company who wishes to manufacture, import and/or wholesale any registered products needs to have Manufacturer's Licence, Import Licence and/or Wholesaler's License.

For more information pertaining application of appropriate licences, please refer Section D: 13. Licensing or contact Licensing Unit, Centre for Compliance and Licensing (CCL), NPRA or NPRA website.

As for processing fee for these applications, please refer to Appendix 1: Fees

5.6 CLINICAL TRIAL IMPORT LICENCE (CTIL)/ CLINICAL TRIAL EXEMPTION (CTX)

For more information pertaining to any matters of clinical trial, please refer to NPRA website.

6. GENERAL CONDITIONS FOR REGISTRATION OF DRUG PRODUCTS UNDER THE CONTROL OF DRUGS AND COSMETICS REGULATIONS 1984

6.1 REGISTRATION CODE/ NUMBER

The product registered with the Registration Number as stated in the Authority database shall have the name, composition, characteristics, specifications and origin as specified in the registration documents and Authority database.

Registration number appears as MALYYMM$$$$@##, e.g. MAL11070001ACERSY:

- MAL refers to “Malaysia”
- YYMM refers respectively to year and month of registration by the Authority (e.g. 1107: July 2011);
- $$$$ refers to a serial number for a product being registered (e.g. 0001);
- @ refers to category of product being registered i.e. A/ X/ N/ T/ H; and
- ## refers to administrative code used by NPRA i.e. C/ E/ R/ S/ Y.
- The symbols @ and ## refer to:
  a) A= Scheduled Poison
  b) X= Non-scheduled Poisons
  c) N= Health Supplements
  d) T= Natural Products/ Traditional Medicines
  e) H= Veterinary Products
  f) C= Contract Manufactured (the product is manufactured by a GMP certified contract manufacturer)
  g) E= For Export Only (FEO) (the product is to be sold for export only and not for sale in the local market)
  h) R= Packed and/or repacked (the product is packed and/or repacked by an approved GMP certified packer and/or repacker)
  i) S= Second source (the product is from a second source/ approved second manufacturer)
  j) Y= Orphan products
  k) Z= Products gazetted as zero-rated under the Goods and Services Tax Act 2014, Goods and Services Tax (Zero-Rated Supplies) Order 2014.

6.2 PRODUCT PARTICULAR

The holder of the registered product shall supply such documents, items, samples, particulars or information as the Authority may require in relation to the registered product.

No change in name, composition, characteristics, origin, specifications, manufacturer, packing, indications, labeling, package insert, product literature or any relevant particulars of the registered product shall be made without prior approval of the Authority.

6.3 LABELLING AND PACKAGING

6.3.1 SHRINK WRAPPING

Shrink wrapping of multiple boxes of approved pack sizes are allowable provided the following conditions are met:

a) This refers to multiple boxes of approved pack sizes of a single or multiple registered products which are shrink wrapped and marketed together for convenience of the consumers.

b) This only applies to registered products from the Health Supplements, Natural Products/ Traditional Medicines and Non-scheduled Poisons category (category T, N and X).

c) The shrink wrap does not come into contact with the dosage form.

d) There are no qualitative or quantitative changes to the approved registered primary packaging and the outer packaging.

e) There are no changes to the label contents of the product, and the label contents are not obscured.

f) The shrink wrap used must be completely transparent and does not contain any stickers/ wordings/ graphics.

6.4 PRODUCT AUTHENTICATION

The registered product shall be affixed with the security device approved by the Authority. The said security device (hologram), which is serialized, shall be used to authenticate and verify that the product is registered with the Authority, and will be affixed to each unit pack of the product, whether locally manufactured or imported.

The security device shall be affixed onto the outer packaging of the product, (or, where there is no outer packaging, on the immediate packaging), on the front panel of the product label. None of the product particulars on the label shall be covered over by the security device.

Please refer to:

a) Appendix 9: Labelling Requirements where the security device/ label may be affixed on the product label;
b) FAQ no. 20 on hologram; and
c) Circulars and directives pertaining to security label (hologram):
   i) Bil (32) dlm BPFK/02/5/1.3
      Keputusan Mengenai Tarikh Perlaksanaan Penggunaan Label Hologram Meditag (6 August 2004)

   ii) Bil (36) dlm BPFK/02/5/1.3
      Keputusan Pihak Berkuasa Kawalan Dadah Berhubung Penggunaan Label Hologram (Product Authentication) (5 November 2004)

   iii) Bil (62) dlm BPFK/02/5/1.3
      Menaiktaraf Ciri-ciri Keselamatan Label Meditag (15 August 2006)

   iv) (1)dlm.BPFK/PPP/07/25 Jld. 1
      Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984. Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 2 Tahun 2013 : Direktif Pelaksanaan dan Pengendalian Label Keselamatan (4 April 2013)

6.5 INDICATIONS, SPECIAL CONDITIONS

The registered product shall only be indicated for use as approved by the Authority. The importation, manufacture, sale and supply of the registered product shall comply with all other specific conditions imposed by the Authority.

6.6 ADVERSE REACTIONS, COMPLAINTS

The product registration holder or any person who possesses any registered product shall inform the Senior Director of Pharmaceutical Services immediately of any adverse reactions arising from the use of the registered product.

6.7 HOLDER OF REGISTERED PRODUCT

The holder of the registered product shall inform the Authority of any change in his name or address.

6.8 WITHDRAWAL FROM REGISTRATION

The holder of the registered product shall notify the Authority with regards to any decision to withdraw registration of a product and shall state reasons for the decision.

The holder shall also notify the Authority when he is no longer authorized to be the holder of the registered product

6.9 CANCELLATION, SUSPENSION, AMENDMENT BY THE AUTHORITY

The Authority may, at any time and without assigning any reason suspend or cancel the registration of any product, and may amend the conditions of registration.

6.10 DIRECTIVES

The Senior Director of Pharmaceutical Services may issue written directives or guidelines to any person or a group of persons as he think necessary for the better carrying out of the provisions of these Regulations and which in particular relate to:

a) Product quality, safety and efficacy;
b) Labeling;
c) Change of particulars of a product;
d) Transfer of licenses;
e) Manufacturing;
f) Storage includes requirements as to containers;
g) Retailing;
h) Promotion of sale including product information;
i) Product recall;
j) Product disposal;
k) The cost of product recall or product disposal;
l) Clinical trials; or
m) Records and statistics pertaining to manufacture, sale, supply, import or export of any products.

7. USE OF *HALAL* LOGO

Halal logo may be used voluntarily on registered product label for the following categories, for both local and export market, provided that such products have been certified and approved *halal* by the Malaysia Department of Islamic Development (*Jabatan Kemajuan Islam Malaysia*, JAKIM):

a) Non-scheduled poison, excluding veterinary products;
   Reference:
   Circular (95)dlm.BPFK/PPP/01/03 Jld. 2
   Penggunaan Logo Halal Bagi Produk Farmaseutikal Berdaftar Kategori Produk Bukan Racun (Over The Counter, OTC) (26 December 2012).
   Directive (6)dlm.BPFK/PPP/07/25
   Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984. Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 7 Tahun 2013 : Direktif Perluasan Skop Penggunaan Logo Halal Bagi Produk Farmaseutikal Berdaftar Kategori Produk Bukan Racun Berjadual Dalam Bentuk Parenteral. (8 November 2013).

b) Health supplements;
c) Natural products; and
d) Cosmetics.

However, the logo is **NOT** allowed to be used on label of registered products other than the categories as listed above.

Only *halal* logo issued by JAKIM or any Islamic Body which is recognized by JAKIM shall be accepted.

Consideration by the Authority for use of *halal* logo on product label of such products shall be based on application as it is not a mandatory requirement.

Applicant shall submit an application for product registration variation to NPRA for approval to affix *halal* logo on product label of a registered product, of which a *halal* certification has been granted. A copy of the *halal* certificate must be submitted as supporting document.

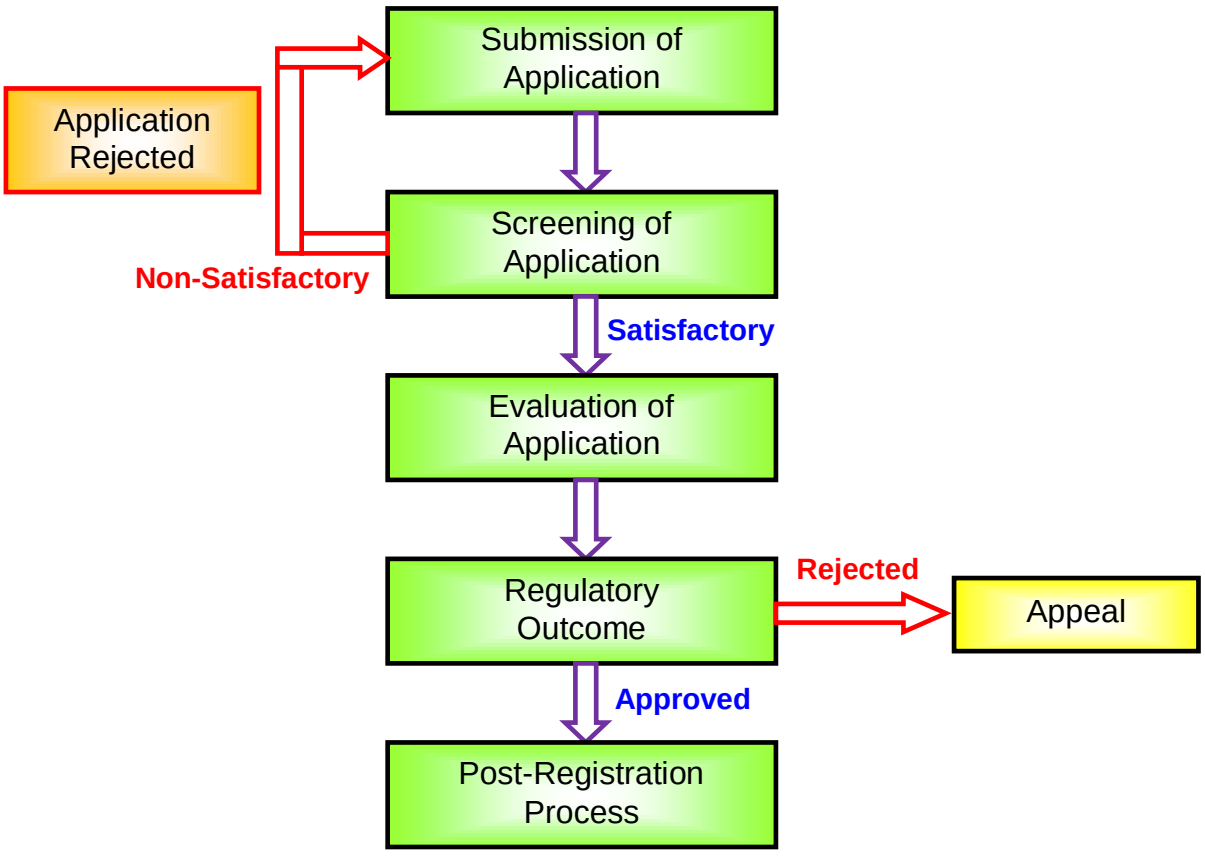
SECTION B: PRODUCT REGISTRATION PROCESS

The process of product registration ensures that pharmaceutical products are evaluated for its safety, efficacy and quality, whereas natural products are evaluated for its safety and quality, prior to being registered by the Authority and finally released into the market.

8. FLOW OF REGISTRATION PROCESS

Figure 4:

Process of Product Registration



8.1 PRE-SUBMISSION OF APPLICATION

Prior to submission of an application for product registration, applicant shall determine/ understand:

a) The category of the product (different product category requires different data);
b) Method of evaluation;
c) General and specific requirements;
d) Conditions applied;
e) Multiple applications;
f) Variants; and
g) Language.

A product shall only be registered if it fulfills regulatory requirements imposed by the Authority, especially **with respect to quality, efficacy and safety** of the product and taking into consideration on the following criteria:

a) Necessity of the product;
b) Potential for abuse; and
c) Therapeutic advantages.

8.1.1 CATEGORY OF PRODUCT

Applicant shall determine on the category of a product, as described under Section A - General Overview.

If the product category is uncertain, applicant may submit a Classification Form to Section of Regulatory Coordination, Centre for Product Registration, NPRA for verification.

8.1.2 METHOD OF EVALUATION

Method of evaluation for registration of a product is divided into two (2) types, which are:

a) Full Evaluation; and
b) Abridged Evaluation.

Table VI: Method of Evaluation According to Product Categories

No.	Product Category	Method of Evaluation	
		Full Evaluation	**Abridged Evaluation**
1.	New Drug Products	√	Not Applicable
2.	Biologics	√	Not Applicable
3.	Generics (Scheduled Poison)	√	Not Applicable
4.	Generics (Non-Scheduled Poison) [or known as OTC]	* All products from this category, unless stated in Abridged Evaluation	Includes, but not limited to the following: • Antiseptics/ skin disinfectants; • Locally-acting lozenges/ pastilles; • Topical analgesic/ counter-irritants; • Topical nasal decongestants; • Emollient/ demulcent/ skin protectants; • Keratolytics; • Anti-dandruff; • Oral care; • Anti-acne; • Medicated plasters/ patch/ pad; and • Topical antibacterial.
5.	Health Supplements a) General or Nutritional Claims b) Functional Claims (Medium) c) Disease Risk Reduction Claims (High)	Not Applicable Not Applicable √	√ √ Not Applicable
6.	Natural Products	Not Applicable	√

* **Table VII:**

Products containing Glucosamine, Chondroitin and Methylsulphonylmethane (MSM)

No.	Product		Product Category	Route of Evaluation	Condition on Product Indication	Remark
1.	Products containing Glucosamine	As single active ingredient	OTC	Full evaluation	As adjuvant therapy for osteoarthritis	Products containing glucosamine in combination with other health supplement ingredients are only allowed to be registered for therapeutic purposes and NOT allowed to be registered as Health Supplement Product.
		As combination with Chondroitin and/ or MSM	OTC	Full evaluation	As adjuvant therapy for osteoarthritis	
2.	Products containing Chondroitin	As single ingredient OR In combination with other supplement ingredients	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-
3.	Products containing MSM	As single ingredient OR In combination with other supplement ingredients	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-

		As combination with Chondroitin	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-

Reference: Circular

1) Bil (66) dlm BPFK/02/5/1.3
   Produk yang Mengandungi Glucosamine dan Chondroitin (14 November 2006).
2) Bil. (20) dlm.BPFK/PPP/01/03
   Produk yang mengandungi Glucosamine, Chondroitin dan Methylsulfonylmethane (MSM) (31 Disember 2008).

8.1.3 REQUIREMENTS FOR PRODUCT REGISTRATION

Applicant shall submit the following requirements to support an application for product registration, applicable according to different category of product:

a) General requirements (either for full or abridged evaluation);

i) Full Evaluation;
(In accordance to ASEAN ACTD/ ACTR or ICH guidelines)

- Part I - Administrative data and product information;
- Part II - Data to support product quality (Quality Document);
- Part III - Data to support product safety (Nonclinical Document); and
- Part IV - Data to support product safety and efficacy (Clinical Document).

OR

ii) Abridged Evaluation.

For details, please refer Appendix 2: Requirements for Product Registration.

b) Specific requirements according to category of product (biologics, health supplements and natural products).

- Biologics : Refer Appendix 3: Guideline on Registration of Biologics
- Health supplements : Refer Appendix 4: Guideline on Registration of Health Supplements
- Natural products : Refer Appendix 5: Guideline on Registration of Natural Products

For regulatory control of active pharmaceutical ingredient (API), it is applicable to all pharmaceutical products either locally manufactured or imported, excluding biologics, health supplements and natural products.

The implementation began with voluntary submission for New Drug Products in April 2011 and was followed by;

- Phase 1 - New Drug Products (NDP) : January 2012
- Phase 2 - Generics (Scheduled Poison) : July 2014 (by phases)
- Phase 3 - Generics (Non-scheduled Poison): (to be determined)

No separate application for registration of the API is required. However, the required technical documentation pertaining to each API at Part 2.S ACTD (Part II Quality: Drug Substance) shall be submitted as part of the application for product registration.

For details pertaining to regulatory control of API, please refer Appendix 6: Guideline on Regulatory Control of Active Pharmaceutical Ingredients (API).

8.1.4 CONDITIONS APPLIED ON PRODUCT REGISTRATION

Applicant shall comply with the following conditions applied on product registration. Failure to do so shall results in rejection of the application by the Authority.

a) Applicant shall comply with all requirements as specified in the following appendices and directions from the Authority:
   i) Appendix 7:

      Special Conditions for Registration for a Particular Product or Group of Products;

   ii) Appendix 8:

      List of Permitted, Prohibited and Restricted Substances;

   iii) Appendix 9:

      Labelling Requirements;

   iv) Appendix 10:

      Guideline on Patient Dispensing Pack for Pharmaceutical Products in Malaysia *(Applicable to pharmaceutical products only).*

b) Applicant shall provide supplementary data/ information, documentation or samples, if requested by the Authority;

c) Applicant shall respond and provide feedback for the requested supplementary data/ information, documentation or samples by the Authority within the specified timeframe. If the applicant is unable to submit the requirements within the specified timeframe, a written request for an extension shall be submitted to NPRA;

d) Application shall be rejected if the applicant fails to submit required supplementary data/ information or documentation within six (6) months from the first correspondence date;

e) Applicant shall submit sample of natural product for laboratory testing to the Centre for Quality Control, NPRA within fourteen (14) working days from date of confirmed payment. Failure to do so within thirty (30) days from the date of the payment shall result in rejection of the application.

8.1.5 MULTIPLE APPLICATIONS

Separate application for product registration shall be required for each product for the following conditions:

a) Products containing the same ingredients but made to different specifications, in terms of strength/ content of ingredient(s), dosage form, description, etc.; or
b) Different manufacturer.

However, different packings (materials) or pack sizes (quantity/ volume) of a product made by the same manufacturer to the same specifications, formulation and dosage form (including parenteral preparations, peritoneal dialysis fluids and haemofiltration solutions which are introduced into human bodies) shall require only one application for product registration. The product registration shall be for the packings and pack sizes stated in the registration documents only.

Note:
Registration of same product in all aspects but with different product name by the same PRH is not allowed by the Authority.

8.1.6 SECOND OR THIRD SOURCE

It is defined as product which is the same as the product from first source in all aspects, except for the site of manufacture.

An application for a second source may be considered by the Authority but only with justification.

A second source product, excluding biologic products, may differ for the following aspects:

a) equipments/ machines;
b) minor manufacturing process (e.g. blending time, number of sub-parts);
c) batch size;
d) packaging materials, thickness of same packaging materials, pack sizes;
(Note: Use of different packaging material shall be supported with stability study report.)
e) manufacturer of API; and
f) source of excipients;

EXCEPT differences in shape, embossment and thickness of tablet, in order to avoid change in product identity and subsequently causing confusion.

The manufacturer shall declare with support of manufacturing validation process data that there is no change in formulation, specification of active ingredient(s) and excipient(s), and finished product for the second source product compared to the first source.

For pharmaceutical product, no third source is allowed for same product unless in emergency situation such as outbreak of infectious disease.

A second source product is defined as a product which is the same as product from the first source in all aspect, except for the site of manufacture. Similarly to Biologics,an application for a new product from a second source may be considered by the Authority but with justification. A third source may be also be considered if justified.

The manufacturer shall declare with support of manufacturing validation process data that there is no change in formulation, specification of active ingredient(s) and excipient(s), and finished product for the second source product compared to the first source. There is no difference in product identity and presentation, to avoid confusion.

Biologics are highly sensitive to manufacturing condition. Therefore if any of the conditions outlined are not fulfilled, the application is automatically considered as new application.

a) The following application procedures apply:

Second or third source for biologic products		
Conditions	**All** the following **conditions are fulfilled:** 1. The proposed facility is approved for manufacturing activities for the same company/sponsor 2. No change in the composition, manufacturing process and drug substance & drug product specifications 3. No change in the container/closure system 4. The same validated manufacturing process is used 5. The newly introduced product is in the same family of product(s) or therapeutic classification as the one of those already approved at the site and uses the same filling process/equipment 6. Only one Final Release Site	Conditions 1. to 6. are **not fulfilled**
Supporting data	1. GMP certification 2. Updated relevant sections in ACTD Part II (P) 3. Confirmation that information on the drug product has not changed as a result of the submission (e.g. other than change in facility) or revised information of the drug product, if any of the attributes have changed 4. Name, address and responsibility of the proposed production facility involved in manufacturing and testing 5. Process validation and/or evaluation studies (e.g. equipment qualification, media fills, as appropriate), to demonstrate comparability between both current and	1. A complete product dossier specific to the new drug product manufacturing site can be made available (ACTD Parts I, II; ACTD Parts III, IV can refer to the first source product registered with DCA) 2. Manufacturer's declaration of no change in formulation, specification of active ingredient(s) and excipient(s), and finished product for the second source compared to the first source 3. Quality comparability data (manufacturing process validation data, batch analyses, stability) 4. Real-time stability data to

	proposed manufacturing sites 6. Process validation study reports. The data should include transport between sites, if relevant. 7. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least 3 consecutive commercial scale batches of the approved and proposed drug product, to demonstrate comparability between both current and proposed manufacturing sites 8. Summary of stability testing and results (e.g. studies conducted, protocols used, results obtained), to demonstrate comparability between both current and proposed manufacturing sites 9. Stability test results from: accelerated testing (usually a minimum of 3 months) or, preferably, forced degradation studies under appropriate time and temperature conditions for the product; and 3 months of real time testing at time of submission (6 months real time testing data at time of registration approval) on three commercial scale batches of the drug product manufactured using the proposed manufacturing facility, or longer if less than 3 time points are available (including the zero time point), as well as commitment to notify NPRA of any failures in the ongoing long term stability studies. 10. Certificates of analysis for drug products manufactured at the	support proposed shelf-life (no extrapolation allowed by *ICH Q5C: Stability Testing of Biotechnological/Biological Products)*

	new manufacturing site 11. Rationale for considering the proposed formulation/filling suite as equivalent 12. Information on the proposed production facility involved in the manufacture of the drug product, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems), as well as the cleaning and shipping validation, as appropriate [if applicable] 13. Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as applicable. If no revisions, a signed attestation that no changes were made to the change-over procedures [if applicable] 14. Results of the environmental monitoring studies in classified areas [if applicable]	
Fees	RM1000 (processing fee) + RM3000 (analysis fee – single active ingredient) OR + RM4000 (analysis fee – two or more active ingredients)	
Processing timeline	120 working days	245 working days
NOTE: There can be only **<u>one</u>** Final Release Site for each MAL no.		

8.1.7 VARIANTS

Variants refer to products with differences in terms of fragrance/ flavour or consequently colour.

When variants are registered:
a) The variants should only differ in terms of fragrance/ flavour and colour.
b) Product name of the variants shall remain the same, with the addition of an identifying variant name.
c) Each variant shall be registered as one (1) product with a different registration number.

Variants to the registered product may be considered for the following dosage forms:

a) Products Containing Scheduled Poison

   ONLY for pediatric oral liquid preparations

b) Products Containing Non-Scheduled Poison

   i) Lozenges;
   ii) Chewable tablets;
   iii) Effervescent powders/ tablets;
   iv) Powder;
   v) Granule;
   vi) Oral liquid;
   vii) Dental preparations (rinses, dentifrices);
   viii) Medicated soaps (bar, liquid); and
   ix) Vaginal creams and douches.

8.1.8 LANGUAGE

All data and information including supporting documents for product registration such as certificates, letters and product labels shall be in English or *Bahasa Malaysia*.

8.2 SUBMISSION OF APPLICATION

Application of product registration shall be submitted via the online QUEST system at http://npra.moh.gov.my/.

Applicant shall ensure all data requirements needed to support the application is fulfilled before submission.

Upon submission, the application shall be given a call number for reference, which is specific to a particular product. Applicant shall refer to this call number during all correspondence pertaining to the registration of the product.

Applicants are advised to read the explanatory notes as stated in Appendix 11: Guideline on Filling the Online Application Form for Product Registration via Quest System, and also relevant ASEAN or ICH guidelines and checklists, for full information on requirement for product registration.

8.3 SCREENING OF APPLICATION

After an online submission of the product registration application has been done, the application shall be undergone an initial evaluation (or known as screening process) which shall ensure the required data/ information of the submitted application are complete. Further evaluation shall be done after payment for the application has been made.

8.3.1 SATISFACTORY

Only a complete application shall be accepted and approved for payment. Upon screening approval, the applicant is requested to proceed for payment and submission of hard copy documents (if applicable).

Submission of hard copy documents:

No.	Category of Product	Online Submission	Hard copy submission
1.	NDPs	All documents as required under Part I – IV	- A copy of CD and a copy of documents as required under Part I – IV; - Nine (9) copies of indexed folders containing proposed package insert and published clinical papers and/or in-house synopses; - A copy of CD and a copy of documents as required under Appendix 6, Table 1 (*for drug substance/ API*); - Further documentations may be requested from case-to-case as deemed necessary.
2.	Biologics	All documents as required under Part I – IV	Part I – IV including published clinical papers (6 sets – indexed, listing with summary/ abstracts of each paper)
3.	Generics (Scheduled Poison)	All documents	As requested e.g. big file size, unable to be submitted online

No.	Category of Product	Online Submission	Hard copy submission
4.	Generics (Non-Scheduled Poison)	All documents	As requested e.g. big file size, unable to be submitted online
5.	Health Supplements	All documents	As requested e.g. big file size, unable to be submitted online
6.	Natural Products	All documents	All Sections (Section A-F)

For payment, applicant shall submit two (2) copies of printed payment voucher together with appropriate fees to the Finance Department, NPRA for payment confirmation. The applicant is advised to keep a copy of the payment voucher as reference. A product reference number shall be given to the application upon payment confirmation.

Payment has to be made within thirty (30) days from the date of approval for screening. The application form will be deleted from the system if payment has not been made within this stipulated time.

8.3.2 NON-SATISFACTORY

If the application is found incomplete during the screening process, the application shall be rejected and the applicant shall be notified via the system.

Note:

If there is any decision made by the applicant/ required by the Authority in certain cases to withdraw a submitted application for registration of a product, at any stage of evaluation prior to its approval, the applicant shall notify the Authority and shall state the reasons for the decision.

8.4 EVALUATION OF APPLICATION

8.4.1 INITIATION OF REVIEW

Upon confirmation of payment, the application with the submitted data shall be evaluated. Review of applications shall follow a queue system. There shall be separate queues for the different categories of products and/or according to level of claims i.e. general, medium or high claim.

Priority review may be granted for product which is intended for treatment of a serious or life-threatening disease, where the likelihood of death is high unless the course of the disease is interrupted.

8.4.2 CORRESPONDENCE

Correspondence via the system shall be sent to the applicant if there is any clarification and further supplementary data/ information or documentation pertaining to the application, if deemed necessary by the Authority.

Application shall be rejected if the applicant fails to respond to the correspondence from NPRA to submit the required supplementary data/ information or documentation within six (6) months from the first correspondence date.

8.4.3 STOP CLOCK

Under review.

8.4.4 TIMELINE FOR PRODUCT REGISTRATION

Table VIII:

No.	Product Category	* Duration (Inclusive screening process)
(A)	**Full Evaluation**	
1.	New Drug Products	245 working days
2.	Biologics	245 working days
3.	Generics (Scheduled Poison)	210 working days
4.	Generics (Non-Scheduled Poison)	210 working days
(B)	**Abridged Evaluation**	***Duration** (Inclusive screening process)
5.	Generics (Non-Scheduled Poison) (Product categories as stated in Table V above) a) Single active ingredient b) Two (2) or more active ingredients	 a) 116 working days b) 136 working days
6.	Natural Products a) Single active ingredient b) Two (2) or more active ingredients	 a) 116 working days b) 136 working days
7.	Health Supplements a) ** Single active ingredient b) ** Two (2) or more active ingredients ** *Applicable for:* *i) General or Nutritional Claims; and* *ii) Functional Claims (Medium Claims)* c) Disease Risk Reduction Claims (High Claims)	 a) 116 working days b) 136 working days c) 245 working days

***** Upon receipt of complete application.

8.5 REGULATORY OUTCOME

8.5.1 DECISIONS OF THE AUTHORITY

A regulatory decision shall be made based on the outcome of the evaluation of the submitted documentation, and samples (if applicable). An application may be approved or rejected by the Authority, and the Authority decision will be sent via email/ official letter to the product registration holder.

As stipulated under the CDCR 1984, Regulation 11(1), the Authority may, at any time reject, as well as cancel or suspend the registration of any product if there are deficiencies in safety, quality or efficacy of the product or failure to comply with conditions of registration.

8.5.2 PRODUCT REGISTRATION NUMBER

As stipulated in Regulation 8(8), CDCR 1984, upon registration of a product by the Authority, the product registration holder shall be notified by the Authority and a product registration number (i.e. MAL number) shall be assigned to the registered product via the system.

The registration number is specific for the product registered with the name, identity, composition, characteristics, origin (manufacturer) and product registration holder, as specified in the registration documents. It shall NOT be used for any other product.

8.5.3 CERTIFICATE OF REGISTRATION

Form 1 (Certificate of Registration) for a product with the provisions, conditions, limitations and etc. of the registration, as stipulated in Regulation 8(8) of CDCR 1984, has been deleted from the regulation in year 2006 via amendment of PU(A) 336/06. Therefore, the certificate will no longer be issued by the Authority.

Applicant shall refer to the product registration approval notification sent by the Authority or the Approved Product Registration List in NPRA website.
Reference: Circular (100)dlm.BPFK/PPP/01/03 Jld. 2. Pemansuhan Pengeluaran Sijil Perakuan Pendaftaran (SPP) (21 January 2013).

8.6 POST-REGISTRATION PROCESS

Registration status of a product shall be valid for **five (5) years** or such period as specified in the Authority database (unless the registration is suspended or cancelled by the Authority).

Upon approval for product registration by the Authority, applicants shall fulfill all commitments and conditions imposed during approval of the product registration and shall be responsible for the maintenance of the product in terms of quality, safety and efficacy throughout the validity period of registration. Failure to do so may result in rejection of application for renewal of product registration.

The Authority shall be notified of any changes to the product's efficacy, quality and safety, as described in detail at Section E: Post-Registration Process.

8.7 REJECTED APPLICATION

As stipulated in Regulation 18, CDCR 1984:

a) Any person aggrieved by the decision of the Authority or the Director of Pharmaceutical Services, a written appeal may be made to the Minister of Health Malaysia;

b) **All notice of appeals** shall be made **within fourteen (14) days** from the date of notification from the Authority;

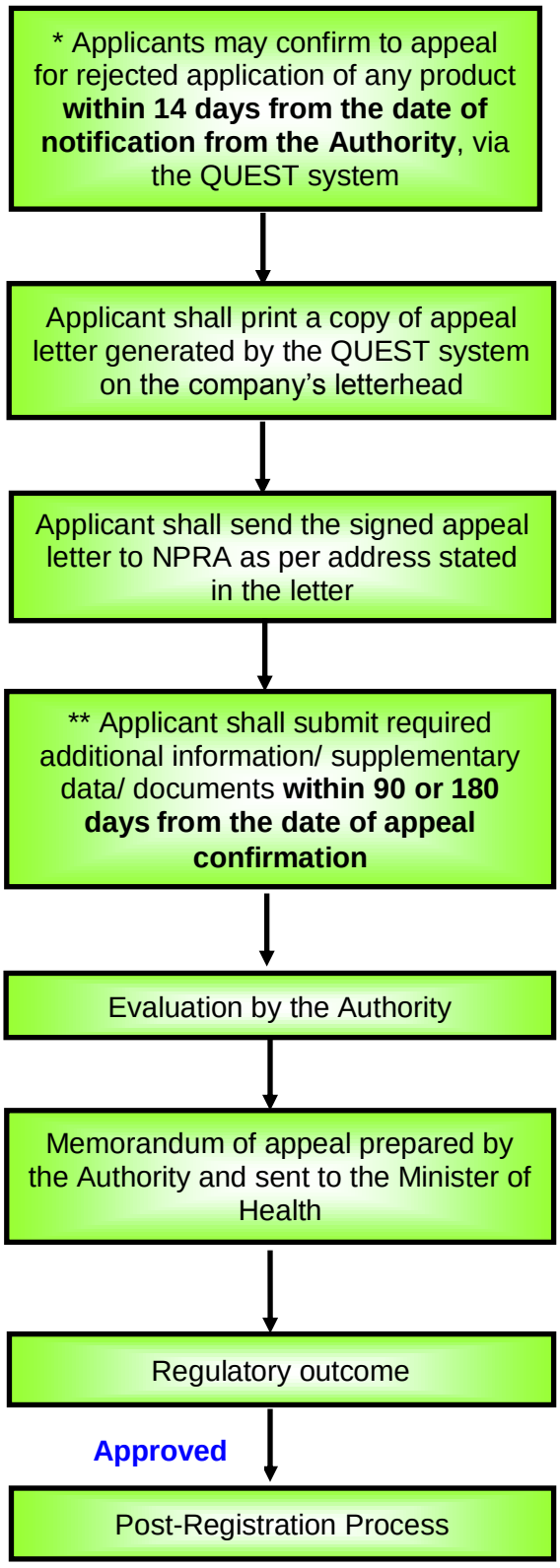
- A period of 180 days from the date of notice of appeal is given for submission of any additional information/ supplementary data/ documents for New Drug Products and Biologics.
- A period of 90 days is allowed for other categories of product.
- The appeal shall not be considered if all the required information is not submitted within the specified timeframe given. **Any request for extension of this period shall not be considered too.**

c) Any decision of the Minister made on an appeal shall be final.

Re-submission for product registration of a rejected application due to reason of safety and efficacy shall not be accepted within **two (2)** years after the rejection. However, if the product is registered in the reference countries, submission of application can be made earlier.

8.7.1 PROCESS OF APPEAL FOR QUEST 2 PRODUCT

Figure 5:



* ***Note:***

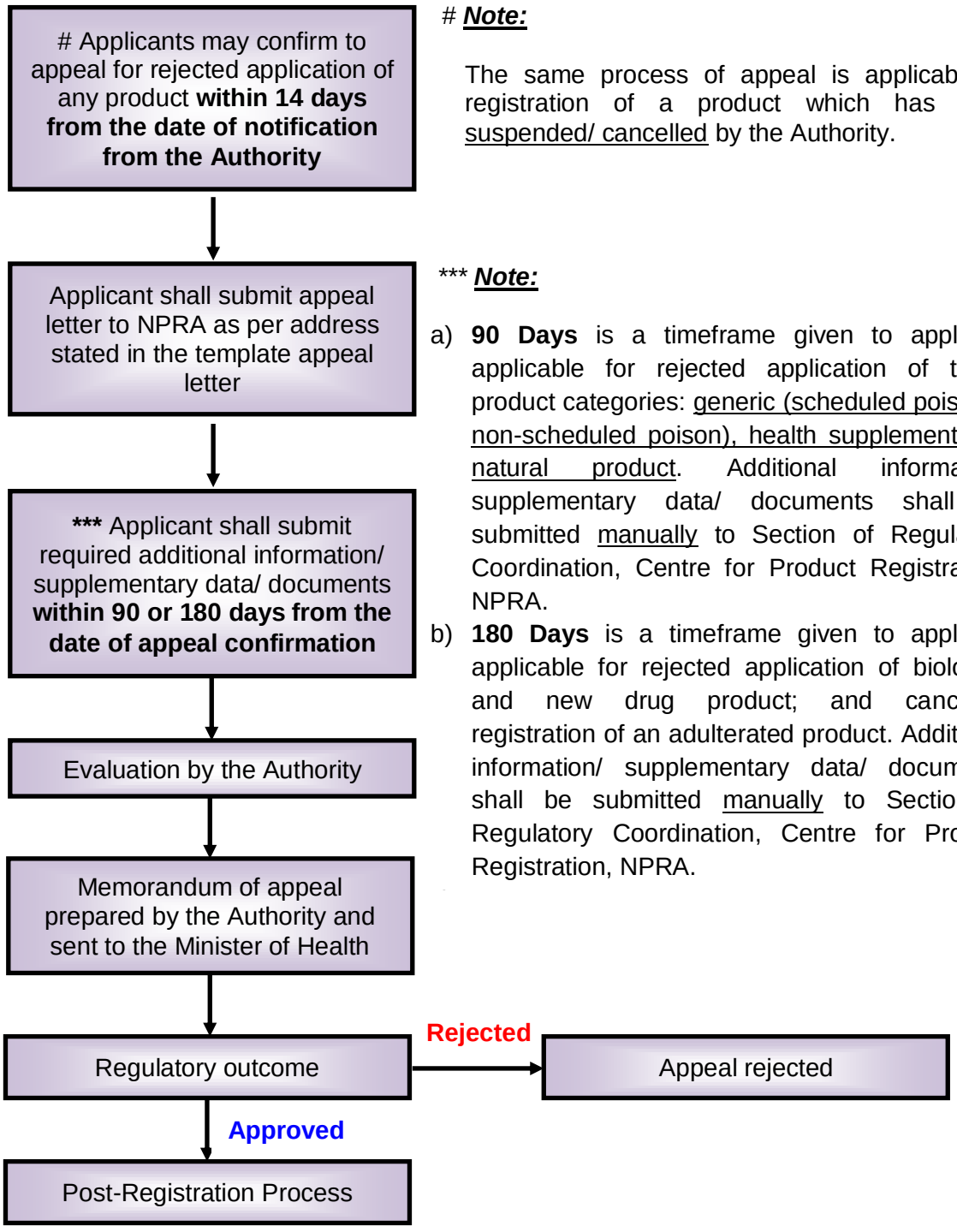
For suspended/ cancelled registration of a product, applicant may confirm to appeal manually by sending an appeal letter to NPRA **within fourteen (14)** days from the receipt of notification letter from the Authority, and it shall be subjected to the same process of appeal.

a) ** **90 Days** is a timeframe given to applicant applicable for rejected application of these product categories: generic (scheduled poison & non-scheduled poison), health supplement and natural product. Additional information/ supplementary data/ documents shall be submitted via QUEST system.

b) ** **180 Days** is a timeframe given to applicant applicable for rejected application of new drug product and biologics; and cancelled registration of an adulterated product. Additional information/ supplementary data/ documents shall be submitted manually to Section of Regulatory Coordination, Centre for Product Registration, NPRA.

8.7.2 PROCESS OF APPEAL FOR QUEST 3 PRODUCT

Figure 6:



Note:

The same process of appeal is applicable to registration of a product which has been suspended/ cancelled by the Authority.

*** ***Note:***

a) **90 Days** is a timeframe given to applicant applicable for rejected application of these product categories: generic (scheduled poison & non-scheduled poison), health supplement and natural product. Additional information/ supplementary data/ documents shall be submitted manually to Section of Regulatory Coordination, Centre for Product Registration, NPRA.

b) **180 Days** is a timeframe given to applicant applicable for rejected application of biologics and new drug product; and cancelled registration of an adulterated product. Additional information/ supplementary data/ documents shall be submitted manually to Section of Regulatory Coordination, Centre for Product Registration, NPRA.

8.7.3 TEMPLATE FOR AN APPEAL LETTER

***LETTERHEAD* SYARIKAT PEMEGANG PENDAFTARAN PRODUK**
Nama dan alamat pemegang

Tarikh:

Y. B. Menteri Kesihatan Malaysia
d/a Agensi Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia
Jalan Universiti, Peti Surat 319,
46730 Petaling Jaya
(u.p. Setiausaha PBKD)

Y. B.,

PERATURAN 18 – RAYUAN TERHADAP PENOLAKAN PERMOHONAN PENDAFTARAN

NAMA PRODUK : Sila nyatakan nama produk (*Please state the product name*)
NO. RUJUKAN : Sila nyatakan nombor pendaftaran produk (*Please state reference number of the product*)

Dengan segala hormatnya, pihak kami ingin membuat rayuan terhadap penolakan permohonan produk seperti di atas.

2. Alasan – alasan rayuan serta data tambahan/ maklumat akan dihantar kepada pihak Y.B. dalam tempoh *90 hari / 180 hari dari tarikh surat ini dikeluarkan.

Sekian, terima kasih.

Yang benar,

Tandatangan Wakil Pemegang

(NAMA WAKIL PEMEGANG)
Jawatan Wakil Pemegang

* Potong mana-mana yang tidak berkaitan.
(Please cross out words that do not apply.)

SECTION C: QUALITY CONTROL

The requirement for the submission of the protocol of analysis (POA), analytical method validation (AMV) and product samples for laboratory testing are presented in this section.

The submission of POA and AMV to the Centre for Quality Control shall be done via the online system (Quest system) and also using hardcopies, once payment for the registration has been confirmed. Documents to be submitted are listed below:

Documents to be submitted via online Quest system

1. E9 : Complete protocol of analysis for finished product including preservatives and diluents (if any).
2. E10 : Summary of AMV which includes all the relevant validation characteristics, its acceptance criteria and results.
3. E11 : Certificate of analysis for active drug substance (1 batch) and recent batches of finished product (3 different batches).

Documents to be submitted as hardcopy:

1. Certificate of analysis for active drug substance (1 batch) and recent batches of finished product (3 different batches)
2. Complete protocol of analysis for active drug substances and finished product (including preservatives and diluents, if any)
3. Complete testing method for the AMV.
4. Complete results for the AMV with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums etc.)

Note:

1. A cover letter consisting of the following information should be enclosed with every hard copy document submission:
    i) Name of product;
    ii) Reference Number/ Protocol Number;
    iii) Contact person (name/ email address/ telephone no.);
    iv) Name and address of company.
2. Documents submitted should be well organized and indexed.

9. GUIDELINE FOR THE SUBMISSION OF PROTOCOL OF ANALYSIS (POA)

This guideline consists of general and specific requirements for the POA submission. The general requirements are referred to POA content whilst details of the test methods are illustrated in the specific requirements

9.1 GENERAL REQUIREMENTS

a) The POA shall be written in *Bahasa Malaysia* or English only.

b) The POA shall contain the following information:

i) Name of product;
ii) Name and address of manufacturer;
iii) Name, signature and designation of authorized person;
iv) Effective date and Review date.

c) The POA shall comply with the following requirements :

i) To provide updated testing methods, shelf-life specifications and certificate of analysis for the intended product to be registered.
ii) References used must be clearly stated.
iii) The latest version of British Pharmacopoeia (BP) and United State Pharmacopeia (USP) shall be used as the main references.
iv) All tests and its specification listed in BP and/or USP shall be the minimum requirement. However, a specific testing method for quantitative analysis shall be accepted.
v) All test specifications set by the manufacturer shall be in line or more stringent than official pharmacopoeias (BP and USP).

d) Details of test methods shall include the following items:
i) List of equipment and apparatus;
ii) List of chemical, reagents and media;
iii) Preparation of solutions such as sample, standard, mobile phase, medium etc.;
iv) Setting up of analytical instrumentation;
v) System suitability tests (resolution, percentage of Relative Standard Deviation (%RSD), tailing factor and theoretical plate for High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) methods);

vi) Complete formula for calculation and interpretation of results;
vii) Specification or acceptance criteria.

e) Photocopies or methods directly copied from pharmacopoeias shall not be accepted. In cases where test methods are adopted from official pharmacopeia, details of specifics requirements should be submitted.

f) All relevant data collected during chemical and microbiological testing such as chromatograms HPLC/ GC, test reports and formulae used for calculating should also be submitted.

g) All documents should be arranged and labeled accordingly.

9.2 SPECIFIC REQUIREMENTS

The specific requirements for test methods are based on type of tests and dosage forms of product as stated in **Table IX** below:

Categories	Type of Tests	Specific Requirements
Physical & Performance Tests	Physical test (friability, uniformity of weight, pH, etc)	Specific method for the intended analysis
	Disintegration test	Specific method for related dosage forms

Categories	Type of Tests	Specific Requirements
	Dissolution test	a. Dissolution parameters should include: i) type of apparatus ii) type and volume of dissolution medium iii) rotation rate iv) temperature of solution v) sampling time b. Complete formula for calculation especially for extended and delayed release products. c. Method of analysis for example HPLC, UV, etc.
Quality Test	Identification test such as color test, Fourier Transform Infrared (FTIR), Thin Layer Chromatography (TLC) etc.	Specific method for the intended analysis
	Impurities/ degradation/ purity test	a. Analysis method should include:- i) Placebo solution (if any) ii) Relative retention times of impurities or degradation product b. Complete formula for calculation c. Method of analysis for example HPLC, TLC, etc.
	Assay and uniformity of content	Specific method for the intended analysis

Categories	Type of Tests	Specific Requirements
	Biological Assay of Antibiotics	a. Procedure for preparation of following solutions/ substances:- i) Culture medium ii) Buffer solutions iii) Diluents iv) Microorganisms used in assay b. Detailed test method (diffusion or turbidimetric method), which includes: i) Preparation of standard solutions (including steps to counteract the antimicrobial properties of any preservatives, etc present in the sample) ii) Preparation of test solutions (including any steps to neutralize the antimicrobial properties of any preservatives, etc present in the sample) iii) Test for Media Sterility and Growth Promotion Test iv) Dilution schemes for test and standard solutions. • Application of test & standard solutions (volume, use of latin squares, etc.) • Incubation temperature & time • Interpretation of result • Detailed calculation for the test including ANOVA table and other data showing validity of test results.

Categories	Type of Tests	Specific Requirements
Safety tests	Pyrogen Test	a. List of depyrogenated or pyrogen-free apparatus, glassware and reagents b. Temperature recording system c. Retaining conditions of the animals d. Selection of animals for test e. Preliminary test/ Sham test procedure f. Detailed test procedure g. Volume and dose of injection h. Interpretation of test results
	Bacterial Endotoxins Test (BET) or Limulus Amebocyte Lysate (LAL) Test	a. Certificate of analysis for endotoxin and LAL (limulus amebocyte lysate) reagent b. List of depyrogenated or pyrogen-free apparatus, glassware and reagent c. Preparation of standard solutions, LAL reagent/ substrate, sample d. Detailed calculation for determination of maximum valid dilution (MVD) e. The product's endotoxin limit concentration (ELC) and source of information f. Detailed calculation for determination of endotoxin limit concentration if the ELC is not in BP, USP, JP or EP g. Detailed test procedure h. Calculation and interpretation of test result

Categories	Type of Tests	Specific Requirements
	Sterility Test	a. List of media and reagent i) Culture media ii) List of rinsing solution, buffer solution and diluent iii) Neutralizing agent (if any) b. Preparation of media & Composition of Rinsing Buffer c. Test for Media Sterility and Growth Promotion Test d. Preparation of test sample (including steps to eliminate antimicrobial activity due to antibiotic samples or samples which contain preservatives). e. Detailed test procedure for sterility test i) Quantity of sample / Volume of sample ii) Membrane filtration / Direct inoculation iii) Open System or Closed System (if uses Membrane filtration method) iv) Volume of rinsing fluid
	* Microbial Contamination Test	a. Preparation of media b. Test for Growth Promoting, Inhibitory and Indicative Properties of Media c. Preparation of test sample (including neutralizing of preservatives for samples that contain preservatives) d. Total Viable Aerobic Count • Detailed test procedure for Total Aerobic Microbial Count TAMC) and Total Yeasts and Moulds Count (TYMC) by Plate Count, Membrane Filtration or Most-Probable Number (MPN) method.

Categories	Type of Tests	Specific Requirements
		e. Test for Specified Microorganisms • Detailed test procedure for each specific microorganism tested (including identification and confirmation test) • Specification and acceptance criteria For details, please refer circular; Bil (4) dlm. BPFK/PKK/12/05. Maklumat Lanjutan Tentang Spesifikasi Baru Untuk Ujian Kontaminasi Mikrobial (30 Mac 2010).
	Microcystin test	For a product containing Aphanizomenonflosaquae, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method

**** Note:***

1. Manufacturer shall ensure that products manufactured locally or overseas are free from any contamination of Burkholderia Cepacia. Please refer to these circulars for details:
   Ref. (90)dlm.BPFK/PPP/01/03/ Jld. 2
   Ujian Kontaminasi *Burkholderia cepacia* (19 December 2012).

2. Products are not allowed to send for gamma radiation treatment for the control of microbial contamination. Please refer to this circular for details:
   Ref. (54)dlm.BPFK/02/5/1.3.
   Aktiviti Pendedahan Produk Berdaftar kepada Sinar Gamma (18 April 2006)

10. GUIDELINE FOR THE SUBMISSION OF ANALYTICAL METHOD VALIDATION (AMV) DOCUMENTS

10.1 TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

a) Identification tests
b) Quantitative tests for impurities' content
c) Limit tests for control of impurities
d) Quantitative tests of the active ingredient in the sample (assay and dissolution)
e) Pyrogen or Bacterial endotoxin test
f) Sterility test
g) Microbial Contamination Test
h) Biological Assay of Antibiotics

10.2 TYPICAL VALIDATION PARAMETERS FOR CHEMICAL TESTS

10.2.1 FULL VALIDATION FOR IN-HOUSE METHODS

Please refer to Table IX on next page.

TABLE IX:

Characteristics	Type of Analytical Method			
	Identification	Testing for Impurities		**Assay:** - **dissolution (measurement only)** - **content/ potency**
		Quantitation	**Limit**	
Accuracy		√		√
Precision **Repeatability** **Interm. Precision**		√ √ (1)		√ √ (1)
Specificity (2)	√	√	√	√
Detection Limit		(3)	√	
Quantitation Limit		√		
Linearity		√		√
Range		√		√

10.2.2 PARTIAL VALIDATION FOR COMPENDIAL/PHARMACOPOEIAL METHODS

TABLE X:

Characteristics	Type of Analytical Method			
	Identification	Testing for Impurities		**Assay:** - **dissolution (measurement only)** - **content/ potency**
		Quantitation	Limit	
Precision **Interm. Precision**				√ (1)
Specificity (2)	√	√	√	√
Detection Limit		(3)	√	
Quantitation Limit		√		

Note:

√ signifies that this characteristic is normally evaluated.

(1) In cases where reproducibility has been performed, intermediate precision is not needed.

(2) Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).

(3) May be needed in some cases.

10.3 TYPICAL VALIDATION CHARACTERISTICS FOR MICROBIOLOGICAL TESTS:

Table XI:

Microbiological tests	Validation characteristics
Bacterial Endotoxin Test	a. Test for Confirmation of Labelled Lysate Sensitivity(Verification of criteria for standard curve) b. Test for Interfering Factors (Inhibition/ Enhancement tests)
Sterility Test	Validation (Bacteriostasis or Fungistasis) Test • Quantity of Sample/ Volume of Sample • Membrane filtration/ Direct inoculation • Open System or Closed System (if uses Membrane filtration method) • Volume of rinsing fluid
Microbial Contamination Test	a. Validation of total viable aerobic count (suitability of the counting method in the presence of product) b. Validation of test for specified microorganism (suitability of the test method)
Microbiological Assay of Antibiotics	Linearity of the dose response relationship

Note:

1. All the analytical validation done by the industry should be in accordance to ASEAN Guidelines for Analytical Procedures, ICH Technical Requirements for Registration of Pharmaceuticals for Human Use under Validation of Analytical Procedures: Text and Methodology Q2 (R1), British Pharmacopoeia (BP), United States Pharmacopoeia (USP), or Japanese Pharmacopoeia (JP).
2. The applicants should ensure all documents available in the online Quest system are of the latest versions. All correspondence on the protocol of analysis and analytical method validation should comply with any relevant circulars regarding the registration process. Failure to do so may cause cancellation or rejection of product registration.

11. GUIDELINE FOR THE SUBMISSION OF PRODUCT SAMPLES FOR LABORATORY TESTING

The submission of sample for laboratory testing is as part of the registration process. This guideline consists of the general and specific requirements for the submission of samples to the Centre for Quality Control for laboratory testing. The general requirements define the condition of the samples to be submitted whereas the specific requirements illustrate the additional details needed according to the category of product.

The applicant is given a period of **14 working days** from the date of confirmed payment to send samples for laboratory testing. If the samples are not submitted within the specified time frame, the product registration application shall be tabled to the Authority for rejection.

The applicants shall comply with these requirements and failure to meet any of these requirements may cause rejection of the samples.

11.1 GENERAL REQUIREMENTS

a) After the registration payment has been approved, applicants must make appointment with the Laboratory Services Unit for the submission of registration samples for laboratory testing.

b) Requirements for samples:

   i) A cover letter consisting of the following information should enclosed with every sample submission :

      - Name and reference no of product;
      - Name and address of holder;
      - Name, email address and contact number of authorized person;

   ii) Samples submitted must be in their original packaging & labeling.

   iii) Samples submitted must be from the same manufacturing premise as stated in the application for registration.

   iv) Samples submitted must have an expiry date of least one (1) year from the date of submission and must be from the same batch number

c) For imported products, applicants are required to submit the original import permit together with the samples for laboratory testing.The import permit will be issued by

the Centre for Registration for natural product and Centre for Quality Control for pharmaceutical products. The applicant should ensure that the import permit is endorsed by the enforcement officer at the entry point.

d) The payment voucher and approved payment application status should also be submitted together with the samples.

11.2 SPECIFIC REQUIREMENTS

11.2.1 NATURAL PRODUCTS

a) Quantity of samples submitted must be:

   i. a minimum of 6 separate containers of all dosage forms with total contents of not less than 200 g or 200 mL; OR

   ii. a minimum of 60 pieces of plasters or patches with total of not less than 200g.

b) Centre For Quality Control will conduct testing for Heavy Metals, Microbial Contamination Test, Disintegration Test, Uniformity Of Weight and screening for adulteration for the samples submitted.

c) The result of the tested sample is final and there is no provision for appeal.

11.2.2 PHARMACEUTICAL PRODUCTS

(Upon request from NPRA)

a) An official certificate of analysis and the recent shelf-life specification from the manufacturer for the same batch of sample must be submitted with the sample.

b) Quantity of samples submitted must be in accordance with the quantity requested.

c) Other materials such as HPLC columns, reagents, etc must be submitted when requested.

d) Reference standards are required to be submitted along with the pharmaceutical products. Requirements for these reference standards are as follows:

   i) The type & quantity of reference standards submitted must be in accordance with the type & quantity requested;

   ii) Reference standards submitted must have an expiry date of least one (1) year from the date of submission. In special situations, an expiry date of not less than six (6) months can be accepted;

   iii) All reference standards must be accompanied by an official certificate of analysis for the same batch with the stated purity (as is, dried, anhydrous etc.) and all other relevant information (water content, loss on drying etc.);

   iv) All reference standards must be properly labeled with name, batch number, purity and expiry date;

   v) All reference standards must be submitted in small sealed air-tight amber glass containers.

SECTION D: INSPECTION & LICENSING

Inspection and licensing of manufacturing premises or facilities, importers and wholesalers of registered products or notified cosmetics on the basis of compliance with Good Manufacturing Practice (GMP) as well as Good Distribution Practice (GDP) are vital element of drug control. Compliance to GMP and GDP are prerequisite for the application of a manufacturing license as well as product registration or cosmetic notification whereas compliance to GDP is a prerequisite for the application of a wholesale license or import license.

12. INSPECTION

Inspection of GMP and GDP are conducted to ensure manufacturers', importers' and wholesalers' compliance towards the current GMP and GDP requirements besides ensuring the registered products and notified cosmetics that are put in the market are safe, efficacious and of quality.

The related GMP and GDP guidelines referred are as below in **Table XIII:**

Guidelines	Product Type/ Category
PIC/S Guide to Good Manufacturing Practice for Medicinal Products *	• Pharmaceuticals (Poison and Non-Poison) • Veterinary Medicinal Products • Investigational Medicinal Products • Active Pharmaceutical Ingredients
GMP Guideline for Traditional Medicines and Health Supplements, 1st Edition, 2008	• Traditional Products • Health Supplements
Guidelines on Good Manufacturing Practice (GMP) for Cosmetic (Annex 1, Part 10)	• Cosmetics
Guideline on Good Manufacturing Practice (GMP) for Veterinary Premixes, 1st Edition, January 2015	• Veterinary Products

Guidelines on Good Distribution Practice (GDP); 2nd Edition 2013 Supplementary Notes For Management Of Cold Chain Products/ Materials Chapter 15 Guidelines On Good Distribution Practice (GDP)	• For activities related to the storage and distribution by manufacturers, importers and wholesalers (where applicable)

** Refer to Pharmaceutical Inspection Co-operation Scheme (PIC/S) website at www.picscheme.org*

Additional Information:

1. For manufacturing activity via campaign basis for carbapenem and monobactam product in area or manufacturing facility for cephalosporin product, please refer circular (1)dlm.BPFK/30/06/2 Bhgn 2.
2. Please refer (8)dlm.BPFK/PPP/07/25 Directive No. 2 Year 2014 for the requirement on Head of Production for pharmaceutical, radiopharmaceutical and veterinary manufacturer.

12.1 FOREIGN GMP INSPECTION

PRH must provide acceptable evidence to show that the manufacturer of the product follows an internationally accepted standard of Good Manufacturing Practice (GMP) and recognized by the Authority in Malaysia.

The Control of Drugs and Cosmetics Regulations 1984 (CDCR) requires that the standard of manufacture and quality control of medicinal products manufactured outside Malaysia be taken into consideration before the products are registered with the Authority. NPRA as the secretariat to the DCA is responsible for ensuring all manufacturers of registered products in Malaysia are able to provide acceptable evidence that the manufacturing premises conform to current GMP requirements. Hence, foreign manufacturers are also subjected to GMP conformity assessments through acceptable GMP evidence or GMP inspection.

For further details and forms, please refer to Guidance Document on Foreign GMP Inspection.

12.2 MANAGING CHANGES OF MANUFACTURERS FACILITY

This section only focuses on changes of manufacturing and its storage / warehouse facilities. Changes on products particulars should be addressed under the Section E of Post Registration Process whereby it discusses on Amendments to Particular of a Registered Products.

Changes at manufacturers' facility can potentially have quality and safety impact. It is the responsibility of the site to assess information on the changes occurs through a formal change control system and risk management, where applicable. Manufacturers are recommended to have a system for categorizing types of changes. All changes to the manufacturing facility are required to be notified to the Centre for Compliance and Licensing (CCL) prior to implementation.

Notification of changes will be reviewed to assess the significance and it may be verified during scheduled GMP inspection. The CCL will communicate further and arrange for an investigative/for-cause inspection focusing on these changes, if deemed necessary.

Additional Information:

1. **This section is applicable to local manufacturer only. Read further on change of importer or wholesaler particulars under Section E of Post Registration Process.**

2. **For further details, please refer to Table of Example Immediate and Periodical Notification.**

Types of notification are as follow:

12.2.1 Immediate Notification

This notification is applicable to manufacturers who plan/undergo a major/significant/substantial change that could have an impact on the product quality and safety. The Immediate Notification shall be made to or approved by the Centre for Compliance and Licensing (CCL) prior to implementation. The Immediate Notification can be submitted as follows:

a) Completing 'Borang Permohonan Penilaian Pelan Susun Atur Premis Pengilang, BPFK-503 for changes related to manufacturing layout and process flow

   OR

b) Official writing which may include at least information such as;
   - Description of changes to the facility
   - Plan of changes (For example: Gantt Chart, Validation Master Plan, etc)
   - Details of the products affected, where applicable

Types of changes are listed in Table A. **Example of Immediate Notification**

12.2.2 Periodical Notification

This notification is applicable to manufacturer that plan/undergo a minor change that would not give any impact to the product quality and safety. The Periodical Notification can be submitted in the form of official writing which may include at least information such as;

- Description of changes
- Plan of changes (For example: Gantt Chart, Validation Master Plan, etc)

Example of changes that require Periodical Notification are as per **Table B. Example of Periodical Notification**

Table A. Example of Immediate Notification

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (If any)
1.	Change of manufacturing site (including drug substance if any)	Require submission of new layout plan	YES	New premise layout (Processing Fee= RM1000.00)	As per BPFK-503 requirement	
2.	Change of warehouse facility	Addition of new warehouse or alternative warehouse which affecting overall manufacturing / operation process e.g. addition of sampling room, cold room, new warehouse block	YES	New premise layout (Processing Fee= RM1000.00) OR Revision of existing premise layout or addition new warehouse in the same licensed premise Processing	As per BPFK-503 requirement	

				Fee= RM500.00)		
3.	**Change of equipment or manufacturing process**	**a. Applicable for changes of critical equipment**	**NO**	**NOT APPLICABLE**	**Notification to CCL, NPRA**	**Please refer further to Section E** **Verification of information by GMP inspection if necessary.**
		c. Change of critical step in manufacturing (including packaging) process	**NO**	**NOT APPLICABLE**	**Notification to CCL , NPRA**	
4.	**Major renovation or introduction of new line**	**a. Addition of new manufacturing and/or packaging line**	**YES**	**Revision of existing premise layout (Processing Fee= RM500.00)**	**As per BPFK-503 requirement**	

		b. New production block	**YES**	**Revision of existing premise layout or addition new production block in the same licensed premise layout** **(Processing Fee= RM500.00)**	**As per BPFK-503 requirement**	**Verification of information by GMP inspection if necessary.**
		d. Change or addition of critical utility such as water system, pharmaceutical gases and HVAC	**NO**	**NOT APPLICABLE**	**Notification to CCL, NPRA**	
5.	**Change of manufacturing rooms**	**Rename or relocate of manufacturing rooms without affecting process flow** **E.g. Tabletting Room to Compression Room**	**YES**	**Revision of existing premise layout** **(Processing Fee= RM500.00)**	**As per BPFK-503 requirement**	

Table B. Example of Periodical Notification

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (If any)
1.	Change of or addition of QC facility	E.g. Retention sample, microbiological laboratory, stability chamber, etc.	NO	NOT APPLICABLE	Notification to CCL, NPRA	Verification of information by GMP inspection if necessary.
2.	Change of key personnel	Applicable to QA/QC Manager, Head of Production, Production Pharmacist	NO	NOT APPLICABLE	Notification to CCL	May involve information for manufacturing license holder
3.	Addition of manufacturing equipments without affecting existing manufacturing layout plan	New capsulation or tabletting machine in the available room	NO	NOT APPLICABLE	Notification to CCL	Verification of information by GMP inspection if necessary.
4.	Change of company name or address	Change of building number, postal code, street name etc.	NO	NOT APPLICABLE	Notification to CCL	Please refer further to Section E May involve information for manufacturing license

13. LICENSING

According to the Controls of Drugs and Cosmetics Regulations 1984, any company that want to manufacture, import or wholesale any registered products need to have a valid Manufacturer's License, Import License or Wholesale License.

13.1 TYPES OF LICENSES

Table XIV:

Type of Licenses	Activity
Manufacturer's License	Licensee is authorized to manufacture the registered products in the premises specified in the license and to sell by wholesale or supply the products
Import License	Licensee is authorized to import and sell by wholesale or supply the registered products from the address of the premises
Wholesaler's License	Licensee is authorized to sell by wholesale or supply the registered products from the address of the business premises specified in the license

13.2 LICENSE APPLICATION FORM

1. The license application for registered products (Manufacturer's License, Import License and Wholesaler's License) shall be submitted by filling Borang BPFK-413 Application for License for Registered Product.

2. The application form must be submitted with the following supporting documents.

   a) A copy of Company/ Business Registration Certificate
   b) A copy of Business License (Local Authority) for business premise or store (if any)
   c) A copy of Applicant's/License Holder's Identity Card

d) A copy of Annual Retention Certificate and/or Type A License (This document is necessary if products manufactured/ imported/ wholesale are Scheduled Poison A products or any other products that require a Pharmacist)
e) A copy of previous license (For renewal application)

3. An application shall only be processed if it is complete and payment has been approved.

4. The processing fee shall not be refundable. The processing fee of an application for a Manufacturer's License is RM 1,000.00 and RM 500.00 for an Import License or a Wholesaler's License.

5. Each license is valid for **one (1) year.**

13.3 ADDITIONAL PRODUCT LIST OF LICENSE FOR REGISTERED PRODUCTS

1. Additional product list of License is issued based on the application submitted when the products are newly registered, change of manufacturer or importer or any registered products which are not listed from the products list of Manufacturer's License and Import License.

2. When submitting the application form for Additional Product List of License for Registered Products the documents that shall be attached together are a copy of Manufacturer's License/ Import License and a copy of approval letter from the Authority (The Authority's meeting result).

3. The application of additional list shall be submitted by filling Borang BPFK-413T Application for (Additional) Product List of License for Registered Product.

13.4 GMP CERTIFICATE

1. GMP Certificate is issued for the purpose of exporting locally manufactured registered products. It endorses that the local manufacturer complies with the current GMP requirements. These certificate are required by the overseas regulatory agencies for products registration in their countries. Thus, when filling in the GMP Certificate

application form, the correct address of the overseas regulatory agencies given by the company is crucial.

2. The application of GMP Certificate shall be submitted online through QUEST3+ which is equivalent to the manual form Borang BPFK-420 *Permohonan Sijil Amalan Perkilangan Baik (APB) that is no longer in used.*

3. A fee of RM50.00 is payable on the issue of such certification.

SECTION E: POST-REGISTRATION PROCESS

14. MAINTENANCE OF REGISTRATION

Registration of a product shall be valid for **five (5) years** or such period as specified in the Authority database (unless the registration is suspended or cancelled by the Authority).

Application for re-registration (renewal of product registration) of a product shall be submitted **within six (6) months prior to the expiry** of the validity period of a product registration. A letter of reminder for product re-registration will be issued to the product registration holder 3 months prior to the expiry date of a product registration.

After the expiry date, the status of product registration shall be automatically changed to 'expired', and applicant will not be able to submit the application for product re-registration. Any form of appeal **shall not be considered** if re-registration application is not submitted before the expiry date of a product registration since reminder letter is issued 3 months prior to the expiry date. A new registration application shall be submitted if applicant wish to continue to market the product.

After the expiry of product registration date, the product is deemed **unregistered.** Products of which their re-registration is on hold due to unmet requirements but has passed its registration expiry date, the new registration date shall be updated according to the DCA Meeting date where the re-registration application is approved by the DCA.

The application for product re-registration shall only be submitted when all of the requirements for product for re-registration have been complied with. Failure to do so shall result in the re-registration application being rejected by the Authority.

The requirements for product re-registration as per stated in the following circulars shall be complied with before the submission of re-registration application:

a) (10) dlm.BPFK/PPP/01/03 Jilid 1
   Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 1 Tahun 2011 : Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens Bagi Semua Produk Generik "Immediate Release, Oral, Solid Dosage Form" Yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian BioEkuivalens (2 March 2011)
b) (27) dlm.BPFK/PPP/07/25
   Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 3 Tahun 2015 : Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens (BE) Bagi Semua Produk Generik Dalam Bentuk Dos Oral Tablet/Kapsul Yang Bersifat Effervercent, Dispersible, Orodispersible, Sublingual, Buccal Dan Chewable Yang Mengandungi Bahan Aktif Racun Berjadual (23 February 2015)
c) (7) dlm.BPFK/PPP/07/25
   Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 8 Tahun 2013 : Direktif Perluasan Skop Pelaksanaan Kawalan Regulatori Ke Atas Bahan Aktif Farmaseutikal Bagi Produk Generik Yang Mengandungi Racun Berjadual (Fasa II) (16 January 2014)
d) (11) dlm.BPFK/PPP/01/03 Jld 3
   Lanjutan Tarikh Pelaksanaan Pengawalan Bahan Aktif Farmaseutikal (API) Bagi Produk Farmaseutikal Berdaftar Yang Mengandungi Racun Berjadual (27 June 2014)

In order to maintain the registration of an imported product, applicant shall comply with GMP requirement as stated in the **directive** issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984. The Authority shall not consider any re-registration application that fails to comply with the stipulated requirement.

Reference:

a) Bil (25) dlm BPFK/PPP/01/03 Jld 1
   Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 1 Tahun 2012 : Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (09 February 2012)
b) Bil (96)dlm.BPFK/PPP/01/03 Jld. 2
   Surat Pekeliling Bagi Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (28 December 2012)

For pharmaceutical products which were submitted for registration before the year 2009, applicants shall ensure that stability study for the products at zone IV B has

been conducted and granted variation approval before submission of re-registration application. Please refer the following circulars for more information:

a) (1)dlm.BPFK/PPP/01/03Jld.3,
   Keperluan Data Kajian Stabiliti Dalam Zon IV B Bagi Produk Farmaseutikal Berdaftar (05 April 2013)
b) (5)dlm.BPFK/PPP/01/03,
   Lanjutan Tarikh Kuatkuasa Untuk Memenuhi Keperluan Data Kajian Stabiliti Dalam Zon IV B Bagi Produk Farmaseutikal Berdaftar (14 August 2013)

14.1 RE-REGISTRATION APPLICATION

a) For a product registered under the QUEST 2 system, the application for re-registration of the product shall be submitted online via the QUEST 2 system.
b) For a product registered under the QUEST 3 system, the application for re-registration of the product shall be submitted manually to NPRA with the following documents;
   i) Re-registration Application Form; BPFK 420.1
   ii) Processing Fee (refer Subsection14.2 as below)

   Please refer the following circulars for more information:
   (37)dlm.BPFK/PPP/01/03Jld.3
   Permohonan Pendaftaran Semula Produk QUEST 3 Melalui Prosedur Manual (29 May 2015)

14.2 RE-REGISTRATION PROCESSING FEE

a) Traditional Product : RM 500.00 per product
b) Poison/ Non-Poison product : RM 1,000.00 per product

c) The processing fee shall be paid in the form of a bank draft/ money order/ postal order, made payable to "Biro Pengawalan Farmaseutikal Kebangsaan".

All processing fees submitted to NPRA are NON-REFUNDABLE.

15. WITHDRAWAL OF PRODUCT REGISTRATION

The Product Registration Holder shall inform the Authority pertaining to decision to withdraw the registration of a product before the end of the validity of such registration and shall state the reasons for the decision. The onus is on the holder to inform the manufacturer/ contract manufacturer.

The registration of a product, once withdrawn, shall not be reinstated and certificate of registration of the withdrawn product, if any, shall be invalid.

A new application shall be submitted if the product registration is required again at a later date.

16. AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

Throughout the life cycle of a registered product, changes to improve the product's efficacy, quality and safety are likely to occur. Therefore, applicant shall inform the Authority pertaining to any changes or amendment made to particulars of a registered product via variation applications.

An applicant who wishes to apply for any application for imported products of which GMP requirement is a consideration, such as change of manufacturing site and variation, shall comply with the requirement, as stated in **directive** issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984. The Authority shall not consider any application in which the requirement is failed to comply with.

Reference:

a) Bil (25) dlm BPFK/PPP/01/03 Jld 1
   Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 1 Tahun 2012 : Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (09 February 2012)
b) Bil (96)dlm.BPFK/PPP/01/03 Jld. 2
   Surat Pekeliling Bagi Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (28 December 2012)

16.1 VARIATION

16.1.1 VARIATION APPLICATION FOR PHARMACEUTICAL PRODUCTS

Variation application for pharmaceutical products shall follow Malaysian Variation Guideline (MVG) as stated in the directive issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984.
Reference: (2) dlm BPFK/PPP/07/25.)
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 3 Tahun 2013 : Direktif untuk melaksanakan Malaysian Variation Guideline (MVG) (29 April 2013)

If deemed necessary, NPRA reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all categories of product.

The registration of a product shall be **reviewed for suspension or cancellation** if changes that fall under Major Variation (MaV) and Minor Variation Prior Approval (MiV-PA) are implemented without prior approval of the Authority.

For drug substance that are yet to be regulated by NPRA, application for variations and supporting documents related to drug substance at Appendix 12 are still applicable until further notice.

MODE OF SUBMISSION

Table XV:

No.	Variation	QUEST 2 Product	QUEST 3 Product
1.	Minor Variation Notification (MiV-N)	Applicant shall submit application for MiV-N via both manual and online QUEST 2 system. For manual submission, applicant can download Form BPFK 416.3 from NPRA's website http://npra.moh.gov.my/ , and shall submit to the respective Sections in Center for Product Registration, NPRA. For submission online, please scan the form and attach together with the revised draft of package insert and labelling as a single file.	Applicant shall submit application **manually** to the respective Sections in Center for Product Registration, until further notice pertaining to online submission.
2.	Minor Variation Prior Approval (MiV-PA) & Major Variation (MaV)	Applicant shall submit application via online QUEST 2 system.	

16.1.2 VARIATION APPLICATION FOR HEALTH SUPPLEMENT AND NATURAL PRODUCTS

Variation application for Health Supplement Products and Natural Products shall follow Malaysian Variation Guideline (MVG) as stated in the directive issued by Director of Pharmaceutical Services under Regulation 29, CDCR 1984; **Directive No. 14 Year 2016.** Ref: BPFK/PPP/07/25(45): Direktif Untuk Melaksanakan *Malaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation*)

Variation refers to change of particulars of a registered product. No change of any particulars of a registered product shall be made without prior approval from NPRA. The registration of a product shall be reviewed for suspension or cancellation if changes are implemented without prior approval of the Authority.

All supporting documents in accordance to the specified conditions laid down for each type of variation should be submitted. For further information pertaining to conditions and supporting documents required for an application of variation, please refer toMalaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation).

If deemed necessary, NPRA reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all categories of products.

MODE OF SUBMISSION

Applicant shall submit the variation application through the current online system.

16.1.3 VARIATION APPLICATION FOR BIOLOGICAL PRODUCTS

Variation application for biologics shall follow the Malaysian Variation Guidelines for Biologics (MVGB) as stated in the directive issued by Director of Pharmaceutical Services under Regulation 29, CDCR 1984; **Directive No. 2 Year 2017. Ref: BPFK/PPP/07/25(7)Jld.1:** Direktif Untuk Melaksanakan *Malaysian Variation Guideline For Biologics (MVGB).*

The MVGB will serve as a main document for all variation applications. The MVG will serve as a secondary document for all administrative changes. If there are variations that are not covered in both MVGB and MVG, the PRH should determine the classification of change based on a change-specific risk assessment using the principles and examples that have been set out in the MVGB. Please refer to section 3.0 (General Considerations) of the MVGB for further details.

All applications submitted either via the QUEST3+ system or manually shall be accompanied by a cover letter, of which the content of the cover letter shall be in accordance to 4.1.2 and 4.1.3 of the MVGB.

16.2 CHANGE OF MANUFACTURING SITE

Change of Manufacturing Site (COS) refers to change of manufacturing site for certain part or all of the manufacturing process of a product, but it does not cover changes related to a new site, where only:

a) batch release takes place OR

b) to a new packager (secondary packaging or labelling), as these changes are covered under applications for amendments to the particulars of a registered product (variation). Please refer to paragraph Section E: 16.1 Variation.

However, a change of manufacturing site for biologics shall require a new product registration if the change is extensive and will have an impact on the quality, safety and efficacy profile of the final product.

Upon receipt of complete application, the application shall be processed within sixty (60) working days.

16.2.1 CONDITIONS ON APPLICATION FOR COS:

Change in Manufacturing Site is only applicable for the following situations:

a) a change in manufacturing site for the same company, including rationalization in the event of mergers; or

b) a company which previously contracts out the manufacture of its product(s), transfers the manufacture of the product to its own manufacturing premises; or

c) a company appoints a contract manufacturer in Malaysia for pharmaceutical products i.e. scheduled poison, non-scheduled poison & health supplement products **except** natural products. This change includes a change from a contract manufacturer to a local contract manufacturer or a change from own manufacturing premise to a local contract manufacturer.

   Note: The change in manufacturing site for this condition will not be considered if the change is made without acceptable justification or submitted too frequently.

A change of manufacturing site under a crisis situation may be considered for the following:

a) A change between contract manufacturers for natural products;

b) A change to a contract manufacturer outside of Malaysia for pharmaceutical products.

Validity of registration for a product which has been approved for change of manufacturing site remains unchanged.

16.2.2 CONDITIONS ON GOOD MANUFACTURING PRACTICE (GMP):

a) The new manufacturing site shall comply with current Good Manufacturing Practice (cGMP);
b) Local manufacturing sites are subjected to pre-licensing inspections by the NPRA inspectors;
c) For manufacturing sites outside Malaysia, certification on GMP by the competent authority is acceptable.
d) The Authority reserves the right to conduct an inspection on any manufacturing site.
e) For further information pertaining to the requirements on GMP, please refer to these circulars and directive.

i) Bil (35) dlm. BPFK/PPP/01/03
Pemeriksaan Amalan Pengilangan Baik Bagi Pengilang Di Luar Negara (03 June 2009)

ii) Bil (40) dlm. BPFK/PPP/01/03
Pekeliling Pemeriksaan Amalan Pengilangan Baik Bagi Pengilang Di Luar Negara (08 September 2009)

iii) Bil (25) dlm BPFK/PPP/01/03 Jld 1
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 1 Tahun 2012 : Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (09 February 2012)

iv) Bil (96)dlm.BPFK/PPP/01/03 Jld. 2
Surat Pekeliling Bagi Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB) (28 December 2012)

16.2.3 TYPES OF MANUFACTURING SITE CHANGES (COS)

Table XVIII:

No.	Types of COS		Description
1.	Type I	Change of manufacturing site within Malaysia	Change in the location of the site of manufacture within Malaysia only. This change may be due to upgrading of facilities, and/or expansion of manufacturing activities or moving to a newly constructed plant, or appointment of a contract manufacturer for pharmaceutical products.
2.	Type II	Change of manufacturing site from foreign country to Malaysia	Change in location of the site of manufacture from outside of Malaysia to a location in Malaysia. This change may be due to the ability of the local counterpart to manufacture the product, or appointment of a contract manufacturer for pharmaceutical products.
3.	Type III	Change of manufacturing site located outside Malaysia	Change of location of the site of manufacture to manufacturing facilities located outside Malaysia. This may be due to a merger or rationalization of manufacturing sites in line with multinationals' manufacturing strategies.

No.	Types of COS		Description
4.	Type IV	Change of manufacturing site for sterile products	i) Transfer of manufacturing of an aseptically processed sterile product to a: a) newly constructed or refurbished aseptic processing facility or area; b) an existing processing facility or area that does not manufacture similar approved products. (For example, transferring the manufacture of a lyophilized product to an existing aseptic process area where there is no approved lyophilized product is manufactured). ii) Transfer of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site.
5.	Type V	Change of manufacturing site in crisis situation	i) Change of location of the site of manufacture that is deemed necessary due to certain circumstances such as natural disasters, closure or suspension of premise (revocation of manufacturing license), bankruptcy and matters related to breach of product quality, safety and efficacy ONLY. ii) Prior to submission of Type V COS, approval letter issued by the secretariat of the Authority shall be obtained. iii) Application for Type V COS must be made within **three (3) months** from the date of the crisis. iv) Type V COS applications for natural products and health supplements are only applicable for local manufacturers.

16.2.4 MODE OF SUBMISSION

Applicant shall submit the application through the current online system.

16.2.5 OTHER INFORMATION

a) Application for COS will be rejected if applicant failed to submit required data within **six (6) months** from the first correspondence date;

b) All supporting documents in accordance to the specified conditions laid down for each type of COS should be submitted. For details, please refer to Appendix 13: Supporting Documents Required for Change of Manufacturing Site Application.

c) If deemed necessary, NPRA reserves the right to request for additional supporting documents.

d) For further information pertaining to COS, please refer these circulars.

i) Bil (59) BPFK/17/VF/9.2
Prosedur Permohonan Pertukaran Tapak Pengilang Produk Berdaftar: Polisi Menolak Permohonan Pertukaran Tapak Pengilang Sekiranya 'Tiada Maklumbalas / Maklumbalas Tidak Lengkap' Dikemukakan Oleh Pemohon Dalam Tempoh Enam (6) Bulan Dari Tarikh Permintaan' (20 May 2009)

ii) Bil (22) dlm. BPFK/PPP/01/03
Keperluan Kajian BioEkuivalens Bagi Produk “Generic Immediate Release Oral Solid Dosage Form” yang Bertukar Tapak Pengilangan (01 February 2009)

iii) Bil (31) dlm. BPFK/PPP/01/03
Makluman Susulan Berkaitan Kajian Bioekuivalens bagi Produk 'Generic Immediate Release Oral Solid Dosage Form' yang Bertukar Tapak Pengilangan (13 May 2009)

iv) Bil (39) dlm. BPFK/PPP/01/03
Permohonan Pertukaran Tapak Pengilang Jenis V Iaitu Pada Situasi Krisis (16 July 2009)

v) (10) dlm.BPFK/PPP/01/03 Jilid 1
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 1 Tahun 2011 : Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens Bagi Semua Produk Generik “Immediate Release, Oral, Solid Dosage Form” Yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian BioEkuivalens (2 March 2011)

vi) Bil (7)dlm.BPFK/PPP/01/03 Jld. 3
Kebenaran Pertukaran Tapak Pengilang Ke Pengilang Kontrak Tempatan (18 February 2014)

16.3 CHANGE OF PRODUCT REGISTRATION HOLDER

[Reference: Directive (3)dlm.BPFK/PPP/07/25]
Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 4 Tahun 2013 : Direktif Untuk Meminda Prosedur Permohonan Pertukaran Pemegang Pendaftaran Produk (03 June 2013)

16.3.1 INTRODUCTION

A transfer procedure shall be used where a product registration for the purpose of marketing authorization to be transferred from the existing product registration holder (PRH) to another holder. This procedure allows the same product to maintain the same registration number.

Upon receipt of complete application, the application shall be processed within forty-five (45) working days.

16.3.2 CONDITIONS

The conditions for the PRH transfer procedure are as follows:

1) An application to transfer the marketing authorization of a product shall be submitted by the **existing PRH**.
2) The new PRH shall be a registered company/ business with Companies Commissioner of Malaysia and a registered QUEST user with National Pharmaceutical Regulatory Division (NPRA).
3) The existing product registration shall have a remaining validity **period of at least six (6) months**. If the period is less than six (6) months, product registration renewal shall be made before the transfer application is submitted.
4) No change/s can be made to the technical data or approved pharmaceutical / pharmacological information, including the texts of the product label and leaflet, **except** the name and address of the approved PRH, unless made through variation procedure.
5) In the interim, the existing PRH is still vested with the marketing authorization of the said registered product.

6) The transfer shall come into effect on the day the DCA makes its decision on the application. Upon the transfer of product registration to the new PRH, the authorization issued to the previous PRH will be cancelled as the product cannot be marketed simultaneously by two different PRHs. The new PRH shall bear responsibility for the said product.
7) However, the existing PRH is allowed to deplete the stocks and still holds the responsibility in the event of pharmacovigilance issues or quality defects associated with the product arises during the interim transfer period.
8) The existing PRH or new approved PRH shall submit a written request to deplete existing stocks after DCA approval for the transfer. The PRH who submitted the request shall hold the responsibility in the event of pharmacovigilance issues or quality defects associated with the product.
9) Application shall be rejected if the applicant fails to provide satisfactory required documents within 30 working days starting from the first correspondence date.

16.3.3 APPLICATION

The existing PRH shall submit the following documents and payment to NPRA:

1. Application Form BPFK-430.5
2. *Borang Penyerahan Permohonan* BPFK-001
3. Processing Fee (refer 16.3.4)
4. Original Supporting Documents (refer 16.3.5)

16.3.4 PROCESSING FEE

1. NON-REFUNDABLE processing fee.
   - For Traditional Product : RM 500.00
   - For Poison/ Non-Poison product : RM 1,000.00

2. The processing fee shall be paid in the form of a bank draft/ money order/ postal order, made payable to "Biro Pengawalan Farmaseutikal Kebangsaan".

3. Application/s without correct processing fee will not be accepted for processing. Foreign currencies are not acceptable.

16.3.5 SUPPORTING DOCUMENTS

1. All supporting documents shall be produced in ORIGINAL copies as listed below:

   LIST OF RE**QUIRED SUPPORTING DOCUMENTS:**

   i) Letter of Authorisation (LOA) issued by overseas product owner **certified by Notary Public from the country of origin of the product owner; or Malaysia Commissioner for Oath for local product owner** and **shall consists** of the following information:

      a. The registered name and registration number of the product(s) concerned.
      b. Company name, business registration number and address of the proposed new PRH.
      c. Company name, business registration number and address of the existing PRH.
      d. Effective date of the appointment and termination given by the product owner. If the effective date is not mentioned, the date of the LOA issued will be considered as the effective date.
      e. Signature of the Managing Director/ Director/ President/ Chief Executive Officer/ General Manager who has overall responsibility for the company or organization.
      f. Full and complete address, email address (if available), telephone and fax number (if available) of the Product Owner.

      **Note:* LOA format example (Please refer 16.3.6 Supporting Document Format Example)

   ii) Resolution by Company Board of Directors of **local product owner** to verify that ALL Board of Directors/ Partners have given their consent to the Change of PRH.

   iii) Certified by Commissioner for Oath of the latest document indicating details of director/s and shareholder/s of **local product owner**; e.g. Form 24 and Form 49.

   iv) Resolution by Company Board of Directors of **existing PRH** to verify that ALL Board of Directors/ Partners have given their consent to the Change of PRH.

   v) Certified by Commissioner for Oath of the latest document indicating details of director/s and shareholder/s of **existing PRH**; e.g. Form 24 and Form 49.

   vi) A certified true copy of the Company/ Business Registration Certificate of proposed new PRH; e.g. Form 9 and/ or Form 13.

vii) Statement of Acceptance as Product Registration Holder, BPFK-430.5(3) to be completed by proposed new PRH.

2. Date of the documents must be recent, i.e. not exceeding six (6) months from the date of application.
3. Each page of attachment of product list (if any) must be endorsed by the signatory.
4. The Secretariat, if necessary, has the right to request for further supplementary information or documentation. Failure to do so may result in the rejection of the transfer application.

16.3.6 SUPPORTING DOCUMENT FORMAT EXAMPLE

This format example is suggested for the applicant in order to produce the required supporting document i.e. Letter of Authorisation (LOA).

PRODUCT OWNER Letter Head (full and complete address, email address, telephone and fax number)

(Please state) Date of LOA (the existing PRH shall submit an application within 6 months from this date)

Drug Control Authority,
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor, Malaysia.

Dear Sir/ Madam,

LETTER OF AUTHORIZATION FOR TRANSFER OF PRODUCT REGISTRATION HOLDER

The above subject matter is referred.

Due to (*please state) reason of the transfer*,

2. We, *Name of registered Product Owner*, the undersigned as the product owner for the said product(s) listed below:

Name of Product(s)	**Registration Number**

(*If number of product > 10, endorsed attachment is allowed.)*

hereby authorize
Company name with business registration number and full address of the proposed new PRH
to be the Product Registration Holder and to act on our behalf/ responsible for all matters pertaining to the registration of the listed product(s) including obtaining approval for any subsequent product variation and maintenance of the product(s) registration.

3. Therefore, we hereby terminate marketing authorization of the existing Product Registration Holder
Company name with business registration number and full address of the existing PRH
for the listed product(s) effectively on *date of authorization / termination.*

4. We shall confirm that the entire dossier of the listed product(s) includes all the data in support of the original application, together with all correspondence with the Drug Control Authority (DCA)/ National Pharmaceutical Regulatory Division concerning the listed product(s), to be transferred from *Company name of the existing PRH* to *Company name of the proposed new PRH* upon the approval from DCA.

Thank you.

Sincerely,

**Company officer's signature(s)*
**Full name & Title/ Positition*
Company stamp

***Certified by Notary Public/ Commissioner for Oath*

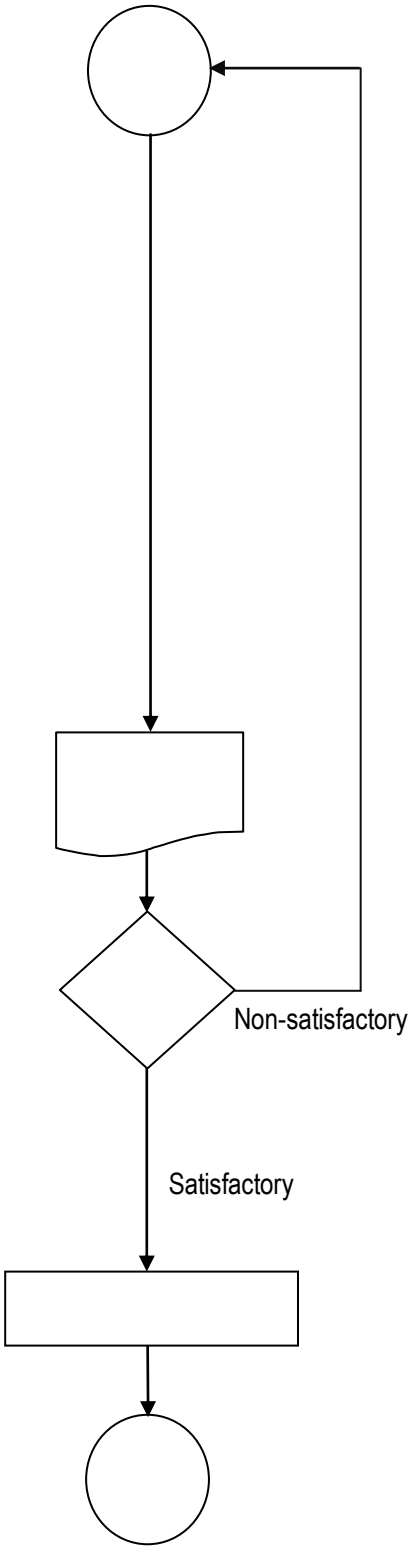
cc: *Company of proposed new PRH*
Company of existing PRH
Product Manufacturer
(A copy of LOA shall be sent to these companies by the Product Owner)

IMPORTANT NOTICE:

1. **LOA shall be signed by Managing Director/ Director/ President/ Chief Executive Officer/ General Manager who has overall responsibility for the company or organization.*
2. ***LOA shall be certified by Notary Public of the country of origin for overseas company or Malaysia Commissioner for Oath for local company.*

N

16.3.7 FLOWCHART FOR THE CHANGE OF PRODUCT REGISTRATION HOLDER



Company (Existing PRH)

Submit completed application to NPRA as below;

1. Application Form BPFK-430.5
2. *Borang Penyerahan Permohonan* BPFK-001
3. Processing Fee
4. Original Supporting Documents consisting of;
   - LOA from product owner certified by Notary Public for overseas company or Commissioner For Oath for local company
   - Resolution by Company Board of Directors of local product owner
   - The latest Form 24 and Form 49 of local product owner certified by Commissioner for Oath
   - Resolution by Company Board of Directors of existing PRH
   - The latest Form 24 and Form 49 of existing PRH certified by Commissioner for Oath
   - Company/ Business Registration Certificate of proposed new PRH
   - Statement of Acceptance As Product Registration Holder; BPFK-430.5(3) completed by proposed new PRH

Secretariat

Receive documentations and evaluation of application

Secretariat

Processing of evaluated application

1. Satisfactory:
   a) Table to DCA meeting for approval
2. Non-satisfactory:
   b) Table to DCA meeting for rejection (processing fee is NON REFUNDABLE in the event that application is being rejected)

DCA Meeting

Secretariat

Processing of DCA meeting outcome

1. Notification of transfer approval to new proposed PRH and termination notification to existing PRH for approved application; OR
2. Notification of transfer rejection to existing PRH for rejected application

16.4 NEW/ ADDITIONAL INDICATION

New/ additional indication is defined as an indication which is not initially approved for a registered pharmaceutical product. This shall include new therapeutic indication or indication for new age group, such as usage in children, and shall not include changing/ rephrasing of sentences.

There are two (2) types of evaluation process available for a new/ additional indication application:

16.4.1 FULL EVALUATION PROCESS

For new indication which has been registered in any one of the Authority's eight (8) reference countries (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan and Switzerland).

This application will require specialists' comments.

16.4.2 VERIFICATION PROCESS

For new indication which has been registered by <u>any two</u> reference country's authorities (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan, Switzerland and EMA).

<u>Note</u>:
The approved new indication in these countries should be the same as that of the proposed new indication.

Other supporting documents that are deemed necessary shall be submitted upon request to support the efficacy and safety of the proposed additional indication.

The supporting documents may include but not limited to the following:

a) Approval of Additional Indication(s) in country of origin;
b) Approval status in reference countries, its corresponding approval letter and approved Package Insert;

c) Approval Indication status in ASEAN Member States and its approved corresponding package insert;
d) Revised Package Insert;
e) World Wide Approval status;
f) Consumer Medication Information Leaflet (RiMUP);
g) Clinical Expert Reports;
h) Synopsis of Individual Studies;
i) Clinical Studies Report/ In-House Clinical Trials;
j) Published Clinical Papers;
k) Current Periodic Safety Update Report (PSUR).

16.5 APPLICATION FOR A CONVENIENT PACK

a) This type of application is referring to registered products which are packed together in a single packaging unit for convenience of the consumers, such as a Confinement Set or *Set Jamu Bersalin*.

b) Individual registered products are allowed to be packed together and marketed as a convenient pack, provided that the application is justified satisfactorily.

c) The convenient pack is applicable for registered products in the categories of;

i) Health supplements.

ii) Natural products.

Or registered products from both categories (i) and (ii)

iii) Non-Scheduled Poison (OTC)

(Only between OTC products with Abridge Evaluation category)

d) Application for a convenient pack shall be made via the process of variation Type II.

The holder has to submit the convenient pack label and also the individual label via application for variation under Part D2 (outer label). The convenient pack label shall contain the same information as in the primary label.

For details of variation, please refer to Section E: 16.1 Variation.

e) Individual registered products involved in the convenient pack can be sold individually or as a pack.

f) Conditions for application:

i) Individual registered products proposed to be packed together as a convenient pack shall be sourced from the same product owner/ PRH;

ii) Submission of the application shall be made by the same PRH.

iii) The manufacturing site for the convenient pack shall be a GMP certified facility.

g) Approved indication of each individual registered product in the convenient pack remains unchanged. There is no common specific indication for the convenient pack.

h) Labelling requirement specifically for convenient pack:

Table XIX:

Outer Label	Immediate Label
Contents in the labelling of each individual registered product have to be included in the outer label of the convenient pack.	As per labelling requirements for registered products.

Note:

For the purpose of application submission, if the individual registered product is also marketed independently, outer label of the packaging sold independently and outer label of the convenient pack shall be submitted together.

i) Additional information on differentiation from Combination Pack (Combo Pack) and Starter Pack/Patient Initiation Pack:

Table XX:

No.	Particulars	Convenient Pack	Combination Pack (Combo Pack)	Starter Pack/ Patient Initiation Pack
1.	New registration number (MAL No.) to be assigned upon approval	No	Yes	No
2.	Mode of application	Variation Type II	Application for registration as a new product	Application for registration as a new product and variation
3.	Purpose of product	For convenience of the consumer	For therapeutic regimen	For dosing regimen
4.	New indication	No	Yes	No
5.	Sale of product	Can be sold individually or as a pack	Only to be sold as a pack	Only to be sold as a pack
6.	Example	Confinement Set or *Set Jamu Bersalin*	Klacid HP7 (for treatment of peptic ulcer diseases associated with H. pylori infection)	Products that require dose tapering either to reduce systemic side effect or for dose adjustment to achieve the desired maintenance dose

17. POST-MARKETING ACTIVITIES

17.1 PHARMACOVIGILANCE

17.1.1 ADVERSE DRUG REACTION REPORTING AND SAFETY UPDATES

In accordance with Regulation 28 : Reporting adverse reaction under Control of Drugs and Cosmetics Regulations 1984, Sale of Drugs Act 1952 (amendment 2006), the product registration holders or any person who possesses any registered product shall inform immediately the Director of Pharmaceutical Services of any adverse reaction arising from the use of the registered product.

All product registration holders must ensure that a pharmacovigilance system is in place by the company and appropriate action is taken, when necessary.

Product registration holders are required to monitor and report any product safety issues that arises locally or internationally to the NPRA and comply with all safety-related directives issued by the Authority.

The product registration may be cancelled if the product registration holder fails to inform the Authority of any serious adverse reactions upon receipt of such reports.

The WHO encourages reporting of ALL adverse drug reactions.

For further information, please refer Malaysian Guidelines for the Reporting & Monitoring.

17.2 POST-MARKET SURVEILLANCE

a) It is the prime responsibility of the holder to ensure products marketed are in accordance to the standards and requirements of the Authority;

b) Registered products may be sampled and tested for compliance with official or pharmacopoeia standards or specifications agreed by the manufacturer. Labels and

package inserts of the samples will also be checked to ensure compliance to the requirements as approved.

c) The Authority will take necessary action on products which do not conform to the standards/ specifications and requirements in the form of warnings or recalls. The product registration holder has up to thirty (30) days to identify the cause of defect and actions to be taken for improvement.

17.2.1 PRODUCT COMPLAINTS

a) The product registration holder should notify the NPRA of any product quality related problems (with registered products) that the holder is aware of;

b) It is also the responsibility of the prescribers, pharmacists, as well as all other health professionals who come into contact with the drug to report to NPRA by using the NPRA complaint form i.e. BPFK 419 / BPFK 418.4 together with complaint sample (if any).

c) All complaints received will be investigated by the NPRA as well as product registration holder/ manufacturer. It is the responsibility of the company to determine the appropriate corrective and preventive action.

Guidelines on Good Distribution Practice, Chapter 9.

17.2.2 PRODUCT RECALLS

a) The decision for recall of a product shall be made when there is or may cause potential risk to the user of the products. Recalls may be done voluntarily by the product registration holder or as directed by the Director of Pharmaceutical Services Division, Ministry of Health Malaysia;

b) The product registration holder is responsible for conducting recalls of defective or unsafe products. No recall should take place without first consulting/ informing the Authority.

Guidelines on Good Distribution Practice, Chapter 10.

17.3 PUNITIVE ACTION FROM THE AUTHORITY

17.3.1 ADULTERATION

As stated in circular Bil (30) BPFK/PPP/01/03, Tindakan Punitif Ke Atas Syarikat Yang Terlibat Dengan Kes Produk Campur Palsu (13 May 2009), punitive action shall be taken against companies who are involved in adulteration.

Any registered products found to have been adulterated, the following action shall be taken by the Director of Pharmaceutical Services:

a) The registration of the related product shall be cancelled and recall of all batches of the product shall be done immediately;

b) The manufacturer's license of the related manufacturer shall be revoked for six (6) months for the first offence and one (1) year for the subsequent offence, from the date of revocation letter;

c) All transactions (including application for product registration, application for change of product registration holder, application for change of manufacturing site) for the adulterated product registration holder shall be frozen for six (6) months for the first offence and one (1) year for the subsequent offence, from the date of cancellation letter from the Authority.

APPENDICES

Appendix 1	**Fees**
Appendix 2	Requirements for Product Registration
Appendix 3	Guidelines on Registration of Biologics
Appendix 4	Guideline on Registration of Health Supplements
Appendix 5	Guideline on Registration of Natural Products
Appendix 6	Guideline on Regulatory Control of Active Pharmaceutical Ingredients (API)
Appendix 7	Special Conditions for Registration for a Particular Product or Group of Products
Appendix 8	List of Permitted, Prohibited and Restricted Substances
Appendix 9	Labelling Requirements
Appendix 10	Guideline on Patient Dispensing Pack for Pharmaceutical Products in Malaysia
Appendix 11	Guideline on Filling the Online Application Form for Product Registration via Quest System
Appendix 12	Conditions and Supporting Documents Required for Application of Variation Type I & Type II
Appendix 13	Supporting Documents Required for Change of Manufacturing Site (COS) Application
Appendix 14	Guidelines On Safety Data Requirements For Complementary Medicine Products

APPENDIX 1: FEES

Outline:

1.1 Charges for USB Token of QUEST Membership;

1.2 Processing and Analysis Fee for Product Registration;

1.3 Charges for Application of Licence;

1.4 Charges for Amendments to Particulars of a Registered Product;

1.5 Fee for Certificates; and

1.6 Charges for Product Classification.

1.1 CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP

	Validity Period	
	1 Year	**2 Years**
Main User – New, Replacement, Change Authorized Person (Certificate + USB Token)	RM 260.00	RM 290.00
Supplementary User – New, Replacement, Change Authorized Person (Certificate + USB Token)	RM 245.00	RM 275.00
Change Authorized Person (Certificate Only)	RM 58.00	RM 105.00
Postage (Semenanjung Malaysia)	RM 10.00	
Postage (Sabah/Sarawak)	RM 20.00	

1.2 PROCESSING AND ANALYSIS FEE FOR PRODUCT REGISTRATION

Every application for registration shall be accompanied with a processing and analysis fee, as specified below (effective 1st January 2007):

No.	Category of Product	* Processing Fees	Analysis Fees	Total Fees
1.	Pharmaceutical a) New Drug Products b) Biologics	RM 1,000.00	Single active ingredient : RM 3,000.00	RM 4,000.00
			Two or more active ingredients : RM 4,000.00	RM 5,000.00
2.	Pharmaceutical a) Generic (Scheduled Poison) b) Generic (Non-Scheduled Poison) c) Health supplement	RM 1,000.00	Single active ingredient : RM 1,200.00	RM 2,200.00
			Two or more active ingredients: RM 2,000.00	RM 3,000.00
3.	Natural Product	RM 500.00	RM 700.00	RM 1,200.00

** As stipulated in the CDCR 1984, Regulation 8.*

1.3 CHARGES FOR APPLICATION OF LICENSES

After a product is registered, the applicant shall apply for a manufacturer/ import/ wholesale license. The processing fees are as specified below:

License	Processing fee	Timeline	Validity
1. Manufacturer	RM 1,000.00	4 working days upon receipt of complete application	1 year
2. Import	RM 500.00	4 working days upon receipt of complete application	1 year
3. Wholesale	RM 500.00	4 working days upon receipt of complete application	1 year

1.4 CHARGES FOR AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

Types of Amendment	Processing fee	
	Pharmaceutical	Natural Product
1. Change of Manufacturing Site (Type I)	RM 1,000.00	RM 100.00
2. Change of Manufacturing Site (Type II, III, IV, V)	RM 1,000.00	RM 500.00
3. Change of Product Registration Holder	RM 1,000.00	RM 500.00
4. Minor Variation Prior Approval (MiV-PA)	RM 150.00	RM 50.00

5. Major Variation (MaV)	RM 300.00	RM 100.00
6. Additional Indication	RM 1000.00	Not applicable

1.5 FEE FOR CERTIFICATES

Under the CDCR 1984, Regulation 16: *"The Director of Pharmaceutical Services may issue such certification on any matter relating to any product where such certification is required by any country importing such a product."*

Certificates	Fee	Validity
Issuance of one (1) Certificate of Pharmaceutical Product	RM 50.00	2 years
Issuance of one (1) Certificate of Good Manufacturing Practice (GMP)	RM 50.00	2 years
Issuance of one (1) Certificate of Declaration *(Sijil Deklarasi)*	RM 50.00	-
Issuance of one (1) Certificate of Indication *(Sijil Indikasi)*	RM 50.00	-

1.6 CHARGES FOR PRODUCT CLASSIFICATION

Category of Products	Processing fee	Timeline
• Food-Drug Interphase (FDI) • Medical Device-Drug-Cosmetic Interphase (MDDCI) • Pharmaceutical products • Health supplements and natural products	RM 300.00	7-14 working days upon receipt of complete application

APPENDIX 2: REQUIREMENTS FOR PRODUCT REGISTRATION

IMPORTANT NOTES:

1. This appendix is for reference purpose only, where applicable, and it may not follow the sequence as in the online product registration application forms (in QUEST system).
2. Online application forms are available for different product categories.
3. Applicant shall follow and comply with all requirements in the online application forms as well as any supplementary documentation requested by the Authority, whichever it may deems fit.

This appendix comprises of two (2) parts which are:

2.1 General requirements for:

2.1.1 Full Evaluation;
(In accordance to ASEAN ACTD/ ACTR or ICH guidelines)

- Part I Administrative data and product information
- Part II Data to support product quality (Quality Document)
- Part III Data to support product safety (Nonclinical Document)
- Part IV Data to support product safety and efficacy (Clinical Document)

2.1.2 Abridged Evaluation.

2.1.3 Additional Information on Requirement of:

- Bioavailability (BA) Study
- Bioequivalent (BE) Study

2.2 Product Specific Requirements

2.1 GENERAL REQUIREMENTS

Data to be submitted as general requirement to support an application for product registration is based on the product category as shown below:

(A) FULL EVALUATION (based on ACTD/ ACTR)					
No.	**Product Category**	**Part I**	**Part II**	**Part III**	**Part IV**
1.	New Drug Products	√	√	√	√
2.	Biologics	√	√	√	√
3.	Generics (Scheduled Poison)	√	√	Not Applicable	Not Applicable
4.	Generics (Non-Scheduled Poison)	√	√	Not Applicable	Not Applicable
5.	Health Supplements: Disease Risk Reduction Claims (High)	√	√	√	√

(B) ABRIDGED EVALUATION	
No.	**Product Category**
1.	* Generics (Non-Scheduled Poison)
2.	Health Supplements: a) General or Nutritional Claims b) Functional Claims (Medium)
3.	Natural Products

* Generics (non-scheduled poison) which are evaluated under abridged evaluation include, but not limited, to the following:

a) Antiseptics/ skin disinfectants;

b) Locally-acting lozenges/ pastilles;
c) Topical analgesic/ counter-irritants;
d) Topical nasal decongestants;
e) Emollient/ demulcent/ skin protectants;
f) Keratolytics;
g) Anti-dandruff;
h) Oral care;
i) Anti-acne;
j) Medicated plasters/ patch/ pad; and
k) Topical antibacterial.

2.1.1 GENERAL REQUIREMENTS FOR FULL EVALUATION

No.	Step I: Product Validation
1.	Is your product has a brand name? (Yes/ No) (If yes, please provide brand name and product name)
2.	Dosage Form
3.	Active Ingredient(s) a) Active Ingredient Name b) Strength of Active Ingredient (Quantity unit/ dose) c) Source of Active Ingredient (Animal – e.g. Bovine, Porcine, Ovine or Others/ Plant/ Others) d) Form of Active Ingredient e) Remarks (if any)
4.	Excipient(s) a) Excipient name b) Strength of Excipient (Quantity unit/ dose) c) Function of excipient (e.g. absorbent, diluents, bulking agent, coating agent, anti-caking agent etc.) d) Source of excipient e) Remarks (if any)
5.	Is there any source of ingredients derived from animal origin, including active ingredient? (Yes/ No)
6.	Manufacturer (Name and Address)
7.	Is the selected manufacturer a contract manufacturer? (Yes/ No)
8.	Is the product from second source? (Yes/ No) If yes, please provide: a) Letter of declaration stating that this product is a second source product b) Registration number and product name of the first source
9.	Is this product containing any premix? (Yes/ No) a) State your premix form b) Manufacturer name c) Manufacturer address d) Certificate of Good Manufacturing Practice (GMP) e) Formulation f) Manufacturing Process g) Specification of Analysis h) Certificate of Analysis (CoA)

No.	Step I: Product Validation
10.	Is this a replacement product? (Yes/ No) If yes, please provide: a) Letter of Declaration stating that this product is a replacement product b) Registration number and product name of the replaced product
11.	Is there any other manufacturer (repacker)? (Yes/ No) a) Manufacturer (repacker) name b) Manufacturer (repacker) address c) Certificate of Good Manufacturing Practice (GMP) d) Packaging Process
12.	Is this an imported product? (Yes/ No)

Step II:	
Part I: Administrative Data And Product Information	
No.	**Section A: Product Particulars**
1.	Product Name
2.	Name & Strength of Active Substance and Excipient
3.	Dosage Form
4.	Product Description
5.	Pharmacodynamics
6.	Pharmacokinetics
7.	Indication
8.	Recommended Dose
9.	Route of Administration
10.	Contraindication
11.	Warning and Precautions
12.	Interaction of Other Medicaments
13.	Pregnancy and Lactation
14.	Side Effects

Step II:	
15.	Symptoms and Treatment of Overdose
16.	Storage Condition
17.	Shelf Life
18.	Therapeutic Code/ ATC Code
No.	**Section B: Product Formula**
1.	Batch Manufacturing Formula
2.	Attachment of Batch Manufacturing Formula Documentation
No.	**Section C: Particulars of Packing** - Please refer Appendix 10: Guide for Implementation of Patient Dispensing Pack for Pharmaceutical Products in Malaysia
1.	Pack Size (Fill details by weight/ volume/ quantity)
2.	Immediate Container Type (Container Type and Description) e.g. Aluminium/ Glass/ Metal/ Paper/ Plastic/ Others
3.	Barcode/ Serial No. (Optional)
4.	Recommended Distributor's Price (RM) (Optional)
5.	Recommended Retail's Price (RM) (Optional)
No.	**Section D: Label (Mock-up) For Immediate Container, Outer Carton, Proposed Package Insert** - Please refer Appendix 9: Labelling Requirements
1.	Proposed Label Mock-up for Immediate Container
2.	Proposed Label Mock-up for Outer Carton
3.	Proposed Package Insert
No.	**Section E: Supplementary Documentation**
1.	Product Owner
2.	Letter of Authorization from Product Owner
3.	Letter of Appointment of Contract Manufacturer from Product Owner (if applicable)

Step II:	
4.	Letter of Acceptance from Contract Manufacturer (if applicable)
5.	Is the active ingredient(s) patented in Malaysia? (Yes/ No) (If yes, please attach the related document)
6.	Certificate of Pharmaceutical Product (CPP)
7.	CPP Issuing Body
8.	Is this product licensed to be placed on the market for use in the exporting country? (Yes/ No) (If no, please state the reason)
9.	Is the product on the market in the exporting country? (Yes/ No) (If no, please state the reason)
10.	Date of Issue of CPP
11.	Date of Expiry of CPP
12.	Certificate of Free Sale (CFS)
13.	CFS Issuing Body
14.	Date of Issue of CFS
15.	Date of Expiry of CFS
16.	Certificate of Good Manufacturing Practice (GMP)
17.	Certificate of GMP Issuing Body
18.	Date of Issue of Certificate of GMP
19.	Date of Expiry of Certificate of GMP
20.	Summary of Product Characteristics (Product Data Sheet)
21.	Consumer Medication Information Leaflet (RiMUP) [Previuosly known as Patient Information Leaflet (PIL)]
22.	***Attachment of Protocol Analysis**
23.	***Attachment of Analytical Validation**
24.	***Certificate of Analysis (CoA)**
25.	Other Supporting Document (if any)

Step II:	
26.	Manufacturer (Name and address)
27.	Importer (if any)
28.	Other manufacturer(s) involved, e.g. repacker (if any) (Please attach Certificate of GMP, if yes)
29.	Store Address
PART II: QUALITY OF PRODUCT	
No.	**Section P: Drug Product (Finished Product)**
1.	Description and Composition
2.	Pharmaceutical Development
	a) Information on Development Studies
	b) Components of the Drug Product
	c) Finished Products
	d) Manufacturing Process Development
	e) Container Closure System
	f) Microbiological Attributes
	g) Compatibility
3.	Manufacturer
	a) Batch Manufacturing Formula
	b) Manufacturing Process and Process Controls
	c) Manufacturing Process Flowchart
	d) Control of Critical Steps & Intermediates
	e) Process Validation and/or Evaluation
4.	Control of Excipients
	a) Specifications
	b) Analytical Procedures
	c) Validation of Analytical Procedures
	d) Justification of Specifications

Step II:	
	e) Excipient of Human or Animal Origin
	f) Novel Excipients
5.	Control of Finished Products
	a) Specifications
	b) Analytical Procedures
	c) Validation of Analytical Procedures
	d) Batch Analyses
	e) Characterization of impurities
	f) Justification of Specifications
6.	Reference Standards or Materials
7.	Container Closure System
8.	Stability
9.	Product Interchangeability/ Equivalent Evidence (Bioavailability/ Bioequivalence, BA/BE) - *Please refer 2.1.3 Additional information on requirements of BA and BE.*
No.	**Section S: Drug Substance**
1.	General Information
	a) Nomenclature
	b) Structure and Attachment for Structure of Drug Substance
	c) General Properties
2.	Manufacturer
	a) Manufacturer Name and Address
	b) Description of Manufacturing Process and Process Controls
	c) Controls of Materials
	d) Controls of Critical Steps and Intermediates

Step II:	
	e) Process Validation and/or Evaluation
	f) Manufacturing Process Development
3.	Characterisation
	a) Elucidation of Structure and Characteristics
	b) Impurities
4.	Control of Drug Substances
	a) Specifications
	b) Analytical Procedures
	c) Validation of Analytical Procedures
	d) Batch Analysis
	e) Justification of Specifications
5.	Reference Standards or Materials
6.	Container Closure System
7.	Stability
PART III: NONCLINICAL DOCUMENT	
	Section A: Table of Contents
No.	**Section B: Nonclinical Overview**
1.	Overview of the Nonclinical Testing Strategy
2.	Pharmacology
3.	Pharmacokinetics
4.	Toxicology
5.	Integrated Overview & Conclusions
6.	List of Literature Citations
	Section C: Nonclinical Written and Tabulated Summaries
	Section D: Nonclinical Study Reports
	Section E: List of Key Literature References

PART IV: CLINICAL DOCUMENT	
	Section A: Table of Contents
No.	**Section B: Clinical Overview**
1.	Product Development Rationale
2.	Overview of Biopharmaceutics
3.	Overview of Clinical Pharmacology
4.	Overview of Efficacy
5.	Overview of Safety
6.	Benefits & Risks Conclusions
No.	**Section C: Clinical Summary**
1.	Summary of Biopharmaceutics Studies and Associated Analytical Methods
2.	Summary of Clinical Pharmacology Studies
3.	Summary of Clinical Efficacy
4.	Summary of Clinical Safety
5.	Synopses of Individual Studies
	Section D: Tabular Listing of all Clinical Studies
	Section E: Clinical Study Reports
	Section F: List of Key Literature References, Published Clinical Papers and Latest Periodic Safety Update Report (PSUR)

Notes:

* Evaluated by Centre for Quality Control. For details, please refer to Section C: Quality Control in the main DRGD.

2.1.2 GENERAL REQUIREMENTS FOR ABRIDGED EVALUATION

No.	Step I: Product Validation
1.	Product Name
2.	Dosage Form
3.	Active Ingredient(s) a) Active Ingredient name b) Strength of Active Ingredient (Quantity unit per dose) c) Source of Active Ingredient (Animal – e.g. Bovine, Porcine, Ovine or Others/ Plant/ Others) d) Form of Active Ingredient e) Remarks (if any)
4.	Excipient(s) a) Excipient name b) Strength of Excipient (Quantity unit per dose) c) Function of excipient (e.g. absorbent, diluents, bulking agent, coating agent, anti-caking agent etc.) d) Source of excipient e) Remarks (if any)
5.	Is there any source of ingredients derived from animal origin, including active ingredient? (Yes/ No)
6.	Manufacturer (Name and Address)
7.	Is the selected manufacturer a contract manufacturer? (Yes/ No)
8.	Is the product from second source? (Yes/ No) If yes, please provide: a) Letter of declaration stating that this product is a second source product b) Registration number and product name of the first source
9.	Is this product containing any premix? (Yes/ No) a) State your premix form b) Manufacturer name c) Manufacturer address d) Certificate of Good Manufacturing Practice (GMP) e) Formulation f) Manufacturing Process g) Specification of Analysis h) Certificate of Analysis (CoA)

No.	Step I: Product Validation
10.	Is this a replacement product? (Yes/ No) If yes, please provide: a) Letter of Declaration stating that this product is a replacement product b) Registration number and product name of the replaced product
11.	Is there any other manufacturer (repacker)? (Yes/ No) a) Manufacturer (repacker) name b) Manufacturer (repacker) address c) Certificate of Good Manufacturing Practice (GMP) d) Packaging Process
12.	Is this an imported product? (Yes/ No)

Step II:	
No.	**Section A: Product Particulars**
1.	Product Name
2.	Product Description
3.	Dosage Form
	a) Source of Capsule Shell
	b) Certificate to verify the source of the capsule shell
	c) Coloring agent used in capsule shell (Please attach COA of the capsule shell)
4.	Product Indication/ Usage
5.	Dose/ Use Instruction
6.	Contraindication
7.	Warning and Precautions
8.	Drug Interaction
9.	Side Effects/ Adverse reaction
10.	Signs and Symptoms of Overdose and Treatment
11.	Storage Condition
12.	Shelf Life

Step II:	
13.	Therapeutic Code/ ATC Code
No.	**Section B: Product Formula**
1.	Batch Manufacturing Formula a) Batch Size b) Unit
2.	Active Ingredients a) Active Ingredients Name b) Quantity c) Source d) Form of Substance e) Overage (%) f) Remarks
3.	Excipients a) Active Ingredients Name b) Quantity c) Function d) Source e) Overage (%) f) Remarks
4.	Attachment of Batch Manufacturing Formula Documentation
5.	Manufacturing Process
6.	Attachment of Manufacturing Process Documentation
7.	In-Process Quality Control
8.	Attachment of Finished Product Specification Documentation
9.	Attachment of Stability Data Documentation *(For two batches) - Compulsory for imported product*
No.	**Section C: Particulars of Packing** - Please refer Appendix 10**:** Guide for Implementation of Patient Dispensing Pack for Pharmaceutical Products in Malaysia
1.	Pack Size (Fill details by weight/ volume/ quantity) Measurement Type

Step II:	
2.	Immediate Container Type (Container Type and Description) e.g. Aluminium/ Glass/ Metal/ Paper/ Plastic/ Others
3.	Barcode/ Serial No. (Optional)
4.	Recommended Distributor's Price (RM) (Optional)
5.	Recommended Retail's Price (RM) (Optional)
6.	Other Related Attachment (if any)
No.	**Section D: Label (Mock-up) For Immediate Container, Outer Carton, Proposed Package Insert** - Please refer Appendix 9: Labelling Requirements
1.	Proposed Label Mock-up for Immediate Container
2.	Proposed Label Mock-up for Outer Carton
3.	Proposed Package Insert
No.	**Section E: Particulars of Product Owner, Manufacturer, Importer and Other Manufacturer(s) Involved and Store address**
1.	Product Owner
2.	Manufacturer
3.	Other Manufacturer(s) involved (if any) a) Manufacturer Name and Address b) Processing Steps Involved c) Certificate of Good Manufacturing Practice (GMP)
4.	Store Name and Address
5.	Importer
No.	**Section F: Supplementary Documentation**
1.	Letter of Authorization from Product Owner
2.	Letter of Appointment of Contract Manufacturer from Product Owner (if applicable)
3.	Letter of Acceptance from Contract Manufacturer (if applicable)

Step II:	
4.	Is the active ingredient(s) patented in Malaysia? (If yes, please attach the related document)
5.	Certificate of Pharmaceutical Product (CPP)
6.	CPP Issuing Body
7.	Is this product licensed to be placed on the market for use in the exporting country? (If no, please state the reason)
8.	Is the product on the market in the exporting country? (If no, please state the reason)
9.	Date of Issue of CPP
10.	Date of Expiry of CPP
11.	Certificate of Free Sale (CFS) (if any)
12.	CFS Issuing Body
13.	Date of issue of CFS
14.	Date of expiry of CFS
15.	Certificate of Good Manufacturing Practice (GMP)
16.	Certificate of GMP Issuing Body
17.	Date of issue of Certificate of GMP
18.	Date of expiry of Certificate of GMP
19.	Summary of Product Characteristics (Product Data Sheet)
20.	Consumer Medication Information Leaflet (RiMUP) [Previously known as Patient Information Leaflet (PIL)]
21.	Attachment of Protocol Analysis
22.	Attachment of Certificate of Analysis (CoA) *(For two batches)* ** Compulsory for imported products*
23.	Attachment of Specifications and Certificate of Analysis of Active Ingredient
24.	Other Supporting Documents (if any)

2.1.3 ADDITIONAL INFORMATION ON:

A) BIOAVAILABILITY (BA) STUDY

For modified-release products, dosage recommendations and regime must be supported by bioavailability studies.

Studies comparing availability or establishing equivalence of similar products would be useful.

B) BIOEQUIVALENCE (BE) STUDY

Note: *This requirement is applicable to generics (scheduled poison) only.*

With the increasing availability of generic products, a mechanism is required to ensure that such products are therapeutically equivalent to the innovators' products and are clinically interchangeable.

In practice, demonstration of bioequivalence (BE) is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products. A list of drug substances, which, when formulated in oral solid dosage forms, require BE data as a prerequisite for registration, has been established by the authority (please refer to NPRA website at http://npra.moh.gov.my/). This list is updated based on the requirements.

Bioequivalence (BE) Study Requirements for Generic Product in Immediate Release, Oral Solid Dosage Form Submitted as a Second Source Application

In general, for a second source application of a generic product (immediate release, oral solid dosage form), BE study report from the actual manufacturing site must be submitted during the submission of application for registration. The base of this requirement is due to the difference in manufacturing site from the first source that may change the characteristic and specifications of a second source product.

However, biowaiver can be considered, provided that Comparative Dissolution Profile (CPD) report against the registered first source product is submitted as a surrogate to bioequivalence study conducted for the second source product and all the following conditions shall be fulfilled:

a) Bioequivalence study conducted using the registered first source product has been evaluated by the NPRA and found satisfactory.

b) The second source product is the same as registered first source product used in the bioequivalence study in terms of:

   i) Product formulation;
   ii) Equipment used in the manufacturing process;
   iii) Source and supplier of raw material;
   iv) Quality control and specifications of raw material;
   v) Manufacturing process of product and standard operating procedures;
   vi) Environmental conditions during the manufacturing process of product;
   vii) Quality control and specifications of finished product.

c) Comparative Dissolution Profile must be conducted in accordance to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies including the calculation of similarity factor (f2) to prove the similarity of these two products.

d) Process validation has been conducted on 3 pilot or commercial batches of the second source product and found satisfactory by the NPRA.

This exemption is not applicable for any new submission of application for registration of a first source product. BE study must be conducted for this product which is manufactured at the actual manufacturing site submitted for registration.
(Reference: Circular Bil.(10)dlm.BPFK/PPP/07/18Jld.1 *, 2 Jun 2011)*

Starting on 1st of January 2012, bioequivalence (BE) study is required for all application of registrations for generic products containing scheduled poison in the form of immediate release, oral, solid dosage form whereas renewal of registered products, the effective date is on 1st January 2013.
(Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Year 2011*, 2 March 2011 Bil (10) dlm BPFK/PPP/01/03 Jld 1)

Sponsors or BE study centers are compulsory to notify the Authority pertaining to all BE studies which do not require Clinical Trial Import Licence (CTIL) or Clinical Trial Exemptions (CTX) and are going to be done at either local or overseas BE study centers for registered products or products to be registered in Malaysia (Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 13 Year 2011*, 14 October 2011, Bil (23) dlm BPFK/PPP/01/03 Jld 1).

Note: The two above directives shall be read in conjunction with the supplementary circular that further explains the procedure for evaluation of BE centre inspection reports in line with the requirement of accreditation of BE Centres. (Reference: Circular dated 12 September 2013; Bil(6)dlm.BPFK/PPP/01/03 Jld 3.)

Effective 1st March 2013, biowaiver may be granted to generic immediate release oral solid dosage form products containing BCS Class I active ingredients listed in the Guidance On Biopharmaceuticals Classification System (BCS) – Based Biowaiver document. BCS Based biowaivers takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into accounts i.e. solubility and permeability of the drug substance/ API, and dissolution characteristics of the dosage form. This BCS approach provides an opportunity to waive *in vivo* pharmacokinetic bioequivalence testing for certain categories of immediate-release drug products.
(Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Year 2013*, 14 October 2011, 28 February 2013, Bil (101)dlm.BPFK/PPP/01/03 Jld 2).

For more information on BE, please refer Bioequivalence (BE).

2.2 SPECIFIC REQUIREMENTS

For biologics, health supplements and natural products, please refer guidelines for the respective product category at:

a) Appendix 3: Guidelines on Registration of Biologics
b) Appendix 4: Guideline on Registration of Health Supplements
c) Appendix 5: Guideline on Registration of Natural Products

Please refer as well on **Appendix 11**: Guideline on Filling the Online Application Form for Product Registration via Quest System before submission of an application for product registration.

APPENDIX 3: GUIDELINES ON REGISTRATION OF BIOLOGICS

IMPORTANT NOTES:

1. This document shall be read in conjunction with the relevant sections of the main guidance document: **Drug Registration Guidance Document (DRGD), which is in accordance to the legal requirements of the Sale of Drugs Act 1952 and the Control of Drugs and Cosmetics Regulations 1984.**

2. The National Pharmaceutical Regulatory Division's (NPRA) requirements for registration of biologics/ biopharmaceuticals products are aligned with the scientific guidelines and recommendations for quality, clinical efficacy and safety and non-clinical of the World **Health Organization (WHO), European Medicines Agency (EMA) and International Conference of Harmonization (ICH).**

3. **Where appropriate, the relevant WHO, EMA and ICH guidelines on biologics/ biopharmaceuticals shall be consulted.**

    - **WHO** *(http://www.who.int/boodproducts/en/index.html)*
    - **EMA** *(http://www.ema.europa.eu)*
    - **ICH** *(http://www.ich.org)*

4. **Every biologic is regulated as a new product and also considered 'high risk', both drug substance and drug product production** must comply to Good Manufacturing Practice strictly. Adoption of GMP as an essential tool of Quality Assurance System.

5. The requirements for registration of biologics/ biopharmaceuticals shall be in accordance to the **ASEAN Common Technical Dossier (ACTD)** format and in adherence to the general regulatory requirement as described in sections of the main DRGD. It covers:

    - Administrative information
    - Product quality data
    - Product safety data
    - Clinical data, demonstrating clinical efficacy and capacity to meet therapeutic claims, through clinical studies.

6. Animal derived materials/ products are commonly used in the manufacture of biologics/ biopharmaceuticals. Please provide detail information regarding the rationale for use of

such material, the source etc., as per **Checklist A** and **Checklist B**; and also provide a confirmation on the presence/ absence of the animal materials in the final product.

7. Since biosimilars are follow-on products of the original biopharmaceutical products (well-characterised recombinant proteins), this document also is applicable to biosimilars. Additionally, a separate Guideline for Registration of Biosimilars is available.

8. Although a CGTP is regulated separately under different framework, the Guidance Document dan Guidelines For Registration of Cell and Gene Therapy Products (CGTPs), December 2015 should be read in conjunction with this document because a high risk CGTP which is categorized as class II, is regulated as a biologic product. A class II cell therapy is "highly processed", used for other than normal function, is combined with non-tissue components, or is used for metabolic purposes". For further details, please refer to **Directive No. 6 Year 2017. Ref: BPFK/PPP/07/25 (11) Jld.1:** Direktif Untuk Menguatkuasakan Penggunaan *Guidance Document And Guideline For Registration Of Cell And Gene Therapy Products (CGTPS), December 2015* Dan *Good Tissue Practice Guideline, 2ND Edition, December 2015).*

9. This document is intended to provide guidance for the registration of biologics. However, the document will serve as a living document that will be updated/ revised further in the line with the progress in scientific knowledge and experience.

Outline:

3.1 General Information

3.1.1 Definitions

3.1.2 Introduction

3.2 Specific Requirements for Registration of Biologics

3.2.1 Requirements for Registration of Biologics (Vaccines and Biotechnology Products)

a) Vaccines

i) Definition of Vaccine

ii) Requirements for Registration of Vaccines (Chemistry, Manufacturing And Controls, CMC)

b) Biotechnology Products

i) Definition of Biotechnology Product

ii) Additional Requirements for Registration of Biotechnology Products

c) References

3.2.2 Requirements for Registration of Blood Products

a) Definition of Blood Product

b) Requirements for Registration of Blood Products

c) Checklist of Plasma Master File for Blood Products

d) References

3.3 Checklists of Registration for Products Containing Materials of Animal Origin:

3.3.1 Checklist A: Products Containing Animal-Derived Materials **with** a valid TSE risk evaluation Certificate of Suitability (CEP)

3.3.2 Checklist B: Products Containing Animal-Derived Materials **without** a valid TSE risk evaluation Certificate of Suitability (CEP)

3.1 GENERAL INFORMATION

3.1.1 DEFINITIONS:

i) Biopharmaceutical/ Biotechnology Product
ii) Biologic/ Biological Product

- The term 'biopharmaceutical' was coined in the 80's to define proteins that were made by recombinant DNA technology [which includes hybridoma technology for monoclonal antibody (mAb) production].

- Biologic/ Biological product refers to a product whose active substance is made by or derived from a living organism (plant, human, animal or microorganism) and may be produced by biotechnology methods and other cutting-edge technologies. This product imitates natural biological substances in our bodies such as hormones, enzymes or antibodies.

- Biopharmaceuticals/ Biologics/ Biological products can also be defined as: "a protein (including antibodies) or nucleic acid-based pharmaceuticals used for therapeutic, which is produced by means other than direct extraction from a native (non- engineered) biological source". This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant/ genetically engineered and mAb-based products).

- The term 'Biotechnology product' and 'Biological product' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view).

Note: *Today, biologics have become inextricably intertwined with biopharmaceuticals, to the point where they are synonymous. The general consensus is that a 'Biologic' and 'Biopharmaceutical' are interchangeable terminology, but a biologic might incorporate some other products (e.g. allergenics, somatic cells etc.).*

Biologics include a wide range of products such as:
1. Vaccines
2. Blood products
3. Monoclonal antibodies (therapeutics)
4. Recombinant proteins:
   - Insulins
   - Hormones
   - Erythropoetins and other hematopoietic factors

- Cytokines: interferons, interleukins, colony-stimulating factors, tumour necrosis factors.

5. Cell and Gene Therapy Products (CGTPs)

But does **not** include:

- Metabolites from microorganisms; e.g antibiotics and some hormones.
- Macromolecules produced by chemical synthesis; e.g peptides/oligo-nucleotides produced by chemical synthesis.
- Whole blood or cellular blood components.

Note: *This document is not intended to apply to the control of genetically-modified live organisms designed to be used directly in humans, e.g. live vaccines.*

3.1.2 INTRODUCTION

It is acknowledged that biological substances used in the practice of medicines make a vital contribution to health care. Nevertheless, because of their nature, biologicals demand special attention with regard to their regulations to assure quality, efficacy and safety.

Biologicals are inherently variable due to their biological nature, produced from biological materials, and often tested in biological test systems, themselves variable, a feature that has important consequences for the safety and efficacy of the resulting product. Each product must be evaluated on its own merits. A prerequisite for the use of biological is therefore to assure the consistency of quality and safety from lot-to-lot.

Today, the biological field is one of enormous expansion and increasing diversity, most especially in the area of new biotechnologies. The revolution of DNA-based and other cell technologies has opened up a new and exciting vista, and in many instances, traditional products are being replaced by equivalents derived by recombinant DNA technologies or other cutting-edge technologies.

It is important to note that the demonstration that a product consistently possesses a desired characteristics of safety and efficacy will depend on a multifaceted approach on the part of manufacturer and the regulatory authority - drawing on thorough characterization of starting materials, demonstration of consistency of production, and appropriate selection of lot release tests - all under the stringent and documented controls imposed by good manufacturing practices - as well as rigorous post marketing surveillance activities.

3.2 SPECIFIC REQUIREMENTS FOR REGISTRATION OF BIOLOGICS

Specific requirements for registration of biologic/ biopharmaceutical are described as follows:

1. Requirements for Registration of Biologics (Vaccines and Biotechnology products);
2. Requirements for Registration of Blood Products.

3.2.1 REQUIREMENTS FOR REGISTRATION OF BIOLOGICS (VACCINES AND BIOTECHNOLOGY PRODUCTS)

a) VACCINES:

i) DEFINITION OF VACCINE

A vaccine contains an active component (the antigen). A vaccine is an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration or therapy of any disease or infection.

Vaccines for human use include one or more of the following:

a) microorganisms inactivated by chemical/ physical means that retain appropriate immunogenic properties;
b) living microrganisms that have been selected for their attenuation whilst retaining immunogenic properties;
c) antigen extracted from microorganisms, secreted by them or produced by recombinant DNA technology; or
d) antigen produced by chemical synthesis *in vitro*.

The antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier to increase immunogenicity. Antigens may be presented plain or in conjunction with an adjuvant, or in combination with other antigens, additives and other excipients.

ii) REQUIREMENTS FOR REGISTRATION OF VACCINES (CHEMISTRY, MANUFACTURING AND CONTROLS, CMC)

A.	DESCRIPTION
	▪ Description - Information on the source materials: source materials include any component/ unformulated active substance used in the manufacture of the product (e.g microorganisms, cells/ cell subtrate, immunogen) including their specifications and the tests used to demonstrate compliance with the specifications. For combination vaccines, each active substance, which will be pooled, combined with other antigens and formulated, shall be described. ▪ Any chemical modification or conjugation of the drug substance shall be described in detail. ▪ List of inactive substances, which may be present in the drug substance.
B.	**METHOD OF MANUFACTURE/ PRODUCTION**
1.	**Manufacturing Formula:** ▪ List of all materials (culture media, buffers, resins for peptide synthesis, chemicals, columns etc.) and their tests and specifications, or reference to pharmacopoeia. ▪ Complete formula inclusive of any adjuvants, diluents, preservatives, additives, stabilisers etc. ▪ Production of each antigen in the vaccine (i.e. fermenter or culture volumes for each bulk batch size as applicable and typical bulk volumes per production run). ▪ Batch formula for each batch size and final formulated bulk product. ▪ Lot numbering system for intermediates and final product.
2.	**Manufacturing Process:** **Flow Charts/ Diagrams be Accompanied by a Descriptive Narrative:** ▪ Detailed description of manufacturing process and characterization of the product. Include complete history and characterization/ characteristics of each species, strain, cell banking systems - Master Cell bank (MCB) and Working Cell Bank (WCB), cell/ seed lot system, cell substrate system, animal sources (including fertilized avian eggs), virus source or cellular sources. **Ref:** WHO TRS 878 (1998) *Annex 1: Requirements for the use of animal cells as in vitro substrates for the production of biologicals.*

	▪ The flow chart should show the steps in production and a complete list of the in-process controls and tests performed on the product at each step. ▪ In-process holding steps, with time and temperature limits indicated. ▪ Description of the manufacturing processes (flow diagram) in detail to support the consistency of manufacture of drug substance - cell growth and harvesting. ▪ Identification of any processes or tests performed by contract manufacturers or testers. ▪ Animal cells: Cells of animal origin may harbour adventitious agents and consequently pose a potentially greater risk to humans. Description of measures taken to remove, inactivate, or prevent contamination of the product from any adventitous agent present. ▪ Information on measures to prevent any catastrophic events that could render the cell banks unusable and to ensure continuous production of vaccines is crucial. For recombinant vaccines: description of the construction and characterization of the recombinant vector as well as source of master cell bank/ constructs.
3.	**Process Validation Program:** ▪ Describe general policy for process validation and provide process validation activities performed.
4.	**Handling, Storage and Packaging:** ▪ All arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.
C.	**QUALITY CONTROL**
1.	**Starting Materials:** ▪ List of all control tests performed on raw materials, with appropriate characterisation on starting materials. ▪ List of raw materials meeting compendia specifications. ▪ List of raw materials meeting in-house specifications including the tests performed and specifications ▪ Biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephlopathies (TSEs) and human diseases (HIV, hepatitis,etc) in the final product including Certificate of Suitability (CEP). *Please refer Checklist A & B* **Ref:** *WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical products (2010).*

2.	**Intermediate Products (as appropriate):** ▪ List the routine tests performed and specifications for intermediates.
3.	**Finished Products (including diluents):** ▪ List routine tests performed and specifications for final product. ▪ Description of the method and retest criteria.
4.	**Analytical Validation Activities Performed:** ▪ Include complete description of the protocol used for each bioassay, the control standards, the validation of inherent variability of test and the establishment of acceptance limits for each assay.
D.	**STABILITY** *(http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/en/)*
	▪ Information on stability of intermediates and final product, quality control methods and rationale for the choice of tests for determining stability. ▪ Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production. ▪ Describe the policy for assigning the date of manufacture of each component as well as the final product (e.g combination vaccine) and diluents, as appropriate. ▪ In addition to final product stability data at the recommended storage temperature, the accelerated stability data at elevated temperatures should be sufficient to justify the choice of Vaccine Vial Monitor (VVM) for use with the product [Vaccine Vial Monitor WHO/PQS/E06/IN05.1]
E.	**LOT SUMMARY PROTOCOL AND LOT RELEASE FOR VACCINE**
	▪ Lot Summary Protocol - a document which describes the key steps and critical test results at each step of the production process must be submitted. ▪ Lot release is a basic principle in the control of vaccine. The aim of lot release is the confirmation of consistency of production as each lot of vaccine is unique. ▪ Submit Lot/ Batch Release Certificate issued by the competent authority. **Reference:** Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities World Health Organization 2010 **Circular** Ref : (23) dlm.BPFK/PPP/07/25 Directive No. 16 Year 2014. Direktif Pelaksanaan Vaccine Lot Release ke atas Semua Produk Vaksin Berdaftar di Malaysia

F.	**NONCLINICAL STUDIES FOR VACCINE**
	▪ Vaccines are a diverse class of biological products and their nonclinical testing programs will depend on product-specific features and clinical indications. ▪ Preclinical testing is a prerequisite to moving a candidate vaccine from the laboratory to the clinic and includes all aspects of testing, product charaterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans. ▪ Some live attenuated vaccines must be tested for safety in animals before they are used in humans. **Ref:** WHO TRS 927 (2005) *Annex 1: WHO guidelines on nonclinical evaluation of vaccines*
G.	**CLINICAL STUDIES FOR VACCINE**
	▪ Clinical studies designed and conducted to meet WHO and international GCP principles. ▪ Tabulated summary of the clinical development program of the vaccine, in which critical parameters that may have changed during the clinical development. ▪ Copies of publications about these trials should accompany the submission. ▪ Clinical summary: Provide detailed summary and intepretation of the safety and efficacy data obtained from clinical studies that supports the current prescribing information. ▪ Clinical Expert Report: Provide an independent clinical expert report on the clinical studies (evidence of expertise and independence should be provided) **Ref:** *3.* WHO TRS 924 (2004) *Annex 1: WHO guidelines on clinical evaluation of vaccines:Regulatory expectations.* *4.* WHO TRS 850 (1995) *Annex 3: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products.*

H.	**POST MARKETING SURVEILLANCE FOR VACCINES**
	▪ Provide an outline of the post marketing pharmacovigilance plan for the vaccine. ▪ Periodic safety update report (PSUR) in accordance to ICH Guideline E2C(R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ▪ In the case of vaccines that have recently been registered/ licensed, provide information on any ongoing phase IV studies or on any active monitoring of the safety profile that is taking place including adverse events following immunization(AEFI). ▪ Risk management plan. **Please also refer to:** *NPRA's Guidelines for Pharmacovigilance on Safety of Vaccines in Malaysia (January 2010) ISBN 978-967-5570-05-6*

b) BIOTECHNOLOGY PRODUCTS

i) DEFINITION

Biotechnological products includes the use of the new genetic tools of recombinant DNA to make new genetically modified organisms or genetic engineering products.

Products of recombinant technology are produced by genetic modification in which DNA coding for the required product is introduced, usually by means of a plasmid or viral vector into a suitable microorganism or cell line, in which DNA is expressed and translated into protein. The desired product is then recovered by extraction and purification.

ii) ADDITIONAL REQUIREMENTS FOR REGISTRATION OF BIOTECHNOLOGY PRODUCTS:

I.	**PRODUCTION PROCESSES**
	▪ The production system shall be well defined and documented. ▪ The effectiveness of the overall purification process for active substance shall be demonstrated. ▪ Validation of procedures for removing contaminating cellular DNA, viruses and impurities.
J.	**HOST CELL AND GENE CONSTRUCT**
	▪ Source of host cells, characterisation, stability, purity and selection. ▪ Information on gene construct, amino acid sequence, vector information and genetic markers for characterisation of production cells. ▪ Cloning process to form the final gene construct and mapping of sited used in constructions of final recombinant gene construct. ▪ Method of gene construct amplication and selection of recombinant cell.
K.	**SPECIFICATIONS**
	▪ Drug substances should include assays for identity, purity, potency, physiochemical and stability. ▪ Identity and quantity of impurities along with analytical data which supports impurities profile ▪ Acceptable limits of impurities and should be included in the specifications if present in finished products.

L.	**CHARACTERISATION**
	▪ Analytical testing performed to characterise the drug substance with respect to identity, purity, potency, and stability. ▪ Characterisation of drug substance include physiochemical characterisation, immunological properties and biological activity. ▪ Sufficient sequence information to characterise the product should be obtained. ▪ Post translational modifications should be identified and adequetly characterised, especially when such modifications are likely to differ from those found in natural counterpart and may influence biological, pharmacological and immunological properties of the product.
M.	**NONCLINICAL STUDIES**
	▪ Preclinical testing is a prerequisite to moving a candidate biotechnology products from the laboratory to the clinic and includes all aspects of testing, product charaterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans. ▪ The primary goals of nonclinical studies/preclinical safety evaluation are to identify an initial safe dose and subsequent dose escalation schemes in humans, potential target organs for toxicity (whether such toxicity is reversible) and safety parameters for clinical monitoring **Ref**: ICH Topic S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.
N.	**CLINICAL STUDIES**
	▪ Clinical studies designed and conducted to meet WHO and international GCP principles. ▪ Overall approach to the clinical developement of a medicinal product. ▪ Overview of the clinical findings and provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies. ▪ Interpretation of how the efficacy and safety findings support the proposed dose and target indication.

O.	POST MARKETING SURVEILLANCE FOR BIOTECHNOLOGY PRODUCT
	▪ Provide an outline of the post marketing pharmacovigilance plan. ▪ Periodic safety update report (PSUR) in accordance to ICH Guideline E2C(R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ▪ All relevant clinical and nonclinical safety data should cover the period of the report with exception of updates of regulatory authority or product registration holder (PRH) actions taken for safety reasons, as well as data on serious, unlisted adverse drug reactions (ADRs), which should be cumulative. ▪ Risk management plan

c) REFERENCES FOR VACCINES AND BIOTECHNOLOGY PRODUCTS:

i) Vaccines:

WHO *(http://www.who.int/biologicals/vaccines)*

i) WHO Technical Report Series: Vaccines

ii) Biotechnology Products:

WHO

i) WHO Technical Report Series 1991 No. 814, Annex 3. Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. *(under revision)*

ii) WHO Technical Report Series 1991 No 822, Annex 3. Guidelines for assuring the quality of monoclonal antibodies for use in humans.

iii) WHO Technical Report Series No 878, Annex 1 and Addendum. Requirements for the use of animal cells as in vitro substrates for the production of biologicals.

iv) WHO Technical Report Series No.786, Annex 3.Requirements for human interferons prepared from lymphoblastoid cells (Requirements for biological substances N0.42)

v) WHO Technical Report Series No.771, Annex 7 Requirements for human interferons made by recombinant DNA techniques (Requirement for biological substance No. 41)

EMA

i) CHMP/BWP/157653/07. Production and Quality Control of Monoclonal Antibodies and Related Substances.
ii) CPMP/BWP/328/99. Development Pharmaceutics for Biotechnological and Biological Products - Annex to Note for Guidance on Development Pharmaceutics.
iii) CHMP/BWP/157653/2007. Guideline on Development, Production, Characterisation and Specifications for Monoclonal Antibodies and Related Products.
iv) EMEA/410/01 Rev. 3 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

ICH

i) ICH Topic Q5A Viral Safety Evaluation Of Biotechnology Products Derived From Cell Lines Of Human Or Animal Origin.
ii) ICH Topic Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products.
iii) ICH Topic Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/ Biological Products.
iv) ICH Topic Q5C Quality of Biotechnological products: Stability Testing of Biotechnological/ Biological Products.
v) ICH Topic Q5D Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products.
vi) ICH Topic Q5E Comparability of Biotechnological/ Biological Products Subject To Changes in Their Manufacturing Process.
vii) ICH Topic Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products.
viii) ICH Topic Q2 Validation of Analytical Procedures: Text and Methodology.
ix) ICH Topic Q8 Pharmaceutical Development.
x) ICH Topic Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/ Biological Entities).
xi) ICH Topic S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

3.2.2 REQUIREMENTS FOR REGISTRATION OF BLOOD PRODUCTS

Note: *This document is applicable to all plasma-derived products containing an active and inactive ingredient that is derived from human blood.*

a) DEFINITION OF BLOOD PRODUCT

Any therapeutic product derived from human blood or plasma and produced by a manufacturing process that pools multiple units.

Plasma-derived therapies and their recombinant analogs are unique among pharmaceuticals and biologics. Their production begins with a biological starting material, human plasma. Each therapy has a unique biochemical profile as a result of differences in production and processing methods that can lead to differing clinical responses and efficacy among patients.

Hence, from the starting material, through manufacturing and final distribution to patients, the complexities of producing blood products places it in a unique class of biologics.

Blood products are regulated as medicinal product. Blood products are inherently variable due to their biological nature, and the biological methods to test them. They are subjected to comprehensive assessment of the quality, efficacy and safety.

Four (4) principal complementary approaches are adopted:

- **Starting material:** Assurance of the quality and safety of the plasma for fractionation.
- **Manufacturing technique:** Control of the fractionation and subsequent manufacturing procedures for isolation, purification, viral inactivation and/or removal steps.
- **Good manufacturing practice (GMP):** Strict adherence to GMP. Adoption of GMP as an essential tool of Quality Assurance System.
- **Product Compliance:** Standardization of biological methods needed in characterisation of in-process and finished products.

Plasma for fractionation and blood products that are regulated by National Pharmaceutical Regulatory Division (NPRA) includes:

- Plasma products derived from plasma collected and fractionated in Malaysia for use in Malaysia;
- Plasma products derived from plasma collected and fractionated overseas for use in Malaysia; and
- Plasma products derived from overseas-sourced plasma fractionated in Malaysia for use overseas.

b) REQUIREMENTS FOR REGISTRATION OF BLOOD PRODUCTS

1.	**QUALITY OF PLASMA SOURCE MATERIAL**
	Plasma Master File (PMF). It can also be a stand-alone document. Document pertaining to the collection and controls of source materials. Key elements of PMF are: ▪ Requirements for a formal contract governing purchase and supply of plasma. ▪ Source plasma. ▪ GMP status of the blood establishments/ collection centers. ▪ Description of the quality assurance system applying to plasma supply and use. ▪ Arrangements for donor selection, selection/exclusion criteria. ▪ Data on population epidemiology and blood-borne infections. ▪ Requirements for testing of samples of donations and pools. Mandatory serology on all plasma donations. Each unit of source material tested for HBsAg, anti-HIV and anti-HCV ▪ Plasma bags, plasma quality and plasma specifications. ▪ Arrangement for communication and review of post-donation information. ▪ Plasma inventory hold. ▪ Traceability from donor to end product and *vice versa.* **Ref:** CHMP/BWP/3794/03 Rev. 1 Scientific data Requirements for Plasma Master File (PMF) and also the checklist.

2.	**MANUFACTURING PROCESS AND CONTROL**

Documents that verify each batch of source material intended for manufacture has been serological tested for hepatitis B (HBV), hepatitis C (HCV) and HIV. Each batch of source material must also be tested for HCV RNA by Nucleic Acid Testing (NAT) and (increasingly for other viruses including HIV, HBV, B19, and HAV) and exclusion of reactive donations.

Characterization: Physicochemical and biological characterization: Specific tests that will provide information regarding identity, purity, potency, stability and consistency of manufacture for the drug substance.

Manufacture and Controls:

i) Formula:

- Include a list of all starting materials, reagents, monoclonal antibodies, intermediate products and auxiliary materials (buffers, sera, antibiotics etc.) with specifications or statement of quality for each.
- Excipients: List of excipients.
- For non-compendial excipients: Describe tests and specifications.
- For novel excipients: Include description for preparation, characterisation and controls.
- When used as excipient in the product, the expiry date of the plasma-derived product should not be earlier than that of the finished product.

ii) Manufacturing:

- Detailed description of manufacturing process and controls to demonstrate proper quality control or prevention of possible contamination with adventitious agents.
- In-process and final controls.
  - Viral inactivation and/ or removal processes
  - Viral validation studies and report
  - Pathogen safety document inclusive of Transmissible Spongiform Encephalopathies (TSEs) risk assessment
  - Information or certification supporting the freedom of reagents, inactive ingredients of human or animal origin from adventitious agents.
  - Process consistency
  - Analytical validation studies
  - Process validation studies (purification, sterility etc.)
  - Batch record and batch release specifications

3.	**THE FINAL PRODUCT**
	▪ Finished product testing and quality control ▪ Stability study program and expiration date ▪ Product history ▪ Container closure system, storage and handling ▪ Package insert and labels ▪ Lot/ batch release protocols ▪ Certificate of batch review and release from a competent authority
4.	**CLINICAL STUDIES**
	▪ Demonstrating product's efficacy
5.	**POST MARKETING SURVEILLANCE – mandatory follow-up**
	▪ Periodic Safety Update Report (PSUR) ▪ Risk Management Plans

c) Checklist of Plasma Master File for Blood Products

Section	Documents	Yes/No
1.	**General Information**	
1.1	Plasma Derived Products' List	
1.2	Overall Safety Strategy • Collection of plasma • Testing • Storage	
1.3	General Logistics • Flowchart of supply chain of plasma	
2.	**Technical Information on Starting Materials/Plasma**	
2.1	Plasma Origin • Information on Collection Centers • Information on Testing Centers • Selection/ Exclusion Criteria for Donors • Traceability	
2.2	Plasma Quality and Safety • Compliance with Ph. Eur. Monographs or relevant monographs • Screening Tests for Markers of Infection • Technical Characteristics of Bags and Bottles for Blood and Plasma Collection, Including Information on Anticoagulant Solutions Used • Storage and Transport • Procedures for any Inventory Hold Period • Characterisation of the Fractionation Pool	
2.3	Contract Between Manufacturer and Blood Collection Establishment(s) • System in place between the manufacturer and/or plasma fractionators/ processor on one hand, and blood collection establishments on the other hand which defines the conditions of their interaction and their agreed specifications	

d) REFERENCES FOR BLOOD PRODUCTS:

The National Pharmaceutical Regulatory Division's requirements for registration of blood products are aligned with the scientific guidelines and recommendations for quality, clinical efficacy and safety and non-clinical of the World Health Organization (WHO), European Medicines Agency and International Conference of Harmonization (ICH).

Where appropriate, the relevant WHO, EMA and ICH guidelines on blood products shall be consulted in particular the followings:

WHO *(http://www.who.int/boodproducts/en/index.html)*

i) WHO Technical report Series 941, Annex 4, Recommendations for production, control and regulation of human plasma for fractionation.
ii) WHO Technical report Series 924, Annex 4, Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human plasma products.
iii) WHO Guidelines on tissue infectivity distribution in Transmissible Spongiform Encephalopathies.

EMA *(http://www.ema.europa.eu)*

i) EMA/CHMP/BWP/706271/2010 Committee for medicinal products for human use (CHMP) Guideline on plasma-derived medicinal products
ii) CHMP/BWP/3794/03 Rev. 1 Scientific data Requirements for Plasma Master File (PMF)
iii) CPMP/BWP/268/953AB8A Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses
iv) EMEA/410/01 Rev. 3 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products
v) Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products, European Medicines Agency, EMA/CHMP/BPWP/144533/2009.
vi) Note for Guidance on the Clinical Investigation of Human Plasma Derived Factor VIII and IX products, European Medicines Agency, CPMP/BPWG/198/95REV.1.
vii) Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg), European Medicines Agency, EMA/VHMP/BPWP/94033/2007 REV.2.

ICH *(http://www.ich.org)*

i) ICH Topic 5QC Quality of Biotechnological products: Stability Testing of Biotechnological/ Biological Products.

3.3 CHECKLISTS

3.3.1 Checklist A:

Products Containing Animal-Derived Materials **WITH** a valid TSE risk evaluation Certificate of Suitability (CEP)

No.	Documents	Yes/ No
1.	TSE Risk Evaluation Certificate of Suitability (CEP)	
2.	Basic information providing a brief description of the following:	
3.	Rationale for using animal-derived materials	
4.	Source of Animals • Declaration of materials of porcine origin • Declaration of materials of other animal origin	
5.	Declaration of the nature of the animal tissue/ parts of animal used.	
6.	Description of the tissue/ organ-collection procedures and measures in place to avoid cross-contamination.	
7.	Nature and quantity of each animal-derived material used: • As a drug substance. • As an excipient or adjuvant. • As a starting material used in the manufacture of a drug substance. • As a starting material used in the manufacture of excipient. • As a reagent or culture media component used in manufacture. • As a reagent or culture media component used in establishing master cell banks. • As a reagent or culture media component used in establishing working cell banks. • Others, please provide details	
8.	Declaration that the final product does not contain any animal-containing materials with the relevant evidence (if applicable)	
9.	Other supporting documents e.g. *Halal* Certification of the animal derived ingredient from a competent *Halal* Certification Authority.	
10.	Labelling of the animal derived materials.	

3.3.2 Checklist B:

Products Containing Animal-Derived Materials **WITHOUT** a valid TSE risk evaluation Certificate of Suitability (CEP)

Section	Documents	Yes/ No
1.	Detailed Assessment Report for the risk of TSE. The scope of this assessment report should include the following:	
2.	Rationale for using animal-derived materials	
3.	Source of Animals • Declaration of materials of porcine origin • Declaration of materials of other animal origin	
4.	Declaration of the nature of the animal tissue/ parts used.	
5.	Description of the tissue/ organ-collection procedures and measure in place to avoid cross-contamination.	
6.	Detail of the risk factors associated with the route of administration and maximum therapeutic dosage of the product.	
7.	Nature and quantity of each animal-derived material used: • As a drug substance • As an excipient or adjuvant • As a starting material used in the manufacture of a drug substance. • As a starting material used in the manufacture of excipient. • As a reagent or culture media component used in manufacture. • As a reagent or culture media component used in establishing master cell banks. • As a reagent or culture media component used in establishing working cell banks. • Others, please provide details.	
8.	Relevant information to support the claim that the manufacturing process is capable of inactivating TSE agents.	
9.	Certificates of analysis for each animal-derived materials used.	
10.	Declaration that the final product does not contain any animal-containing materials with the relevant evidence (if applicable)	

Section	Documents	Yes/ No
11.	Other supporting documents eg. Halal Certification of the animal derived ingredient from a competent Halal Certification Authority.	
12.	Labelling of the animal derived materials.	

APPENDIX 4: GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS

IMPORTANT NOTES:

This guideline will serve as an additional reference guide for the registration of health supplement products which consist of pharmaceutical active ingredients for human use as well as ingredients derived from natural sources.

Applicants are advised to refer to Drug Registration Guidance Document for the common requirements for the preparation of a well-structured dossier application to be submitted for product registration.

Outline:

4.1 DEFINITION

4.1.1 HEALTH SUPPLEMENT (HS)

A Health Supplement (HS) means any product that is used to supplement a diet and to maintain, enhance and improve the health function of human body. It is presented in small unit dosage forms (to be administered) such as capsules, tablets, powder, liquids and shall not include any sterile preparations (i.e. injectable, eyedrops). It may contain one or more, or the following combination:

i) Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics, and other bioactive substances;
ii) Substances derived from *natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolite;
iii) Synthetic sources of ingredients mentioned in (i) and (ii) may only be used where the safety of these has been proven.

4.1.2 INDICATION

i) Used as a Health Supplement;
ii) Vitamin and mineral supplements for pregnant and lactating women.

4.1.3 ROUTE OF ADMINISTRATION

Oral

4.1.4 EXCLUSION AS HEALTH SUPPLEMENTS:

Health Supplements shall NOT include:

i) Any product as a sole item of a meal;
ii) Any injectable and sterile preparation;
iii) Any cells, tissues, organs or any substance derived from the human body;
iv) Any substance listed in the Schedule of the Poison Act;
v) Any other route of administration other than the oral route.

4.1.5 EXEMPTION

Extemporaneous preparations that have been prepared and given directly to the patient by a healthcare practitioner during the course of treatment.

4.2 ACTIVE INGREDIENTS

Listed active ingredients can be checked trough http://npra.moh.gov.my/ of product search.

4.3 MAXIMUM DAILY LEVELS OF VITAMINS AND MINERALS FOR ADULTS ALLOWED IN HEALTH SUPPLEMENTS

NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
1.	Vitamin A	5000 IU
2.	Vitamin D	1000 IU
3.	Vitamin E	800 IU
4.	Vitamin K (K1 and K2) [1]	0.12mg
5.	Vitamin B1 (Thiamine)	100 mg
6.	Vitamin B2 (Riboflavine)	40 mg
7.	Vitamin B5 (Panthothenic Acid)	200 mg
8.	Vitamin B6 (Pyridoxine)	100 mg
9.	Vitamin B12 (Cyanocobalamin)	0.6 mg
10.	Vitamin C (Ascorbic Acid)	1000 mg
11.	Folic Acid	0.9 mg
12.	Nicotinic Acid	15 mg
13.	Niacinamide (Nicotinamide)	450 mg
14.	Biotin	0.9 mg
15.	Boron	6.4 mg
16.	Calcium	1200 mg
17.	Chromium	0.5 mg
18.	Copper	2 mg
19.	Iodine	0.3 mg
20.	Iron [2]	20 mg
21.	Magnesium	350 mg

NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
22.	Manganese	3.5 mg
23.	Molybdenum	0.36 mg
24.	Phosphorus	800 mg
25.	Selenium	0.2 mg
26.	Zinc	15 mg

Note:

1. *Vitamin K (K1 and K2) is restricted only for combination with other vitamins and minerals in oral preparations. Vitamin K (K1 and K2) as a single ingredient in an oral preparation is not allowed.*
2. *For pre and antenatal use, as part of a multivitamin and mineral preparation, levels higher than the 20mg limit established for adults may be permitted at the discretion of the Authority.*
3. *Any form of fluoride as an ingredient is not permitted in formulation of health supplement products.*

4.4 HEALTH SUPPLEMENT CLAIM

4.4.1 CONDITIONS

All claims made for HS shall:

i) be consistent with the definition of HS;
ii) enable consumers to make an informed choice regarding products;
iii) not be misleading or false;
iv) support the safe, beneficial and appropriate use of the product;
v) maintain the level of scientific evidence which is proportional to the type of claims;
vi) be for health maintenance and promotion purpose only;
vii) not be medicinal or therapeutic in nature, such as implied for treatment, cure or prevention of disease.

4.4.2 TYPES AND EVIDENCE OF CLAIMS

i) A health supplement claim refers to the beneficial effects of consuming HS to promote good health and well-being (physical and mental) by providing nutrition, enhancing body structure/ function, relieving physiological discomfort and/or reducing the risk of health related conditions or diseases.

ii) Types of HS claims are:
   - General or Nutritional Claims;
   - Functional Claims (medium);
   - Disease Risk Reduction Claims (high).

iii) For a HS product making a General or Functional Claim on vitamin(s) and/or mineral(s), it must contain minimum of 15% of the Codex Nutrient Reference Value (NRV) per daily dose of the vitamin(s) and/or mineral(s). Other ingredients must be substantiated by the evidences to which it has been supported.

   For example, if vitamin is less than 15% NRV, then the specific claim for this vitamin is not allowed unless there is evidence to support effect below this value.

iv) For a HS product making Disease Risk Reduction Claim, it must be substantiated by the evidences to which it has been supported.

(i) Table 1: General or Nutritional Claims

Level of claim	Definition	Examples/ Wording of claim	Criteria	Evidence to substantiate HS claims
General or Nutritional Claims	▪General Health Maintenance ▪Benefits derived from supplementation beyond normal dietary intake	▪Supports healthy growth and development ▪Nourishes the body ▪Relieves general tiredness, weakness ▪Helps to maintain good health ▪For energy and vitality ▪For strengthening the body	▪ Is in line with established nutrition knowledge in reference texts ▪ Is related to general well-being in line with scientific knowledge ▪ Claim does not refer to the structure and/or function of the human body ▪ In accordance to HS principles and practice in Malaysia	**1 or more of the following evidences:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs ii) Recommendations on usage from reference regulatory authorities or reference organisations

Please refer to Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

(ii) Table 2: Functional Claims (medium)

Claims must be adequately substantiated through ingredient-based evidence and when necessary through product-based evidence.

Types of HS claim	Definition	Examples/ Wording of claims	Criteria	Evidence to substantiate HS Claims
Functional Claims (medium)	▪ Maintains or enhances the structure or function of the human body, excluding disease-related claims	Acceptable claims based on the single ingredient e.g. ▪ Vitamin A helps to maintain growth, vision and tissue development ▪ Vitamin D helps in normal development and maintenance of bones and teeth. ▪ Chondroitin helps to promote healthy joints	For claims on established nutrients and ingredients such as vitamins & minerals with daily recommended values ▪ Meet the conditions for nutrient function claims as set by the Authority ▪ Claims have consistent scientific support according to scientific review and evaluation ▪ In accordance to HS principles and practice in Malaysia	**1 or more of the following evidence:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs ii) Recommendations on usage from reference regulatory authorities or reference organisations iii) Good quality scientific evidence from human observational studies (refer to ASEAN Guidelines on efficacy data requirement) **(only in the event that human experimental study is not ethical, animal studies will be accepted together with epidemiological studies or other scientific literature and documented traditional use)** iv) Peer-reviewed scientific data or meta-analysis

Please refer to Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

(iii) Table 3: Disease risk reduction (high)

Types of HS claim	Definition	Examples/ Wording of claims	Criteria	Evidence to substantiate HS Claims
Disease risk reduction	▪ Significantly altering or reducing a risk factor of a disease or health related condition.	▪ Helps to reduce risk of osteoporosis by strengthening bone ▪ Helps to reduce the risk of dyslipidaemia	▪ The relationship between the HS ingredient or product and disease risk reduction is supported by consistent scientific evidence ▪ Documented in authoritative reference texts ▪ Recognised by the Authority reference or international organisations or regulatory authorities ▪ Adheres to the key principles of HS claims	**Compulsory evidence:** i) Scientific evidence from human intervention study on ingredient and/or product ii) Toxicological study (chronic) iii) Pharmacological study **At least 1 additional evidence:** i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs etc. ii) Recommendations on usage from reference regulatory authorities or reference organisations iii) Evidence from published scientific reviews or meta-analysis iv) Report prepared by expert committees/ expert opinion (subject to the Authority approval)

Please refer to Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

4.4.3 CLAIMS SUBSTANTIATION

Claims must be in line with the respective HS principles and supported by adequate evidence. To reflect the total available usage evidence (including relevant scientific evidence), the evidence shall be summarized as part of the substantiation document for the claim as in the **Table 4** below.

Indication/ claim	Product/ Ingredient studied	Dosage and administration route	Duration of treatment	Type of evidence (scientific evidence)	Study design	Study population	Summary of findings	Limitations of the study	Source of evidence i) Author ii) Title iii) Publication details iv) Year v) Type (text, …)

Note: *Evidence not summarised as in the above format will not be further evaluated.*

4.4.4 ILLUSTRATIVE SUSBSTANTIATION EVIDENCE

i) Reference texts

a. Martindale, latest edition. The Complete Drug. Pharmaceutical Press, 2009.
b. The ABC Clinical Guide to Herbs. American Botanical Council
c. WHO Monographs on Selected Medicinal Plants
d. British Pharmacopoeia
e. United States Pharmacopoeia
f. Indian Pharmacopoeia
g. Chinese Pharmacopoeia
h. Natural Standards (www.naturalstandard.com)
i. Office of Dietary Supplements, National Institutes of Health - Dietary Supplement Fact Sheets (http://ods.od.nih.gov/Health_Information/Information_About_Individual_Dietary_Supplements.aspx)

ii) Organisations

a. American Botanical Council (www.herbalgram.org).
b. American Nutraceutical Association (www.ana-jana.org)
c. CODEX Alimentarius
d. Global Information Hub for Integrated Medicine (http://www.globinmed.com)
e. National Centre for Complementary and Alternative Medicine (http://nccam.nih.gov/)
f. Office of Dietary Supplements, National Institutes of Health (USA) (http://ods.od.nih.gov)

iii) Reference regulatory authorities

a. Australia TGA
b. Chinese Health Authority on Chinese medicinal herbs
c. European Commission
d. Health Canada
e. United States FDA

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority will nonetheless conduct a detailed evaluation of the evidence included in the report to ensure that the health claim is substantiated.*
3. *The Authority will be willing to consider review other than the listed above, if the standards of evidence are consistent with those of the Authority.*
4. *All references must be current.*

4.5 SPECIFIC DOSSIER REQUIREMENT FOR REGISTRATION OF HEALTH SUPPLEMENTS

PRODUCT VALIDATION

1. PRODUCT NAME

- May include product name, dosage form and strength (e.g. XYZ Capsule 500mg)
- Dosage form and strength of product would need to be entered as part of product name to allow for multiple dosage forms (e.g. tablet, capsule) and strengths (e.g. 200mg and 400mg) for any particular named (proprietary or generic) product.
- In any event if found that registered product name is similar to another registered product, NPRA reserve the rights to request for the change in the product name.
- Product with more than 1 active ingredient could not include strength of active ingredients in the product name.
- Product name may be included together with the brand name or trademark name, if applicable.
- Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product is prohibited.

Table 5: List of Non-Permissible Product Name for Health Supplement Products

No.	Issue	Example
1.	**Prohibited use of disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (revised 1983)**	Diabetes, Asthma, Cancer
2.	**Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika**	If the product contain Vitamin C, Vitamin E and Fish Oil Product name: "Vitamin C" is not allowed but product name: "Vitamin C Plus" is allowed.

No.	Issue	Example
3.	**Prohibited use of superlative** Names which indicates superiority inefficacy	Power, Superior, Pure, Mustajab, Safe, Healthy, Penawar, VIP, Good, World Number 1
4.	**Prohibited use of spelling of words which may cause confusion** i)Words which involve names of/part thereof: 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) ii) Other diseases without scientific proof iii) Prohibited indication	Go Out = GOUT (label) Utix
5.	**Prohibited use of names which may cause ambiguity** Ambiguous product name	B For Energy?
6.	**Prohibited use of names which may be offensive or indecent**	SENXBIG=SEnXBIG(label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire
7.	**Product name which is not congruent with the active ingredient.**	The active ingredient is Evening Primrose oil (EPO) and the product name: “Marine tablet” is not allowed.
8.	**Prohibited use of product names which has elements of ludicrous belief** Statements referring to ancient believe/negative spirits/supernatural power	Words such as miracle, magic, magical, miraculous, saintly, heavenly

No.	Issue	Example
9.	**Prohibited use of product names similar to the existing approved product names** Product name similar to the spelling and pronunciation of words of an existing product names	Elegen vs L-gen vs L-jen Forte vs Fort
10.	**Prohibited use of product names which may cause ambiguity in the nature of product (drug/ food/ beverage)** Product name similar to a food/ beverage name	Juice, Health drink, Beverage, Kooky
11.	**Prohibited use of product names which represents professional advice or opinion**	Dr Sunny, Professor
12.	**Product name that symbolize a claim**	Vigour, Youthful, High, Hi
13.	**Product name that uses strength but formulation contains more than one active ingredient.**	If the product contains multivitamins and minerals. Product name: "XXX multivitamins and minerals 500mg" is not allowed.
14.	**Other prohibited product names**	Minda, IQ, Smart, Unique, Ultra Mega, Detox
15.	**Names of organs and brain**	Heart, kidney, skin, liver

Note:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual.*

2. DOSAGE FORM

- Dosage forms allowed:
    a) Tablets
        - Caplet, Lozenge, Chewable tablet, Dispersible tablet, Effervescence tablet, uncoated tablet, enteric coated tablet, Sugar coated tablet, Film coated tablet, extended release tablet;
    b) Capsules
        - Soft capsule, Hard capsule, Enteric coated capsule, Chewable soft capsule, Extended released capsule;
    c) Powder/ Granules;
    d) Liquid
        - Emulsion, syrup, spray, suspension.
- Products in the shape of animal dosage forms are not allowed.
- Supporting data from established reference (e.g. Standard Pharmacopeia) shall be required for new dosage form.
- The form that correctly describes it in terms of its product quality control specifications and performance shall be selected.
- A <u>separate application</u> for registration is required for each dosage form.
- The following documents will have to be provided during submission of product dossier for **Sustained-release/ Extended-release/ Timed-release dosage form**
    i) Protocol of analysis;
    ii) In-Process Quality Control (IPQC);
    iii) Finished Product Specification (FPQC);
    iv) Certificate of Analysis (COA).

3. ACTIVE INGREDIENT

<u>Name of Active Ingredient</u>:

- Please select active ingredient from the search database. If substance is not listed, please select the 'Not Listed Ingredient' button. Automatic e-mail will be send to NPRA for notification.
- Approved names, pharmacopoeia names of ingredients shall be used whenever possible.

Strength of active ingredient :

- To enter the content of active ingredients (numerical) and then select the weights and measures from the given list.
- Content of ingredients shall be expressed as appropriate in the following manner:
  a. quantity per dose unit (e.g. for unit dose formulations - tablet, capsule, lozenge, etc.)
  b. percentage composition - %w/w, %w/v, %v/v, etc.
  c. weight per ml. (e.g. for solutions,suspension etc.)
  d. quantity (percentage or amount) per measured dose (e.g. oral liquids, drops, etc.)
- Metric weights and measures shall be used.

Source of Active ingredient:

- To specify the source such as animal, plant, synthetic or others (to specify)

USE OF PROTECTED/ ENDANGERED INGREDIENTS

a) PROTECTED/ ENDANGERED WILDLIFE SPECIES

It is the responsibility of the applicant to ensure that the ingredient(s) derived from wildlife species its parts and derivtives used in the formulation **COMPLIES** with the Wildlife Conservation Act 2010 (Act 716) and International Trade in Endangered Species Act 2008 (Act 686). Both guidelines can be downloaded through this link http://www.wildlife.gov.my.

The applicant shall contact the following department to obtain the necessary permit/ license. A copy of the permit/ license shall be attached together with the application form for product registration.

Department of Wildlife and National Parks, Peninsular Malaysia
Km. 10, Jalan Cheras,
56100 Kuala Lumpur,
Tel: +603-90866800, Fax: +603-90753873

b) ENDANGERED BOTANICAL SPECIES

It is the responsibility of the applicant to declare the source of the botanical ingredient if it is listed under the International Trade in Endangered Species Act

2008 (Act 686). If the ingredient is from a local source, a special permit/ license shall be obtained from the:
Division of Protection and Quarantine of Plants,
Department of Agriculture,
Tingkat 1-3, Wisma Tani,
Jalan Sultan Salahuddin,
50632 Kuala Lumpur.
Tel: +603 - 20301400, Fax: +603 - 26913550.

Remarks on active ingredient (if any):

- To specify the equivalent/providing amount of active component from the raw material (e.g: Sodium ascorbate 520 mg providing.... Vitamin C)
- Declaration of species name from natural source (plant, animal or others)

Table 6: Additional data to support a new health supplement active ingredients:

No.	Types of documents	Checklist
1.	Standard/ established references	• Martindale, Pharmacopeias, Monograph etc.
2.	Information from the competent authorities of reference countries	• Information shall be provided from the competent authorities of reference countries (Refer to 9.6.5) • Example of supporting documents: ➢ Registration status and maximum registered dosage as health supplement ➢ established monograph ➢ GRAS status
3.	Clinical studies or scientific evidences	• Full published articles • Unpublished data may be considered • Mandatory for high claim
4.	Non-clinical studies to support long term-use	

No.	Types of documents	Checklist
5.	Toxicology studies with the determination of NOAEL (No observed adverse effect level)	
6.	Pharmacological study	
7.	Justification for the use of new active ingredient as health supplement	
8.	Registration status worldwide	• Registered and Marketed Date

Note: *The documentation must support the safety use and dose of new active ingredients as a health supplement.*

4. ANY ANIMAL ORIGIN

Any source from animal origin must be declared and to specify the type of animal.

5. MANUFACTURER

The requirements for Good Manufacturing Practice (GMP) of the premises are in **Table 7** as followed:

Level of claims	Requirements for GMP
General/ Functional	a) Malaysia *Guidelines on Good Manufacturing Practice for Traditional Medicine and Health Supplement latest edition*. Or b) The accepted standards for GMP will be determined by the category the product is classified in the country of origin. For example, if the product is classified as food in the country of origin, GMP certificate of food standard issued by relevant country authority will be accepted on condition that the standards are similar to those practices in Malaysia. Or c) If the product is not regulated in the country of origin and does not require GMP certification, the manufacturer will have to produce a GMP certificate issued by an independent body recognised by the Authority. Information including the standard/ regulations/ legislation to which the inspection was based upon must be mentioned.
Disease Risk Reduction	a) Malaysia *Guidelines on Good Manufacturing Practice for Traditional Medicine and Health Supplement latest edition* Or b) The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Standards. Or c) GMP certificates issued by relevant country authority will be accepted on condition that the standards are similar to PIC/S Standards

6. CONTRACT MANUFACTURER

Contract manufacturer is applicable when product owner is not the product manufacturer

7. SECOND SOURCE INFORMATION

An application for a second source may be considered where deemed necessary. This second source product shall be the same as the first product in all respects except for the site of manufacture.

8. PRODUCT CONTAINING PREMIX

Premixed active ingredient(s) is a combination of two or more active ingredients that are previously manufactured by a different manufacturer.

Certificate of GMP for manufacturer/ supplier is required for the premixed ingredient(s) in formulation. The requirements for GMP are same as in Field 5 as above.

9. REPLACEMENT PRODUCT

A product registration holder is not allowed to register/ hold two or more products with similar formulation (same active ingredient of raw material, strength and dosage form) at any one time unless product variant.

Letter of justification for replacement by product holder is required.

10. OTHER MANUFACTURER

Any manufacturer involved in Assembly, Fill & Finish, Active Ingredients, Packing, Labeling etc.

11. IMPORTED PRODUCTS

Imported product needs to be declared.

SECTION A: PRODUCT PARTICULARS

Product Description:

State, briefly, **visual and physical characteristics** of the product, including as in the following **Table 8** (where applicable):

No.	Dosage Form	Description
1.	Tablet	Shape, size, colour, odour, taste, marking, emboss, type of tablet (e.g. coated, uncoated, film, sugar etc.)
2.	Capsule	Shape, size, colour, odour, taste, marking, emboss, coating, content of capsule, type of capsule (e.g.: soft, hard, chewable etc.)
3.	Liquid	Clarity, type (e.g. solution/ suspension/ emulsion etc.), taste, odour, colour.
4.	Powder	Colour, odour, taste etc.
5.	Pill	Colour, odour, taste, size etc.
6.	Granules	Colour, odour, taste, size etc.

- **Indication/ Usage**

  State briefly recommended use(s) of product. The following indications are allowed:

  - Used as a Health Supplement; or
  - Vitamins and mineral supplements for pregnant and lactating women.

- **Recommended Dose (Dose/ Use Instruction) & Route of administration**

  State the dose (normal dose, dose range) and dosage schedule (frequency, duration if applicable). Dosage for adults and children (where appropriate) shall be stated.

- **Contraindication**

  State conditions for which or under which the product shall not be used.

  Note 1: Indicate clearly which conditions are:

  - absolutely contraindicated,
  - contraindicated but may be used under special circumstances and what precautions to be taken in such cases.
  - If there is no information available for this section, please state as 'Unknown'.

- **Warnings and Precautions**

  State briefly precautions and warnings necessary to ensure safe use of the product e.g. caution against giving to children and elderly; use in pregnancy and lactation; in infants; etc.

  Note : If there is no information available for this section, please state as 'Unknown'.

- **Drug Interactions**

  State only interactions which are observed and/or for which there is potential clinical significance. Interactions may occur with

  - other medicinal products used;
  - other herbs/ substance;
  - meals, or specific types of food.

  Note : If there is no information available for this section, please state as 'Unknown'.

- **Side Effects/ Adverse Reactions**

  State in order of severity and frequency, the side effects, adverse reactions, toxic effects, etc. (i.e. reactions, toxic effects, other than those desired therapeutically) including reactions such as allergy, hypersensitivity, dependence, addiction, carcinogenicity, tolerance, liver/ kidney toxicity etc.

  Indicate also symptoms and sites of effects/reactions.

  Note 1 : Reactions, whether minor or serious, shall be stated.

  Note 2 : Severity, reversible, frequency of occurrence shall be indicated wherever possible.

Note 3 :Clinical tests for detection of 'sensitive' patients, measure for management of adverse reactions developed shall be described wherever possible.

Note : If there is no information available for this section, please state as 'Unknown'.

- **Pregnancy and Lactation**

  Please state any effect on pregnancy and lactation if applicable.

- **Signs and Symptoms of Overdose and Treatment**

  State briefly symptoms of overdose/ poisoning, and where possible, recommended treatment and antidotes for overdose/ poisoning.

  Note : If there is no information available for this section, please state as 'Unknown'.

- **Storage Conditions**

  State the recommended storage conditions (specific temperature eg: 30^{o}C, humidity, light etc.).

  Information shall also include storage condition before first opening, after reconstitution and/or after opening and for all the listed pack types where applicable. Stability data to support such storage condition shall be available.

- **Shelf Life**

  The shelf life for all the listed pack types shall be supported by stability data.

  Information shall also include shelf life before first opening, after reconstitution and/or after opening where applicable. Stability data to support such shelf life shall be available.

  Evidence is required to demonstrate that the product is stable (meets the finished product shelf life specifications throughout its proposed shelf-life).

- **Therapeutic Code (If any)**

  Please select "Health Supplement"

SECTION B: PRODUCT FORMULA

Change of formulation whether for active ingredient or excipient is not allowed during product evaluation.

- **Batch Manufacturing Formula**

  State the batch size and actual batch manufacturing master formula. Data from validation step will be captured in terms of substance name, type (active ingredient or excipient), function and quantity per unit dose. Other information will need to be entered.

  An **attachment** of the Batch Manufacturing Formula documentation must be provided. The documents must be verified by authorized personel.

Example of BMF documentation:

ABC Sdn. BHD.
Batch Manufacturing Formula

Product Name:
Batch Quantity: 1,000,000 capsules

Name	Function	Quantity per capsule	Batch quantity	Overage
Pyridoxine HCl	Active	_ mg	_ kg	_ %
Cholecalciferol	Active	_ mg	_ kg	_ %
Glycerin	Excipient	_ mg	_ kg	None
Gelatin	Excipient	_ mg	_ kg	None
Purified water	Excipient	0 mg *	_ kg	None
		Total: _ mg	Total: _ kg	

* evaporated, does not exist in final formulation

(Signature)
Post of authorized person
Name of authorized person
Date:

- **Manufacturing process**

  State a brief description of the manufacturing process. Essential points of each stage of manufacturing process and a description of the assembling of the product into final containers shall be covered. If the product is repacked/assembled by another manufacturer, details of repacking/assembly and quality control must be supplied.

  An **attachment** of the manufacturing process, in the form of a flow chart can be made.

- **In Process Quality Control (IPQC)**

  To provide a summary of the tests performed, stages at which they are done, and the frequency of sampling and number of samples taken each time. Specifications for quality assurance of the product shall be supplied.

Example of In Process Quality Control:

Company Name/ Address:

Applicant/ Client Name/ Address:

Date:

In-Process Quality Control: Test performed during manufacturing process

No.	Test Done (example)	Stage Done (example)	Frequency of testing (example)	Quantity sample taken (example)	Specifications (example)	Method (example)
1.	Appearance	Before weight, after encapsulation	2	10 gram	Blue like orange	Organoleptic test
2.	Disintegration	After compression	2	10 tablet	NMT 30 minutes	Equipment etc
3.	Uniformity of weight	After tableting, Packaging	4	20 Tablets	1 gram/tab	

* Declaration (if any)
Signature (authorized personnel)
Name:
Designation:

*** The above parameters are only as an example; other test may be required for specific product.**

- **Finished Product Quality Specification**
- **Provide details of quality control specifications including a list of tests for both release and shelf life specifications (if they are different) and state the limits of acceptance.**

Example of Finished Product Quality Specification

Finished Product Quality Control (FPQC) - Finished product Specification/ Specification Sheet

Company name/Address:
Product Name:
Batch no.
Dosage form:
Packaging:
Date of manufacture:
Date of expiry:

No.	Test	Method	Specification	Reference
1.	Appearance/ Organoleptic: Odour Colour	Ex: Macroscopic/ Microscopic	To describe the characteristic	In-house/ pharmacopoeia (e.g. BP/USP etc)
2.	Assay: List the active ingredients	HPLC/ GC/ MS/ UV	To specify	To specify
3.	Disintegration/Dissolution	To specify	DRGD	DRGD
4.	Uniformity of weight	To specify		
5.	Water content	To specify		
6.	Microbial contamination TAMC, TYMC, specified microorganism	To specify	DRGD	DRGD
7.	Heavy Metal Contamination: Lead, Arsenic, Cadmium, Mercury	To specify	DRGD	DRGD
8.	Etc:			

Signature:
Name:
Designation: (At least by Quality Assurance Manager or equivalent)
Date of signature:

*** The above parameters are only as an example; other test may be required for specific product.**

- **Stability Data**

Table 9:

No.	Stability Study	Shelf Life
1.	i) 2 batches of complete real-time stability study at 30 ± 2 ºC / RH 75± 5% for the claimed shelf-life. OR ii) 2 batches of on-going real time stability study (at least 6 months) at 30 ± 2 ºC / RH 75 ± 5% + Letter of commitment (LOC) to submit complete real time stability data when study is complete/ when requested. AND 2 batches of 6 months accelerated stability study at 40ºC.	- Shelf life will be based on data stability at 30^{o}C of not more than 5 years. - 3 years
2.	i) 2 batches of complete real time stability study at a temperature and relative humidity (RH) different from the Zone IVB for at least 2 years + LOC to conduct real time stability study at Zone IVB and submit when the study is complete/ when requested OR ii) 2 batches of on-going real time and accelerated stability study (at least 6 months) at a temperature/ relative humidity (RH) different from Zone IVB + LOC to conduct real time stability study at Zone IVB and submit when the study is complete/ when requested.	- Shelf life will be based on data stability at specified temperature. - 2 years at specified temperature in the stability study.

3.	2 batches of complete real-time stability study at temperature and RH other than zone IVB for very unstable active ingredient(s)/ product (must be substantiated).	- Shelf life will be based on data stability at specified temperature.

Storage Conditions with Type of Container Closure System/ Stability Study

Table 10:

No.	Type of Container Closure System/ Study	Storage Condition
1.	Products in primary containers permeable to water vapour	30°C ± 2°C/75% RH ± 5%RH
2.	Products in primary containers impermeable to water vapour	30°C ± 2°C
3.	Accelerated studies	40°C ± 2°C/75% RH ± 5%RH

Reports of stability studies shall provide details of:

- the batches placed under study (a minimum of 2 batches are required).
- containers/ packaging type.
- conditions of storage during study (temperature, humidity, etc).
- duration of study and frequency (interval) of the tests/ observations.
- the tests performed and acceptance limits.

Example of Stability Data

STABLITY DATA

PRODUCT NAME: TABLET ABC 500MG **BATCH NO.:**

MANUFACTURING DATE: dd/mm/yy **TEMPERATURE:** 30 °C ± 2 °C

EXPIRY DATE: dd/mm/yy **RELATIVE HUMIDITY**: 75 % ± 5%

Tests	Specification	0	3	6	9	12	18	24	36
Product description	Film-coated tablet, brownish in colour								
Disintegration test	NMT 30 minutes								
Assays	eg: 90% -120% (ref….)								
Microbial Contamination test: Total Aerobic Microbial Count Total Yeasts & Moulds Count Test for Specified Microorganisms	 NMT 2 x 10^4 NMT 2 x 10^2 ➢ NMT 2 x 10^2 CFU of bile-tolerant gram- negative bacteria in 1g or 1ml ➢ Absence of Salmonella in 10g or 10ml ➢ Absence of Escherichia coli in 1g or 1ml ➢ Absence of Staphylococcus								
Heavy metal test: Lead Arsenic Mercury Cadmium	 ≤10.0 mg/kg (≤ 10ppm) ≤5.0 mg/kg (≤ 5ppm) ≤0.5 mg/kg (≤ 0.5ppm) ≤0.3 mg/kg (≤ 0.3ppm)		NA						

Conclusion ----------

Analyst name: (signature) Verified by: (signature)

Name: Name:

Designation Designation

Date: Date:

Stability study data checklists are as in **Table 11** below:

Data Required	Remarks
Company name	- From product holder/ manufacturer/ third party lab
Product name	- To be same with other documentation
Dosage form	- To be same with A3
Packaging particulars	- Material and pack size must be stated - To be same with C1
Storage condition	- Temperature and humidity must be stated - Shall comply with ASEAN Zone IV requirement (30±2°C/75±5%RH) - If different storage condition (e.g. 25°C, 2-8°C), must provide justification/ supporting data.
Frequency of testing	For example: - 0, 3, 6, 9, 12, 18, 24 months and annually for the proposed shelf life
List of relevant tests	- All tests required for each dosage form shall be conducted, for example: o Physical appearance changes o Disintegration test (if applicable) o Chemical Assays for active ingredients (if applicable) o Microbial tests
Specifications	- Acceptance limit for each test must be stated - To be supported by established references (e.g. USP, BP) if available
Results for each test	- Must meet the specifications
Approval by authorized person	- Must have the name, post and signature of authorized person

Testing Parameters of Stability Study for each type of dosage forms are shown in **Table 12** below:

Testing Parameters / Dosage Form	Appearance/ organoleptic (odor, color, taste)	Assay*	Hardness/ friability	Disintegration or dissolution rate	Moisture content	Viscosity	pH	Microbial content	Granules/ Particle Size variation	Re-suspendability
Oral powder	√	√			√			√		
Hard capsule	√	√		√	√			√		
Soft capsule	√	√		√				√		
Coated and Uncoated Tablet	√	√	√ (uncoated)	√	√			√		
Coated and Uncoated Pill/ Pellet	√	√		√	√			√		
Suspension	√	√				√	√	√	√	√
Solution	√	√				√	√	√		
Emulsion	√	√				√	√	√		
Granules	√	√			√			√	√	

Notes:

1. The list of tests for each product is not intended to be exhaustive, nor is it expected that every listed test to be included in the design of the stability study protocol for a particular finished product.

** Assay to determine the stability of a single active ingredient or a single marker/surrogate indicator that is susceptible to change during storage and is likely to influence quality shall be sufficient to infer the overall stability of the TM/HS product irrespective of whether the finished product contains single or multiple active ingredients.*

2. Justification must be given if one of the tests is not conducted for relevant dosage form.

SECTION C: PARTICULARS OF PACKING

- **Packaging**

➢ Maximum pack size allowed for tablets, pills, capsules is based on daily dosing for a quantity not exceeding six (6) months usage.

➢ Maximum pack size allowed with disease risk reduction claim for 1 month supply of products unless justified.

➢ Product with dosage form of softgel with tail (twist and squeeze) shall come with children proof cap.

- Packing particulars to the listing of packing as follows ;
  - C1: pack size and fill details by weight, or volume or quantity;
  - C2 : container type
  - C3 : Barcode/ serial No (optional);
  - C4 : recommended distributor's price (optional);
  - C5 : recommended retail price (optional);

SECTION D: LABELLING REQUIREMENTS

- The information shall present on the label of a product at outer carton, immediate container or blister/ strips:

  Please refer *Appendix 9: Labelling Requirements* **for:**

  a) **General Labelling Requirements - Label (mock-up) for immediate container and outer carton;**
  b) **Consumer Medication Information Leaflet (RiMUP);**
  (For health supplement with high claims/ disease risk reduction)
  c) **Specific Labelling Requirement**
  (For specific substances, e.g. alfalfa, arginine, bee pollen, chitosan, Boswellia serrata etc.)

- **Additional Requirements for Labelling**
  - Information on the Product Name; and Name and Strength of active ingredient(s) must be printed repeatedly (for blister/ strip).
  - Product with dosage form of soft gel with tail (twist and squeeze) shall include the statement 'Under parent supervision' in the label.
  - For products containing animal origin(s), please add this statement: *This product contains substance(s) from animal origin.*
  - For products containing porcine, please add this statement: *This product contains animal part(s) (porcine/pig).*

- Health supplement products with disease risk reduction claims (high) are encouraged to be dispensed under the supervision of pharmacists or medical practitioners. At such, the label and package insert of health supplement products with disease risk reduction claims (high) shall have the following statement**:**

  "Please consult a doctor/ pharmacist before taking this product".

- **Standard Labelling for Health Supplements**

- Name and Strength of active substances
- RDA (optional)
- Preservative(s) (where present)
- Alcohol (where present)

- Indication
- Dose / Usage Instruction

- Functional Claim (if applicable)
- Warnings (If applicable)

PRODUCT NAME

GRAPHIC

- Storage Condition
- Keep out of reach of children / Jauhkan daripada capaian kanak-kanak

- Pack Size
- Dosage Form

- Name & address of Product Registration Holder
- Name & address of Manufacturer

- Sources (animal origin)
- Source of capsule shell (if applicable)

- Batch Number
- Manufacturing Date
- Expiry Date

MAL ……...

Note:

- *Product label shall follow the standard labelling for Health Supplement.*
- *Information stated in the left and right panel is interchangeable.*
- *All information on the label must be truthful and not misleading to the consumers.*
- *Batch number, manufacturing date, expiration date: can be stated on label, on top of cap or bottom of bottle.*
- *The front panel must contain the information as above. However, the information on the side panels is interchangeable. Additional cautionary labelling relating to the safety of the product may be imposed.*

- **Package inserts (Optional**)

The following information is required to be included in a package insert:

(i) Brand or Product Name
(ii) Name and Strength of Active Substance(s)
(iii) Product Description
(iv) Indication
(v) Dose/ Use Instruction
(vi) Contraindications
(vii) Warnings and Precautions
(viii) Interactions with Other Medications
(ix) Statement on usage during pregnancy and lactation
(x) Adverse Effects/ Undesirable Effects
(xi) Overdose and Treatment
(xii) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
(xiii) Dosage Forms and packaging available
(xiv) Name and Address of manufacturer/ product registration holder
(xv) Date of Revision of Package Insert

- **Prohibited Visual/ Graphics on Label,** as shown in **Table 13** below:

No.	Issue	Example	Note
1.	Marketing strategy	**Example:** "Money back guarantee" "Buy 1 free 1" "Backed by RM5 million product Liability Insurance"	Such statements are prohibited on labels, as per Medicines (Advertisement and Sale) Act 1956 guideline requirements
2.	Usage guide which promotes use of other product(s)	**Example:** "After consumption of this product (Product A), for better results, it is recommended to take Product B"	Prohibited on product label
3.	Consumer testimonial		Prohibited on product label
4.	Clinical Trial results or any information on clinical trial done on product	Example : "Clinically Tested" "Randomized Double Blind Placebo Control Clinical Study"	Such statements are prohibited on labels (as per Medicines (Advertisement and Sale) Act 1956 guideline Requirement
5.	Reference to Hadith/ Al-Quran/ Bible/ Religious books		Prohibited on product label
6.	Opinion of prominent figure(s) on product or its active ingredient/ content	**Example:** Opinion of product/formulation inventor	Prohibited on product label

No.	Issue	Example	Note
7.	Label design (graphic and color) similar to labels from another company		Prohibited on product label
8.	Statement on active ingredient origin	**Example:** Source from the Mountains of Alps	Allowed if proven true
9.	Introduction of founder/ Manufacturer		Prohibited on product label
10.	Logo with certification	**Example:** SIRIM/ ISO / GMP/ HACCP	Prohibited on product label because certification renewal is on a yearly basis
11.	Name/ Statement/ Logo/ registered trademark which does not satisfy the specifications	**Example:** “Dr.ABC’s Formula” “Nothing like it”	Prohibited on product label
12.	Patency claim/ Patency number/ Special technique used/ superiority in ingredients (Example: capsule coat)	**Example:** Patented technique	Allowed if proven true
13.	Nutritional claims with analysis certificate attached	**Example:** Calorie, Fat, Protein and others	Prohibited on product label
14.	Graphics or picture of internal organs	**Example:** Kidney, Heart, Nerves.	Prohibited on product label

No.	Issue	Example	Note
15.	Gender symbol (male or female)	(♀ and/or ♂)	Prohibited on product label
16.	Indecent photographs/ pornography		Prohibited on product label
17.	Graphics which are incoherent with the indication	**Example:** - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose.	Prohibited on product label
18.	Highlighting unnecessary body parts	**Example:** Indication is for general health but graphics on label highlights male and female sexual organ parts	Prohibited on product label
19.	Graphics of plants or animal which may cause confusion	**Example:** Radix Ginseng which is improvised as a male sexual part	Prohibited on product label
20.	Photograph of celebrities	**Example** **-** Artiste, sports person(s), politician	Prohibited on product label
21.	Statement on sugars	**Example** - This product contains no added sugar	Allowed on product label provided the product contains no fructose, glucose, sucrose, or other kind of sugars with a

No.	Issue	Example	Note
			potential to affect diabetics are not included in the formulation
22.	Negative statement	**Example** - No gluten, yeast etc	Prohibited on product label
23.	Other statements	**Example:** - This product is blended with premium quality - Certified chemical residue free	Prohibited on product label

Notes:

1. *The list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual.*

SECTION E: PARTICULAR OF PRODUCT OWNER, MANUFACTURER, IMPORTER AND OTHER MANUFACTURER

- Please select whether the product owner is the product holder, manufacturer or both product holder and the manufacturer.
- If the product owner is neither product holder nor the manufacturer, please select name and address of the product owner (applicable for imported product only).
- Other details such as product owner, manufacturer, repacker, other manufacturer involved in the manufacturing process, store address and importer (If any) have to filled. It is mandatory for the repacker to acquire GMP certificate.

SECTION F: SUPPLEMENTARY DOCUMENTS

- **Letter of authorization of product owner**

This is applicable for imported product in which the product owner appoints the product holder (in Malaysia) as their product holder in Malaysia

- **Letter of appointment of contract manufacturer and/ or repacker**

Applicable if the product is contract manufactured by a manufacturer who is not the product holder.

- **Letter of acceptance as contract manufacturer and/ or repacker**

Applicable if the product is contract manufactured by a manufacturer who is not the product holder.

- **Certificate Of Pharmaceutical Product (CPP), Free Sale Certificate (CFS) and Good Manufacturing Practice (GMP)**

CPP can be attached as a replacement of CFS and GMP certificate if the product is classified as pharmaceutical product in the country of origin:

GMP/ CFS Template

Authority name, address, country

Type of certificate

Company name (product owner/ manufacturer)
Product name
Product formulation if available
Dosage form

Statement of freely sold (similar meaning) if for CFS certificate
Standard of GMP and compliance status if for GMP certificate
Duration of certification

Name, signature and designation of authorized personnel
Date of signature

Note: The certificate must be in English or translated into English (certified true by issuance or embassy or notary public)

- **Attachment of Protocol Analysis**

Protocol analysis is attached here.

- **Finished Product Quality Control (FPQC)**
  - The certificate must be complete with the product specification and result. The list of tests and specifications must be same with finished product specification document.
  - Quality Control Test For Health Supplement Product are as follows:

1. Limit Test for Heavy Metals

a) Lead : NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm)
b) Arsenic : NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm)
c) Mercury : NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm)
d) Cadmium : NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm)

** Required for products with ingredients from natural sources.*
The test shall be conducted either on the raw material or finished product.

2. Disintegration Test (for tablets, capsules and pills)

Disintegration time:

a) Uncoated tablets : NMT 30 minutes
b) Film-coated tablets : NMT 30 minutes
c) Sugar-coated tablets : NMT 60 minutes
d) Enteric-coated tablets : Does not disintegrate for 120 minutes in acid solution but to disintegrate within 60 minutes in buffer solution
e) Capsules : NMT 30 minutes
f) Pills : NMT 120 minutes

3. Test for Uniformity of Weight (tablets and capsules only)

i) Tablet

- For tablet with average weight of 130mg or less: Not more than 2 tablets differ from the average weight by more than 10% AND no tablets differ from the average weight by more than 20%
- For tablet with average weight between 130-324mg: Not more than 2 tablets differ from the average weight by more than 7.5% AND no tablet differs from the average weights by more than 15%
- For tablets with average weight more than 324mg: Not more than 2 tablets differ from the average weight by more than 5% AND no tablet differs from the average weight by more than 10%

ii) Capsule

Individual weight of the capsule to be within the limit of 90-110% of the average weight.

4. Tests for Microbial Contamination, as shown in **Table 14** below:

Route of Administration	TAMC (CFU/g or CFU/ml)	TYMC (CFU/g or CFU/ml)	Specified micro-organisms
Non-aqueous preparations for oral use	NMT 2 x 10^3	NMT 2 x 10^2	Absence of *Escherichia coli* (1 g or 1 ml)
Aqueous preparations for oral use	NMT 2 x 10^2	NMT 2 x 10^1	Absence of *Escherichia coli* (1 g or 1 ml)
Special Ph. Eur. provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU/g or CFU/mL.	NMT 2 x 10^4	NMT 2 x 10^2	Not more than 10^2 CFU of bile-tolerant gram-negative bacteria (1 g or 1 ml) Absence of *Salmonella* (10 g or 10 ml) Absence of *Escherichia coli* (1 g or 1 ml) Absence of *Staphylococcus aureus* (1 g or 1 ml)

Notes:

TAMC : Total Aerobic Microbial Count

TYMC : Total Yeasts & Moulds Count

NMT : Not more than

[Reference: British Pharmacopoeia 2012]

- **Specifications and Certificate of Analysis of Active Ingredient**

Certificate of analysis for each active ingredient (raw material) is required pre-registration. The certificate must consist of specifications and results of analyses.

- **Other Supporting documents**

  - For the submission of other supporting documents.

  - Additional requirement for safety and quality of active ingredient/ product (e.g.; dose for children, pregnant etc.)

  - Quality testing for specific ingredient:
    - For product containing Aphanizomenon flos-aquae, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method

  - Quality testing for specific product:
    - Certificate of Analysis for Dioxin level is required for product containing ingredient(s) derived from seafood
    - Certificate of Analysis for proof of hormone-free is required for product containing placenta

ATTACHMENT 1

CHECKLIST OF DOSSIER REQUIREMENT FOR HEALTH SUPPLEMENTS

- Depending on the level of claims, submission may follows the route as outlined:
  i) General/ Nutritional and Medium Claims - Abridge evaluation
  ii) Disease Risk Reduction Claims - Full evaluation

Table 15: Checklist for General/ Nutritional and Medium Claim

No.	Field	General or Nutritional Claims	Functional Claims
A1	Product Name	√	√
	Brand name and product name		
A2	Product Description	√	√
	- Describe visual and physical characteristics of the product including shape, size, superficial markings, colour, odour, taste, type of coating, type of capsule etc where applicable		
	- Animal shape is only allowed for 'For Export Only' (FEO) Products		
A3	Dosage Form	√	√
	- COA capsule shell is required		
	- Colouring agent used in capsule		
	- Letter to verify the source of gelatin used		
A4	Product indication/ Usage	√	√
A5	Dose/ Use Instruction	√	√
	- Quantity and frequency		
	- Dosing schedule must be stated (e.g. take before/ after/ with meal)		
A6	Contraindication, if applicable	√	√
A7	Warning/ Precautions, if applicable	√	√
A8	Drug Interaction, if applicable	√	√
A9	Side Effects/ Adverse Reactions, if applicable	√	√
A10	Signs and Symptoms of overdose and treatment, if applicable	√	√

No.	Field	General or Nutritional Claims	Functional Claims
A11	Storage Condition - According to stability data	√	√
A12	Shelf life - Must be supported by stability study - Please refer to B5	√	√
A13	Therapeutic Code - As a health supplement	√	√
B1.1	Batch Manufacturing Formula	√	√
B1.2	List of Active ingredient(s)	√	√
B1.3	List of excipient(s)	√	√
B1.4	Attachment of Batch Manufacturing Formula - Shall be on the product owner's/ manufacturer's original letterhead, product details, date and signature & designation of authorized personnel	√	√
B2.1	Manufacturing Process	√	√
B2.2	Attachment of Manufacturing Process Document or Manufacturing Flow Diagram	√	√
B3	In-Process Quality Control (IPQC)	√ *LOC to submit data during post registration	√
B4	Finished Product Specification (FPQC)	√ * LOC to submit data during post registration	√
B5	Stability Data (Please refer page 24)	√	√
D1	Label for immediate container	√	√
D2	Label for outer carton (if applicable)	√	√
D3	Proposed package insert / Product information leaflet (if applicable)	√	√

No.	Field	General or Nutritional Claims	Functional Claims
E1	Company name and address of product owner	√	√
E2	Company name and address of manufacturer(s)	√	√
E3	Company name and address of repacker (if applicable)	√	√
E4	Company name and address of other manufacturer (if applicable)	√	√
E5	Store address(s)	√	√
E6	Importer(s)	√	√
F1	Letter of authorization from product owner to product registration holder (if applicable)	√	√
F2	Letter of Appointment of Contract Manufacturer/ Repacker from Product Owner (if applicable)	√	√
F3	Letter of Acceptance from Contract Manufacturer/ Repacker (if applicable)	√	√
F4	Certificate of Pharmaceutical Product (CPP) - Applicable to imported products, must be issued by the competent authority in the country of origin. CPP issued by reference country may be considered.	√	√
F5	Certificate of Free Sale (CFS) - Applicable if CPP is not available, must be issued by the competent authority in the country of origin/ products owner country.	√	√
F6	Certificate of Good Manufacturing Practice (GMP) - Applicable if CPP is not available, must be issued by the competent authority in the manufacturing country.	√	√

No.	Field	General or Nutritional Claims	Functional Claims
F9	Attachment of protocol analysis	√ - dosage form extended release * LOC to submit during post for other types of dosage form	√ - dosage form extended release - validation of analytical method for new actives or new combination dosage
F10	Attachment of Certificate of finished product (COA of finished product)	√ * LOC to submit during post registration	√
F11	Attachment of Specifications and Certificate of Analysis (COA) of Active Ingredient	√	√
F12	Examples of supporting documents		
	Dioxin level test results (for product containing ingredients derived from seafood)	√	√
	Certificate of Good Manufacturing Practice (GMP) for premixed active ingredients		
	Hormone free test results (for placenta products)		
	Declaration letter from product manufacturer on the hormone - free status for product containing placenta		
	Manufacturing process validation report if applicable		
	Letter of commitment if applicable		
	Etc.		

No.	Field	General or Nutritional Claims	Functional Claims
* Complete stability study conducted at 30 ± 2 ºC / RH 75 ± 5%, IPQC, FPQC, protocol analysis and COA of finished product are required to be submitted 2 years after product registration with SAMPLE of the products. Failure on submission will cause the product be suspended until the complete documents are submitted, the registration of the product will be terminated if the complete documents still cannot be produced upon renewal of product registration.			

- Dossier Requirement for Disease risk reduction as in **Table 15 above** and **Table 16** below:

Table 16: Additional Quality Data Checklist for Disease Risk Reduction Claim

No.	Field	Disease Risk Reduction Claim
PART P	**P. HEALTH SUPPLEMENT PRODUCT** P1. Description and Composition P2. Pharmaceutical Development P2.1 Information on Development Studies P2.2 Components of the Health Supplement Product P2.3 Finished Product P2.4 Manufacturing Process Development P2.5 Container Closure System P2.6 Microbiological Attributes P2.7 Compatibility P3. Manufacturer P3.1 Batch Manufacturing Formula P3.2 Manufacturing Process & Process Control P3.2.1 Manufacturing Process Flowchart P3.3 Control of Critical Steps & Intermediates P3.4 Process Validation and Evaluation P4. Control of Excipients P4.1 Specifications	√

No.	Field	Disease Risk Reduction Claim
	P4.2 Analytical Procedure P4.3 Validation of Analytical Procedures P4.4 Justification of Specification P4.5 Excipient of Human or Animal Origin P4.6 Novel Excipients P5. Control of Finished Product P5.1 Specification P5.2 AnalyticalProcedures P5.3 Validation of Analytical Procedures P5.4 Batch Analyses P5.5 Characterization of impurities P5.6 Justification of Specification P6. Reference Standards or Materials P7. Container Closure System P8. Stability P9. Product Interchangeability/Equivalent evidence	
PART S	**S. HEALTH SUPPLEMENT SUBSTANCE** S1. General Information S1.1 Nomenclature S1.2 Structure S1.3 General Properties S2. Manufacture S3. Characterisation S4. Control of Health Supplement Substance S4.1 Specification S4.2 Analytical Procedures S4.3 Validation of Analytical Procedure S4.4 Batch Analysis S4.5 Justification of Specification S5. Reference Standards or Materials S6. Container Closure System S7. Stability	√

PART III: NON-CLINICAL DATA

- Applicable to disease risk reduction claims
  (For new active ingredient, new combination of active ingredients and new dose)

Table 17:

No.	Field	Disease Risk Reduction Claims
1.	Overview of non-clinical testing strategy	√
	- nomenclature	
	- structure	
	- general properties	
2.	Pharmacology	√
	- related information (including academic literature) of pharmacology studies on the declared efficacy	
3.	Pharmacokinetics	√
	- related information (including academic literature) of pharmacokinetics studies on the declared efficacy	
4.	Toxicology	√
	- related information (including academic literature) of toxicology studies	
5.	Integrated overview and conclusions	√
6.	Other toxicity studies if available	√
7.	References	√
	- List of references used	

- All information must be provided in the following format/ table:

Study Title	Type of Study	Product (formulation)	Study Summary - Study Design (e.g. case control, randomised placebo controlled, in vitro data, cohort study) - Dosage - Subject - Study Duration - Outcome parameters	Summary findings (Includes scientific details such as strength of evidence [e.g. p-values], conclusions, any shortcomings, etc. For traditional evidence include enough information to demonstrate relevance)

PART IV: CLINICAL DOCUMENTS

- Applicable to disease risk reduction claims (for new active ingredient, new combination of active ingredients and new dose).

Table 18:

No.	Field	Disease Risk Reduction Claims
1.	Clinical overview	√
2.	Production Development Rational	√
3.	Overview of Bio-pharmaceutics	√
	- To include associated analytical methods	
4.	Overview of Clinical Pharmacology	√
	- Summary of clinical pharmacology studies	
5.	Overview of Efficiency	√
	- Summary of clinical efficacy	
6.	Overview of Safety	√
	- Summary of clinical safety	
7.	References	√
	- List of all clinical studies	
	- List of key literature references	
	- Published clinical papers	

- All information must be provided in the following format/table:

Forms of study	Sample size	Duration	Randomisation of groups	Endpoint	Statistical analysis of data
Randomised, controlled, and preferably blinded intervention studies	Must be justified and must involve sufficiently large number of subjects to estimate incidence and nature of potential adverse reactions	Must be justified and must be of sufficient duration to ensure no safety concerns with respect to long term use	All groups shall have comparable baseline values, particularly for those factors that are known to be, or may be, confounders or risk factors	As a decrease incidence of the disease or a reduction of a factor, or a surrogate thereof, of the many that contribute to the development of a disease	Methods to calculate the sample size, setting the power and the significance level at conventional 80% and $p<0.05$ respectively shall be utilised Meta-analysis shall combine only studies with similar design, populations, interventions and outcome measure

ATTACHMENT 2

Table 19: Allowable claims for specific active ingredients in HS products

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Vitamin A	• Maintenance of good health	• Helps to maintain growth, vision and tissue development • Aids in maintaining the health of the skin and mucous membrane	
Vitamin C		• For healthy bones, **(cartilage),** teeth, gums as well as general make-up of the body	
Vitamin D	• Maintenance of good health	• Helps in normal development and maintenance of bones and teeth • Helps the body utilize calcium and phosphorus • Claim for specific population subgroups: Elderly people who are confined indoors	
Vitamin E	• Maintenance of good health		

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Beta Carotene	• Maintenance of good health	• Helps in maintenance of growth, vision and tissue differentiation	
Vitamin B1 (Thiamine)	• Helps to maintain good health	• Helps in maintenance of growth, vision and tissue differentiation	
Riboflavin (Vitamin B2)	• A factor in maintenance of good health	• Helps the body to utilize energy from food/ metabolize protein, fats and carbohydrates • Claim for specific population subgroups: -Additional amounts of Riboflavin are required during pregnancy and breast feeding when diet does not provide a sufficient daily intake	
Niacin (Vitamin B3)	• A factor in maintenance of good health	• Helps normal growth and development • Helps the body in utilization of energy from food	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Pyridoxine (Vitamin B6)	• A factor in maintenance of good health	• Helps the body to metabolize proteins, fats and carbohydrates	
Cyanocobalamine (Vitamin B12)	• Helps in maintenance of good health	• Helps in the formation of red blood cell	
Folic Acid		• Helps in formation of red blood cell	• Helps prevent neural tube defects for women who are planning a pregnancy before conception and during 12 weeks of pregnancy at a dose of 400 mcg daily
Biotin	• Helps in maintenance of good health	• Helps to metabolize fats and carbohydrates	
Panthothenic Acid	• Helps in maintenance of good health	• Helps to metabolize fats and carbohydrates	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Calcium	• Helps in maintenance of good health	• Helps in the formation and maintenance of bones and teeth • Claim for specific subgroup: - Additional calcium is required for pregnant and lactating women, when diet does not provide a sufficient daily intake to help in proper bone formation in developing baby	
Phosphorus	• Helps in maintenance of good health	• Helps in the formation and maintenance of bones and teeth	
Magnesium	• Helps in maintenance of good health	• Helps the body to metabolize carbohydrate	
Iron	• Helps in maintenance of good health	• Helps in the formation of red blood cell	• Helps to prevent iron anemia • Helps to prevent anemia due to iron deficiency
Iodine	• Helps in maintenance of good health	• Helps in the function of the thyroid glands	

Ingredients	Claims		
	General	**Functional**	**Reduced Risk Reduction Claim**
Zinc	• A factor in maintenance of good health	• Helps to metabolize carbohydrates, fats and protein	
Copper	• A factor in maintenance of good health	• Helps in the formation of red blood cell	
Manganese	• A factor in maintenance of good health	• Helps to metabolize carbohydrates and proteins	
Probiotics		• Helps to improve a beneficial intestinal microflora	

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority will nonetheless conduct a detailed evaluation of the evidence included in the report to ensure that the health claim is substantiated.*
3. *The Authority will be willing to consider review other than the listed above, if the standards of evidence are consistent with those of the Authority.*
4. *All references must be current.*

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Industries/ Associations:

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ii) Direct Selling Association of Malaysia (DSAM)
iii) Federation of Chinese Physician and Medicine-Dealers Association of Malaysia (FCPMDAM)
iv) Malaysian Biotechnology Corporation (BiotechCorp)
v) Malaysian Dietary Supplement Association (MADSA)
vi) Malaysian Direct Distribution Association (MDDA)
vii) *Persatuan Industri Farmaseutikal Malaysia (MOPI)*
viii) *Persatuan Pengeluar-pengeluar Ubat Tradisional Melayu Malaysia (PURBATAMA)*
ix) *Perubatan Traditional India Malaysia (PEPTIM)*
x) Pharmaceutical Association of Malaysia (PhAMA)

APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS

IMPORTANT NOTES:

1. This document shall be read in conjunction with the relevant sections of the main DRGD.
2. Natural products will be evaluated based on the criteria for safety and quality of the product and where appropriate efficacy/ claimed benefits.
3. This document is intended to provide guidance for the registration of natural products. However, the document will serve as a living document that will be updated/ revised further in the line with the progress in scientific knowledge and experience.
4. The following lists are by no means exhaustive. It may be reviewed as and when it is deemed necessary.

Outline:

2. General Requirements for Registration of Natural Products

2.1 Ingredients

- 2.1.1 Active Ingredients
- 2.1.2 Premix
- 2.1.3 Prohibited/ Banned Ingredients
- 2.1.4 Use of Protected/ Endangered Ingredients

2.2 Excipients

2.3 Indications

- 2.3.1 Indications Acceptable for Natural Products
- 2.3.2 Non-Permissible Indications

2.4 Product Name

2.5 Quality Control

- 2.5.1 Sample for Testing
- 2.5.2 Quality Testing for Specific Ingredient
- 2.5.3 Limit Test for Heavy Metals
- 2.5.4 Disintegration Test
- 2.5.5 Test for Uniformity of Weight (For Tablets and Capsules Only)
- 2.5.6 Tests for Microbial Contamination

2.6 Stability Data

2.7 Labelling Requirement

- 2.7.1 Statements to be stated on Product Label
- 2.7.2 Specific Labelling Statements/ Warning & Precautions
- 2.7.3 Cautionary Statement for Products Specially Used in Women
- 2.7.4 Prohibited Visual/ Graphics/ Statement on Label of Natural Products in Women

2.8 Particulars of Packing

3. Product Specific Requirements:

3.1 Foot Patch

3.2 Herbal Tea

3.3 Homeopathic Products

1. GENERAL INFORMATIONS

1.1 DEFINITIONS

1.1.1 Traditional medicine

As defined under the CDCR 1984, traditional medicine refers to any product used in the practice of indigenous medicine, in which the drug consist solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof, in the unextracted or crude extract form, and a homeopathic medicine. It shall not include any sterile preparation, vaccines, any substance derived human parts, any isolated and characterized chemical substances.

1.1.2 Finished Herbal Product

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term “mixture herbal product” can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substance have been added, including synthetic compounds and/ isolated constituents from herbal materials, are not considered to be herbal.

1.1.3 Herbal Remedy

Any drug consisting of a substance or a mixture of substances produced by drying, crushing or comminuting, but without subjecting to any other process, a natural substance or substances of plant, animal or mineral origin, or any part of such substance or substances.

1.1.4 Homeopathic Medicine

Any pharmaceutical dosage form used in the homeopathic therapeutic system in which diseases are treated by the use of minute amounts as of such substances which are capable of producing in healthy persons symptoms similar to those of the disease being treated.

1.2 EXEMPTION FROM PRODUCT REGISTRATION

The following preparations do not require registration with the Authority:

a) Extemporaneous preparation that has been prepared and given directly to the patient by any traditional practitioner during the course of treatment;

b) Traditional preparation containing plants, animal parts or mineral substance or a mixture of these substances of natural origin that is produced only through drying, without any treatment/process involved. For example, raw herbs;

c) Traditional preparation containing plants, animal parts, mineral substance/ extracts or a mixture of these substances of natural origin traditionally used as food, spices or flavouring of food which do not have any medicinal claim;

d) Traditional preparation that is used for cosmetic purposes such as to whiten or improve the appearance of skin, hair, teeth, etc has to be registered as cosmetic product.

1.3 PREPARATIONS WHICH ARE NOT ALLOWED TO BE REGISTERED

a) Traditional preparation with the indication as listed in **"**List of Non Permissible Indications for Natural Product"
(Reference: Medicine Advertisement and Sale Act 1956)

b) Traditional preparation containing herbal ingredients as listed under Poison Act 1952 except for those exempted for homeopathic preparation. Please refer to Section 4 - General guidelines for the registration of homeopathic products.

c) Traditional preparation containing ingredient known or reported to cause any adverse effect on humans. Please refer to List of Botanicals (& botanical ingredients) which are banned due to reported adverse event.

d) Traditional preparation containing combination of plants, animal parts or mineral substance of natural origin with chemical/ synthetic substance with therapeutic effect.

e) Traditional preparation containing combination of plants, animal parts or mineral substance of natural origin with vitamins and amino acids.

f) Traditional products are prohibited from containing ingredients derived from human origin. For examples:

i) CRINIS CARBONISATUS = Carbonised human hair
(Reference: Pharmacopoeia Of The People's Republic Of China: English Edition 1992)

ii) HUMAN PLACENTA

1.4 CLASSIFICATION FOR SPECIFIC ACTIVE INGREDIENTS

1.4.1 PRODUCTS CONTAINING CASSIA/ SENNA:

Finished products containing cassia/senna as an active ingredient with a daily dose of less than 0.5g of the crude drug or 20 mg sennoside (standardized preparation) shall be classified as traditional products and restricted to traditional claims. Active ingredient consumed more than this daily limit will be classified as pharmaceutical product, depending on the product formulation.

1.4.2 PRODUCTS CONTAINING PSYLLIUM HUSK/ PLANTAGO OVATA

Finished products containing psyllium husk as an active ingredient and with a total daily consumption of less than 3.5g per day shall be classified as a non-drug. However, daily doses above this amount and up to 6.9 g will require this product to be registered under the traditional product category.

(Reference: Circular on 14 May 2010 - Bil (24) dlm.BPFK/PPP/07/11Jld 5)

2. GENERAL REQUIREMENTS FOR REGISTRATION OF NATURAL PRODUCTS

2.1 INGREDIENTS

2.1.1 ACTIVE INGREDIENTS

a) Active ingredients are those substances that have a therapeutic role in the formulation. Substances that are included in the formulation as active ingredients must make a contribution to the proposed indications for the product. Where a claim links the presence of an ingredient to the product indication, that ingredient must contribute to that indication. The evidence may be scientific and or traditional.

b) Overages of active ingredient
Overages may be used during manufacture. An overage is where the amount of an ingredient added during manufacturing that is greater than the nominated on the product label. Details of the overage used must be available

c) Listed active ingredients can be checked through http://npra.moh.gov.my/ of product search. Ingredients not listed will require safety and/or efficacy data evaluation prior to addition to this list.

d) For new active ingredients or new combination products, the following information shall be required:

- Product containing new single ingredient:

i) Extract form

- Information on the taxonomy of the ingredient;
- Techniques and methods in preparing/ processing the extract and subsequently the product;
- Information on the use and safety of the ingredient and the product Quality standard.

ii) Powder/ Granules

- Information on the taxonomy of the ingredient;
- Techniques and methods in preparing/ processing the extract and subsequently the product;
- Information on the use and safety of the ingredient and the product.

- Product containing multiple ingredients (contains ingredients which are known to be used traditionally):
  - The source of the product formulation;
    e.g. Chinese Pharmacopoeia
  - Proof or evidence of the use, traditionally.

- Product containing multiple ingredients (contains ingredients which are not known to be used traditionally):
  - Information on the use and safety of every new ingredient;
  - Safety data on the new formulation;
  - Regulatory status in other countries.

2.1.2 PREMIX

Effective from 1 December 2007, premixed ingredient(s) shall not be used in a traditional product formulation, as directed in circular Bil (71) dlm BPFK/02/5/1.3, 1 Jun 2007

2.1.3 PROHIBITED/ BANNED INGREDIENTS

The following lists are prohibited/ banned ingredients which are not allowed in the formulation of natural products registered by the Authority:

a) Botanicals (and botanical ingredients) containing scheduled poisons as listed under the Poisons Act 1952;

b) Botanicals (& botanical ingredients) which are banned due to reported adverse event;

c) Ingredients (botanicals and substance derived from animals) which are banned due to safety reasons.

Table 1: Botanicals (and botanical ingredients) containing scheduled poisons as listed under the Poisons Act 1952

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
Aconitum	All species			Aconite
Asidosperma	*quebracho*	White quebracho		Asidospermine, yohimbine
Atropa	*belladonna*	Deadly nightshade		Atropine, hyoscine (scopolamine), hyoscyamine
Cabola	*albarrane*	Squill		Glycoside
Cannabis *(controlled under Dangerous Drug Act 1952)*	*All species*	Marijuana		Cannabinoids
Catharanthus	*roseus*	Periwinkle Madagascar, Old Maid, *Vinca rosea,* Myrtle Syn: ***Vinca balcanica***, ***Vinca difformis***, ***Vinca heracea***, ***Vinca major***, ***Vinca minor***, ***Vincae***		Vinca, Vincristine, Vinblastine

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
		minoris herba		
Chondodendron	*tomentosum*	Curare, Velvet leaf, Ice Vine,		Tubocurarine
Claviceps	*purpurea*	Ergot		Ergometrine
Colchicum	*autumnale*	Autumn Crocus/ Meadow Saffron/ Naked Lady)		Colchicine
Datura	*metel*	Devil's Trumpet, Metel, J California Jimson Weed Syn.: *Datura wrightii*		Atropine, Scopolamine
Datura	*stramonium*	Jimson Weed/ Gypsum Weed,Loco Weed		Atropine, Hyoscyamine, Scopolamine
Delphinium	*staphysagria*	Lice bane, Stavesacre		Delphinine
Digitalis	*purpurea*	Common Foxglove, Purple Foxglove, Kecubung	Leaf	Glycoside
Drimia	*maritima*	Squill		Glycoside

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
		Syn.:*Urginea maritima, Scilla maritima* Related substance: *Urginea indica, Urginea pancreatium, Urginea scilla*		
Ephedra	All species	Ma Huang		Ephedrine, Pseudoephedrine
Gelsemium	*sempervirens*	Yellow Jessamine,Evening Trumpet,Carolina Jessamine		Gelsemine
Hyoscyamus	*muticus*	Egyptian henbane		Hyoscyamine
Hyoscyamus	*niger*	Black henbane		Hyoscyamine-atropine
Lobelia	*inflata*	Lobelia, pokeweed, Indian tobacco, gagroot, asthma weed, vomitwort, bladderpod,rapuntium inflatum.		Lobeline
Lobelia	*nicotianifolia*	Wild Tobacco		Lobeline

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
Mitragyna	*speciosa*	Daun Ketum		Mitragynine
Nicotiana	*tabacum*	Common tobacco		Nicotine
Papaver	*somniferum*	Opium poppy		Morphine, codeine, hydrocodone, meperidine, methadone, papaverine
Pausinystalia	*yohimbe*	Yohimbe, Johimbe Syn. *Corynanthe johimbi,Corynanthe yohimbi*		Yohimbine
Physostigma	*venenosum*	Calabar bean		Physostigmine
Pilocarpus	*microphyllus*	Pilocarpus jaborandi, jaborandi		Pilocarpine
Punica	*granatum*	Pomegranate	Bark	Iso-Pellatrierine
Rauwolfia	*serpentina*	Indian snakeroot, Serpentine root		Reserpine
Rauwolfia	*vomitoria*	African serpentwood		Reserpine
Schoenocaulon	*officinale*	Veratrum		Sabadilla,

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
		officinale		Veratrine
Scillae	*bulbus*	Sea onion, Squill		
Solanum	*nigrum*	Black nightshade		Solanine
Strychnos	*nux-vomica*	Poison nut, Quaker button, strychnine tree, ma qian zi/maqianzi		Strychnine
Valerian	All species		All parts except for root part	Valepotriates
Veratrum	All species			
Vinca	All species	Including *Catharanthus roseus*		Vinca, Vincristine, Vinblastine, Vinpocetin

a) Table 2: Botanicals (& botanical ingredients) which are banned due to reported adverse event

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
Aristolochia	All species			Contain **Aristolochic Acid** reported to cause kidney toxicity **(**Please refer to footnote below)**
Berberis	All species			Berberine *Other herbs containing naturally-occuring berberine are allowed to be registered with specific requirements. Please refer to Appendix 9 Notes: Only prohibited for oral preparation.
Dioscorea	*hispida*	Ubi gadong, Gadong, Gadog, Gadong Lilin, Gadong Mabok, Ubi Arak, Ubi Akas, Taring Pelanduk, Susur Gadong, Gadongan, Kedut dan Ubi Bekoi	All parts	Contain dioscorine and dioscorinine reported to cause burning sensation in the throat, giddiness, followed by haematemesis, sensation of suffocation, drowsiness and exhaustion Not allowed for oral preparation
Drybalanops	aromatica	Borneo	Whole herb	Contain camphor- not

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
		/Malay/Sumatra Camphor, Pokok Kapur		allowed for oral preparation
Borneolum	syntheticum	Bingpian,borneol		Contain borneol- not allowed for oral preparation
Larrea	tridenata	Chapparal		Reported to cause liver toxicity
	mexicana			
Hydrastis	canadensis	Goldenseal,Eye Balm, Indian Dye		Reported to cause disturbance of the nervous system
Magnolia	officinalis	Houpu, Magnolia		Reported to cause kidney toxicity
Stephania	tetrandra			
Piper methysticum		Kava-kava		Reported to cause liver toxicity
Symphytum	officinale	Comfrey		
	asperum			
	x. uplandicum			
Senecio	aureus	Life root		
	jacobaea	Tansy ragwort, Tansy Butterweed		
	bicolor	Silver ragwort		
	nemorensis	Alpane ragwort, Wood ragwort		

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
	vulgaris	Common groundsel, Groundsel, Old-man-in the-spring		
	longilobus -syn .with douglasii, filifolius	Threadleaf groundsel, Threadleaf ragwort		
	Scandens Buch.-Ham	German/African/ Cape Ivy, Climbing Groundsel		

** To identify the Botanicals which may contain Aristolochic Acid besides the Aristolochia genus, please refer the following lists on the next page:

a. **List A - Botanicals Known or Suspected to contain Aristolochic Acid**
b. **List B - Botanicals which may be Adulterated with Aristolochic Acid**

Notes:

Products containing any of the listed herbs (EXCEPT for Aristolochia spp. which is totally banned) will have to be sent to any governmental doping centre for testing and the result shall be attached with the registration form.

(Source for Lists A and B)

U. S. Food and Drug Administration

Center for Food Safety and Applied Nutrition

Office of Nutritional Products, Labeling, and

Health Supplements

[Revised April 9, 2001]

List A: Botanicals Known or Suspected to Contain Aristolochic Acid

Table 3:

Botanical Name*	Common or Other Names
Asarum canadense Linn. Syn. Asarum acuminatum (Ashe) E.P. Bicknell Syn. Asarum ambiguum (E.P. Bicknell) Daniels Syn. Asarum canadense var. ambiguum (E.P. Bicknell) Farw. Syn. Asarum canadense var. reflexum (E.P. Bicknell) B.L. Rob. Syn. Asarum furcatum Raf. Syn. Asarum medium Raf. Syn. Asarum parvifolium Raf. Syn. Asarum reflexum E.P. Bicknell Syn. Asarum rubrocinctum Peattie	Wild ginger Indian ginger Canada snakeroot False coltsfoot Colic root Heart snakeroot Vermont snakeroot Southern snakeroot
Asarum himalaicum Hook. f. & Thomson ex Klotzsch or Asarum himalaycum Hook. f. & Thomson ex Klotzsch	Tanyou-saishin (Japanese)
Asarum splendens (F. Maek.) C.Y. Cheng & C.S. Yang	Do-saishin (Japanese)

Botanical Name*	Common or Other Names
Bragantia wallichii R.Br. Specimen exists at New York Botanical Gardens. Tropicos does not list this species as a synonym for any Thottea species. Kew Gardens Herbarium does not recognize the genera Bragantia. Until additional information is obtained we will use the name as cited in J. Nat. Products 45:657-666 (1982)	

List B: Botanicals which may be Adulterated with Aristolochic Acid

Table 4:

Botanical Name*	Common or Other Names
Akebia spp.	Akebia Mu tong Ku mu tong Zi mutong Bai mu tong Mokutsu (Japanese) Mokt'ong (Korean
Akebia quinata (Houtt.) Decne. Syn. Rajania quinata Houtt.	Chocolate vine Fiveleaf akebia Mu tong

Botanical Name*	Common or Other Names
	Yu zhi zi Mokutsu (Japanese)
Akebia trifoliata (Thunb.) Koidz.	Mu tong Three leaf akebia Yu zhi zi
Asarum forbesii Maxim.	Batei-saishin (Japanese)
Asarum heterotropoides F. Schmidt Syn. Asarum heterotropoides F. Schmidt Syn. Asiasarum heterotropoides (F. Schmidt) F. Maek.	Keirin-saishin (Japanese) Chinese wild ginger Manchurian wild ginger Bei xi xin Xin xin
Asarum sieboldii Miq. Syn. Asarum sieboldii fo. seoulense (Nakai) C.Y. Cheng & C.S. Yang Syn. Asarum sieboldii var. seoulensis Nakai Syn. Asiasarum heterotropoides var. seoulense (Nakai) F. Maek. Syn. Asiasarum sieboldii (Miq.) F. Maek.	Usuba-saishin (Japanese) Chinese wild ginger Xi Xin Hua Xi Xin Manchurian wild ginger Siebold's wild ginger

Botanical Name*	Common or Other Names
Clematis spp.	Clematis Mufangji Clematidis Ireisen (Japanese) Wojoksum (Korean)
Clematis armandii Franch. Syn. Clematis armandii fo. farquhariana (W.T. Wang) Rehder & E.H. Wilson Syn. Clematis armandii var. biondiana (Pavol.) Rehder Syn. Clematis biondiana Pavol. Syn. Clematis ornithopus Ulbr.	Armand's clematis Chuan mu tong (stem) Xiao mu tong Armand's virgin bower
Clematis chinensis Osbeck.	Chinese clematis Wei ling xian (root)
Clematis hexapetala Pall.	
Clematis montana Buch.-Ham. ex DC. Syn. Clematis insulari-alpina Hayata	

Botanical Name*	Common or Other Names
Clematis uncinata Champ. ex Benth. Syn. Clematis alsomitrifolia Hayata Syn. Clematis chinensis var. uncinata (Champ. ex Benth.) Kuntze Syn. Clematis drakeana H. Lév. & Vaniot Syn. Clematis floribunda (Hayata) Yamam. Syn. Clematis gagnepainiana H. Lév. & Vaniot Syn. Clematis leiocarpa Oliv. Syn. Clematis ovatifolia T. Ito ex Maxim. Syn. Clematis uncinata var. biternata W.T. Wang Syn. Clematis uncinata var. coriacea Pamp. Syn. Clematis uncinata var. floribunda Hayata Syn. Clematis uncinata var. ovatifolia (T. Ito ex Maxim.) Ohwi ex Tamura Syn. Clematis uncinata var. taitongensis Y.C. Liu & C.H. Ou	
Cocculus spp.	Cocculus
Cocculus carolinus (L.) DC. Syn. Cebatha carolina Britton Syn. Epibaterium carolinum (L.) Britton Syn. Menispermum carolinum L.	
Cocculus diversifolius DC. Syn. Cocculus madagascariensis Diels	
Cocculus hirsutus (L.) Diels Syn. Cocculus villosus DC. Syn. Menispermum hirsutum L.	

Botanical Name*	Common or Other Names
Cocculus indicus Royle Syn. Anamirta paniculata Colebr.	Indian cockle
Cocculus laurifolius DC. Syn. Cinnamomum esquirolii H. Lév.	
Cocculus leaebe DC.	
Cocculus madagascariensis Diels Syn. Cocculus diversifolius DC.	
Cocculus orbiculatus DC. Syn. Cissampelos pareira Linn. Cocculus orbiculatus (L.) DC. Syn. Cocculus cuneatus Benth. Syn. Cocculus sarmentosus (Lour.) Diels Syn. Cocculus sarmentosus var. linearis Yamam. Syn. Cocculus sarmentosus var. pauciflorus Y.C. Wu Syn. Cocculus sarmentosus var. stenophyllus Merr. Syn. Cocculus thunbergii DC. Syn. Cocculus trilobus (Thunb.) DC. Syn. Menispermum orbiculatus L. Syn. Menispermum trilobum Thunb. Syn. Nephroia sarmentosa Lour.	Moku-boui (Japanese)
Cocculus palmatus (Lam.) DC.	Columba Columbo
Cocculus pendulus Diels Syn. Cebatha pendula (J.R. & C. Forst.) Kuntze Syn. Epibaterium pendulus Forst. f. Syn. Cocculus Epibaterium DC.	

Botanical Name*	Common or Other Names
Cocculus pendulus (Forst. & Forst.) Diels	
Cocculus palmatus Hook. Syn. Jateorhiza Miersii Oliver	Colombo
Cocculus thunbergii DC.	
Diploclisia affinis (Oliv.) Diels Syn. Diploclisia chinensis Merr. Syn. Cocculus affinis Oliv.	
Diploclisia chinensis Merrill	Xiangfangchi
Menispernum dauricum	
Saussurea lappa (Decne.) Sch. Bip. / Aucklandia Lappa	Mokkou (Japanese)
Sinomenium acutum (Thunb.) Rehder & E.H. Wilson Syn. Cocculus diversifolius var. cinereus Diels Syn. Cocculus heterophyllus Hemsl. & E.H. Wilson Syn. Menispermum acutum Thunb. Syn. Sinomenium acutum (Thunb.) Rehder & E.H. Wilson var. cinereum (Diels) Rehder & E.H. Wilson Syn. Sinomenium diversifolium (Diels) Diels	Orientvine Xunfengteng Dafengteng Daqingmuxinag Zhuigusan Da ye qingshener Mufangji Hanfangji Tuteng Zhuigufeng Maofangji
Stephania spp. (except for Stephania Tetrandra which is banned)	Stephania
Vladimiria souliei (Franch.) Ling	Sen-mokkou

b) Ingredients (Botanicals and Substance Derived from Animals) which are banned due to safety reasons:

Table 5:

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
Abrus	*precatorius*	Seed	Abrin, Agrus, Agglutinin	- Potent inhibitor of protein and DNA synthesis - Severe diarrhea - Severe stomach cramp - Severe gastroenteritis
Adonis	*vernalis*		Adonitoxin	Uncontrolled dose can damage heart and cause death
Animal parts containing hormones (All species)				
Antiaris	*toxicaria*	Latex, sap	Cardiac glycoside (antiarin), Cardenolides & alkaloids with cardiac arresting potential	- Latex is highly poisonous - Paralyze heart muscle and cause death
Aristolochia	*All species*		Aristolochic acid	Reported to cause kidney toxicity, interstitial nephropathy
Calotropis	*gigantean*	Latex	Cardiac glycosides, calotropin	Severe mucous membrane irritation characterized by vomiting, diarrhea, bradycardia, convulsion and
	procera			

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
				death
Catharanthus	*roseus*		Vinca alkaloids	Bone marrow depression, central and peripheral (including autonomic) neurotoxicity
Cerbera	*manghas*	Seed	Digitoxynglycoside, Cerberine, Cerberoside, thevetin	- Drastic purgative and emetic - Burning in the stomach sensation, vertigo, nausea, violent purgation and colic - Heart failure
	odollam	Seed	Cerberine, Cerberoside, odollin, odolotoxin, thevetin and cerapain	- Gastro intestinal symptoms - cardiac toxicity - Nausea, severe retching, vomiting, abdominal pain, blurring of vision - Arterial block and nodal rhtym, hyperkalaemia - Irregular respiration, collapse and death from heart failure
Cinchona	*All species*		Quinine and derivatives	- Resistance of malarial vector - Use of bark is contraindicated in pregnancy and ulcers, intestinal or gastric, and if taken concommitantly with anticoagulants can increased their effects - Can elicit thrombocytopenia

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
				with purpura - Cinchona alkaloids are toxic. Can cause symptoms such as blindness, deafness, convulsions and paralysis
Citrullus	*Colocynthis*	Seed, fructus	Curcubitacin	- Carcinogenic effects, induce infertility in both sexes - Enterohepatonephro-toxicity
Dryopteris	*filix-mas*	Rhizome	Filicin, aspidinol	Hepatotoxic and blindness
Euphorbia	*antiquorum*	Latex	Apha euphorbol, Beta amyrin cycloartenol Euphol	Inflammation of the gastrointestinal mucous membrane, irritate skin, difficult respiration, eyes pupil dilated
	trigona			
Excoecaria	*agallocha*	Latex	Excoecaria phorbol	- Highly irritant to skin - Cause blindness if it enters the eye - Biocidal
Garcinia	*acuminate*	Gum resin	Cambogic acid, β-guttiferin, α-1 guttiferin	Vomiting, hypercarthasis, sympathetic irritation of sympathetic nervous system, caused death by gastro-enteritis
	hanburyi			
	morella			
Gelsemium	*elegans*	Root, leaf, rhizome	Gelsemine & gelseminine (Gelsemium indole alkaloid)	Paralysis, shortness of breath, muscle stiffeningcoma, hypocyclosis
Hyoscyamus	*muticus*		Hyoscyamine, atropine, hyoscine	Difficulty in swallowing and talking, transient bradycardia followed by tachycardia with palpitation and arrhythmias,

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
				CNS depression, coma
Jatropha	*multifida*	Fruit, seed	Phytotoxin (toxalbumin - Curcin	Nausea, vomiting, serious purgative action
Lantana	*camara*		Lantadene, Lancamaron	Cause toxicity in buffalo, cattle, sheep and goat. Symptoms include photosensitive dermatitis, jaundice and yellowing of mucous membrane and loss of appetite with a decrease in ruminal motility
Lobelia	*chinensis*		Lobeline	- Stimulant and has peripheral and central effects - Excessive use can cause nausea, vomiting and dizziness
	tupa			- Stimulant and has peripheral and central effects - Caused arrhythmias
Lytta	*vesicatoria*	Whole body, tincture	Cantharidin	- Excessive salivation, abdominal pain, swelling of kidney and urogenital system, headache, vomiting and diarrhea accompanied by bleeding - Burning of the mouth, dysphagia, nausea, hematemesis, gross hematuria and dysuria - Renal dysfunction and related to acute tubular

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
				necrosis and glomerular destruction
Melaleuca	*alternifolia*		Tea tree oil	Skin irritation, respiratory distress, vomiting, diarrhea and cytotoxic for oral administration. *** Banned in oral preparation**
Papaver	*All species*		Morphine and derivatives, codeine	- Potential abuse - Dependence, palpitation, hallucination, euphoric activities, CNS depression - Nervous system toxicity - Possible death from circulatory and respiratory failure
Pilocarpus	*pinnatifolius*	Bark	Pilocarpine	Bronchospasm, ocular problem, miosis, blurred vision
	jaborandi			
Podophyllum	*emodii*	Root, leaf	Podophyllin resin	- Serious systemic toxicity with excessive amounts (persistent nausea and vomiting, tachypnea, fever, stupor, coma, tachycardia, neuropathy and death) - Renal failure and hepatotoxicity
	peltatum			
Solanum	*dulcamara*	Leaf, flowering tops	Solanaceous alkaloids	Typical antimuscarinic effect e.g. dry mouth, mydriasis

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
Strophantus	*All species*		Strophantus alkaloids	Cardiac effect similar to digoxin
Symphytum	*pregrinum*		Pyrrolizidine alkaloid	Reported to cause liver toxicity

2.1.4 USE OF PROTECTED/ ENDANGERED INGREDIENTS

c) PROTECTED/ ENDANGERED WILDLIFE SPECIES

It is the responsibility of the applicant to ensure that the ingredient(s) derived from wildlife species its parts and derivatives used in the formulation **COMPLIES** with the Wildlife Conservation Act 2010 (Act 716) and International Trade in Endangered Species Act 2008 (Act 686). Both guidelines can be downloaded through this link http://www.wildlife.gov.my.

The applicant shall contact the following department to obtain the necessary permit/ license. A copy of the permit/ license shall be attached together with the application form for product registration.

Department of Wildlife and National Parks, Peninsular Malaysia
Km. 10, Jalan Cheras,
56100 Kuala Lumpur,
Tel: +603-90866800, Fax: +603-90753873

d) ENDANGERED BOTANICAL SPECIES

It is the responsibility of the applicant to declare the source of the botanical ingredient if it is listed under the International Trade in Endangered Species Act 2008 (Act 686). If the ingredient is from a local source, a special permit/ license shall be obtained from the:

Division of Protection and Quarantine of Plants,
Department of Agriculture,
Tingkat 1-3, Wisma Tani,
Jalan Sultan Salahuddin,
50632 Kuala Lumpur.
Tel: +603 - 20301400, Fax: +603 - 26913550.

2.2 EXCIPIENTS

a) Excipients are substances used to assist in the manufacture of active substance into dosage forms suitable for administration to consumers. Each excipient ingredient included in a formulation must have a justifiable excipient role and shall be controlled by specifications. The intended use of an excipient shall be appropriate.

b) New excipient will require safety and/or other additional data to support the function in the product prior to addition into the Quest 3 database.

c) LIST OF RESTRICTED EXCIPIENTS:

Specific Excipient	Limits (Not allowed)
1. Menthol	- Oral (>10mg/day) - External (>10%)

2.3 INDICATIONS

General note: The indications listed below will serve as a guide for the applicant. For traditional medicines, only low level claim (s) will be accepted. Other indication with the same level of claims may be considered if supported with traditional use.

2.3.1 INDICATIONS ACCEPTABLE FOR NATURAL PRODUCTS

a) General Health Maintenance*/ Kesihatan Am*

"Traditionally used…./ *"Digunakan secara tradisional….*
"Digunakan secara homeopati untuk.../ *"Homeopathically used....*

1. For general health/ for health/ *untuk kesihatan*.
2. General health maintenance/ for general well being.
3. For health and strengthening the body/ *untuk kesihatan dan menguatkan badan*.
4. For relief of body heatiness/ *untuk melegakan panas badan*.
5. For general debility, weakness after illness or childbirth/ *untuk letih lesu/ kelesuan badan selepas sakit atau selepas bersalin.*
6. For loss of appetite/ *untuk kurang selera makan.*
7. For difficulty in sleep/ *bagi melegakan kesukaran untuk tidur.*
8. For relief of fatigue/ *untuk melegakan kepenatan.*
9. As an aid to overcome fatigue during physical exertion/ *membantu melegakan kepenatan fizikal.*
10. To expel wind and invigorate vital energy/ *untuk membuang angin dan menambah tenaga.*
11. To improve appetite/ *untuk menambah selera makan.*
12. For relieving waist ache and body weakness/ *untuk melegakan sakit pinggang dan lemah anggota badan.*
13. For relieving dizziness, sweating, and difficulty in sleep/ *untuk melegakan pening, berpeluh berlebihan dan sukar untuk tidur.*
14. For reducing body odour/ *untuk mengurangkan bau badan.*
15. For reducing toothache/ *untuk mengurangkan sakit gigi.*
16. To relieve tired eyes/ *untuk melegakan kepenatan mata.*
17. For healthy eyes/ *untuk kesihatan mata.*

b) Blood & Body Fluid/ *Darah & Cecair Badan*

"Traditionally used…./ *"Digunakan secara tradisional….*

1. For improving blood circulation/ *untuk melancarkan perjalanan darah.*
2. To improve urination/ *untuk melawaskan kencing/ buang air kecil.*
3. For improving bowel movement/ *untuk melawaskan buang air besar.*
4. For relieving mild vomiting/ *untuk melegakan muntah ringan.*
5. For reducing minor swelling/ *untuk melegakan bengkak-bengkak ringan.*

c) Bone, Muscle & Joint/ *Tulang, Otot & Sendi*

"Traditionally used…./ *"Digunakan secara tradisional….*

1. For strengthening muscle and bone/ *untuk menguatkan otot dan tulang.*
2. For relieving muscular ache/ *untuk melegakan sakit otot.*
3. For relieving waist ache and backache/ *untuk melegakan sakit pinggang dan sakit belakang.*
4. For relief of joints and muscular pain/ *untuk melegakan sakit sendi dan otot.*
5. For relieving muscles sprain/ *untuk melegakan terseliuh/ terkehel.*

d) Pain & Fever/ *Sakit Am & Demam*

"Traditionally used…./ *"Digunakan secara tradisional….*

1. To relieve/ alleviate pain/ *untuk melegakan kesakitan.*
2. For relieving fever/ *untuk melegakan demam*.
3. For relieving headache/ *untuk melegakan sakit kepala.*
4. For relieving pain and itchiness related to piles/ *untuk melegakan kesakitan dan rasa gatal akibat buasir.*
5. For symptomatic relief of body heatiness/ body heat / *untuk melegakan panas badan.*

e) Cough & Cold/ *Batuk & Selsema*

"Traditionally used……/ *"Digunakan secara tradisional…..*

1. For relief of fever, cough and cold/ *untuk melegakan demam, batuk dan selsema.*
2. For relief of sore throat/ *untuk melegakan sakit tekak.*
3. For reducing phlegm and relief of cough, sore throat and body heatiness/ *untuk mengurangkan kahak dan melegakan batuk, sakit tekak dan panas badan.*
4. For relief of throat irritations and cough/ *untuk melegakan sakit tekak dan batuk.*
5. For relief of nasal congestion/ *untuk melegakan hidung tersumbat.*
6. For relief of sore throat and cough/ *untuk melegakan sakit tekak dan batuk.*
7. For relief of mouth ulcers due to heatiness/ *untuk melegakan sakit mulut akibat panas badan.*
8. To relieve sinusitis/ *untuk melegakan resdung.*

f) Digestive System/ *Sistem Pencernaan*

"Traditionally used…./ *"Digunakan secara tradisional….*

1. For relief of stomach ache, mild diarrhoea/ *untuk melegakan sakit perut, cirit-birit ringan.*
2. For relief of flatulence, stomach ache, mild diarrhoea, and loss of appetite/ *untuk melegakan kembung perut, sakit perut, cirit-birit ringan dan kurang selera makan.*
3. For relief of mild diarrhoea, vomiting and improve appetite/ *untuk melegakan cirit-birit, muntah ringan dan menambah selera makan.*
4. For relief of mild constipation/ *untuk melegakan sembelit ringan.*
5. To improve appetite and digestion/ *untuk menambah selera makan dan pencernaan.*
6. For relieving abdominal pain and flatulence/ *untuk melegakan sakit perut dan kembung perut.*
7. For relief of stomach ache, constipation, mild vomiting and indigestion/ *untuk melegakan sakit perut, sembelit, muntah ringan dan makanan tidak hadzam*.
8. Aid in digestion/ *untuk membantu penghadzaman.*

g) Women's Health/ *Kesihatan Wanita*

"Traditionally used…../ *"Digunakan secara tradisional….*

1. To relieve menstrual pain, headache and to regulate menstruation/ *untuk melegakan senggugut, sakit kepala dan melancarkan perjalanan haid.*
2. To reduce body weight/ *untuk mengurangkan berat badan.*
3. For relief of vaginal discharge/ *untuk melegakan keputihan.*
4. For women after childbirth/ *untuk wanita lepas bersalin.*
5. For general wellbeing and strengthen the body after childbirth/ *untuk kesihatan dan menguatkan badan wanita selepas bersalin.*
6. For women after childbirth to reduce body weight/ *untuk ibu-ibu selepas bersalin untuk mengurangkan berat badan.*
7. For symptomatic relief of vaginal discharge and mild itch/ *untuk melegakan keputihan dan gatal-gatal ringan.*
8. To improve menstrual flow, for relief of menstrual pain, vaginal discharge and flatulence/ *untuk melancarkan haid, melegakan senggugut, keputihan dan kenbung perut.*
9. For strengthening body muscle and reducing body weight/ *untuk mengencangkan otot-otot tubuh dan mengurangkan berat badan.*
10. For general health of women after childbirth/ *untuk menyihatkan rahim selepas melahirkan anak.*
11. To relieve symptoms of menopause/ *untuk melegakan simptom menopause. [**Note:** For specific active ingredient only, examples: red clover (trifolium pratense) and black cohosh (cimicifuga racemosa)]*

h) Men's Health/ *Kesihatan Lelaki*

"Traditonally used…./ *"Digunakan secara tradisional….*

1. For energy and men's health/ for vitality/ *untuk memulihkan tenaga dan kesihatan lelaki.*

i) Skin And External Usage*/ Kulit Dan Kegunaan Luar*

"Traditionally used…../ *"Digunakan secara tradisional…*

1. For symptomatic relief of pain and itch associated with insect bites/ *untuk melegakan sakit dan gatal-gatal digigit serangga.*
2. For relief of minor burns/ *untuk melegakan melecur ringan.*
3. For relief minor cuts/ *untuk melegakan luka-luka ringan.*
4. For relief of minor bruises/ *untuk melegakan lebam yang ringan.*
5. For reducing pimples/ *untuk mengurangkan jerawat.*
6. To help maintaining healthy skin, nail and hair/ *untuk kesihatan kulit, kuku dan rambut.*
7. For reducing pimples and mild itch/ *untuk melegakan jerawat dan gatal-gatal ringan.*

2.3.2 NON-PERMISSIBLE INDICATIONS

Table 6:

NO.	NON-PERMISSIBLE INDICATIONS
1.	*Penyakit atau kecacatan ginjal* / Disease or defects of the kidney
2.	*Penyakit atau kecacatan jantung* / Disease or defects of the heart
3.	*Kencing manis* / Diabetes
4.	*Epilepsi atau sawan* / Epilepsy or fits
5.	*Kelumpuhan* / Paralysis
6.	*Tibi* / Tuberculosis
7.	*Asma* / Asthma
8.	*Kusta* / Leprosy
9.	*Kanser* / Cancer
10.	*Kepekakan* / Deafness

NO.	NON-PERMISSIBLE INDICATIONS
11.	*Ketagihan dadah* / Drug addiction
12.	*Hernia atau pecah* / Hernia or rupture
13.	*Penyakit mata* / Disease of the eye
14.	*Hipertensi (Darah Tinggi)* / Hypertension
15.	*Sakit otak* / Mental disorder
16.	*Kemandulan* / Infertility
17.	*Kaku* / Frigidity
18.	*Lemah fungsi seks atau impoten* / Impairment of sexual function or impotency
19.	*Penyakit venerus* / Venereal disease
20.	*Lemah urat saraf atau aduan atau kelemahan lain timbul daripada atau berhubungkait dengan perhubungan seks* / Nervous debility or pother complaint of infirmity arising from or relating to sexual intercourse.

2.4 PRODUCT NAME

a) If the product owner wishes to use a formulary name, any amendments made to the product formulation such as the addition of active ingredients, removal of active ingredients or change in strength of active ingredients will not be permitted.

b) A brand name in front of the formulary name shall be required to be added, in order to differentiate and identify that their product from products with the same formulary name.

c) Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product is prohibited.

d) For products in which the product name is the name of active ingredient or the product name is a common name, e.g. *Kapsul Kacip Fatimah; Misal Kucing Tea*; Ortosiphon Capsule; Herbal Rub; Natural Herb Capsule, a brand name shall be added to the product name, in order to differentiate and identify this specific product.

e) For single-ingredient products, in the case where the product name bears the name of the active ingredient, strength should be added to the product name. Example: Sunsky Tongkat Ali 500 mg Capsule

f) The dosage form is required to be added to the product name in the system (i.e in section A1)

g) Justification will be required to prove the "claim" made in the product name. Example: "Double Strength/ Acticoat/WaterSol"

h) Product name supported by a registered trade mark certificate will not be accepted if deemed inappropriate by the Authority/ not following the regulations stated in this Appendix.

i) Replacement product may used the same product name as a previously registered provided that the formulation (strength of active ingredient), product registration holder and dosage form of the product remains the same.

j) The name of the active ingredient is not allowed to be used as brand name.

k) The name of active ingredient combined with product indication is not allowed to be used as product name.

l) Product names which are not permitted to be registered are as specified in **Table 7** below:

Table 7 :

No.	Non-Permissible Product Names	Example
1.	**Prohibited use of disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983)**	**Example :** Diabetes, Asthma, Cancer
2.	**Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika**	**Example :** Tongkat Ali Capsule ---- But product contains tongkat ali, ginseng, ect.
3.	**Prohibited use of superlative - Names which indicates superiority in efficacy**	**Example :** Power/ Kuasa, Superior, Pure, Mustajab, Safe, Healthy/ Sihat, Penawar/ Shifa, VIP, Good, Heal/ Sembuh, Premium, Mustajab, Men/ Women/ Children Complete, Men/ Women/ Children Enriched, Paradise/ Syurga, Menawan, Booster
4.	**Prohibited use of spelling of words which may cause confusion** **Words which involve names of/part thereof:** i) 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) ii) Diseases without scientific evidence of efficacy/ prescription medication to treat diseases/ parameters that indicate certain diseases (e.g. insulin, glucose) iii) Prohibited indication (e.g. to detoxify body)	**Example :** a) Go Out = GOUT b) UTix = Urinary Tract Infection c) Diabecine = Diabetes d) Metformon = Metformin e) Insuprem = Insulin f) Glucosey = Glucose g) DetoxB = Detox body
5.	**Prohibited use of names which may cause ambiguity** Ambiguous product name	**Example:** B For Energy?

No.	Non-Permissible Product Names	Example
6.	**Prohibited use of names which may be offensive or indecent**	**Example:** SENXBIG=SEnXBIG(label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire*(Dezire),Sensual (Xenxual),Asmara,Syok*
7.	**Prohibited use of product names which are incoherent with the approved indication** Name containing a product claim whereas product is indicated for more than the approved indication	**Example:** Cough Syrup X= Approved indication for cough, dizziness, flu and itch
8.	**Prohibited use of product names which has elements of ludicrous belief** Statements referring to ancient believe/ negative spirits/ supernatural power	**Example:** Words such as miracle, magic, magical, miraculous, saintly, heavenly
9.	**Prohibited use of product names similar to the existing approved product names** Product names similar to the spelling and pronunciation of words of the existing product names	**Example:** Tenormin vs Tenormine vs Tenormy Re-Liv vs Re-Lif
10.	**Prohibited use of product names which may cause ambiguity in the nature of product (drug/ food/ beverage)** Product names similar to a food/ beverage product	**Example:** Juice, Health drink, Beverage, Kooky
11.	**Prohibited use of product names which represents professional advice or opinion or referring to the profession**	**Example:** Dr Sunny, Dr Noortier Rooibose Tea, Professor, Herbalist, Doctor
12.	**Prohibited use of product names which represent weight loss/ slimming properties/ names that can be associated with weight loss/ slim**	**Example:** Slim, Langsing, Trim, Trimnfit, *Sleen, Kurus, Susut perut,Xlim, Weight watcher*

No.	Non-Permissible Product Names	Example
13.	**Prohibited use of product names referring to any religious content**	**Example:** Maksum, Mahmudah, Arifbillah
14.	**Name of internal organ**	**Example:** Liver, Brain, Kidney, etc.
15.	**Use of abbreviation as a product name unless it carries no meaning**	**Example:** TB, UTI, HB, etc.
16.	**Other prohibited product names**	**Example:** Minda, IQ, Smart, Genius, Ultra Mega, Detox

Note:

1. This list is not meant to be exhaustive and will be reviewed from time to time
2. The Authority reserves the right to disallow any other words or phrases for product names which in its opinion is misleading, improper or not factual.

2.5 QUALITY CONTROL

2.5.1 SAMPLE FOR TESTING

Sample for testing shall be submitted to the Drug Analysis Division, NPRA within 14 working days of payment confirmation by the NPRA.

For further information, please refer **Section C: Guideline for Submission of Product Samples for Laboratory Testing** in the main DRGD.

2.5.2 QUALITY TESTING FOR SPECIFIC INGREDIENT

i) For product containing Aphanizomenon flosaquae, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method;

ii) For products containing Red Yeast Rice (*Monascus purpureus*), applicants shall provide certificates of analysis (for both raw material and finished product) showing the Monacolin-K content. The percentage of Monacolin-K shall not exceed 1% and the Monakolin-K consumed shall not exceed 10 mg per day.

2.5.3 LIMIT TEST FOR HEAVY METALS

Limit for heavy metals:

i)	Lead	:	NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm)
ii)	Arsenic	:	NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm)
iii)	Mercury	:	NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm)
iv)	Cadmium	:	NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm)

2.5.4 DISINTEGRATION TEST

Disintegration time **for tablets, capsules and pills**

i)	Uncoated tablets	:	NMT30 minutes
ii)	Film-coated tablets	:	NMT 30 minutes
iii)	Sugar-coated tablets	:	NMT 60 minutes
iv)	Enteric-coated tablets	:	Does not disintegrate for 120 minutes in acid solution but to disintegrate within 60 minutes in buffer solution
v)	Capsules	:	NMT 30 minutes
vi)	Pills	:	NMT 120 minutes

2.5.5 TEST FOR UNIFORMITY OF WEIGHT (FOR TABLETS AND CAPSULES ONLY)

i) Tablet

- For tablet with average weight of 130mg or less: Not more than 2 tablets differ from the average weight by more than 10% AND no tablets differ from the average weight by more than 20%
- For tablet with average weight between 130-324mg: Not more than 2 tablets differ from the average weight by more than 7.5% AND no tablet differs from the average weights by more than 15%
- For tablets with average weight more than 324mg: Not more than 2 tablets differ from the average weight by more than 5% AND no tablet differs from the average weight by more than 10%

ii) Capsule

Individual weight of the capsule to be within the limit of 90 - 110% of the average weight.

2.5.6 TESTS FOR MICROBIAL CONTAMINATION

TABLE 8:

A. Herbal medicinal products containing herbal drugs, with or without excipients, intended for the preparation of infusions and decoctions using boiling water (for example herbal teas, with or without added flavourings)

Microbiological Quality	Acceptance Criteria
TAMC	NMT 5 x 10^7 CFU/g
TYMC	NMT 5 x 10^5 CFU/g
Escherichia coli	NMT 1 x 10^3 CFU/g
Salmonella	Absence (25 g)

B. Herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where the method of processing (for example, extraction) or, where appropriate, in the case of herbal drugs, of pre-treatment reduces the levels of organism to below those stated for this category

Microbiological Quality	**Acceptance Criteria**
TAMC	NMT 5 x 10^4 CFU/g or CFU/mL
TYMC	NMT 5 x 10^2 CFU/g or CFU/mL
Bile-tolerant gram-negative bacteria	NMT 1 x 10^2 CFU/g or CFU/mL
Escherichia coli	Absence (1 g or 1 mL)
Salmonella	Absence (25 g or 25 mL)

C. Herbal medicinal products containing, for example, extracts and/or herbal drugs, with or without excipients, where it can be demonstrated that the method of processing (for example, extraction with low strength ethanol or water that is not boiling or low temperature concentration) or, in the case of herbal drugs, of pre-treatment, would not reduce the level of organisms sufficiently to reach the criteria required under B

Microbiological Quality	**Acceptance Criteria**
TAMC	NMT 5 x 10^5 CFU/g or CFU/mL
TYMC	NMT 5 x 10^4 CFU/g or CFU/mL
Bile-tolerant gram-negative bacteria	NMT 1 x 10^4 CFU/g or CFU/mL
Escherichia coli	Absence (1 g or 1 mL)
Salmonella	Absence (25 g or 25 mL)

D. Special Ph. Eur. provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU/g or CFU/mL.

Microbiological Quality	**Acceptance Criteria**
TAMC	NMT 2 x 10^4 CFU/g or CFU/mL
TYMC	NMT 2 x 10^2 CFU/g or CFU/mL
Bile-tolerant gram-negative bacteria	NMT 1 x 10^2 CFU/g or CFU/mL
Salmonella	Absence (10 g or 10 mL)
Escherichia coli	Absence (1 g or 1 mL)
Staphylococcus aureus	Absence (1 g or 1 mL)

E. Herbal Medicine for External use

Route of Administration	**TAMC (CFU/g or CFU/ml)**	**TYMC (CFU/g or CFU/ml)**	**Specified micro-organisms**
Oromucosal use Gingival use Cutaneous use Nasal use Auricular use	NMT 2 x 10^2	NMT 2 x 10^1	Absence of *Staphylococcus aureus* (1 g or 1 ml) Absence of *Pseudomonas aeruginosa* (1 g or 1 ml)
Transdermal patches (limits for one patch including adhesive layer and backing layer)	NMT 2 x 10^2	NMT 2 x 10^1	Absence of *Staphylococcus aureus* (1 patch) Absence of *Pseudomonas aeruginosa* (1 patch)

Notes:

TAMC: Total Aerobic Microbial Count

TYMC: Total Yeasts & Moulds Count

NMT : Not more than

[Reference: British Pharmacopoeia 2012]

2.5.7 CERTIFICATE OF ANALYSIS

Applicants will have to submit a certificate of analysis for each active ingredient used, which may be purchased from the supplier. This requirement is not applicable for raw materials that are processed in-house.

2.6 STABILITY DATA

General:

- The stabilityof the product is important to ensure the quality of the traditional medicines and health supplement
  (TMHS) product. This is to ensure that the product specifications are maintained throughout the shelf life of product.

- Effective from 27 Nov 2014, a shelf life of 2 years will be approved for both local and imported products. Proposed shelf life exceeding this period will have to be supported by stability study data conducted in Malaysia under zone IVb conditions (30±2 °C, 75±5%). For further information, please refer to the circular Bil (27).dlm BPFK/PPP/06/04Jld.7 Tempoh Hayat Simpanan (Shelf-Life) Bagi Produk Tradisional dan Suplemen Kesihatan (27 November 2014).

- Should the applicant wish to declare the percentage or content of the isolated compound of a standardized extract, the stability study should state the results of the assay of the isolated compound which is conducted along the proposed shelf-life. If results of the assay are not provided, the shelf life period approved will be not more than 2 years.

- The testing frequency of the stability data is as described below:

Storage condition	Testing frequency
Real time	Time 0, 3, 6, 9, 12, 18, 24 months and annually there after through
Accelerated	0, 3 and 6 months

Please refer to the ASEAN Guidelines on Stabiliy Study and Shelf Life of Traditional Medicines and Health Supplements for further details

Stability data as shown in the following example shall be submitted for evaluation.

EXAMPLE:

STABILITY DATA

PRODUCT NAME	: TABLET ABC 500MG	**BATCH NO.**	:
DOSAGE FORM	:	**STRENGTH/ VOLUME**	:
CONTAINER/ PACKAGING	:	**DATE OF REPORT**	:
MANUFACTURING DATE	: dd/mm/yy	**TEMPERATURE**	: 30 °C ± 2 °C
EXPIRY DATE	: dd/mm/yy	**RELATIVE HUMIDITY**	: 75 % ± 5%

PERIOD OF STUDY:

Tests	**Acceptance Criteria/ Specification**	**Frequency of Test, in month (*Kekerapan Ujian, bulan*)**							
		0	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Product description	Film-coated tablet, brownish in colour								
Disintegration test	NMT 30 minutes								
Microbial Contamination Test: - Total Aerobic Microbial Count - Total Yeasts & Moulds Count - Test for Specified Microorganisms	NMT 2 x 10^4 NMT 2 x 10^2 ➢ NMT 2 x 10^2 CFU of bile-tolerant gram-negative bacteria in 1g or 1ml ➢ Absence of Salmonella in 10g or 10ml ➢ Absence of Escherichia coli in 1g or 1ml ➢ Absence of Staphylococcus								

Tests	Acceptance Criteria/ Specification	Frequency of Test, in month (*Kekerapan Ujian, bulan*)							
		0	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Heavy Metal Test: - Lead - Arsenic - Mercury - Cadmium	 ≤10.0 mg/kg (≤ 10ppm) ≤5.0 mg/kg (≤ 5ppm) ≤0.5 mg/kg (≤ 0.5ppm) ≤0.3 mg/kg (≤ 0.3ppm)		NA						

Conclusion ----------

Prepared by: (signature)
Name:
Designation:
Date:

Checked by: (signature)
Name:
Designation:
Date:

Approved by: (signature)
Name:
Designation:
Date:

2.7 LABELLING REQUIREMENT

a) The following information as shown in **Table 9** shall be included in the product label. Please refer example of label for natural products approved by the Authority, as shown below.

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
1.	Product name	√	√	√	√
2.	Dosage Form	√	√	√	√
3.	Name of active ingredients, including part of plant used	√	√	√	
4.	Strength of active ingredient in weight	√	√	√	
5.	Indication	√	√		
6.	Batch number	√	√		√
7.	Manufacturing date	√	√		
8.	Expiry date	√	√		√
9.	Dosage/ Use instruction	√	√	√	
10.	Storage condition(s) - state temperature used in the stability study - state “Protect from light and moisture” (If product is not packed in moisture resistant container)	√	√	√	
11.	Registration number (MAL)	√	√		√

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
12.	Name and address of product registration holder (Example: Product Registration Holder: XXXXX)	√	√		
13.	Name and address of manufacturer (Example: Manufacturer: XXXXX)	√ At least name of town/ city and country of manufacturer	√ At least name of town/ city and country of manufacturer	√	
14.	Warning label (if applicable) e.g. Ginseng, Bee Pollen etc. as required under 2.7.2 Specific Labelling Statements/ Warning & Precautions *Note: Please refer **Appendix 9: Labelling Requirements***	√	√	√	
15.	Pack size (unit/ volume)	√	√	√	
16.	Name and strength of preservative	√	√	√	
17.	Name and content of alcohol,where present	√	√		
18.	To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine (capsule shell).	√	√		
19.	Additional statement (if applicable)	√	√	√	

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
20.	Contraindication/ Precaution (if any)	√	√	√	
21.	Security Label (Hologram)		√ #		

b) All labels and package inserts must be in *Bahasa Malaysia* or English. In additional to this, translation to another language will be allowed.

c) # In case of a product without an outer carton, the security label shall be applied onto the immediate label. The security label shall however not be applied onto the outer shrink wrap of the product.

d) Font size of the product name on the label, including alphabets and numbers, should be equal in size.

e) For a product containing 2 or more active ingredients, font size of each active ingredient that is highlighted on the inner/ outer carton must be of equal size and equal prominence (Note: this is not referring to the product name, but the statement made on the label).Justification for highlighting certain ingredients only on the product name / label must be provided and subject to approval by the Evaluation Committee.

f) Please ensure all requirements as specified below are stated on the labels and package inserts:

- State the weight per dosage form
- State the quantity/ content of active ingredients per dosage form
- For products in liquid form (syrup), content of active ingredients shall be stated as follows:

  "Each ____ml (per dosage) product contains extract of the following ingredients"

  Herb X = ___mg

  Herb Y = ___mg
- Check and correct all spelling/ grammar and translations.

g) For products meant for traditional practitioner/ physician use, please state its primary use by the related traditional physician/ practitioner on the label.

For example: 'For Chinese Physician Use Only' OR
'For Ayurvedic Practitioner Use Only'.

Example of label approved by the Authority:

This is a traditional medicine Please consult your pharmacist/ doctor before taking this product Jauhkan daripada capaian kanak-kanak *Keep out of reach of children* **Indication**: Traditionally used for women's health **Warning**: Pregnancy and breastfeeding: Insufficient reliable data Keep below 30 ° celcius Protect from light and moisture Manufacturing date: Expiry date:	KAPSUL PQR 500MG MALXXXXXXXXT 50 CAPSULE Hologram	Each Capsule (Vegetable capsule) contains : Folium XX 200mg Fructus QY 300mg Dosage : 2 capsule taken twice a day after food Marketing authorization holder: Syarikat XYZ Sdn Bhd 18, Jalan Utama 47000 Sungai Buloh Selangor Manufactured by: Syarikat ABC Sdn Bhd 3, Jalan Universiti 46730 Petaling Jaya

2.7.1 STATEMENTS TO BE STATED ON PRODUCT LABEL

The following statements shall also be stated on the product label, where applicable:

- For product with an indication "For general health/ well being" **or** "*Untuk kesihatan umum*", please state:
  - "Please consult your pharmacist / doctor before taking this product **or** *Sila merujuk kepada ahli farmasi/ doktor sebelum mengambil produk ini."*

- For product with an indication "To relieve symptoms for…. (any illness)" **or** "*untuk mengurangkan tanda-tanda/ simptom*….", please state:

- "Please consult your pharmacist/ doctor if symptoms persist/ worsen **or** *Sila merujuk kepada ahli farmasi/ doktor jika simptom berlarutan/ bertambah teruk."*

- For product with indication "To regulate menstruation/ To improve menstrual flow", please state:
  "Contraindicated in pregnant women."

- For product with indication 'To reduce body weight', please state these statements, (unless proven otherwise):
  - **"Balanced diet and regular exercise are essential."**
  - **"Safety on long term use has not been established."**

- "This is a traditional medicine/*Ini adalah ubat tradisional*." **OR** "This is a homeopathy medicine/*Ini adalah ubat homeopati."*

- Unless otherwise supported, all herbal/ traditional products label shall state the following general cautionary statement, **EXCEPT** for product with indication for men's health or product for children use only:
  "Pregnancy and breastfeeding: Insufficient reliable data"

- For product with an indication to be taken/ used **specially for women,** please refer to para **2.7.3 Cautionary Statement for Products Specially Used in Women.**

- "Keep out of reach of children & *Jauhkan daripada capaian kanak-kanak"* (in both *Bahasa Malaysia* and English).

- "Protect from light and moisture."

- Please state the storage condition according to the temperature stated in stability data.

- For products containing <u>ingredients</u> as specified below, please add the required statements:

  i) **Animal part(s):**
  "This product contains animal part(s)."

  ii) **Animal origin(s):**

Example: for active ingredients such as pearl, shell of oyster (Concha), pearl, etc
"This product contains substance(s) from animal origin."

iii) **Porcine:**
"This product contains animal part(s) (porcine/ pig)."

iv) **Alcohol:**
- "This product contains alcohol."
- Please declare the percentage of alcohol contained in the product.

- For the following dosage forms, please add this statement:
  i) **Topical preparations:** "For external use only."
  ii) **Liquids and suspensions:** "Shake well before use"

- Labels that have the picture/graphic of the herb/ animal, should not have the picture/graphic of only 1 particular active ingredient if the product formulation contains more than 1 ingredient. For multiple ingredients exceeding 2, the label should have picture/graphics of at least 2 ingredients on the label.

- Any patent/ special/specific name of active ingredient/extract stated on the label should be positioned away from name of the active ingredient in the product formulation

- For products to be sold in Kedai Rakyat 1 Malaysia (KR1M), logo of the KR1M is allowed to be printed on the label.However, the application has to be supported with the approval letter from Ministry of Economic Trade and Consumer Affairs Malaysia.

2.7.2 SPECIFIC LABELLING STATEMENTS/ WARNING & PRECAUTIONS

- Please refer **Appendix 9: Labelling Requirements** for common substance (e.g. alfalfa, bee pollen, black cohosh etc.)
- For products containing the following substances, specific cautionary statement as specified shall be included:

No.	Substance	Specific Cautionary Statement
1.	For product containing **'Anti-diarrhoea'**, please state:	**"Contraindicated in children below 1 year old" (to be stated for products with children dosing only)**
2.	For product containing **Benzyl Alcohol/ Phenylmethanol (as preservative)**, please state:	**As this preparation contains benzyl alcohol, its use shall be avoided in children under 2 years**
3.	For products containing **Camphor**:	i) The following warning shall be stated on the label: **WARNING:** **CAN CAUSE CONVULSION** **CONTRAINDICATED IN CHILDREN BELOW 2 YEARS OF AGE.** **CAUTION MUST BE EXERCISED WHEN OLDER CHILDREN ARE TREATED.** **AVOID DIRECT APPLICATION INTO NOSTRILS** **PRECAUTION:** It is dangerous to place any camphor – containing product into the nostril of children. A small amount applied this way may cause immediate collapse. - Avoid contact with the eyes. - Do not apply to wounds or damaged skin. ii) The following warning and precaution shall be stated on product leaflet:

No.	Substance	Specific Cautionary Statement
		WARNING: "This product is contraindicated in children under 2 years of age. Caution must be exercised when older children are treated." **PRECAUTION: "It is dangerous to place any camphor containing product into the nostrils of children. A small amount applied this way may cause immediate collapse."**
4.	For product containing **St. John's Wort (*Hypericum perforatum)***, please state:	**The product may interact with other medicines. Please consult a doctor/ pharmacist before using it.**
5.	For pack size meant as samples, please state:	**Sample not for sale**

2.7.3 CAUTIONARY STATEMENT FOR PRODUCTS SPECIALLY USED IN WOMEN

Special precaution shall be given to ingredients taken during pregnancy. The Authority urges pregnant women to consult their medical/ traditional health care provider prior to taking any herbal or traditional products.

Unless otherwise supported, all herbal/ traditional products label shall state the following general cautionary statement:

"Pregnancy and breastfeeding: Insufficient reliable data"

However, for products containing any ingredients as listed in the following lists, i.e. List of Prohibited Ingredients in Pregnancy and List of Restricted Ingredients in Pregnancy, the following cautionary statement shall be stated in the product label:

i) Prohibited Ingredients in Pregnancy:
"Contraindicated in pregnant women. Insufficient reliable data in breastfeeding women"

ii) Restricted Ingredients in Pregnancy:
"To be used with caution in pregnancy. Insufficient reliable data in breastfeeding women"

The list of herbs contraindicated in pregnancy is rarely in agreement as most herbal products are used in combination. The following list has been compiled based on well documented information as an aid to the industry to comply with the labelling requirement for products used during pregnancy.

Table 10: List of Prohibited Ingredients in Pregnancy

	Latin Compendium Name	Common/ Chinese Name	Remarks
A	Acorus Calamus	Calamus	
	Achillea Millefolium	Yarrow	
	Aloe barbadensis	Aloe vera	
	Angelica Archangelica	Angelica	
	Angelica sinensis	Dong Quai	When taken orally
	Artemisia Vulgaris	Mugwort	
	Arctostaphylos Uva Ursi	Uva Ursi	
	Artemisia Absinthium	Wormwood	
	Astragalus gummifer	Tragacanth	
B	Bryonia Alba	White Bryony	
	Bupleurum chinense, **Bupleurum falcatum**	Bupleurum	
C	Calendula Officinalis	Calendula	
	Calomelas	Qing fen	
	Capsella Bursa-Pastoris	Shepherd's Purse	
	Cassia Marilandica	Senna	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Caulophyllum Thalictroides	Blue Cohosh	When taken orally
	Chamaemelum nobile (Anthemis nobilis)	Roman Chamomile	When taken orally
	Chenopodium Ambrosioides	Epazote	
	Cichorium intybus	Chicory	
	Cimicifuga Racemosa	Black Cohosh	When taken orally
	Cnicus Benedictus	Blessed Thistle	
	Conium maculatum	Hemlock	
	Convalaria Majalis	Lily of the Valley	
	Cortex Cinnamomi	Rou Gui	
	Cortex Moutan	Mu Dan Pi	
	Crocus Sativus	Saffron	
	Croton tiglium	Ba dou	
E	Epimedium grandiflorum	Horny goat weed	
	Equisetum arvense L.	Horsetail	
F	Flos Carthami	Hong Hua	
	Flos Genkwa	Yuan Hua	
	Folium Sennae	Fan Xie Ye	
	Fructus Aurantii	Zhi Ke	
	Fructus Aurantii Immaturus	Zhi Shi	
G	Gentiana lutea	Gentian	
	Ginkgo Biloba	Ginkgo	
	Glycyrrhiza glabra/ Glycyrrhiza uralensis	Licorice	
H	Helleborus spp.	Hellebore	
	Hyssopus officinalis	Hissopo	
I	Iris Versicolor	Blue Flag	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Ipecac Ipecachuana	Ipecac	
J	Juglans Canadensis	Butternut	
	Juglans nigra	Black Walnut	
	Juniper (***Juniperus communis)***	Juniper Berries	
L	Leonurus Cardiaca	Motherwort	
M	Marrubium Vulgare	Horehound	
	Mentha Pulegium	Pennyroyal	When used orally or topically
	Monarda didyma	Bee Balm	
	Moschus berezovskii Flerov, Moschus sifanicus Przewalski, Moschus moschferus Linnaeus (Moschus)	She xiang / musk	
	Mylabris / Radix Sacchari Arundinacei	Ban Mao	
N	Natrii Sulfas	Mang Xiao	
	Nepeta cataria	Catnip	
	Nigella sativa	Black seed/ black cumin	
O	**Oenothera biennis** *L.*	Evening Primrose	
P	Panax Ginseng, Panax Quinquefolius	Ginseng	
	Passiflora incarnata *L.*	Passion Flower	When taken orally
	Petroselinum Crispum	Parsley	
	Podophyllum Peltatum	American Mandrake	
	Polygala Senega	Senega Snakeroot	
R	Radix Euphorbiae Pekinensis	Jing Da Ji	
	Radix et Rhizoma Rhei	Da Huang	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Radix Kansui/ Radix Euphorbiae Kansui	Gan Sui	
	Radix Phytolaccae	Shang Lu	
	Rhizoma Sparganii	San Leng	
	Resina Toxicodendri/ Resina Rhois Praeparata	Gan Qi	
	Rhizome et Radix Veratri	Li Lu	
	Radix Achyranthis Bidentatae	Niu Xi	
	Rhizome Chuanxiong	Chuan Xiong	
	Rhizome Curcumae Longae	Jiang Huang	
	Rhamnus Purshiana	Cascara Sagrada	
	Rhamnus Frangula	Buckthorn	
	Rheum Palmatum	Rhubarb Root	
	Ruta Graveolens	Rue	
	Rheum Australe	Turkey Rhubarb	
S	Sanguinaria Canadensis	Bloodroot	
	Semen Pharbitidis	Qian Niu Zi	
	Semen Strychni	Ma Qian Zi	
	Semen Persicae	Tao Ren	
	Serenoa repens	Saw Palmetto	When taken orally
T	Tabebuia impetiginosa	Pay D' Arco	When taken orally
	Tanacetum parthenium	Feverfew	
	Tanacetum Vulgare	Tansy	
	Thuja Occidentalis	Arbor Vitae	
	Turnera Diffusa	Damiana	
	Trigonella foenum-graecum	Fenugreek	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Trillium Erectum	Bethroot	
	Tussilago Farfara	Coltsfoot	
V	Venenum Bufonis	Chan Su	
	Viscum Album	European Mistletoe	
W	Whitmania pigra Whitman, Hirudo nipponica Whitman, Whitmania acranulata Whitman (Hirudo)	Shui Zhi	
X	Xanthoxylum Americanum	Prickley Ash	

Note: The list is not to be exhaustive and will be reviewed from time to time'.

Table 11: Restricted in Pregnancy

No.	Latin Compendium Name	Common/ Chinese Name	Remarks
1.	Zingiber Officinalis	Ginger	> 1g dry weight/day

Note: The list is not to be exhaustive and will be reviewed from time to time'.

2.7.4 PROHIBITED VISUAL/ GRAPHICS/ STATEMENT ON PACKAGING MATERIAL (LABEL, BOX, PACKAGE INSERT OR CONSUMER MEDICATION INFORMATION LEAFLET)

General requirement:

The graphics printed on outer and inner label has to be standardized to avoid confusion to the customers.

Table 12:

No.	Subject Matter	Example(s)	Notes
1.	Marketing strategy	**Example:** "Money back guarantee" "Buy 1 free 1" " Backed by RM5 million product Liability Insurance"	Such statements are prohibited on labels, as per Medicines (Advertisement and Sale) Act 1956 guideline requirements
2.	Usage guide which promotes use of other product(s)	**Example:** "After consumption of this product (Product A), for better results, it is recommended to take Product B"	Not allowed
3.	Consumer testimonial		Prohibited on product label
4.	Clinical Trial results or any information on clinical trial done on	Example:	Such statements are prohibited on labels, as per Medicines

No.	Subject Matter	Example(s)	Notes
	product	"Clinically Tested" "Randomized Double Blind Placebo Control Clinical Study"	(Advertisement and Sale) Act 1956 requirement
5.	Opinion/ Name of prominent figure(s)/ professionals on product or its active ingredient/ content	**Example:** Opinion of product/ formulation inventor	Prohibited on product label
6.	Label design (graphic and color) similar to labels from another company		Prohibited on product label
7.	Statement on herbal origin	**Example:** Source from the Mountains of Alps	Allowed if proven true

No.	Subject Matter	Example(s)	Notes
8.	Introduction/ description of founder/ manufacturer/ professionals i.e. elaboration on the identity of the founder or manufacturer	**Example:** "Manufacturer ABC is a GMP certified manufacturer and has manufactured many products." "Founder Dr. ABC is a world renowned surgeon."	Prohibited on product label
9.	Logo with certification	**Example:** SIRIM/ ISO / GMP /HACCP	Prohibited on product label because certification renewal is on a yearly basis
10.	Name/ Statement / Logo/ registered trademark which does not satisfy the specifications of the Traditional Unit	**Example:** "Dr.ABC's Formula" "Nothing like it"	Prohibited on product label
11.	Patency claim/ Patency number/ Special technique used/ superiority in ingredients (Example: capsule coat)	**Example:** Patented technique	Allowed if proven true
12.	Nutritional claims with analysis certificate attached	**Example:** Calorie, Fat, Protein and others	Prohibited on product label This is not a food supplement.

No.	Subject Matter	Example(s)	Notes
13.	Graphics or picture of internal organs	**Example:** Kidney, Heart, Nerves.	Prohibited on product label
14.	Photograph of celebrities	**Example:** Artiste, Sports person(s), Politician	Prohibited on product label
15.	Gender symbol (male or female)	(♀ and / or ♂)	Prohibited on product label
16.	Indecent photographs/ pornography		Prohibited on product label
17.	Graphics which are incoherent with the indication	**Example:** - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose.	Prohibited on product label
18.	Highlighting unnecessary body parts	**Example:** Indication is for general health but graphics on label highlights male and female sexual organ parts	Prohibited on product label

No.	Subject Matter	Example(s)	Notes
19.	Graphics of plants or animal which may cause confusion	**Example:** Radix Ginseng which is improvised as a male sexual organ	Prohibited on product label
20.	Statement on sugars in traditional products	**Example:** This product contains no added sugar	Allowable on product label provided the product contains no fructose, glucose, sucrose or other kind of sugars with a potential to affect diabetics are not included in the formulation
21.	Negative statements	**Example:** **-**No active ingredient -No gluten, yeast, etc	Prohibited on product label
22.	Other statements	**Example:** - This product is blended with premium quality - Certified chemical residue free	Prohibited on product label

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time*
2. *The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual.*

2.8 PARTICULARS OF PACKING

- The maximum pack size allowed for all dosage forms is based on the daily dosing for a quantity not exceeding six (6) months usage.

- Packing particulars to the listing of packing as follow:

  C1: Pack size and fill details by weight, or volume or quantity.

  C2: Container type

  C3: Barcode/ serial number (optional)

  C4: Recommended distributor's price (optional)

  C5: Recommended retail price (optional)

- Measuring spoon/ device must be provided for all products in bulk powder form unless it is for physician use only.

3. PRODUCT SPECIFIC REQUIREMENTS

3.1 FOOT PATCHES

A foot patch which contains herbs with a health claim needs to be registered with the Authority.

Summary of registration for foot patches is described below:

a) Product Indication

- Traditionally used for
  a) General health;
  b) Promoting blood circulation;
  c) Relieve fatigue.

- If there are other indications other than those mentioned above, applicant is required to submit clinical study data to support the proposed indication.

b) Active ingredient/ Excipient

- May only contain active ingredient which are classified under the category of Natural Products (Traditional).
- Pharmaceutical ingredients which have dual-function as an active ingredient and excipient, e.g. Vitamin C can be used as excipient.
- However the maximum allowable amount for the excipient in the traditional product has to follow the pharmacopoeia limits established. If for example in this case the amount of Vitamin C is more than 0.1%, the product shall be classified as an OTC product. The product will then have to fulfill the requirement for the registration of an OTC product.

c) Certificate of Analysis for Finished Product

- It is required with at least one batch data for registration.

d) Certificate For Free Sale

- CFS from the regulatory authority of the country of origin of the product depending on the product classification of that product in that country.

e) Good Manufacturing Practice

- GMP from the governmental issuing body declaring manufacturer adherence to GMP/ ISO or other standards depending on the classification of the product in the country of origin.

3.2 HERBAL TEA

Please refer to Circular Ref: (19)dlm.BPFK/PPP/01/03 Jld.3. Pekeliling Kriteria Baru Pengkelasan Produk Food-Drug Interphase (FDI).

3.3 HOMEOPATHIC PRODUCTS

The following guidance notes are published as First Edition in October 2010 and the latest revision is on October 2012.

This guidance notes serve as an additional reference on the requirements for the registration of homeopathic products. Other aspects of registration requirements are covered in the Drug Registration Guidance Document. Applicants for product registration are also requested to refer to the latest edition on the Guidelines of Good Manufacturing Practices (GMP) for Traditional Medicines.

2nd Revision

Acknowledgements

The National Pharmaceutical Regulatory Division acknowledges its indebtedness to the Malaysia Homeopathic Medical Council and the Traditional & Complementary Medicine Division, Ministry of Health who provided comments and advice during the preparation of these guidelines.

Outline:

1. Introduction
2. Exemptions
3. Preparations not considered by the Authority for registration
4. Ingredients
5. Quality
6. Good Manufacturing Practice
7. Labelling
8. Indications for use

Attachments:

- Attachment 1: List of exempted Single Homeopathic Potentised Dilutions
- Attachment 2: Negative List
- Attachment 3: List of acceptable references
- Attachment 4: List of endangered animal species/ protected wildlife

1. INTRODUCTION

Regulation 7(1)(a) of the Control of Drugs and Cosmetics Regulations (CDCR) 1984 requires all products to be registered with the Authority prior to being manufactured, sold, supplied, imported or possessed for sale, unless the product is exempted under the specific provisions of the regulations.

Under Regulation 2, CDCR 1984, "**Homeopathic medicine**" means any pharmaceutical dosage form used in the homeopathic therapeutic in which diseases are treated by the use of minute amounts of such substances which are capable of producing in healthy persons symptoms similar to those of the disease being treated. This would include preparations that are to be chewed, sucked, swallowed whole and applied topically.

Applicants are reminded that it is their responsibility to ensure that their products comply with these regulations and also other related legislations namely:

(i) Sale of Drugs Act 1952

(ii) Dangerous Drugs Act 1952

(iii) Poisons Act 1952

(iv) Medicines (Advertisement & Sale) Act 1956

(v) Wildlife Protection Act 1972

2. EXEMPTION

All homeopathic products are registrable under the *Control of Drugs and Cosmetics Regulations 1984*. Exemption to this are:

i) single homeopathic potentised dilution;

ii) extemporaneous preparation for an individual patient by a registered/ licensed homeopathic practitioner;

iii) All Mother Tinctures;

iv) Unmedicated sugar globules and tablets.

3. PREPARATION NOT CONSIDERED BY THE AUTHORITY FOR REGISTRATION

The Authority will only register homeopathic products used for oral administration, nasal or mouth sprays and external application only. The following dosage forms will not be considered for registration.

- Sterile preparations such as eye-drops and injectables;
- Suppositories and vaginal tablets;
- Transdermal patch;
- Sublingual preparations;
- Preparation in combination with non-homeopathic active ingredient, such as vitamins, minerals and herbs.
- Preparations containing substance listed in the Poison List (except **Attachment 1**).

4. INGREDIENTS

Homeopathic products are prepared from natural or synthetic sources that are referenced in pharmacopoeia monographs or other recognized documents. Not considering imponderable, the source materials for homeopathic medicines may consist of the following:

- Plant material such as: roots, stems, leaves, flowers, bark, pollen, lichen, moss, ferns and algae;
- Microorganisms such as: fungi, and plant parasites;
- Animal materials such as: whole animals, animal organs, tissues, secretions;
- Minerals and chemicals.

For each medicinal ingredient, a copy of the monograph from the pharmacopoeia to which the applicant attests must be provided. Also for homeopathic medicines with a specific claim, it must be supported by the same level of evidence as for traditional products.

Products containing a combination of homeopathic and non-homeopathic medicinal ingredient will not be evaluated as a homeopathic product.

4.1 POSITIVE LIST

Homeopathic medicinal ingredients are allowed as multi ingredient in homeopathic products and the active ingredient must be documented in a monograph as a homeopathic medicinal ingredient as stated in the current edition of Homeopathic Pharmacopoeias recognized by the Authority listed in **Attachment 3**.

Homeopathic products are allowed to be registered when the homeopathic medicinal ingredients used in their products are more than 2C or 4X.

4.2 NEGATIVE LIST

Homeopathic products containing single or multiple ingredients in **Attachment 2** and **Attachment 4** will not be registered by the Authority.

4.3 LIMIT OF HOMEOPATHIC INGREDIENTS IN MULTI INGREDIENT HOMEOPATHIC PRODUCTS

Homeopathic Products are allowed to contain a maximum of 12 potentised single homeopathic dilutions.

5. QUALITY

A certificate of analysis (CoA) for raw material potentised dilution and finished product must be provided as proof on the dilution used.

6. GOOD MANUFACTURING PRACTICE

The requirements for Good Manufacturing Practice of the premises as outlined in the Guidelines on Good Manufacturing Practice (GMP) for Traditional Medicines apply to all homeopathic products.

7. LABELLING

The labelling of homeopathic products is the same as for traditional products in DRGD with the following additional requirements:

On the label of this homeopathic product:

a) The word ‘homeopathic product’, ‘homeopathic medicine’, ‘homeopathic preparation’, ‘homeopathic remedy’ (either one) - must appear on the innermost label of the container.

b) The scientific name or common name of the active ingredient.
c) Potency and type of scale use.
d) Declare the percentage of alcohol contained in the product.

8. INDICATIONS FOR USE

Indications allowed for homeopathic product is the same as those allowed for traditional products in the DRGD.

Recommended use or indications for specific claims must be supported by evidence for the multi ingredient homeopathic products.

No indication will be allowed for single homeopathic potentised dilution in the form of raw material and finished homeopathic product. No indications are also allowed for mother tinctures.

ATTACHMENTS

Attachment 1:

List of "Single Homeopathic Potentised Dilution (2C or 4X or 1:10000)" exempted from the Poisons List.

No.	Ingredient
1.	Aconite
2.	Amyl nitrite
3.	Antimony
4.	Apomorphine
5.	Arsenic
6.	Barium
7.	Belladonna
8.	Bismuth
9.	Boric Acid
10.	Caffeine

No.	Ingredient
11.	Cantharidin
12.	Colchinine
13.	Coniine
14.	Creosote
15.	Curare
16.	Digitalis
17.	Ephedra
18.	Ergot
19.	Gelsemium
20.	Hydrogen Cyanide
21.	Hyoscine
22.	Iodine
23.	Jaborandi
24.	Lead Acetate
25.	Lobelia Inflata
26.	Mercury
27.	Morphine
28.	Nicotine
29.	Nux Vomica
30.	Phosphorus
31.	Physostigmine
32.	Picric Acid
33.	Piper Methysticum (Kava-kava)
34.	Quebracho
35.	Quinine
36.	Radium
37.	Rauwolfia
38.	Sabadilla

No.	Ingredient
39.	**Santonin**
40.	**Sparteine**
41.	**Stavesacre**
42.	**Strophanthus**
43.	**Thallium**
44.	**Veratrum**
45.	**Vinca**
46.	**Yohimba**

Attachment 2:

Negative List

NO.	SUBSTANCES
1.	**Mother tincture of Narcotics**
	Homeopathic Products
	Cannabis
	Cocainum
	Cocainum muriaticum
	Coca leaves
	Narceinum
	Opium
2.	**Mother tincture of Radiopharmaceuticals**
	Uranium
	X-ray
3.	**Mother tincture of Animal materials: Nosodes, toxins and blood products**
4.	**Mother tincture of human or human organ**
5.	**Mother tincture of Bacteria**
6.	**Mother tincture of Viruses**

Attachment 3:

Homeopathic Pharmacopoeia from the Following Countries Will Be Accepted as References

NO.	COUNTRIES
1.	Germany (GHP)
2.	Britain
3.	France (Phf)
4.	USA (HPUS)
5.	Pakistan
6.	India (HPI)
7.	European Pharmacopoeia

Attachment 4:

List of Endangered Animal Species/ Protected Wildlife

As listed in the Wildlife Protection Act.

Notes:

These lists are not exhaustive and will be amended from time to time as and when the need arises

REFERENCES

a) List of Ingredients Prohibited and Restricted in Pregnancy

1. Benchmarks for training in traditional Chinese medicine (WHO)
2. American Pregnancy Association
3. Natural Standards
4. Health Canada
5. TCM Discovery (Contraindication of Chinese Medicinal Herbs)
6. Motherlove Herbal Company (Herbs to avoid while Pregnant)
7. Green Earth Herbs (Herbs Contraindicated in Pregnancy)
8. Home. Caregroup.Org (Herbs during Pregnancy and Lactation)

b) Homeopathic Products:

1. Safety Issues in the Preparation of Homeopathic Medicines, World Health Organization, 2009.

APPENDIX 6 : GUIDELINE ON REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

(Version 2.3)

Outline:

1. INTRODUCTION

1.1. A significant part of the quality of a finished product is dependent on the quality of the Active Pharmaceutical ingredients (APIs) used for its formulation. Thus, a proper system of qualification of suppliers is necessary to ensure a constant sourcing of APIs of appropriate quality and to safeguard the public health interests. This will be done through standardized quality assessment and inspection procedures.

1.2. The National Pharmaceutical Regulatory Division (NPRA) under the purview of the Ministry of Health Malaysia has introduced mandatory control of APIs as part of the requirements in the product registration application.

1.3. The implementation began with voluntary submission for New Drug Products in April 2011 and followed by;

- **Phase 1** - New Drug Products (January 2012)

- **Phase 2** - Scheduled Poison

a) New Application (Generic Product):-

i. Parenteral Dosage Form : 1July 2014
ii. Oral Dosage Form : 1July 2016
iii. Others : 1 July 2018

b) Registered Product (Pharmaceutical products containing Scheduled Poison):-
All Dosage Form :Expire on 1 January 2020 onwards

* API Information must be submitted at least **one year before the expiry date.**

Reference:

i) Bil (12) dlm BPFK/PPP/01/03 Jld1 17 March 2011
ii) BPFK/PPP/07/25 (7) 16 January 2014
iii) Bil (11) dlm BPFK/PPP/01/03 Jld3 27 June 2014

- **Phase 3** - Generic Product NOT containing Scheduled Poison (to be determined)

1.4 The procedure for control of APIs established by the NPRA is based on the following principles:

- A general understanding of the production and quality control activities of the manufacturer;
- Assessment of APIs data and information, including changes and variations, submitted by the product registration holder (PRH)/API Manufacturer. These data should include the manufacturing process, material specifications and test data and results;
- Assessment of the manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key raw materials and APIs during and after purification through compliance with Good Manufacturing Practice(GMP);
- Random sampling and testing of APIs (post-marketing surveillance);
- Handling of complaints and recalls; and
- Monitoring of complaints from other agencies and countries.

1.5. This guideline is intended to provide guidance regarding the requirements to be included for APIs in the quality part of the product dossier (Part II-S).

2. DEFINITION

2.1 DEFINITION OF ACTIVE PHARMACEUTICAL INGREDIENT (API)

- Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body (WHO Technical Report Series No.970,2012).

2.2 CLASSIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENT (API)

API classification can be divided into:

- Inorganic substances;
- Organic substances (isolated from materials of animal or human origin); and
- Organic substances (synthetic or semi-synthetic or isolated from herbal sources or micro-organisms).

3. SCOPE

3.1. This Guideline encompasses the final APIs of new products for registration and current/exist in registered products. This is applicable to all pharmaceutical products (excluding traditional products, veterinary products, and health supplement products) both locally manufactured and imported.

3.2. Biological active substances and immunological active substances are excluded from the scope of this Guideline. Please refer to relevant guidelines available for Biologics.

3.3. APIs used in products for export only (FEO) are exempted from the requirement for submission of the Drug Master File (DMF) and Certification of Suitability (CEP) in the product application.

3.4. Premixing of API is part of the product manufacturing process; therefore information on premixed API should be submitted under Part II-P. Submission for Part II-S solely includes information on API only.

3.5. Separate registration of the API is not requirement for the purpose of product registration. However, the required technical documentation pertaining to each API should be submitted with the new product registration application.

3.6. Assessment of an API will be performed once submission of a new product registration application has been done.

3.7. Assessment of an API will also be performed for a registered product prior to a product renewal application (as stated in item 1.3).

4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION

4.1 HOW TO SUBMIT

The API(s) information can be submitted to NPRA through one of the following three options:

- Option 1: Drug Master File (DMF) procedure; or
- Option 2: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 3: Full details of "Part II-S ACTD" in the Product Dossier

Note:

- The PRH should attach:
  i) a cover letter (clearly indicating the product name, API name, option for API submission) and
  ii) API submission checklist
  http://npra.moh.gov.my/index.php/guidelines-central

- The PRH shall submit Part II-S ACTD as part of product application. In cases where required information as per ACTD is not available, the DMF is accepted.

- The DMF must be submitted via electronic copy (CD) directly to the NPRA to maintain confidentiality of the contents.

- The NPRA may accept a CEP issued by European Directorate for the Quality of Medicine (EDQM) in lieu of the DMF of an API.

4.2 REQUIRED INFORMATION

4.2.1 Documents required for each option of API Information submission are summarized as in table 1:

Table 1:
Summary of documents required for API Information Submission:

Option	Documents required
Option 1 (DMF)	• Part II-S ACTD via the online system (Open Part only) • DMF (*See Section 5 for details*) • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and • Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).
Option 2 (CEP)	• Part II-S ACTD via the online system (as deemed appropriate) • CEP (*See Section 6 for details*); and, • Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).
Option 3 (Full ACTD)	• Full details of Part II-S ACTD via the online system.(See Section 7 for details) • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and, • Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).

*GMP certificates for **ALL** manufacturers involved in manufacturing process of API.

4.2.1 Separate API information must be provided for <u>each</u> API for:

i. Finished product contains more than one API
ii. API from different manufacturing site
iii. API from different synthesis route

4.2.2 In order to gain approval for an API;

- The data should be sufficient to justify the specifications and testing of the API (including validated analytical methods);
- The information should confirm the identity and stability of the API by providing appropriate structure elucidation and stability studies; and
- The control of the API manufacturing process as well as the ability to produce an API with reproducible physical properties and impurity profiles should be demonstrated.

4.2.3 The NPRA reserves the right to request for **any** additional information about the API when deemed appropriate.

4.3 OTHER CONSIDERATIONS

In the spirit of harmonisation of regulatory activities and optimisation of efficient assessment, The NPRA may take into consideration the evaluation of relevant APIs by the regulatory authorities of the reference countries (Australia, Japan, France, Switzerland, United Kingdom, Canada, Sweden, and the United State of America) and, other PIC/S countries and World Health Organization (WHO).

4.4 PROCESSING FEE

Not required as the API application is already incorporated in the application for product registration.

5. OPTION 1 :DRUG MASTER FILE (DMF)

5.1. The Drug Master File (DMF) is a document that may used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

5.2. The DMF submitted to the NPRA should contain the information as required under sections listed in Part II-S ACTD.

5.3. DMF is generally created to allow an authorized party other than the holder of the DMF to refer the DMF without disclosing the contents of the file to any other party.

5.4. The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR) / ACTD provide details on the information to be included in the API sections of an application dossier.

5.5. Where the API and the finished product are manufactured by the same manufacturer, information on the production, quality control and stability of the API may be submitted as part of the dossier for the finished product (ACTD) rather than in a separate DMF. However, the company is not precluded from submitting a DMF for the API.

5.6. The DMF is divided into two parts, namely the Open (or PRH's) part and the Closed (or restricted) part.

5.7 The documents required for an application making a reference to a DMF are as follows:

- **From the PRH:**
  - Open part of the DMF, as part of the submitted product dossier (the open part contains most of the information in Part II-S (ACTD) - i.e. sections S1, S2.1 and S3 to S7);
    - S1 General Information
      1.1 Nomenclature
      1.2 Structure
      1.3 General Properties

- S2 Manufacture
  - 2.1 Manufacture(s)/Site of Manufacture
  - **ALL** manufacturers involved in manufacturing process of API.

- S3 Characterisation
  - 3.1 Elucidation of Structure and other Characteristics
  - 3.2 Impurities

- S4 Control of API/Drug Substance

  From API manufacturer:
  - 4.1 Specification of API
  - 4.2 Analytical Procedures
  - 4.3 Validation of Analytical Procedures
  - 4.4 Batch Analysis-minimum three batches

  Certificate of Analysis (COA)-minimum two batches.
  - 4.5 Justification of Specification

  From Finished product manufacturer:
  - 4.1 Specification of API

  Certificate of Analysis (COA)-minimum two batches.

- S5 Reference Standards or Materials
  (from API manufacturer AND finished product manufacturer).

- S6 Container Closure System

- S7 Stability

- **From the API Manufacturer:**
  - The Complete DMF (open part AND closed part); S1-S7.
    The closed part contains the confidential information in section Part II-S ACTD - i.e. section S2);
    - S2 Manufacture
      - 2.1 Manufacture(s)/ Site of Manufacture
      - 2.2 Description of Manufacturing Process and Process Controls
      - 2.3 Control of Materials
      - 2.4 Controls of Critical Steps and Intermediates
      - 2.5 Process Validation and/or Evaluation
      - 2.6 Manufacturing Process Development

- An original Letter of Access.
  The Letter of Access from API Manufacturer/ holder of the DMF authorizes the NPRA to refer to the DMF, in support of the application for a finished product. Thus, the Letter of Access must state the following:

  - The name of the finished product (product name, dosage form and product strength) to be registered;
  - The PRH responsible for finished product registration; and,
  - A declaration that both the PRH and the NPRA shall be notified of any change in the API specification or in the manufacturing process that will likely affect the product's quality or safety.

The PRH is responsible to ensure that the complete DMF (i.e. both the *Open part* and the *closed part*) submitted to NPRA directly by the API Manufacturer.

5.8. The API Manufacturer may submit the DMF via electronic copy (CD) directly to the NPRA to maintain confidentiality of the contents. The information contained in the closed part of the DMF will be regarded as confidential and will only be evaluated in support of the applications mentioned in the Letter of Access. The confidential information will not be disclosed to any third party without a written authorization from the API Manufacturer.

5.9. Separate DMF must be provided for each API for:

i. Finished product contains more than one API
ii. API from different manufacturing site
iii. API from different synthesis route

5.10. Upon receipt of the DMF, a BPFK/NPRA DMF number will be assigned to the application for product registration. For future correspondences, the PRH and the API Manufacturer should make a reference to the BPFK/NPRA DMF number. The NPRA will directly contact API Manufacturer for any correspondence pertaining to API information in closed part. The PRH is required to include a copy of the API Manufacturer's Letter of Access in the application.

5.11. API Manufacturer is responsible to maintain and update the DMF. The PRH should file a variation once they are notified with the changes to the DMF.

5.12. API Manufacturer Obligations:

- Any change or addition, including a change in authorization related to specific PRH, shall be submitted to the NPRA in duplicate and adequately cross-referenced to previous submission(s). The reference should include the date(s), volume(s), section(s), and/or page number(s) affected.
- Should any change to a DMF is necessary, the API Manufacturer shall notify each affected PRH who has referenced the DMF of the pertinent change. Such notice should be provided well before making the change in order to permit the PRH to supplement or amend any affected application(s) as needed.

5.13. The DMF is not required for common inorganic salts (for example, sodium chloride, and other common electrolytes) used and regarded as API in products such as injections and dialysis solutions, and simple organic compounds available commercially in high purity (for example, natural occurring organic acids and their salts, including ascorbic acid and sodium citrate, and simple mono- and disaccharides such as glucose and sucrose). Although a DMF is not required for these API, evidence needs to be submitted by the PRH that the API is obtained from a reliable source and consistently comply with the applicable pharmacopoeial specifications. Any non-pharmacopoeial specifications need to be assessed by the NPRA to determine their appropriateness and adequacy to ensure the quality of the API.

5.14. Where a DMF is submitted for an API controlled according to a pharmacopoeia monograph, the DMF should include a discussion of the potential impurities most likely to arise during synthesis using the actual manufacturing process described in the DMF together with evidence that these impurities are adequately controlled by the test procedures described in the pharmacopoeia monograph. Where particular impurities found in the substance are not listed in the monograph, a justification (including toxicological data, if appropriate) should be provided. Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3Aand Q3C guidelines.

6. OPTION 2 : CERTIFICATES OF SUITABILITY (CEP)

6.1. CEP stands for certification of suitability of European Pharmacopoeia monographs/Certificate of Pharmacopoeia.

6.2. The CEP is a document that used to demonstrate the purity of a given API produced by a given manufacturer is suitably controlled by the relevant monograph(s) of the European Pharmacopoeia. By demonstrating grant a CEP for given API, the suppliers of the API can prove such suitability to their pharmaceutical industry clients and the NPRA.

6.3. The PRH should submit a copy of the most current CEP including all annexes, together with the following:

- A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision and
- A declaration from the API Manufacturer that the PRH and the NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety.

Note: *All such written statements must state the name of the finished product (product name, dosage form and product strength) to be registered and the PRH shall responsible for finished product registration.*

6.4. Along with the CEP, the PRH should submit the following information in the product dossier.

- ***S1 General Information***
- ***S.1.1 Nomenclature***
- ***S.1.2 Structure***

- ***S.1.3 General properties*** - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section.

- ***S2 Manufacture***

  2.1 Manufacture(s) / Site of Manufacture

  - ALL manufacturers involved in manufacturing process of API.

  2.5 Process Validation and/or Evaluation

  In the case of sterile APIs, data on the sterilization process of the API, including validation data, should be included in the product dossier(S 2.5).

- ***S.3.1Elucidation of structure and other characteristics***- studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.

- ***S.4.1 Specification***

  i. The specification from the API manufacturer
  ii. The specification of the finished product manufacturer

  Note: Specification should include all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that were not controlled in the CEP and Ph.Eur. monograph, such as polymorphs, impurities and/or particle size distribution.

- ***S.4.2/ S.4.3 Analytical procedures and validation***– for any methods used by the API manufacturer and in addition to those in the CEP and Ph.Eur. monograph.

- ***S.4.4 Batch analysis***

  i. Results from minimum three batches of at least pilot scale, demonstrating compliance with Ph. Eur. monograph and including any additional tests/limits listed on the CEP (e.g. residual solvents, additional impurity tests).
  ii. Certificate of Analysis (COA)-minimum two batches each from **both** API manufacturer and finished product manufacturer.

- ***S.5 Reference standards or materials*** – information on reference standards from **both** API manufacturer and finished product manufacturer.

- ***S.6 Container closure system***- specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container closure system and the PRH declares to use the same container closure system.

- ***S.7 Stability***
  i. Proposed retest period, or shelf life
  ii. Proposed storage condition (temperature and packaging)
  iii. Stability data
  Exception: where the CEP specifies a re-test period that is the same as or of longer duration, and storage conditions which are the same or higher temperature and humidity as proposed by the PRH.

6.5 The NPRA reserves the right to request for any additional information about the API when deemed appropriate.

6.6 The PRH is responsible to submit the latest CEP updates, with annexes, as soon as it is available from the API Manufacturer.

6.7 Separate CEP must be provided for each API for:
i. Finished product contains more than one API
ii. API from different manufacturing site
iii. API from different synthesis route

7. OPTION 3 : FULL DETAILS OF "PART II-S : ACTD" IN THE PRODUCT DOSSIER

7.1. Information on the API sections (ACTD Part II-S: S1-S7),including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the product dossier.

7.2. The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR) / ACTD provide details on the information to be included in the API sections of an application dossier.

- S1 General Information
  - 1.1 Nomenclature
  - 1.2 Structure
  - 1.3 General Properties

- S2 Manufacture
  - 2.1 Manufacture(s)/ Site of Manufacture
  - **- ALL** manufacturers involved in manufacturing process of API.
  - 2.2 Description of Manufacturing Process and Process Controls
  - 2.3 Control of Materials
  - 2.4 Controls of Critical Steps and Intermediates
  - 2.5 Process Validation and/or Evaluation
  - 2.6 Manufacturing Process Development

- S3 Characterisation
  - 3.1 Elucidation of Structure and other Characteristics
  - 3.2 Impurities

- S4 Control of API/Drug Substance
  (submission should include information from API manufacturer AND finished product manufacturer).
  - 4.1 Specification of API
  - 4.2 Analytical Procedures
  - 4.3 Validation of Analytical Procedures
  - 4.4 Batch Analysis-minimum three batches,
  Certificate of Analysis (COA)-minimum two batches.
  - 4.5 Justification of Specification

- S5 Reference Standards or Materials
  (from API manufacturer AND finished product manufacturer).

- S6 Container Closure System

- S7 Stability

7.3. Separate dossier (Part II-S : ACTD) must be provided for each API for:

i. Finished product contains more than one API
ii. API from different manufacturing site
iii. API from different synthesis route

7.4. Where the API and the finished product are manufactured by the same company, information on the production, quality control and stability of the API may be submitted as part of the dossier for the finished product (ACTD) rather than in a separate DMF. However, the company is not precluded from submitting a DMF for the API.

8. STABILITY DATA OF API

8.1. Current stability test data for an API should be provided, for at least 3 primary batches. These data should include:

- The type of stability study and stability protocol
- API name, API manufacturer, packaging particular
- Batch details (e.g., batch number, date of manufacture, batch size
- The general test methodology (e.g., duration of study, storage conditions of temperature and humidity, list of relevant testing, testing frequency, etc.);
- Proposed retest period or shelf-life;
- Proposed storage condition;

  A storage temperature must be specified, e.g:
  - Do not store above 25 °C
  - Do not store above 30 °C
  - Store in a refrigerator (2 °C to 8 °C)
  - Store in freezer

  Other special storage condition, e.g:
  - Protect from light
  - Protect from moisture

- The analytical test methods (e.g., assay method of quantitation, determination of degradation products, moisture etc) with reference;
- Validation of test methods;
- Specification;
- Results of tests; and,
- Conclusions.

8.2. In circumstances where an API retest period has not been established and complete long term stability data is not available at the time of submission, the <u>minimum</u> stability data required are as follows:

- At least 12 months of long term data <u>and</u> 6 months of accelerated data on at least 3primary batches of the API ;
- The batches should be at least pilot scale-sized and manufactured by a method that simulates the final commercial process.

** In view of this, the re-test date may be extended beyond the end of long term studies which can be extrapolated not more than 12 months covered by the long term data.*

A letter of commitment (to provide complete long term stability data when study is completed/when requested) should be submitted.

8.3. Where the API is sourced from multiple sites or from different route of synthesis, stability data from each source should be provided.

8.4. The NPRA may request for additional stability data if deemed necessary for the evaluation of the application.

8.5. Stability data is not required where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the PRH.

9. MANUFACTURINGSITE INSPECTION

9.1. Depending on the outcome of the evaluation of the API dossier, a risk-based approach will be used in the planning of manufacturing site inspections; the approach will take into account the type of APIs as well as the outcome, results and reports of inspections conducted by other regulatory authorities or competent organizations.

9.2. The NPRA shall plan and coordinate the performance of inspections at the manufacturing site of the API and that of the key intermediate (if relevant) to assess compliance with the relevant sections of the relevant GMP Guidelines, and to compare the technical information on the manufacturing process given in the API dossier with the manufacturing process actually carried out on the manufacturing site.

9.3. All such inspections shall be performed by inspectors deemed to possess sufficient qualifications and experience. In order to perform such inspections, the inspectors have to be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in the area of GMP. Such inspectors shall perform the inspections and report on its findings in accordance with established Standard Operating Procedures (SOPs) so as to ensure a standard harmonized approach.

10. MAINTENANCE OF APPROVAL STATUS

10.1. Manufacturer of finished product should establish a mechanism by which manufacturers/suppliers of an API shall provide information on any changes (i.e., variations) in manufacture and control that may have impact on the safety, purity and quality of the API. The PRH is responsible to provide the NPRA with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have an impact on the safety, purity and quality of the API that has been previously approved. For those APIs approved by the NPRA, an evaluation of such variations shall be performed with accordance to the Malaysian Variation Guidelines (MVG).

10.2. Random samples of APIs supplied to manufacturers of finished products may be taken for independent testing if needed. Certificates of Analysis released by the API Manufacturer as well as specifications for test methods shall be provided by the API Manufacturer or the PRH to the NPRA for review upon request. In the event of failure to meet the established criteria for testing, the NPRA shall proceed to investigate and communicate this problem to the manufacturer concerned.

10.3. The NPRA may conduct a re-evaluation of the APIs at a 5 years interval. If, as a result of this re-evaluation, found that an API and/or specified manufacturing site(s) no longer complies with the recommended standards, such APIs and manufacturing sites will be removed from the approved list. Prior notice to the PRH and API Manufacturer shall be issued from the NPRA regarding such decision.

10.4. Re-evaluation may also be done in any situation deemed necessary, including the following:

- If any omissions by the manufacturer in the initial assessment procedure or during the follow-up activities is evident in relation to the requirements. This includes compliance with GMP.

- If any batch(s) of supplied API is considered not to be in compliance with the agreed specification of the API;

- If the CEP, or an API for which a CEP dossier was submitted, is cancelled or refused based on the assessment of the dossier for any other reason; and,

- If in the opinion of the NPRA, changes made in the sourcing of key intermediates, route of synthesis, facility or other production, require that reassessment be made.

REFERENCES AND GUIDELINES

a) Guidelines on the Technical Requirements Related to the Quality of Active Pharmaceutical Ingredients

The technical requirements related to the quality of active pharmaceutical ingredients have already been addressed elsewhere, (such as in the ASEAN, WHO, ICH, EDQM and EMA guidelines), and PRH are advised to refer to these guidelines available at the relevant website such as:

- Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part
  http://apps.who.int/prequal/info_general/documents/TRS970/TRS_970-Annex4.pdf

- Guideline on Active Pharmaceutical Ingredient Master File (APIMF) Procedure.
  (http://apps.who.int/prequal/info_applicants/Guidelines/APIMF_Guide.pdf)

- The ASEAN Common Technical Dossier (ACTD) For The Registration Of Pharmaceuticals For Human Use Organization Of The Dossier
  http://npra.moh.gov.my/index.php/guidelines-central

- The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: Quality – M4Q(R1)
  (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf)

- Impurities in New Drug Substances
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2__Guideline.pdf

- Impurities: Guideline For Residual Solvents
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Step4/Q3C_R6_Step4.pdf

- Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A
  http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

- Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

- Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf

- **Guideline on Summary of Requirements for Active Substances**. *In The* **Quality Part of the Dossier**.
  (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002813.pdf)

- Content of the Dossier for Chemical Purity and Microbiological Quality (PA/PH/CEP 04 1 4R)
  http://www.edqm.eu/medias/fichiers/Content_of_the_Dossier_for_Chemical_Purity_Microbiological_Quality.pdf

- Content of the Dossier for a Substance for TSE Risk Assessment (PA/PH/CEP (06) 2)
  http://www.edqm.eu/medias/fichiers/Content_of_the_Dossier_for_a_Substance_for_TSE_Risk_Assessment.pdf

- Certificates of Suitability for Sterile Active Substances (PA/PH/Exp. CEP/T (06) 13, 1R)
  http://www.edqm.eu/en/New-Applications-29.html

- Certification database for information on Certificates of Suitability (CEPs) granted by the EDQM.
  https://extranet.edqm.eu/publications/recherches_CEP.shtml

- WHO List of Prequalified Active Pharmaceutical Ingredients
  http://apps.who.int/prequal/info_applicants/API_PQ-List.htm

b) Guidelines on Stability Testing

The following Guidelines may be consulted in the context of stability testing:

- WHO Technical Report Series, No. 953, 2009 Annex 2: Stability testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products (http://www.who.int/medicines/publications/pharmprep/PDF_TRS953_WEB.pdf)

- International Conference on Harmonisation. *ICH Q1A* (*R2*)*: Stability testingof new drug substances and products*
  (http://www.ich.org/LOB/media/MEDIA419.pdf)

- International Conference on Harmonisation. *ICH Q1B: Photostability testing of new drug substances and products*
  (http://www.ich.org/LOB/media/MEDIA412.pdf)

- International Conference on Harmonisation. *ICH Q1C: Stability testing of newdosage forms* (http://www.ich.org/LOB/media/MEDIA413.pdf).

- International Conference on Harmonisation. *ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products* (http://www.ich.org/LOB/media/MEDIA414.pdf).

- International Conference on Harmonisation. *ICH Q1E: Evaluation for stabilitydata* (http://www.ich.org/LOB/media/MEDIA415.pdf).

- Note for Guidance on Stability Testing: Stability Testing Of New Drug Substances And Products (CPMP/ICH/2736/99) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002651.pdf)

- **Note for Guidance** *on* **Stability** *Testing of* **Existing Active Substances and Related Finished Products** (www.ema.europa.eu/pdfs/vet/qwp/084699en.pdf)

- ASEAN Stability Guideline http://npra.moh.gov.my/index.php/guidelines-central

APPENDIX 7: SPECIAL CONDITIONS FOR REGISTRATION FOR A PARTICULAR PRODUCT OR GROUP OF PRODUCTS

1. BLOOD PRODUCTS

a) Each batch of the products must comply with WHO requirements for the product.

b) Each batch of the product imported into Malaysia must be accompanied with a Batch Release Certificate from the relevant authority in the country of manufacture.

c) Each batch of the product must be accompanied with a certificate confirming that the blood or plasma used in the production of the lot is tested and found to be negative for HIV antibody, HbsAg, HCV and high-risk donors are excluded.

d) Each batch of the product must be accompanied with a certificate of analysis.

2. ETRETINATE/ ACITRETIN

a) The product shall only be sold or supplied to:

   i) Dermatologist (Skin Specialist) who are gazetted with the Ministry of Health, Malaysia, or registered with the Academy of Medicine, Malaysia, Specialist Registry and Approved by the Drug Control Authority.

   ii) A hospital or Institution maintained by the government, having the services of a skin specialist or registered medical practitioner with experience in dermatology.

b) The container of the product shall be labeled in a conspicuous and distinct manner, with the following statements:

   i) "Etretinate/ Acitretin is **highly teratogenic**.

   ii) Pregnancy must be avoided during treatment and for at least **three years** after **completing** treatment."

c) A proper record of product supplied stating the product name, product registration number, name, address and contact number of purchaser (prescriber) shall be kept and submitted to the Authority upon request.

d) The following records shall be maintained for the product and well kept for auditing by the Authority.

Name of Product :				Reg. No :
Date	**Quantity**			Name & Address of Purchaser
	Received	Supplied	Balance	
Name and Address of : Importer/Manufacturer/Wholesaler : Import/Manufacturer's/Wholesaler's Licence No :				

3. HUMAN GROWTH HORMONE (Somatotropin, Somatropin)

A proper record of product supplied stating the product name, product registration number, name, address and contact number of purchaser (prescriber) shall be kept and submitted to the Authority upon request.

4. ISOTRETENOIN/ TRETINOIN

a) The product shall only be sold or supplied to:

i) Dermatologist (Skin Specialist) who are gazetted with the Ministry of Health, Malaysia, or registered with the Academy of Medicine, Malaysia, Specialist Registry and Approved by the Drug Control Authority.

ii) A hospital or institution maintained by the government, having the services of a skin specialist or registered medical practitioner with experience in dermatology.

b) The container of the product shall be labelled in a conspicuous and distinct manner, with the following statements:

i) "Isotretinoin/ tretinoin is **highly teratogenic**.

ii) Pregnancy must be avoided during treatment and for at least **1 month** after **completing** treatment."

c) A proper record of product supplied stating the product name, product registration number, name, address and contact number of purchaser (prescriber) shall be kept and submitted to the Authority upon request.

5. KETOCONAZOLE

Products containing oral ketoconazole are restricted for hospital use only.

6. MIDAZOLAM

Products containing midazolam are restricted for use in government and private hospitals and specialist clinics only.

7. PARACETAMOL IN COMBINATION WITH CAFFEINE

a) For products containing a combination of paracetamol and caffeine, dose unit of caffeine for adults is 65mg and maximum dose of caffeine is 520mg per day, meanwhile, dose unit for paracetamol is 500mg with the maximum dose of 4,000mg per day or 8 tablets daily.

b) Products containing caffeine for pediatrics are not allowed.

c) Allowable packing size should not exceed 20 tablets/ capsules.

8. PARACETAMOL INTRAVENOUS INJECTION

a) Products containing paracetamol in the form of intravenous injection are restricted for hospital use only.

9. VACCINES

a) Each batch of the product must comply with WHO requirements for the product.

b) Each batch of the product imported into Malaysia must be accompanied with a batch release certificate.

APPENDIX 8: LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES

IMPORTANT NOTES:

The following lists are by no means exhaustive.

Outline:

8.1 List of Prohibited and Restricted Active Ingredients and Combination

8.1.1 List of Prohibited Active Ingredients and Combinations

a) Specific Active Ingredients

b) Combinations

8.1.2 List of Restricted Active Ingredients and Combinations

a) Specific Active Ingredients

b) Combinations

8.2 List of Prohibited and Restricted Excipients

8.2.1 List of Prohibited Excipients

8.2.2 List of Restricted Excipients

8.3 List of Permitted and Restricted Colouring Agents

8.3.1 List of Permitted Colouring Agents

8.3.2 List of Restricted Colouring Agents

8.1 LIST OF PROHIBITED AND RESTRICTED ACTIVE INGREDIENTS AND COMBINATION

8.1.1 LIST OF PROHIBITED ACTIVE INGREDIENTS AND COMBINATIONS

a) <u>Prohibited Active Ingredients</u>

NO.	PROHIBITED ACTIVE INGREDIENTS
1.	1,3-dimethylamylamine (DMAA)
2.	Aristolochic Acid
3.	Aminopyrine/ Amidopyrine
4.	Astemizole
5.	Bacillus Coagulans
6.	Berberine
7.	Butobarbitone
8.	Chlormezanone
9.	Cisapride
10.	Conjugated Linoleic Acid
11.	Crinis Carbonisatus
12.	Danthron
13.	Dipyrone
14.	Enterococcus Faecalis
15.	Enterococcus Faecium
16.	Ethenzamide
17.	Euflavine
18.	Furazolidone
19.	Fenfluramine/ Dexfenfluramine

NO.	PROHIBITED ACTIVE INGREDIENTS
20.	Gentian Violet
21.	Gamma-Butyrolactone (GBL)
22.	Gamma-Aminobutyric Acid (GABA)
23.	Gamma-Hydroxybutyric Acid (GHB)
24.	Haloquinol
25.	Hexachlorophene
26.	Mercurochrome
27.	Nimesulide
28.	Novobiocin
29.	Oxyphenisatin Acetate/ Acetophenolisatin
30.	Oxyphenbutazone
31.	Pergolide
32.	Phenacetin
33.	Phenazone/ Antipyrine - Propylphenazone - Isopropylphenazone
34.	Phenylbutazone
35.	Phenylpropanolamine
36.	Piperazine
37.	Prenylamine
38.	Quinalbarbitone
39.	Salicylamide
40.	Sibutramine
41.	Stanozolol

NO.	PROHIBITED ACTIVE INGREDIENTS
42.	Sulphaguanide
43.	Thioridazine
44.	Tegaserod
45.	Terfenadine

b) <u>Prohibited Combinations</u>

NO.	PROHIBITED COMBINATIONS
1.	Ampicillin + Cloxacillin
2.	Antibiotics + Papain/ Prolase
3.	Antacid + Charcoal
4.	Combinations With Any Barbiturates
5.	Combinations of Two or More Analgesic with the Same Mode of Action
6.	Combinations Of Vitamin (S) With Other Drugs: a. Vitamin (S) + Appetite Suppressant b. Vitamin (S) + Corticosteroid c. Vitamin (S) + Analgesic d. Vitamin (S) + Laxative e. Vitamin (S) + Slimming Agents
7.	Cough, Cold and Allergy Products Containing: a. Four or More Pharmacological Groups in One Product. b. Two or More Drugs from the Same Pharmacological Group c. Antypyretic - Analgesic + Expectorant d. Anticholinergic + Bronchodilator e. Codeine + Ephedrine/ Pseudoephedrine f. Methapyrilene

NO.	PROHIBITED COMBINATIONS
	g. Paracetamol + Mucolytic/ Expectorant
8.	Combinations Containing Antacid and Surface Local Anaesthetic Agent
9.	Combinations Containing Dextropropoxyphene
10.	Combinations Containing Spironolactone
11.	Corticosteroids + Antihistamines
12.	Eye Drops Containing Vitamin
13.	Gripe Water Containing Alcohol
14.	Propanolol + Hydralazine
15.	Propanolol + Spironolactone
16.	Topical Preparation Containing Combination of Antibiotic, Antifungal and Steroid

8.1.2 LIST OF RESTRICTED ACTIVE INGREDIENTS AND COMBINATIONS

Specific Active Ingredients	Not Allowed in the Specified Preparation(s) or Condition
1. Acetic Acid	Expectorant
2. Allantoin	Eye Drop
3. Allergen Extracts	Vaccines, Diagnostics
4. Amphetamine	Cough Mixtures, Appetite Suppressants
5. Animal Organ	All Preparations Except Natural Products
6. Antihistamine	Topical Use
7. Bismuth Salts Except Bismuth Subcitrate	Oral Preparations
8. Boric Acid/ Borax And Related Salts	Oral, Topical (Skin), Vaginal, Nasal Dosage Form
9. Buprenorphine	Single Active Ingredient Sublingual Tablet Formulation
10. Caffeine	All Preparations Except for an Oral Preparation in Combination with Paracetamol/ Acetaminophen or Combination with Ergotamine
11. Camphor	- Oral - External (>11%)
12. Chloroform	Expectorant
13. Codeine	Cough Syrup
14. Cocillana Liq. Extract	Expectorant
15. Cyproheptadine	Appetite Stimulant
16. Dextromethorphan	Single Active Ingredient in Tablet Form, including lozenges
17. Dihydrostreptomycin	Oral Antidiarrhoeals
18. Diphenoxylate	Liquid Oral Dosage For Anti-Diarrhoeal
19. Quinestrol, Oestrogen	Lactation Suppressant
20. Ethynodiol Diacetate	Oral Contraceptives

21. Euphorbia Liquid Extract	Expectorant
22. Gatifloxacin	All Preparations Except for Eye Drop
23. Germanium	Non Naturally Occurring
24. Hydroquinone	Oral
25. Lactobacillus Acidophillus	Antidiarrhoeal
26. Loperamide	Liquid Oral Dosage For Anti-Diarrhoeal
27. Lovastatin	In Red Yeast Rice: > 1 % w/w and > 10mg/Day
28. Lynooestrenol	Oral Contraceptives
29. L-Tryptophan	All Preparations Except Parenteral Nutrition Products And Enteral Feeding Products
30. Magnesium Ascorbryl Phosphate	Antipigmentation
31. Menthol	External Preparations >16%
32. Mestranol	Oral Contraceptives
33. Methylene Blue	Oral Preparations
34. Midazolam	All oral preparations, except 7.5mg coated tablet
35. Morphine	Cough Mixtures
36. Neomycin	Oral Antidiarrhoeal, Vaginal Tablets, Topical Powders, Aerosols, Nasal Preparations
37. Noradrenaline	Dental Preparations
38. Norgestrel	Oral Contraceptives
39. Paracetamol	Liquid Oral 500mg/5ml
40. Penicillin	Topical Use
41. Phenazopyridine	Urinary Analgesics
42. Phenolphthalein	Stimulant Purgative
43. Pizotifen	Appetite Suppressant
44. Podophyllum Resin	Oral Preparations

45. Pseudoephedrine	All Single Active Ingredient Formulations
46. Sulphonamides	Topical Use
47. Sulphur	All preparations Except External Preparation
48. Squill	Expectorant
49. Terpene Hydrate	Expectorant
Combinations	**Not Allowed in the Specified Preparation(s)**
1. Cough, Cold And Allergy Products Containing:	
i) Antimony Potassium Tartrate	Expectorant
ii) Allylisothiocyanate/ Mustard Oil	Nasal Decongestant
iii) Turpentine Oil	Expectorant/ Antitussive
2. Vitamin(s)	Eye Drops

8.2 LIST OF PROHIBITED AND RESTRICTED EXCIPIENTS

8.2.1 LIST OF PROHIBITED EXCIPIENTS
1. Colouring Agents **(Including in Capsule Shells)**
a) Amaranth (CI= 16185, FD & C Red No. 2, E123)
2. Others
a) Chlorofluorocarbons (CFC)

8.2.2 LIST OF RESTRICTED EXCIPIENTS	
Excipients	**Restrictions**
1. Colouring Agents (Including in Capsule Shells)	
a) Tartrazine (CI= 19140, FD & C Yellow No.5, E102)	Not allowed in the following preparations: – Oral; – Rectal; – Vaginal or – Nasal Preparations
b) Red 2G	Not allowed in the following preparations: – Oral Preparations; and – Preparations Used for Mucosa Membrane
2. Sweeteners/ Flavouring Agent	
a) Menthol	Limited to not more than 10mg/day
b) Saccharin and Salts	Limited to not more than 5mg/kg/day
c) Cyclamates	Limited to not more than 1.5mg/kg body weight/day

3. Preservatives		
a) Chloroform	Limited to not more than 0.5% in Pharmaceuticals for Internal Use	
b) Thiomersal *	Not allowed in ophthalmic Preparations	
4. Others		
a) Phthalates	Variant	Maximum Limit of Daily Exposures (mg/kg body weight/day)
	Dibutyl Phthalate (DBP)	0.01mg/ kg/ day
	Diethyl Phthalate (DEP)	4mg/ kg/ day
	Polyvinyl Acetate Phthalate (PVAP)	2mg/ kg/ day

** For other preparations, warning as specified in **Appendix 9**: Labelling Requirements, shall be included in the package insert and product literature of products containing thiomersal.*

Additional Information

1. **Methylene Chloride/ Dichloromethane** are not allowed as solvent in film-coating for locally manufactured products.

   For detail on implementation, please refer circular (2)dlm.BPFK/30/06/2 Bhgn 2.

2. **Alcohol** is not allowed unless it is essential to the formulation and no suitable alternatives to alcohol are available. Content of alcohol shall be at the minimum level as possible.

8.3 LIST OF PERMITTED AND RESTRICTED COLOURING AGENTS

8.3.1 List of Permitted Colouring Agents

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
1.	Allura Red AC/ FD & C Red No.40	16035
2.	Anthocyanins a. Those glycosides of 2-phenylbenzopyrylium salts which are anthocyanins b. The following anthocyanidin aglycones : i. Pelargonidin ii. Cyanidin iii. Peonidin iv. Delphinidin v. Petunidin vi. Malvidin	
3.	Black PN (Brilliant Black BN)	28440
4.	Brilliant Blue FCF	42090
5.	Calcium Carbonate	
6.	Carbo Medicinals/ Vegetalis; (Charcoal)	
7.	Caramel	
8.	Carmoisine (or Azorubine)	14720
9.	Carotenoids a. Alpha, Beta, Gamma-Carotene b. Bixin, Noribixin, Roucou c. Annatto d. Capsanthin, Capsorubin, (paprika extract) e. Lycopene f. Beta-Apo-8' carotenal (C 30) g. Ethyl ester of Beta-Apo-8 Carotenoic Acid (C30) i. Chlorophyll ii. Copper complexes of Chlorophyll and Chlorophyllins	 75120 40820 75810
10.	Chocolate Brown HT	20285

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
11.	Cochineal or Carminic Acid, Carmine from Cochineal	75470
12.	Curcumin	75300
13.	Fast Green FCF (FD & C Green No.3)	42053
14.	Green S (Acid Brilliant Green BS, Lissamine Green)	
15.	Indigo Carmine (Indigotine)	73015
16.	Lactoflavin, Riboflavin	
17.	Patent Blue V	42051
18.	Ponceau 4R (Cochineal Red A)	16255
19.	Quinoline Yellow	47005
20.	Xanthophylls a. Flavoxanthin b. Lutein c. Cryptoxanthin (Kryptoxanthin) d. Violoxanthin e. Rhodoxanthin f. Canthaxanthin	40850
21.	The Following Colouring Matters Natural to Edible Fruits or Vegetables: a. Alkannin b. Annatto (including eye) c. Carotene (including eye) d. Chlorophyll e. Flavine f. Indigo g. Osage h. Orange i. Persian Berry j. Safflower k. Saffron l. Sandalwood m. Turmeric n. or their pure coloring principles whether isolated from such natural colors or produced synthetically	75530

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
22.	Bole or Iron Oxide, Carbon Black (or Vegetable Origin), Titanium Dioxide	77891
23.	The Aluminium Salts (Lakes) of Any of the Scheduled Synthetic Dyes Approved for Use, (a) Alumina (Dried Aluminium Hydroxide)	
24.	Talc	
25.	Indigo Carmine/ FD & C Blue No. 2	73015
26.	Brilliant Blue FCF Ammonium Salt/ D & C Blue No. 4	42090
27.	Alizarin Cyanine Green F/ D & C Green No. 5	61570
28.	Toney Red/ D & C Red No. 17	26100
29.	Eosin YS Acid Form/ D & C Red No. 21	45380:2
30.	Eosinys Sodium Salt/ D & C Red No. 22	45380
31.	Phloxine B Acid Form/ D & C Red No. 27	45410:1
32.	Phloxine B Sodium Salt/ D & C Red No. 28	45410
33.	Helindone Pink CN/ D & C Red No. 30	73360
34.	Erythrosine/FD & C Red No. 3	45430
35.	Yellow 2G (Food Yellow)	
37.	Orange Yellow S Sunset Yellow FCF (FD & C Yellow No. 6, E110)	15985

8.3.2 List of Restricted Colouring Agents

The following colouring agents are **ALLOWED** in preparations as stated in the parentheses:

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
1.	Dihydroxyacetone (external use with specific drugs only)	
2.	Bismuth Oxychloride (external use only, including eye)	77163
3.	Ferric Ammonium Ferrocyanide (external use only, including eye)	
4.	Ferric Ferrocyanide (external eye only)	
5.	Chromium Hydroxide Green (external use only)	77289
6.	Chromium Oxide Green (external use only, including eye)	
7.	Guanine (external use only)	75170
8.	Prophyllite (external use only)	
9.	Mica (external use only, including eye)	77019
10.	Bronze (external use only, including eye)	
11.	Copper (external use only, including eye)	
12.	Zinc Oxide (external use only, including eye)	77947
13.	Quinizarine Green SS/ D & C Green No. 6 (external use only)	61565
14.	Pyranine Concentrated/ D & C Green No. 8 (external use only)	59040

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
15.	Orange II/ D & C Orange No. 4 (external use only)	15510
16.	Dibromofluorescein/ D & C Orange No. 5 (mouth wash, dentifrices, external use only)	45370
17.	Diiodofluorescein/ D & C Orange No. 10 (external use only)	45425
18.	D & C Orange No. 11 (external use only)	
19.	Ponceau SX/ FD & C Red No. 4 (external use only)	14700
20.	Lithol Rubin B/ D & C Red No. 6 (may be use in combination; total not more than 5mg/day)	15850
21.	Lithol Rubin B CA/ D & C Red No. 7 (may be used in combination; total not more than 5mg/day)	15850:1
22.	D & C Red No. 31 (external use only)	
23.	Deep Maroon/ D & C Red No. 34 (external use only)	15880:1
24.	D & C Red No. 39 (external use only, not more than 0.1%)	
25.	Uranine Acid Form/ D & C Yellow No. 7 (external use only)	45350:1
26.	EXT. D & C Yellow No. 7 (external use only)	
27.	Uranine Sodium Salt/ D & C Yellow No. 8 (external use only)	45350
28.	Tartrazine/ FD & C Yellow No. 5/MA Yellow A-2/ Aluminic Lake (external use only)	19140

APPENDIX 9: LABELLING REQUIREMENTS

This appendix comprises of two (2) parts:

a) General Labelling Requirements for:

i) Section D : Label (Mock-Up) for Immediate Container and Outer Carton

ii) Section D : Proposed Package Insert (PI)

iii) Section E8/ F8 : Consumer Medication Information Leaflet (RiMUP)

b) Specific Labelling Requirements

9.1 GENERAL LABELLING REQUIREMENTS

The following information in **Table 1** shall present on the label of a product at outer carton, immediate container or blister/ strips:

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
1.	Product Name	✓	✓	✓
2.	Dosage Form	✓	✓*	NA
3.	Name of Active Substance(s)	✓	✓	✓**
4.	Strength of Active Substance(s)	✓	✓	✓**
5.	Batch Number	✓	✓	✓
6.	Manufacturing Date	✓	✓*	NA
7.	Expiry Date	✓	✓	✓
8.	Route of Administration	✓	✓	NA
9.	Storage Condition	✓	✓*	NA
10.	Country's Registration Number	✓	✓*	NA
11.	Name & Address of Product Registration Holder (PRH)	✓	✓*	Name/ Logo of Manufacturer/ Product Owner
12.	Name & Address of Manufacturer	✓ At least name of town/ city and country of manufacturer	✓* At least name of town/ city and country of manufacturer	NA
13.	Warnings and/or Specific Labelling (if applicable)	✓	✓*	NA
14.	Pack Sizes (unit/ volume)	✓	✓	NA

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
15.	Name & content of preservative(s) where present	✓	✓	NA
16.	Name & content of alcohol, where present	✓	✓	NA
17.	To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine.	✓	✓	NA
18.	To declare the source of capsule shell (if applicable)	✓	✓	NA
19.	Recommended daily allowance (RDA) for vitamins/ multivitamins/ mineral preparations used as dietary supplements (optional)	✓	✓	NA
20.	The words “Keep medicine out of reach of children” or words bearing similar meaning in both *Bahasa Malaysia* & English	✓	✓*	NA
21.	Other country specific labelling requirements (if applicable)	✓	✓*	NA
22.	The words “Controlled Medicine/ *Ubat Terkawal*” **(For scheduled poison only)**	✓	✓*	NA
23.	Security Label (Hologram)	✓ #	-	NA

NA : Not Applicable

* Exempted for small labels (i.e. 5ml and less) used for ampoules/ cartridge, vials, eye drops, ear drops, and nose drops.

** For multi-vitamins and minerals preparations it is suggested to label as multi-vitamins and minerals.

i. In case of a product without an outer carton, the security label shall be applied onto the immediate label. The security label shall however not be applied onto the outer shrink wrap of the product.

ii. Exemption will be for small labels (i.e. volume of 5ml and less) such as for ampoules/ cartridge/vials.

No. 15, 20, 22 & 23 of the above are country specific requirements for Malaysia.

- Declaration of nutrition information per serving (for example energy, carbohydrate, protein and fat) is not permitted in a health supplement product label.

ADDITIONAL INFORMATION:

a) All labels and package inserts must be in *Bahasa Malaysia* or English. In additional to this, translation to another language will be allowed.

b) If the product is without an outer carton, the inner label shall bear all the information that is required.

c) Official website of the company or website for any purpose of product promotion from the PRH/ product owner/ manufacturer is not allowed to be printed on the product label (applicable to all categories of products inclusive of imported products). However, the email address of the company is permissible on the label.

d) The colours of labels shall be differentiated between strengths of products as well as between products containing different active ingredients which belong to the same holder.

e) Only a single label artwork is permitted for all pack sizes of a registered product.

f) No stick-on label is permitted. Any usage of stick-on label shall have prior approval by the Authority. The Authority will only consider the following situations:

   i) Stick-on label of such information and printing of registration number for label redressing of a registered product is permitted:

      Words with "Controlled Medicine/ *Ubat Terkawal", "Keep out of reach of children/ Jauhkan daripada capaian kanak-kanak"*, information of Product Registration Holder, and Malaysia Specific Labelling Requirements (if any) shall be printed in a single label.

ii) The label shall be made from good quality material and not easy to be torn out.

iii) Registration number shall be printed permanently on the product (ink-jet) and it is not allowed to be printed on the stick-on label.

g) Use of QR code is permitted only for the purpose of monitoring inventory of the product, such as batch number, expiry date and manufacturing date, BUT NOT for linkage to any website. The addition of QR code on registered product labels without variation approval from NPRA can be considered only if that is the only proposed change to the currently approved labels.

h) The label of a registered product containing any Scheduled Poison shall not have colourful atrwork or graphics that can be misleading or will adversely influence caregivers'/patients'/children's perceptions of the appropriateness of the medication.

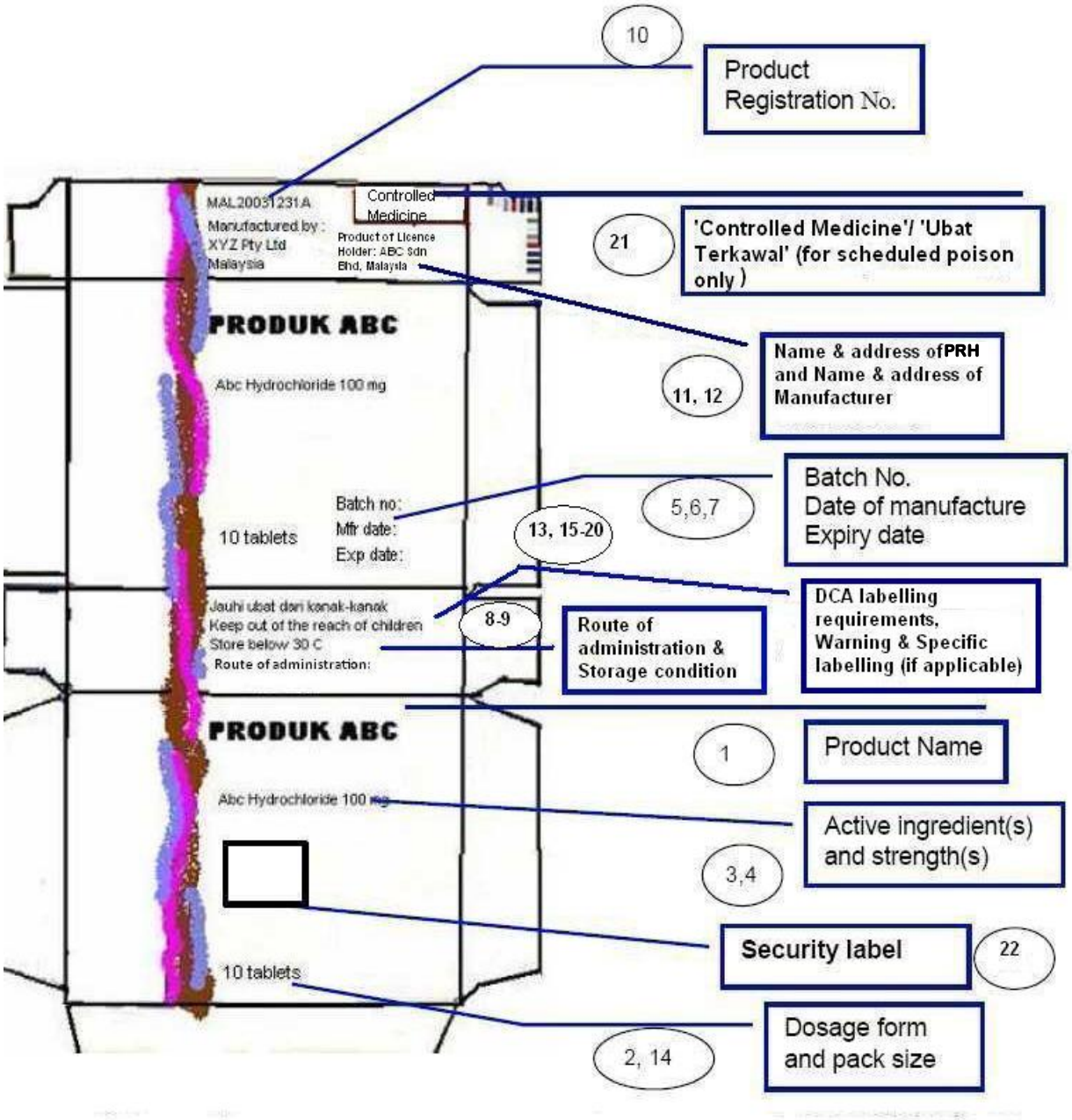
i) Font size of the product name on the label, including alphabets and numbers, should be equal in size.

j) For a product containing 2 or more active ingredients, font size of each active ingredient that is highlighted on the inner/ outer carton must be of equal size and equal prominence (Note: this is not referring to the product name, but the statement made on the label).Justification for highlighting certain ingredients only on the product name / label must be provided and subject to approval by the Evaluation Committee.

9.1.1 LABEL (MOCK-UP) FOR IMMEDIATE CONTAINER AND OUTER CARTON

Please refer to **Figure 1** as an example of a product label which in accordance to the labelling requirements.

Figure 1:



Note:

Numerical notations shown in the above figure are in line with the numbering for the parameters, shown in Table 1 above, to be included in the product label (as identified and adopted by the ACCSQ-PPWG).

9.1.2 PROPOSED PACKAGE INSERT

Package insert (PI) is required for products containing scheduled poison and for injectable OTC products. PI may also be submitted for other OTC products. The draft copy of the PI shall be submitted for evaluation.

Sharing of PI is only allowed for products having the same active ingredient(s) but with different strengths.

The following information is required to be included in the PI:

a) Brand or Product Name
b) Name and Strength of Active Substance(s)
c) Product Description
d) Pharmacodynamics/ Pharmacokinetics
e) Indication
f) Recommended Dosage
g) Route of Administration
h) Contraindications
i) Warnings and Precautions
j) Interactions with Other Medicaments
k) Statement on usage during pregnancy and lactation
l) Adverse Effects/ Undesirable Effects
m) Overdose and Treatment
n) Incompatibilities (For injections only)
o) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
p) Dosage forms and packaging available
q) Name and address of manufacturer/ product registration holder
r) Date of revision of PI

9.1.3 CONSUMER MEDICATION INFORMATION LEAFLET (RiMUP)

Consumer Medication Information Leaflet or in *Bahasa Malaysia* known as *Risalah Maklumat Ubat untuk Pengguna (RiMUP),* is compulsory for products which are self-administered by patients, including:

a) Scheduled poisons (Category A);
b) Over-the-Counter, OTC products (Category X);
c) Herbal products; and health supplements with high claims (disease risk reduction).

For details, please refer to:

i) *Direktif Penguatkuasaan Keperluan Mengemukakan Risalah Maklumat Ubat untuk Pengguna (RiMUP) Bil. 5 Year 2011* Bil (15) dlm BPFK/PPP/01/03 Jld 1
ii) *Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna (RiMUP)*

The draft copy of the RiMUP in both English and *Bahasa Malaysia* shall be submitted for evaluation.

Note:

RiMUP is not compulsory to be distributed with the product. All approved RiMUP will be uploaded onto NPRA website as reference for consumers. Healthcare professionals can access the RiMUP and disseminate to patients if necessary.

For OTC Products, if the product is intended to be sold without a PI or RiMUP, the information required to be included in the PI or RiMUP shall be printed on the unit outer-carton of the product. However, submission of the RiMUP softcopy is compulsory as mentioned above.

9.1.4 PRODUCT NAME

Product name is defined as a name given to a product which may either be a proprietary name (an invented name); or a generic name (common name) or scientific name, together with a trade mark or the name of the manufacturer.

- Product name shall consist of dosage form and strength (for single active ingredient product). (e.g. X Brand Paracetamol Tablet 500mg)
- The generic name cannot be used alone as product name but in combination with another name, other than the generic name.
  - The generic name means the international non-proprietary name recommended by WHO (rINN), or if one does not exist, the usual approved name.
- The invented name shall not be liable to confusion with the common name.
- Font size of the product name on the label, including alphabets and numbers, should be equal in size.
- If a product name is found similar in terms of spelling and pronunciation to another registered product or any other name which deemed inappropriate by the Authority, NPRA reserves the rights to request for the change of the product name.

Product names which are not permitted to be registered are as specified in **Table 2** below:

No.	Non-Permissible Product Names	Example
1.	**20 disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983)**	**Example :** Diabetes, Asthma, Cancer
2.	**Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika**	**Example :** Tongkat Ali Capsule ---- But product contains tongkat ali, ginseng, ect.

No.	Non-Permissible Product Names	Example
3.	**Use of Superlatives - Names which indicates superiority in efficacy**	**Example :** Power/ Kuasa, Superior, Pure, Mustajab, Safe, Healthy/ Sihat, Penawar/ Shifa, VIP, Good, Heal/ Sembuh, Premium, Mustajab, Men/ Women/ Children Complete, Men/ Women/ Children Enriched, Paradise/ Syurga, Menawan, Booster
4.	**Use of spelling of words which may cause confusion** **Words which involve names of/part thereof:** iv) 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) v) Diseases without scientific evidence of efficacy/ prescription medication to treat diseases/ parameters that indicate certain diseases (e.g. insulin, glucose) vi) Prohibited indication (e.g. to detoxify body)	**Example :** a) Go Out = GOUT b) UTix = Urinary Tract Infection c) Diabecine = Diabetes d) Metformon = Metformin e) Insuprem = Insulin f) Glucosey = Glucose g) DetoxB = Detox body
5.	**Use of names which may cause ambiguity** Ambiguous product name	**Example:** B For Energy?
6.	**Use of names which may be offensive or indecent**	**Example:** SENXBIG=SEnXBIG(label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire*(Dezire),Sensual (Xenxual),Asmara,Syok*

No.	Non-Permissible Product Names	Example
7.	**Use of product names which are incoherent with the approved indication** Name containing a product claim whereas product is indicated for more than the approved indication	**Example:** Cough Syrup X= Approved indication for cough, dizziness, flu and itch
8.	**Use of product names which has elements of ludicrous belief** Statements referring to ancient believe/ negative spirits/ supernatural power	**Example:** Words such as miracle, magic, magical, miraculous, saintly, heavenly
9.	**Use of product names similar to the existing approved product names** Product names similar to the spelling and pronunciation of words of the existing product names	**Example:** Tenormin vs Tenormine vs Tenormy Re-Liv vs Re-Lif
10.	**Use of product names which may cause ambiguity in the nature of product (drug/ food/ beverage)** Product names similar to a food/ beverage product	**Example:** Juice, Health drink, Beverage, Kooky
11.	**Use of product names which represents professional advice or opinion or referring to the profession**	**Example:** Dr Sunny, Dr Noortier Rooibose Tea, Professor, Herbalist, Doctor
12.	**Use of product names which represent weight loss/ slimming properties/ names that can be associated with weight loss/ slim**	**Example:** Slim, Langsing, Trim, Trimnfit, *Sleen, Kurus, Susut perut,Xlim, Weight watcher*
13.	**Use of product names referring to any religious content**	**Example:** Maksum, Mahmudah, Arifbillah
14.	**Use of product names referring to internal organs**	**Example:** Leever, Brainey, Kidnee, etc.

No.	Non-Permissible Product Names	Example
15.	**Use of abbreviation as a product name unless it carries no meaning**	**Example:** TB, UTI, HB, etc.
16.	**Use of product name which carries 'traditional' and/ or 'non-professional' image for Pharmaceutical products**	**Example:** Cap Ikan Emas, Brand Ayam Jati, Tablet Kuat Badan
17.	**Other prohibited product names**	**Example:** Minda, IQ, Smart, Genius, Ultra Mega, Detox

Note:

1. *This list is not meant to be exhaustive and will be reviewed from time to time*
2. *The Authority reserves the right to disallow any other words or phrases for product names which in its opinion is misleading, improper or not factual.*

9.1.5 PROHIBITED VISUAL/ GRAPHICS/ STATEMENTS ON LABEL

The lists are as shown in **Table 3** below:

No.	Issue	Example	Note
1.	Marketing strategy	**Example:** "Money back guarantee" "Buy 1 free 1" "Backed by RM5 million product Liability Insurance"	-
2.	Usage guide which promotes use of other product(s)	**Example:** "After consumption of this product (Product A), for better results, it is recommended to take Product B"	-

No.	Issue	Example	Note
3.	Consumer testimonial	-	-
4.	Clinical Trial results or any information on clinical trial done on product	Example : “Clinically Tested” “Randomized Double Blind Placebo Control Clinical Study”	-
5.	Reference to Hadith/ Al-Quran/ Bible/ Religious books	-	-
6.	Opinion of prominent figure(s) on product or its active ingredient/ content	**Example:** Opinion of product/formulation inventor	-
7.	Label design (graphic and color) similar to labels from another company	-	-
8.	Statement on active ingredient origin	**Example:** Source from the Mountains of Alps	Allowed if proven true
9.	Introduction of founder/ Manufacturer	-	-

No.	Issue	Example	Note
10.	Logo with certification	**Example:** SIRIM/ ISO / GMP/ HACCP	Prohibited on product label because certification renewal is on a yearly basis
11.	Name/ Statement/ Logo/ registered trademark which does not satisfy the specifications	**Example:** “Dr.ABC’s Formula” “Nothing like it”	-
12.	Patency claim/ Patency number/ Special technique used/ superiority in ingredients (Example: capsule coat)	**Example:** Patented technique	Allowed if proven true
13.	Nutritional claims with analysis certificate attached	**Example:** Calorie, Fat, Protein and others	-
14.	Graphics or picture of internal organs	**Example:** Kidney, Heart, Nerves.	-
15.	Gender symbol (male or female)	(♀ and/or ♂)	-
16.	Indecent photographs/ pornography	-	-

No.	Issue	Example	Note
17.	Graphics which are incoherent with the indication	**Example:** - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose.	-
18.	Highlighting unnecessary body parts	**Example:** Indication is for general health but graphics on label highlights male and female sexual organ parts	-
19.	Graphics of plants or animal which may cause confusion	**Example:** Radix Ginseng which is improvised as a male sexual part	-
20.	Negative Statements/ Visual	**Example:** - This product is GMO/ LMO free - This product is free from animal origin - Free from Preservative	-
21.	Other statements deemed relevant to be prohibited by the authority	**Example:** - This product is blended with premium quality	-

Notes:

3. *This list is not meant to be exhaustive and will be reviewed from time to time*
4. *The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual*

9.2 SPECIFIC LABELLING REQUIREMENTS

Please refer Table 4: List of Substances Which Requires Specific Labelling Requirements and Table 5: Details of Specific Labelling Requirements.

Table 4: List of Substances Which Requires Specific Labelling Requirements:

NO.	SUBSTANCES
1.	5-ALPHA REDUCTASE INHIBITOR (5-ARI)
2.	ACE INHIBITORS
3.	ACETYLSALICYLIC ACID (ASPIRIN)
4.	ACTIVATED CHARCOAL/ ATTAPULGITE
5.	ALBENDAZOLE & BENZIMIDAZOLE ANTIHELMINTICS
6.	ALFALFA (*MEDICAGO SATIVA*)
7.	ALLOPURINOL
8.	ALPHA DIHYDROERGOCRYPTINE
9.	ALPRAZOLAM
10.	AMIODARONE
11.	ANTIDEPRESSANTS
12.	ANTIEPILEPTICS
13.	ANTIPSYCHOTIC AGENTS
14.	APOMORPHINE
15.	ARGININE
16.	ARIPIPRAZOLE
17.	ARTESUNATE
18.	ASPARTAME
19.	ATORVASTATIN

20.	AZITHROMYCIN
21.	BEE POLLEN
22.	BENZOYL PEROXIDE
23.	BENZYL ALCOHOL
24.	BERBERINE ALKALOIDS – NATURAL OCCURING BERBERINE E.G. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA ETC.
25.	BLACK COHOSH (*CIMICIFUGA RACEMOSA*)
26.	BOSWELLIA SERRATA (FOR HEALTH SUPPLEMENT PRODUCTS ONLY)
27.	BROMAZEPAM
28.	BROMOCRIPTINE
29.	BROMPHENIRAMINE
30.	CAMPHOR
31.	CARBAMAZEPINE
32.	CARBIMAZOLE
33.	CABERGOLINE
34.	CEFTRIAXONE
35.	CETIRIZINE
36.	*CHELIDONIUM MAJUS*
37.	CHITOSAN
38.	CHLORHEXIDINE
39.	CHLORPHENIRAMINE
40.	CHORIONIC GONADOTROPHIN
41.	CLEMASTINE
42.	CLINDAMYCIN

43.	CLOBAZAM
44.	CLOPIDOGREL
45.	CLOZAPINE
46.	CODEINE
47.	COLCHICINE
48.	CORTICOSTEROID (INHALATION)
49.	COX-2 INHIBITORS
50.	CYPROTERONE ACETATE
51.	CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION
52.	CYTOTOXIC AGENT
53.	DEXBROMPHENIRAMINE
54.	DEXTROMETHORPHAN
55.	DIAZEPAM
56.	DICLOFENAC SODIUM
57.	DICYCLOMINE
58.	DIPHENHYDRAMINE
59.	DIPHENOXYLATE
60.	DOMPERIDONE
61.	DOPAMINERGIC INGREDIENT
62.	EPHEDRINE
63.	ETHINYLESTRADIOL
64.	ETORICOXIB
65.	FAMOTIDINE
66.	FIBRATES

67.	FILGRASTIM
68.	FLUCLOXACILLIN
69.	FLUORIDE
70.	FLUOROQUINOLONES
71.	FLURAZEPAM HYDROCHLORIDE
72.	GADOBENIC ACID
73.	GADOBUTROL
74.	GADODIAMIDE
75.	GADOLINIUM OXIDE
76.	GADOTERIC ACID
77.	GADOVERSETAMIDE
78.	GADOXETIC ACID
79.	GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
80.	GAMAT/ STICHOPUS spp.
81.	GENTAMICIN TOPICAL PREPARATIONS
82.	GINKGO BILOBA/ GINKGO EXTRACT
83.	GINSENG
84.	GLUCOSAMINE
85.	HIV PROTEASE INHIBITORS
86.	HYDROQUINONE
87.	IMMUNOSUPPRESANTS
88.	INSULIN
89.	INGREDIENTS DERIVED FROM SEAFOOD
90.	INTERFERON ALPHA

91.	INTERFERON BETA
92.	KAOLIN, PECTIN, KAOLIN-PECTIN
93.	KETOCONAZOLE
94.	KETOROLAC TROMETHAMOL (KETOROLAC TROMETHAMINE)
95.	LEVODOPA
96.	LEVONORGESTREL
97.	LINCOMYCIN
98.	LISURIDE
99.	LIQUID PARAFFIN
100.	LOPERAMIDE
101.	LORAZEPAM
102.	LOVASTATIN
103.	MEFLOQUINE
104.	MELALEUCA LEUCADENDRA
105.	METHYL SALICYLATE
106.	METHYLPHENIDATE HCL
107.	METOCLOPRAMIDE
108.	MICONAZOLE
109.	MIDAZOLAM
110.	MINOXIDIL
111.	MOMORDICA CHARANTIA
112.	MONTELUKAST
113.	MUCOLYTIC AGENT
114.	NEVIRAPINE

115.	NIFEDIPINE
116.	NITRATES
117.	NITRAZEPAM
118.	NORFLOXACIN
119.	NORMAL GLOBULIN
120.	NOSCAPINE
121.	NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)
122.	OLANZAPINE
123.	ONDANSETRON
124.	PALIPERIDONE
125.	PARACETAMOL
126.	PARACETAMOL WITH CAFFEINE IN COMBINATION
127.	PEGFILGRASTIM
128.	*PELARGONIUM SIDOIDES*
129.	PENICILLIN
130.	PHENIRAMINE
131.	PHENYLEPHRINE
132.	PIRIBEDIL
133.	PIROXICAM
134.	PRAMIPEXOLE
135.	PRAVASTATIN
136.	PROMETHAZINE HCL
137.	PROPAFENONE
138.	PROPOFOL

139.	PROPOLIS (ORAL)
140.	PROPOLIS (TOPICAL)
141.	PROPYLTHIOURACIL
142.	PSEUDOEPHEDRINE
143.	PROTON PUMP INHIBITORS (PPI)
144.	PSYCHOTROPIC PRODUCTS
145.	PSYLLIUM/ PLANTAGO (SEED/ HUSK)
146.	QUETIAPINE
147.	QUINAGOLIDE
148.	RED YEAST RICE (MONASCUS PURPUREUS)
149.	RISPERIDONE
150.	ROPINIROLE
151.	ROSIGLITAZONE
152.	ROSUVASTATIN
153.	ROYAL JELLY
154.	SALBUTAMOL
155.	SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)
156.	SEDATIVE – HYPNOTIC PRODUCTS
157.	SELENIUM SULPHIDE
158.	SENNA (CASSIA SPP.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part
159.	SIMVASTATIN
160.	SODIUM METABISULPHITE (EXCIPIENT)
161.	SODIUM VALPROATE

162.	ST. JOHN'S WORT *(Hypericum perforatum)*
163.	STATINS
164.	STRONTIUM RANELATE
165.	SULPHONAMIDES/ TRIMETHOPRIM
166.	SYNTHETIC SALMON CALCITONIN
167.	TABEBUIA SPP. (PAU D'ARCO)
168.	TEMOZOLAMIDE
169.	TERBUTALINE
170.	TETRACYCLINE SYRUP
171.	THIOMERSAL
172.	THROMBOLYTIC AGENTS
173.	TIAPROFENIC ACID
174.	TOPIRAMATE
175.	TRETINOIN (TOPICAL)
176.	TRIAZOLAM
177.	TRIMETAZIDINE
178.	TRIPROLIDINE
179.	VARENICLINE
180.	VITAMIN K
181.	WARFARIN
182.	ZIPRASIDONE
183.	ZOLPIDEM TARTRATE
184.	ZOPICLONE

Table 5: Details of Specific Labelling Requirements

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
1.	**5-ALPHA REDUCTASE INHIBITOR (5-ARI)** The following statement shall be included in the package inserts of products containing 5-ARI: **1.1 PRODUCT CONTAINING FINASTERIDE 5MG** **WARNINGS AND PRECAUTIONS** **Increased Risk of High-Grade Prostate Cancer** Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo). 5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established. **Increased Risk of Breast Cancer** Breast cancer has been reported in men taking finasteride 5 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge. **ADVERSE EVENTS: POST MARKETING EXPERIENCE** Male breast cancer **1.2 PRODUCT CONTAINING FINASTERIDE 1MG** **WARNINGS AND PRECAUTIONS** **Increased Risk of High-Grade Prostate Cancer** Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of [Brand Name]) in the 7-year Prostate Cancer Prevention Trial (PCPT) had

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo).

5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

Increased Risk of Breast Cancer

Breast cancer has been reported in men taking finasteride 1 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

ADVERSE EVENTS: POST MARKETING EXPERIENCE

Male breast cancer

1.3 <u>PRODUCT CONTAINING DUTASTERIDE</u>

WARNINGS AND PRECAUTIONS

Increased Risk of High-Grade Prostate Cancer

In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus placebo 0.5%). In a 7-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (finasteride 5 mg, PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%).

5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

Reference:

a) Circular Bil (19) dlm BPFK/PPP/01/03 Jld 1: *Direktif untuk Memuatkan Kenyataan Amaran Berkaitan dengan Risiko High-Grade Prostate Cancer dalam Sisip Bungkusan*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Semua Produk 5-Ari ***Circular Bil (64) dlm BPFK/PPP/01/03 Jld 1:*** *Direktif untuk Memuatkan Kenyataan Amaran Berkaitan dengan Risiko Kanser Payudara Di Kalangan Pesakit Lelaki dalam Sisip Bungkusan Semua Produk Yang Mengandungi Finasteride*
2.	**ACE INHIBITORS** The following statement shall be <u>included in the package inserts</u> of products containing ACE inhibitors: **WARNING** • INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY **USE IN PREGNANCY** • INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY ***Reference: Circular Bil (65) dlm BPFK/02/5/1.3:*** *Produk yang Mengandungi 'ACE Inhibitors'*
3.	**ACETYLSALICYLIC ACID (ASPIRIN)** For products containing Acetylsalicylic acid, the following <u>warning shall be included on the labels</u> in two languages (*Bahasa Malaysia* and English): ***AMARAN*** *TIDAK BOLEH DIBERI KEPADA KANAK-KANAK BERUMUR KURANG DARIPADA 16 TAHUN.* **WARNING** NOT TO BE GIVEN TO CHILDREN UNDER 16 YEARS OF AGE.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
4.	**ACTIVATED CHARCOAL/ ATTAPULGITE** 4.1 The following boxed warning shall be included on the labels of products containing Activated charcoal/ attapulgite: **NOT RECOMMENDED FOR TREATMENT OF DIARRHOEA IN CHILDREN UNDER 6 YEARS OF AGE** 4.2 The following statements shall be included in the package inserts of products containing Activated charcoal/ attapulgite: **Not recommended for treatment of diarhoea in children under 6 years of age** **WARNING** Activated charcoal/ attapulgite may interfere with the absorption of other drugs, including antibiotics, when administered concurrently. **PRECAUTION** Appropriate fluid and electrolyte therapy should be given to protect against dehydration. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative.
5.	**ALBENDAZOLE & BENZIMIDAZOLE ANTIHELMINTICS** The following statement shall be included on the labels and in the package inserts of products containing Albendazole or Benzimidazole antihelmintics: SHOULD NOT BE ADMINISTERED DURING CONFIRMED OR SUSPECTED PREGNANCY

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
6.	**ALFALFA (*MEDICAGO SATIVA*)** The following boxed warning shall be included on the labels of products containing Alfalfa (*Medico sativa*): This product contains **Alfalfa** (*Medico sativa*). Individual with a predisposition to **systemic lupus erythematosus** should consult their physician before consuming this product.
7.	**ALLOPURINOL** The following statement shall be included in the package inserts of products containing Allopurinol: **WARNING** Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction. Hypersensitivity to allopurinol usually appears after some weeks of therapy, and more rarely immediately after beginning treatment. In some instances, a skin rash may be followed by more severe reactions such as exfoliative, urticarial and purpuric lesion as well as Stevens-Johnson syndrome, and/or generalized vasculitis, irreversible hepatotoxicity and even death.
8.	**ALPHA DIHYDROERGOCRYPTINE** Please refer to DOPAMINERGIC INGREDIENT
9.	**ALPRAZOLAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
10.	**AMIODARONE** The following boxed warning shall be included on the package inserts of products containing Amiodarone: **This product is to be used only by a registered medical practitioner with experience in cardiology.**
11.	**ANTIDEPRESSANTS** The following statement shall be included in the package inserts of products used as antidepressants: **WARNING** Suicidality in Children and Adolescents • Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. • Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need. • Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. • Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber. • The indication(s) approved in paediatric for the particular drug should be clearly stated / included. ***Reference: Circular Bil(41)dlm BPFK/02/5/1.3:*** *Keputusan Pihak Berkuasa Kawalan Dadah (PBKD) Berhubung Tambahan Amaran Berkaitan Dengan 'Suicidality In Children And Adolescents Treated With Antidepressants'*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
12.	**ANTIEPILEPTICS** The following statement shall be included in the package inserts of products used as antiepileptics: **WARNING AND PRECAUTION** Potential for an increase in risk of suicidal thoughts or behaviors. ***Reference: Circular Bil (43) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berkaitan Dengan "Potential for an Increase in Risk of Suicidal Thoughts or Behaviours" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Antiepileptik*
13.	**ANTIPSYCHOTIC AGENTS** **13.1 ALL ANTIPSYCHOTIC AGENTS** The following statement shall be included in the package inserts of products containing antipsychotic: **PREGNANCY AND LACTATION** Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation. [BRAND NAME] should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. ***Reference: Circular Bil (16) dlm BPFK/PPP/01/03 Jld 1:*** *Directive Kenyataan Amaran Berkaitan Dengan Risiko Extrapyrimidal And/or Withdrawal Symptoms Bagi Neonat Yang Terdedah Kepada Produk Antipsikotik Semasa Trimester Ketiga Kehamilan Pada Sisip Bungkusan Semua Produk Antipsikotik*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

13.2 ATYPICAL ANTIPSYCHOTIC AGENTS

The following statement shall be included in the package inserts of products containing atypical antipsychotic agents:

a. Clozapine
b. Olanzepine
c. Risperidone
d. Quetiapine
e. Ziprasidone
f. Aripiprazole

WARNING

Hyperglycemia and Diabetes Mellitus

Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	discontinuation of the suspect drug. ***Reference: Circular Bil (31)dlm BPFK/02/5/1.3:*** *Tambahan Amaran Berkaitan Dengan Hyperglycemia Bagi Keluaran 'Atypical Antipsychotic Agents'*
14.	**APOMORPHINE** Please refer to DOPAMINERGIC INGREDIENT
15.	**ARGININE** The following statement shall be included on the labels and in the package inserts of oral preparations containing Arginine for **health supplement products**: **WARNING** Arginine is not recommended for patients following a heart attack. ***Reference: Circular Bil (64) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran Produk Mengandungi 'Arginine'*
16.	**ARIPIPRAZOLE** Please refer to ANTIPSYCHOTIC AGENTS
17.	**ARTESUNATE** Please refer to MEFLOQUINE for products containing Mefloquine in combination with other active ingredients (mefloquine/artesunate)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
18.	**ASPARTAME** The following statement shall be included on the labels and in the package inserts of products containing Aspartame: **WARNING** Unsuitable for phenylketonurics.
19.	**ATORVASTATIN** The following statement shall be included in the package inserts of products containing Atorvastatin: **DOSAGE AND ADMINISTRATION** Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors – In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with [Product Name] should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing [Product Name] and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with [Product Name] should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with [Product Name] should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. **WARNINGS AND PRECAUTIONS**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Skeletal Muscle Effects Physicians considering combined therapy with atorvastatin and fibrates, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin (≥1g/day) should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy. All generic products containing Atorvastatin should update their package inserts respectively according to the innovator's information such as parts for Interactions, Pharmacokinetics and other parts deemed relevant. ***Reference: Circular Bil (17) dlm BPFK/PPP/07/25. Directive Bil 10 Year 2014.*** **DIREKTIF UNTUK SEMUA PRODUK ATORVASTATIN: MENGEHADKAN DOS PENGGUNAAN ATORVASTATIN UNTUK MENGURANGKAN RISIKO KECEDERAAN OTOT**
20.	**AZITHROMYCIN** The following statement shall be included in the package insert of product that contains Azithromycin: ***Special Warnings and Precautions for Use*** ***Hypersensitivity*** *As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.* *If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued. ***Prolongation of the QT interval*** *Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see section 4.8). Prescribers should consider the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including:* • *Patients with congenital or documented QT prolongation* • *Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones* • *Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia* • *Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency* • *Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval* ***Adverse Drug Reactions*** ***Post-marketing experience:*** *Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see* ***Special Warnings and Precautions for Use)****.* *Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, SJS, TEN and DRESS have been reported.* ***Reference: Circular Bil (34) dlm BPFK/PPP/07/25. Directive Bil 3 Year 2016.*** **DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI AZITHROMYCIN (FORMULASI SISTEMIK) : PENGEMASKINIAN SISIP BUNGKUSAN DENGAN MAKLUMAT KESELAMATAN BERKAITAN KESAN ADVERS QT *PROLONGATION* DAN *DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS* (DRESS)**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
21.	**BEE POLLEN** The following statement shall be included on the labels and in the package inserts of product containing bee pollen: This product contains Bee Pollen and may cause severe allergic reactions, including fatal anaphylactic reactions in susceptible individuals. Asthma and allergy sufferers may be at greater risks.
22.	**BENZOYL PEROXIDE** The following statement shall be included on the labels and in the package inserts of products containing Benzoyl peroxide: **WARNING** Do not use this medication if you have sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possible swelling.
23.	**BENZYL ALCOHOL** The following statement shall be included on label and in package insert of parenteral products containing Benzyl alcohol: **As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age.** **Not to be used in neonates.**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
24.	**BERBERINE ALKALOIDS – NATURAL OCCURING BERBERINE E.G. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA ETC.** **The** following statement shall be included on the label and in the package insert of products containing the berberine alkaloid: **WARNING** Not to be taken by babies, children under 12 years of age, pregnant women or lactating mothers. Consult your practitioner if you have conditions such as : -Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency -Haemolytic anemia -Glaucoma -Diabetes -High Blood Pressure -History of cardiovascular disease -If you are using Paclitaxel, Cyclosporin, or other chemotherapeutic agents. ***Reference :*** *Circular: Bil.(22)dlm.BPFK/PPP/06/12 Jld.26. Kawalan produk mengandungi bahan aktif yang mempunyai berberine secara semulajadi.*
25.	**BLACK COHOSH (*CIMICIFUGA RACEMOSA*)** The following statement shall be included on the labels and in the package inserts of products containing Black Cohosh (*Cimicifuga Racemosa*): **WARNING** Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine and consult your doctor immediately. Patients using herbal medicinal products should tell their doctor about it. ***Reference: Circular Bil (61) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran Produk Mengandungi 'Black Cohosh'*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
26.	**BOSWELLIA SERRATA** The following statement shall be included on label and package inserts of health supplement products containing Boswellia serrata: **WARNING:** Please consult your doctor/pharmacist before using this product if you are on other medicines.
27.	**BROMAZEPAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS
28.	**BROMOCRIPTINE** Please refer to DOPAMINERGIC INGREDIENT
29.	**BROMPHENIRAMINE** The following statement shall be included on the labels and in the package inserts of liquid oral products containing Brompheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference: Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
30.	**CAMPHOR** 25.1 The following boxed warning shall be included on the labels of products containing Camphor: CAN CAUSE CONVULSION **CONTRAINDICATED** IN CHILDREN BELOW 2 YEARS OF AGE. CAUTION MUST BE EXERCISED WHEN OLDER CHILDREN ARE TREATED **AVOID DIRECT** APPLICATION INTO THE NOSTRILS 25.2 The following warning and precaution shall be included in the package insert of products containing Camphor: **WARNING** This product is contraindicated in **children** below 2 years of age. Caution must be exercised when older children are treated. **PRECAUTION:** It is dangerous to place any camphor containing product into the nostril of children. A small amount applied this way may cause immediate collapse.
31.	**CARBAMAZEPINE** The following statement shall be included in the package insert of products containing Carbamazepine: Severe dermatologic reactions including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) have been reported with carbamazepine. Patients treated with carbamazepine should closely be monitored for signs of hypersensitivity reactions, particularly during the first month of therapy. Immediate discontinuation of therapy should be made when cutaneous reactions occur. Potential for an increase in risk of suicidal thoughts or behaviours.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
32.	**CARBIMAZOLE** The following statement shall be included in the package inserts of products containing Carbimazole: **WARNING** Carbimazole may cause white cell disorders such as neutropenia and agranulocytosis, which may be fatal if treatment with carbimazole is not stopped promptly. These reactions usually occur during the first 3 months of therapy, and in most cases, are reversible on stopping treatment. Since agranulocytosis can develop very rapidly, periodic leucocyte counts alone may not be effective in the early detection of these reactions.
33.	**CABERGOLINE** Please refer to DOPAMINERGIC INGREDIENT
34.	**CEFTRIAXONE** The following statement shall be included in the package inserts of products containing Ceftriaxone: **CONTRAINDICATION** Ceftriaxone is contraindicated in neonates (≤28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium. **WARNING** • In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. • Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: Circular Bil (48) dlm. BPFK/PPP/01/03: *Pindaan Pada Kenyataan Amaran Berkaitan Dengan "Potential Risk Associated With Concomitant Use Of Ceftriaxone With Calcium - Containing Intravenous Solutions" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Ceftriaxone*
35.	**CETIRIZINE** The following statement shall be included in the package insert of products containing Cetirizine: **PRECAUTION** Activities Requiring Mental Alertness: In clinical trials the occurrence of somnolence has been reported in some patients taking Cetirizine: due caution should therefore be exercised when driving a car or operating potentially dangerous machinery.
36.	***CHELIDONIUM MAJUS*** The following statement shall be included on the label of products containing *Chelidonium majus* in 2 languages (*Bahasa Melayu* and English) in bold font: **WARNING** This product may cause adverse reaction to the liver. ***AMARAN*** *Produk ini mungkin boleh menyebabkan kesan sampingan pada hepar (hati).* ***Reference: Circular (bil 17) dlm bpfk02/5/1.3:*** *Label Amaran Tentang Penggunaan Bahan Chelidonium majus*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
37.	**CHITOSAN** The following statement shall be included on the labels and package inserts of products containing chitosan. **"DERIVED FROM SEAFOOD"** ***Reference: Circular Bil (52) dlm BPFK/02/5/1.3:*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Daripada Sumber Laut'*
38.	**CHLORHEXIDINE** The following statements shall be included in the package insert, label and RiMUP of pharmaceutical products containing Chlorhexidine: **Package Insert** **a) Warnings and Precautions:** [Product Name] contains chlorhexidine. Chlorhexidine is known to induce hypersensitivity, including generalised allergic reactions and anaphylactic shock. The prevalence of chlorhexidine hypersensitivity is unknown, but available literature suggests this is likely to be very rare. [Product Name] should not be administered to anyone with a possible history of an allergic reaction to chlorhexidine. If any signs or symptoms of a suspected hypersensitivity reaction such as itching, skin rash, redness, swelling, breathing difficulties, light headedness, and rapid heart rate develop, immediately stop using the product. Appropriate therapeutic countermeasures must be instituted as clinically indicated. **b) Undesirable Effects/Side Effects:** Immune system disorders Frequency not known: Hypersensitivity including anaphylactic shock **Label and Consumer Medication Information Leaflet (RiMUP)**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	[Product Name] contains chlorhexidine. Inform your healthcare provider if you have a known allergy to chlorhexidine. Stop using this product and seek immediate medical assistance if you experience rash, itching, swelling, breathing difficulties, light-headedness or rapid heartbeat. **Reference : Directive No. 8 Year 2017. Ref.** BPFK/PPP/07/25 (13) Jld 1. Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Chlorhexidine : Pengemaskinian Sisip Bungkusan, Label Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Reaksi Hipersensitiviti
39.	**CHLORPHENIRAMINE** The following statement shall be included on the labels and package inserts of liquid oral products containing Chlorpheniramine: **WARNING** When used for treatment of cough and cold; (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference: Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
40.	**CHORIONIC GONADOTROPHIN** The following statement shall be included in the package inserts of products containing Chorionic gonadotrophin: **The ovulation cycle should be monitored with oestriol levels and ultrasonography**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
41.	**CLEMASTINE** The following statement shall be included on the labels and package inserts of liquid oral products containing Clemastine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference: Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
42.	**CLINDAMYCIN** The package insert must emphasize the possibility of pseudomembranous colitis with the use of the drug. The package insert must include the **following boxed or emphasized statements/ warning:** • Clindamycin therapy has been associated with severe colitis which may end fatally. • It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. • It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. • Its use in newborns is contraindicated.
43.	**CLOBAZAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
44.	**CLOPIDOGREL** The following statement shall be included in the package inserts of products containing Clopidogrel: **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE** Pharmacogenetics: Based on literature data, patients with genetically reduced CYP22C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function. **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g proton pump inhibitors) should be discouraged. **PHARMACOKINETIC PROPERTIES** The oxidative step is regulated primarily by Cytochrome P450 ISOENZYMES 2B6, 3A4, 1A1, 1A2 and 2C19. ***Reference: Circular Bil (42) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berkaitan Dengan "Possible Interaction Between Clopidogrel and Proton Pump Inhibitors" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Clopidogrel*
45.	**CLOZAPINE** Please refer to ANTIPSYCHOTIC AGENT
46.	**CODEINE** The following safety information/ statements shall be included in the package inserts of products containing Codeine: **Therapeutic Indications** [Product name] is indicated for the relief of painful disorders such as headache, dysmenorrhea, conditions involving musculoskeletal pain, myalgias

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	and neuralgias. It is also indicated as an analgesic and antipyretic in conditions accompanied by discomfort and fever, such as the common cold and viral infections. [Product name] is an effective analgesic after dental work and tooth extractions. Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone). Pada bahagian **Dosing and Administrations** <u>Paediatric population:</u> • <u>Children aged less than 12 years:</u> Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine. [Product name] is contraindicated in children below the age of 12 years for the symptomatic treatment of cold. • <u>Children aged 12 years to 18 years:</u> [Product name] is not recommended for use in children aged 12 years to 18 years with compromised respiratory function. **Contraindications** • In children below the age of 12 years for the symptomatic treatment of colds due to an increased risk of developing serious and life-threatening adverse reactions. • In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to increased risk of developing serious and life-threatening adverse reactions. • In women who are breastfeeding. • In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers. **Special Warnings and Precautions for use** <u>CYP2D6 metabolism</u> Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4 to 6.5%
Asian	1.2 to 2.0%
Caucasian	3.6 to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1.0 to 2.0%

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function

Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Pregnancy and Lactation

Pregnancy

Careful consideration should be given before prescribing the product for pregnant patients. Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers.

As a precautionary measure, use of [Product name] should be avoided during the third trimester of pregnancy and during labor.

Breastfeeding

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	[Product name] is contraindicated in women during breastfeeding. At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal. **Reference : Directive No. 16 Year 2016. Rujukan BPFK/PPP/07/25 (2) Jld 1.** DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI CODEINE DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO KESAN ADVERS RESPIRATORY DEPRESSION
47.	**COLCHICINE** The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Colchicines: **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:** Potential risk of severe drug interactions, including death, in certain patients treated with colchicine and concomitant P-glycoprotein or strong CYP3A4 inhibitors such as clarithromycin, cyclosporin, erythromycin, calcium channel antagonists (e.g Verapamil and Diltiazem), telithromycin, ketoconazole, itraconazole, HIV protease inhibitors and nefazodone. P-Glycoprotein or strong CYP3A4 inhibitors are not to be used in patients with renal or hepatic impairment who are taking colchicine. A dose reduction or interruption of colchicine treatment should be considered in patients with normal renal and hepatic function if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required. Avoid consuming grapefruit and grapefruit juice while using colchicine. ***Reference: Circular Bil (45) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berkaitan Dengan "Severe Drug Interaction Between Colchicine and P-Glycoprotein or Strong CYP3A4 Inhibitors" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Colchicine*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
48.	**CORTICOSTEROID (INHALATION)** The following statements shall be <u>included in the package insert and RiMUP</u> of inhaled corticosteriod used for treatment of Chronic Obstructive Pulmonary Disease (COPD) such as **budesonide** and **fluticasone** (product containing single active ingredient and in combination) and **beclomethasone** (only for combination product): **<u>Package Insert</u>** **a) Special Warnings and Precautions for Use:** <u>Pneumonia in patients with COPD</u> An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. Physicians should remain vigilant for the possible development of pneumonia in patient with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking status, older age, low body mass index (BMI) and severe COPD. **b) Undesirable Effects:** "Pneumonia (in COPD patients)" to be listed as "Common" adverse drug reaction in the "Infections and Infestations" SOC. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Possible Side Effects** <u>Pneumonia (infection of the lung) in COPD patients (common side effect)</u> • Tell your doctor if you have any of the following while

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	taking <product name> they could be symptoms of a lung infection: - Fever or chills; - Increased mucus production or change in mucus colour; - Increased cough or increased breathing difficulties. **Reference : Directive No. 9 Year 2017. Ref.** BPFK/PPP/07/25 (14) Jld 1. Direktif Untuk Semua Produk Inhalasi Kortikosteroid Yang Digunakan Untuk Rawatan *Chronic Obstructive Pulmonary Disease (COPD)* : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Tambahan Berkenaan Peningkatan Risiko *Pneumonia*
49.	**COX-2 INHIBITORS** The following statement shall be included in the package insert for COX-2 Inhibitors products containing Celecoxib and Etoricoxib: • Contraindication for patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke). • Warning to prescriber when prescribing COX-2 Inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia, diabetes, smoking patient and patient with peripheral arterial disease. • Statement on limiting the period and dosing is written as 'Given the association between cardiovascular risk and exposure to COX-2 Inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment'. • Contraindication for patient using Etoricoxib is written as 'Contraindication for Etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control'. ***Reference: Circular Bil (46) dlm BPFK/02/5/1.3:*** *Keputusan Mesyuarat PBKD - Tindakan-tindakan regulatori terhadap Cox-2 Inhibitors: Celecocib dan Etoricoxib*
50.	**CYPROTERONE ACETATE** The following statement shall be included in the package inserts of products containing Cyproterone acetate: **WARNING** Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	has been fatal in some cases, has been reported in patients treated with 100mg or more of cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.
51.	**CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION** **CYPROTERONE ACETATE 2MG AND ETHINYLESTRADIOL 0.035MG** The following statement shall be included in the package inserts of products containing Cyproterone acetate 2mg and Ethinylestradiol 0.035mg **INDICATION:** - Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age. - For the treatment of acne, [product name] should only be used after topical therapy or systemic antibiotic treatments have failed. - Since [product name] is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives. **DOSAGE AND METHOD OF ADMINISTRATION** (At the beginning part with **bold** formatting) **Note: [Product name] should not be prescribed for the purpose of contraception alone. However, when taken as recommended, [product name] will provide reliable contraception in patients treated for the above clinical conditions. If patient compliance is uncertain and contraception is necessary, then a supplementary non-hormonal contraceptive method should be considered.** **UNDESIRABLE EFFECTS:** - Vascular Disorders - Rare: Thromboembolism

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
52.	**CYTOTOXIC AGENT** The following boxed statement shall be included on the label of products containing Cytotoxic agents: **CAUTION : CYTOTOXIC AGENT** ***Note:*** *The label caution should be printed prominently on the label.*
53.	**DEXBROMPHENIRAMINE** The following statement shall be included on the labels and package inserts of liquid oral products containing Dexbrompheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference: Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
54.	**DEXTROMETHORPHAN** The following statement shall be included on the labels and package inserts of liquid oral products containing Dextromethorphan: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference: Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
55.	**DIAZEPAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS
56.	**DICLOFENAC SODIUM** The following statement shall be included in the package inserts of products containing Diclofenac sodium: **PRECAUTION** Severe cutaneous reactions, including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs. Adverse effects: Dermatological: Occasional - rashes or skin eruptions Cases of hair loss, bullous eruptions, erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported. **DOSAGE AND ADMINISTRATION** **DOSAGE** As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section WARNINGS AND PRECAUTIONS). **ESTABLISHED CARDIOVASCULAR DISEASE OR SIGNIFICANT CARDIOVASCULAR RISK FACTORS** Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes melilitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily if treated for more than 4 weeks (see section WARNINGS AND PRECAUTIONS).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	CONTRAINDICATIONS Severe cardiac failure (see section WARNINGS AND PRECAUTIONS). **WARNINGS AND PRECAUTIONS** **CARDIOVASCULAR EFFECTS** Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, maybe associated with an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke). Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes melilitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks. Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event. **ADVERSE DRUG REACTIONS** **Cardiac Disorders** Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain. * The frequency reflects data from long-term treatment with a high dose (150 mg/day). **DESCRIPTION OF SELECTED ADVERSE DRUG REACTIONS** **Arteriothrombotic events** Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see section WARNINGS AND PRECAUTIONS). ***Circular :*** *(30)dlm.bpfk/ppp/07/25 ; Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 7 Year 2015 : Direktif Untuk Semua Produk Yang Mengandungi Diclofenac (Formulasi sistemik) : Pengemaskinian Sisip Bungkusan Dengan MaklumatKeselamatan Berkaitan Kesan Advers Kardiovaskular*
57.	**DICYCLOMINE** The following boxed warning shall be included on the labels and in the package inserts of products containing Dicyclomine: **WARNING** Dicyclomine is not recommended for use in infants under the age of six month
58.	**DIPHENHYDRAMINE** The following statement shall be included on the labels and in the package inserts of products containing Diphenhydramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference: Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
59.	**DIPHENOXYLATE** 1. The following boxed warning shall be included on the labels of products containing Diphenoxylate: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE.** 2. The following statement shall be included in the package insert of products containing Diphenoxylate: **WARNING** **Not recommended for children under 6 years of age.** **PRECAUTION** Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid detention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes, especially in young children. If severe dehydration of electrolyte imbalance is present, diphenoxylate should be withheld until appropriate corrective therapy has been initiated.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

60. **DOMPERIDONE**

The following statement shall be included on the package inserts of products containing Domperidone:

THERAPEUTIC INDICATIONS

Domperidone is indicated for the relief of the symptoms of nausea and vomiting.

This includes:

- Nausea and vomiting of functional, organic, infectious or dietary origin.
- Nausea and vomiting induced by:
  - radiotherapy or drug therapy.
  - dopamine agonists (such as L-dopa and bromocriptine) used in the treatment of Parkinson's disease.

DOSAGE AND ADMINISTRATION

It is recommended to take [product name] 15-30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed.

Adults and adolescents ≥ 12 years and weighing ≥35 kg and children weighing ≥ 35 kg

The dose of [product name] should be the lowest effective dose for the individual situation (typically 30 mg/day) and can be increased if necessary to a maximum daily oral dose of 40 mg.

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. If nausea and vomiting persists for longer than one week, patients should consult their physician. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Film-coated tablets (10 mg/tablet)	1 tablet three to four times per day	40 mg (4×10 mg tablet)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Oral suspension (1 mg/ml)	10 mL three to four times per day	40 mg (40 mL of 1 mg/mL oral suspension)

<u>Neonates, Infants and children < 12 years of age and weighing < 35 kg, and adults and adolescents weighing < 35 kg</u>

The dose of [product name] should be the lowest effective dose. The total daily dose is dependent on weight (see table below). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life, the risk of neurological side effects is higher in young children. Overdosing may cause nervous system disorders in children. The dose should be determined accurately based on body weight and not exceed the recommended maximum individual and daily dose in neonates, infants, toddlers and children.

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed. Film-coated tablets and orodispersible tablets are unsuitable for use in children, adults and adolescents weighing less than 35 kg. Suppositories are unsuitable for use in children.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Oral suspension (1 mg/mL)	0.25 mg/kg three to four times per day	1 mg/kg but no more than 35 mL (35mg)

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L), the dosing frequency of [product name] should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Patients with severe renal impairment should be reviewed regularly.

Hepatic impairment

[Product name] is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh >9) hepatic impairment. Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	CONTRAINDICATIONS [Product name] is contraindicated in the following situations: • Known hypersensitivity to domperidone or any of the excipients. • Prolactin-releasing pituitary tumour (prolactinoma). • In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see Warnings and Precautions). • co-administration with QT-prolonging drugs • co-administration with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects). • Whenever stimulation of gastric motility might be dangerous, e.g., in the presence of gastro-intestinal haemorrhage, mechanical obstruction or perforation. • In patients with moderate or severe hepatic impairment). **WARNINGS AND PRECAUTIONS** **Cardiovascular effects** Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT-prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see Adverse Reactions). Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see Adverse Reactions). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors. Domperidone should be used at the lowest effective dose in adults and children. Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Contraindications). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk. Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician. Patients should be advised to promptly report any cardiac symptoms. **ADVERSE REACTIONS** {information to be included} **Postmarketing:** **Cardiac Disorders** Frequency: Very rare Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, Sudden cardiac death (see Warnings and Precautions) **Reference Directive : (28)dlm.bpfk/ppp/07/25 ;** **ARAHAN PENGARAH KANAN PERKHIDMATAN FARMASI BILANGAN 4 YEAR 2015 : DIREKTIF UNTUK SEMUA PRODUK DOMPERIDONE UNTUK MENGEHADKAN PENGGUNAAN BERIKUTAN RISIKO KESAN ADVERS JANTUNG**

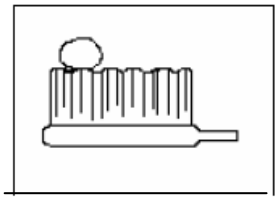
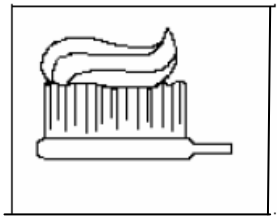
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
61.	**DOPAMINERGIC INGREDIENT** The following warning/ statement related to "Sudden sleep onset" shall be included in the package insert and product literature of products containing dopaminergic ingredients: a. alpha-dihydroergocryptine b. apomorphine c. bromocriptine d. cabergoline e. levodopa f. lisuride g. piribedil h. pramipexole i. quinagolide j. ropinirole **SPECIAL WARNING & SPECIAL PRECAUTIONS FOR USE** ……. has been associated with somnolence and episodes of sudden onset, particularly in patients with Parkinson's diseases. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ……. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES** Patients being treated with ……. and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also section on special warnings and special precautions for use). **UNDESIRABLE EFFECTS** ……. is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes. ***Reference: Circular (bil 14) dlm bpfk02/5/1.3:*** *Keluaran yang mengandungi bahan aktif dopaminergik- tanda amaran berkaitan dengan ' sudden sleep onset'*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
62.	**EPHEDRINE** The following statement shall be included on the labels and in the package inserts of products containing Ephedrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference: Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
63.	**ETHINYLESTRADIOL** Please refer to CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION for products containing cyproterone acetate 2mg with ethinylestradiol 0.035mg in combination.
64.	**ETORICOXIB** (Please also refer to COX-2 INHIBITORS) The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Etoricoxib: **Package Insert** **Dosage and Administration:** Rheumatoid arthritis The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Ankylosing spondylitis The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered. **Consumer Medication Information Leaflet (RiMUP)** **Recommended Dose/How Much to Use** Rheumatoid arthritis The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. Ankylosing spondylitis The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. **Reference : Directive No. 13 Year 2017. Ref.** BPFK/PPP/07/25 (18) Jld 1. Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Etoricoxib : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Perubahan Dos Permulaan Bagi Rawatan Rheumatoid Arthritis Dan Ankylosing Spondylitis
65.	**FAMOTIDINE** The following statement shall be included in the package inserts of products containing Famotidine: **DOSAGE** Dosage adjustment is required for patients with moderate to severe renal insufficiency. Since CNS adverse effects have been reported in patients with moderate to severe renal insufficiency, to avoid excess accumulation of the drug, the dose of famotidine may be reduced to half the recommended dose or the dosing interval may be prolonged to 36 - 48 hours as indicated by the patient's clinical response. **PRECAUTION** As elderly patients are more likely to have decreased clearance of famotidine, care should be taken in dose selection and it may be useful to monitor renal function.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
66.	**FIBRATES** The following statement shall be included in the package inserts of products containing Fibrates: a. Clofibrate, b. Bezafibrate c. Ciprofibrate, Etofibrate d. Fenofibrate e. Simfibrate f. etc. **DRUG INTERACTION** Concurrent use of fibrates with HMG-CoA reductase inhibitors may cause severe myositis and myoglobinuria.
67.	**FILGRASTIM** The following statement shall be included in the package inserts of ALL biosimilar products containing FILGRASTIM **WARNINGS AND PRECAUTIONS** Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care. **UNDESIRABLE EFFECTS** Clinical Trials **In Cancer Patients** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥1/1000 to < 1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony stimulating factors. **In Normal Donors undergoing peripheral blood progenitor cell mobilization** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed,

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony stimulating factors. Post Marketing **Vascular disorders** Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. **Reference: Circular Bil (20) dlm. BPFK/PPP/07/25. Directive No. 13 Year 2014. Direktif Untuk Semua Produk Yang Mengandungi Filgrastim Dan Pegfilgrastim : Amaran Berkaitan Risiko *Capillary Leak Syndrome (Cls)* Bagi Pesakit Kanser Dan *Healthy Donor* (Filgrastim) Dan Bagi Pesakit Kanser (Pegfilgrastim)**
68.	**FLUCLOXACILLIN** The following warning shall be included in the package insert of products containing Flucloxacillin: **WARNING** Liver Toxicity Flucloxacillin can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in older patients and those who take the drug for prolonged periods (see Precaution, Adverse Reactions)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
69.	**FLUORIDE** All toothpastes containing Fluorides should be labeled with the following additional information: a. **DIRECTIONS ON USE** • Do not swallow – spit and rinse after use. b. **FOR CHILDREN BELOW 6 YEARS** • Use a pea-sized amount of toothpaste (less than 5mm). • Supervise child's brushing. c. **DIRECTIONS ON DENTAL HEALTH** • Brush at least twice a day. • Restrict the amount and frequency of sugary food. • Visit your dentist at least once a year. d. **GRAPHICS AS SHOWN** • *Child's use* • *Adult's use*  *Child's use*  *Adult's use*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
70.	**FLUOROQUINOLONES** The following statement shall be included in the package inserts of products containing fluoroquinolones: **WARNING AND PRECAUTION** Exacerbation of myasthenia gravis Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with flouroquinolones use in persons with myasthenia gravis. Avoid flouroquinolones in patients with known history of myasthenia gravis **ADVERSE REACTIONS/SIDE EFFECTS** Exacerbation of myasthenia gravis Post Marketing Experience ***Reference: Circular Bil (20) dlm BPFK/PPP/01/03 Jld 1:*** *Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Exacerbation of Myasthenia Gravis dalam Sisip Bungkusan Semua Produk Antibiotik dalam Kumpulan Fluoroquinolones*
71.	**FLURAZEPAM HYDROCHLORIDE** Please refer to SEDATIVE – HYPNOTIC PRODUCTS
72.	**GADOBENIC ACID** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
73.	**GADOBUTROL** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
74.	**GADODIAMIDE** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
75.	**GADOLINIUM OXIDE** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
76.	**GADOTERIC ACID** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
77.	**GADOVERSETAMIDE** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
78.	**GADOXETIC ACID** Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
79.	**GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING** The following boxed warning and warning shall be included in the package inserts of products containing: a. Gadobenate Dimeglumine b. Gadobenic acid c. Gadobutrol d. Gadodiamide e. Gadolinium oxide f. Gadoteric acid

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

g. Gadoversetamide
h. Gadoxetic acid

BOXED WARNING

- Exposure to gadolinium – based contrast agents (GBCAs) increases the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with:
  - acute or chronic severe renal insufficiency (glomerular filtration rate < 30mL/min/1.73m²), or
  - acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs

- Avoid use of GBCAs unless the diagnotic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).

- Screen all patients for renal dysfunction by obtaining a history and/ or laboratory tests.

- When administering a GBCA, do not exceed the dose recommended in product labelling. Allow sufficient time for elimination of the GBCA prior to any readministration.

WARNING

- Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA.

- For patients receiving haemodialysis, healthcare professionals may consider prompt haemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if haemodialysis prevents NSF.

- Determine the renal function of patients by obtaining a medical history of conducting laboratory tests that measure renal function prior to using

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	GBCA. • The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown. • Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. ***Reference: Circular Bil (2) dlm. BPFK/PPP/01/03 Jld. 1:*** *PENAMBAHAN AMARAN BERKOTAK DAN AMARAN TERKINI KE DALAM SISIP BUNGKUSAN SEMUA AGEN "CONTRAST MEDIUM" YANG BERASASKAN GADOLINIUM (GADOLINIUM BASED) UNTUK TUJUAN 'MAGNETIC RESONANCE IMAGING' "*
80.	**GAMAT/ STICHOPUS spp.** For products containing Gamat/ Stichopus spp. for **ORAL USE ONLY**, please state: **"Please consult your pharmacist, doctor, or other healthcare providers about any other supplements/ medications you are taking and other health care problems. There may be a potential for interactions or side effects."**
81.	**GENTAMICIN TOPICAL PREPARATIONS** The following boxed statement shall be included in the package inserts of topical Gentamicin preparations: Use of topical gentamicin preparations in closed hospital settings is actively discouraged
82.	**GINKGO BILOBA/ GINKGO EXTRACT** The following statements shall be included on the labels and in the package inserts of products containing *Gingko biloba*/ Gingko extract: As the use of Ginkgo may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/dental procedure. (*Memandangkan Ginkgo boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau akan*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	menggunakan ubat lain dan sebelum prosedur pembedahan / dental dijalankan). ***Reference: Circular Bil (47) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran Pada Label Dan Sisip Bungkusan Produk Yang Mengandungi Ginkgo Biloba / Ginkgo Ekstrak*
83.	**GINSENG** The following <u>statements</u> shall be <u>included on the labels and in the package inserts</u> of products containing Ginseng (including all Panax genus): • Contraindicated in pregnant women. • Safe use in lactating women and children has not been established. • Do not exceed the stated dose. • Safety on long term use has not been established.
84.	**GLUCOSAMINE** 71.1 The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of products containing Glucosamine (derived from seafood); **"DERIVED FROM SEAFOOD"** 71.2 The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Glucosamine: **SIDE EFFECT** • Cardiovascular Peripheral oedema, tachycardia were reported in a few patients following larger clinical trials investigating oral administration in osteoarthritis. Causal relationship has not been established. • Central nervous system Drowsiness, headache, insomnia have been observed rarely during therapy (less than 1%). • Gastrointestinal Nausea, vomiting, diarrhoea, dyspepsia or epigastric pain, constipation, heartburn and anorexia have been described rarely during oral therapy with glucosamine. • Skin

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Skin reactions such as erythema and pruritus have been reported with therapeutic administration of glucosamine. ***Reference:*** *a)* ***Circular Bil (52) dlm BPFK/02/5/1.3:*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Daripada Sumber Laut'* *b)* ***Circular Bil (72) dlm BPFK/02/5/1.3:*** *Mengemaskini dan menyelaraskan maklumat mengenai kesan sampingan pada label & sisip bungkusan produk yang mengandungi glucosamine*
85.	**HIV PROTEASE INHIBITORS** The following statement shall be included in the package inserts of products containing HIV Protease inhibitors: **ADVERSE REACTION** Although a causal relationship has not been definitively established, protease inhibitors may contribute to increase in blood sugar levels and even diabetes in HIV patients. Close monitoring of blood glucose level is recommended.
86.	**HYDROQUINONE** The following warning shall be included on the outer labels of products containing Hydroquinone: **WARNING:** Some users of this product may experience skin irritations. Should this occur, stop using and consult a medical doctor. For hydroquinone products that do not contain any sun screening agent, a statement should be included in the package insert to advise users to either use a sun screening agent or protect themselves from sunlight or to use the products only at night. ***Reference: Circular (bil 26) dlm bpfkweb.bpkp.3.2000:*** *Amaran bagi Produk Mengandungi Hydroquinone*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
87.	**IMMUNOSUPPRESANTS** The following information shall be included in the package inserts of products containing the following immunosuppressants: a) Sirolimus b) Cyclosporin c) Mycophenolate mofetil d) Mycophenolic acid e) Tacrolimus **WARNINGS AND PRECAUTIONS** Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes. ***Reference: Circular Bil (44) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berkaitan Dengan "Increased Risk For Opportunistic Infections Such As Activation of Latent Viral Infections Including BK Virus – Associated Nephropathy" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Immunosuppressant*
88.	**INSULIN** The label of the product shall state clearly the source of insulin.
89.	**INGREDIENTS DERIVED FROM SEAFOOD** The following statement shall be included on the labels and package inserts of products. **"DERIVED FROM SEAFOOD"** ***Reference: Circular Bil (52) dlm BPFK/02/5/1.3:*** *Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Daripada Sumber Laut'*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
90.	**INTERFERON ALPHA** The following statements shall be included in the package insert and RiMUP of products containing Interferon Alpha: **Package Insert** **a) Adverse Drug Reactions:** **Respiratory, thoracic and mediastinal disorders:** Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alpha products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alpha. **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects** Tell your doctor immediately if you experience: • Shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen. These may indicate pulmonary arterial hypertension (high blood pressure in the arteries that supply the lungs). **Reference : Directive No. 1 Year 2017. Ref. BPFK/PPP/07/25 (6) Jld 1.** Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa Dan Interferon Beta : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers *Pulmonary Arterial Hypertension (PAH)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
91.	**INTERFERON BETA** The following statements shall be <u>included in the package insert and RiMUP</u> of products containing Interferon Beta: **<u>Package Insert</u>** **a) Adverse Drug Reactions:** **Respiratory, thoracic and mediastinal disorders:** Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **a) Side Effects** Tell your doctor immediately if you experience: • Shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen. These may indicate pulmonary arterial hypertension (high blood pressure in the arteries that supply the lungs). **Reference : Directive No. 1 Year 2017. Ref. <u>BPFK/PPP/07/25 (6) Jld 1.</u>** Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa Dan Interferon Beta : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers *Pulmonary Arterial Hypertension (PAH)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
92.	**KAOLIN, PECTIN, KAOLIN-PECTIN** The following boxed warning shall be included on the labels: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE.** The following statement shall be included in the package inserts of products containing kaolin and/ or pectin: **WARNING** **Not recommended for children under 6 years of age.** Severe constipation, which may lead to faecal impaction, may rarely occur in children and the elderly patients taking kaolin and pectin. Kaolin and pectin may interfere with the absorption of other drugs, including antibiotics, administered concurrently. **PRECAUTION** Appropriate fluid and electrolyte therapy should be given to protect against dehydration. Oral rehydration therapy with the use of appropriate fluids including oral rehydration salts - remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

93. **KETOCONAZOLE**

a) Indication of products containing oral ketoconazole is restricted as follows, and the package insert of the product shall be amended accordingly:

[BRAND NAME] (ketoconazole) Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

[BRAND NAME] (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis.

[BRAND NAME] (ketoconazole) Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid.

Reference: ***Directive (9)dlm.BPFK/PPP/07/25:*** *Direktif untuk memperketatkan indikasi semua produk ketoconazole oral dan mengehadkan penggunaan di hospital sahaja berikutan risiko kesan advers hepatotoksisiti*

b) The following statement shall be included in the package inserts of products containing oral ketoconazole:

CONTRAINDICATIONS

In patients with acute or chronic liver disease.

WARNINGS & PRECAUTIONS

Because of the risk for serious hepatotoxicity, [BRAND NAME] should be used only when the potential benefits are considered to outweigh the potential risks, taking into consideration the availability of other effective antifungal therapy.

Assess liver function, prior to treatment to rule out acute or chronic liver disease, and monitor at frequent and regular intervals during treatment, and at the first signs or symptoms of possible hepatotoxicity.

Hepatotoxicity

Very rare cases of serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation have occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Cases have been reported that occurred within the first month of treatment, including some within the first week.

The cumulative dose of the treatment is a risk factor for serious hepatotoxicity.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
94.	**KETOROLAC TROMETHAMOL (KETOROLAC TROMETHAMINE)** The following statements shall be included in the package inserts of products containing Ketorolac tromethamol: **THE PRODUCT SHALL BE INDICATED FOR THE FOLLOWING** For short-term management of moderate to severe acute post-operative pain following surgical procedures associated with low risk of haemorrhage. **DOSAGE AND DURATION OF TREATMENT** Parenteral administration: The starting dose should be 10mg with subsequent doses of 10-30mg four to six hourly as required. The lowest effective dose should be used. The total daily dose of 90mg for the non-elderly and 60mg for the elderly should not be exceeded. Maximum duration of parenteral treatment is 2 days for all age groups. In patients who have received parenteral ketorolac and are converted to oral tablets, the total combined daily dose of all forms of ketorolac should not exceed 90mg for non-elderly and 60mg for the elderly. Maximum duration of treatment for the oral formulation is 7 days. **CONTRAINDICATIONS** • A history of peptic ulceration or gastrointestinal bleeding • A history of haemorrhagic diathesis • A history of confirmed or suspected cerebrovascular bleeding • Operations associated with a high risk of haemorrhage • A history of asthma • Moderate or severe renal impairment (serum creatinine > 160❍mol/L) • Hypovolaemia or dehydration from any cause • Hypersensitivity to NSAIDs or aspirin • During pregnancy, labour, delivery or lactation • Concomitant administration with other NSAIDs, anticoagulant including low dose heparin
95.	**LEVODOPA** Please refer to DOPAMINERGIC INGREDIENT

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
96.	**LEVONORGESTREL** The following statements shall be <u>included in the package insert, label and RiMUP</u> of emergency contraceptives containing Levonorgesteral: **<u>Package Insert</u>** **a) Recommended Dose:** Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to use a non-hormonal emergency contraceptive, i.e. Cu-IUD or take a double dose of levonorgestrel (i.e. <number of> tablets taken together) for those women unable or unwilling to use Cu-IUD. **b) Interaction of Other Medicaments:** The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers, mainly CYP3A4 enzyme inducers. Concomitant administration of efavirenz has been found to reduce plasma levels of levonorgestrel (AUC) by around 50%. Drugs suspected of having similar capacity to reduce plasma levels of levonorgestrel include barbiturates, phenytoin, carbamazepine, herbal medicines containing Hypericum perforatum (St. John's wort), rifampicin, ritonavir, and griseofulvin. For women who have used enzyme-inducing drugs in the past 4 weeks and need emergency contraception, the use of non-hormonal emergency contraception (i.e. a Cu-IUD) should be considered. Taking a double dose of levonorgestrel (i.e. 3 mg within 72 hours after the unprotected intercourse) is an option for women who are unable or unwilling to use a Cu-IUD, although this specific combination (a double dose of levonorgestrel during concomitant use of an enzyme inducer) has not been studied. **<u>Label</u>** *If you have used certain **other medicines in the last 4 weeks**, in particular treatment for epilepsy, tuberculosis, for HIV infection or herbal medicines containing St. John´s wort (see leaflet), <product name> may work less effectively. If you use these medicines take <number of>tablets of <product name>. If you are unsure or to ask for an alternative treatment speak to your doctor or pharmacist before using <product name>.*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Consumer Medication Information Leaflet (RiMUP) **a) Before you use <product name>** **-Taking other medicines** If you have used any of the medicines below during the last 4 weeks, <product name> may work less effectively.Your doctor may prescribe another type of (non-hormonal) emergency contraceptive, i.e. a copper intrauterine device (Cu-IUD). If this is not an option for you or if you are unable to see your doctor promptly, you can take a double dose (i.e. <number of> tablets) of <product name>: • medicines used to treat epilepsy (e.g. phenobarbitone, phenytoin, carbamazepine) • medicines used to treat tuberculosis (e.g. rifampicin) • medicines used to treat HIV (e.g. ritonavir, efavirenz) • medicines used to treat fungal infections (e.g. griseofulvin) • herbal remedies containing St. John's wort (Hypericum perforatum) Speak to your doctor or pharmacist if you need further advice on the correct dose for you. Consult your doctor as soon as possible after taking the tablets for further advice on a reliable form of regular contraception and to exclude a pregnancy. **Reference : Directive No. 11 Year 2017. Ref.** BPFK/PPP/07/25 (16) Jld 1. Direktif Untuk Semua Produk Kontraseptif Kecemasan Yang Mengandungi Levonorgestrel Dengan Maklumat Berkaitan Interaksi Antara Ubat-Ubatan Yang Dikelaskan Sebagai *Hepatic Enzyme Inducer* Dan Keberkesanan Kontrasepsi

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
97.	**LINCOMYCIN** For all products containing Lincomycin: The package insert must emphasize the possibility of pseudomembranous colitis with the use of the drug and must include the following boxed or emphasized statement/ warning: a. Lincomycin therapy has been associated with severe colitis which may end fatally. b. It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. c. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. d. Its use in newborns is contraindicated.
98.	**LISURIDE** Please refer to DOPAMINERGIC INGREDIENT
99.	**LIQUID PARAFFIN** The following statement shall be included on the labels of products containing Liquid paraffin as laxative: • Not recommended for use in children below 3 years of age; • Not recommended for use in pregnant women; • Repeated use is not advisable; • Consult your doctor if laxatives are needed every day, if you have persistent abdominal pain or have a condition which makes swallowing difficult.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

100. **LOPERAMIDE**

1. The following boxed warning shall be included on the label of products containing Loperamide:

NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE

2. The following statement shall be included in the package insert of products containing Loperamide:

a) WARNING

Not recommended for children under 6 years of age. Its use has been associated with fatal episodes of paralytic ileus in infants and young children.

Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes. If severe dehydration or electrolyte imbalance is present Loperamide should be withheld until appropriate corrective therapy has been initiated.

c) Warnings and Precautions

The use of higher than the recommended doses for control of the diarrhea may cause abnormal heart rhythms and serious cardiac events leading to death. However, in adult patients receiving the recommended dosage of loperamide, cases of syncope and ventricular tachycardia have been reported. Some of these patients were taking other drugs or had other risk factors that may have increased their risk of cardiac adverse reactions.

Abuse and misuse of loperamide, as an opioid substitute, have been described in individuals with opioid addiction (see Overdose).

d) Adverse Reactions

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Post-marketing Experience Cardiac Disorders: QT/QTc interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death (see Warnings and Precautions). **e) Overdose** In individuals who have intentionally ingested overdoses (reported in doses from 40 mg up to 792 mg per day) of loperamide HCl, prolongation of the QT/QTc interval, Torsades de Pointes, other ventricular arrhythmias and cardiac arrest, have been observed (see Warnings and Precautions). Fatal cases have also been reported. 3. The following statement shall be included in the RiMUP of products containing Loperamide: **a) If you use too much (overdose)** If you have taken more than the recommended dose of [product name], immediately contact your doctor or go to the Emergency Department of your nearest hospital for advice. Symptoms may include : • changes to your heartbeat such as increased heart rate and irregular heart rhythm (these symptoms can have potentially serious, life-threatening consequences) • muscle stiffness • uncoordinated movements • drowsiness • difficulty urinating • weak breathing **Reference : Directive No. 14 Year 2017. Ref.** BPFK/PPP/07/25 (19) Jld 1. Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Loperamide : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Pada Jantung Yang Serius Susulan Pengambilan Loperamide Melebihi Dos Yang Disyorkan Dan Isu Penyalahgunaan
101.	**LORAZEPAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
102.	**LOVASTATIN** The following statement shall be included in the package inserts of products containing Lovastatin: **1. Contraindications:** • Concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone). • Concomitant administration of cyclosporine. **2. Dosage and Administration:** Concomitant Therapy The combined use of lovastatin with gemfibrozil should be avoided. In patients taking danazol, verapamil, diltiazem, fibrates (except gemfibrozil) or lipid-lowering dose of niacin (≥1g/day) concomitantly with [Product Name], the dose of [Product Name] should not exceed 20mg/day. In patients taking amiodarone concomitantly with [Product Name], the dose of [Product Name] should not exceed 40mg/day. **3. Warnings and Precautions:** Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine. **4. Interactions:** Contraindicated Drugs Strong inhibitors of CYP3A4: Concomitant use with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) is contraindicated. Cyclosporine: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine. Concomitant use of this drug with lovastatin is contraindicated.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Other Drugs • Gemfibrozil, other fibrates, niacin ≥1g/day: These drugs increase the risk of myopathy when given concomitantly with lovastatin, probably because they can produce myopathy when given alone. There is no evidence to suggest that these agents affect the pharmacokinetics of lovastatin. Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of lovastatin with fibric acid derivatives or niacin. • Danazol, verapamil, diltiazem: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, verapamil, or diltiazem particularly with higher doses of lovastatin. • Amiodarone: The risk of myopathy/rhabdomyolysis is increased when amiodarone is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class. • Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine.
103.	**MEFLOQUINE** The following statement shall be included in the package inserts of products containing Mefloquine as single ingredient or in combination with other active ingredients: **1. SPECIAL WARNINGS AND PRECAUTIONS FOR USE** a) Products containing Mefloquine as single ingredient**:** In chemoprophylaxis the safety profile of mefloquine is characterized by a predominance of neuropsychiatric adverse reactions. If acute anxiety, depression, restlessness or confusion occur during prophylactic use, **[Brand name] (mefloquine)** should be discontinued and an alternative prophylactic agent should be recommended. Because of the long half-life of mefloquine, adverse reactions to **[Brand name] (mefloquine)** may occur or persist up to several weeks after discontinuation of the drug. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with **[Brand name] (mefloquine)**.

b) Products containing Mefloquine in combination with other active ingredientas (mefloquine/artesunate):

If acute anxiety, depression, restlessness or confusion occur during treatment, **[Brand name] (mefloquine/artesunate)** should be discontinued and an alternative agent should be recommended. Because of the long half-life of mefloquine, adverse reactions to **[Brand name] (mefloquine/artesunate)** may occur or persist up to several weeks after discontinuation of the drug. In a small number of patients it has been reported that dizziness or vertigo and loss of balance may continue for months after discontinuation of the drug.

Eye disorders, including but not limited to optic neuropathy and retinal disorders, have been reported during treatment with mefloquine. Any patient presenting with a visual disorder should be referred to the treating physician, as certain conditions may require stopping treatment with **[Brand name] (mefloquine/artesunate).**

2. **POSTMARKETING ADVERSE EVENT**

Nervous system disorders	
Common	Dizziness, headache
Not known	Balance disorder, somnolence, syncope, convulsions, memory impairment, peripheral sensory neuropathy and peripheral motor neuropathy (including paraesthesia, tremor and ataxia), encephalopathy
Eye disorders	
Common	Visual impairment
Not known	Vision blurred, cataract, retinal disorders and optic neuropathy which may occur with latency during or after treatment

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	References: Circular (13)dlm.BPFK/PPP/01/03 Jld.3: *Pengemaskinian sisip bungkusan semua produk antimalaria yang mengandungi mefloquine (termasuk produk kombinasi) dengan maklumat keselamatan berkaitan kesan advers pada sistem saraf (neurologik) yang berpanjangan dan gangguan penglihatan*
104.	**MELALEUCA LEUCADENDRA** The following statement shall be included on the labels of products containing Melaleuca Leucadendra (cajeput oil) in topical dosage form: a) Malay language:- **AMARAN** **Produk ini tidak boleh disapu pada muka, khususnya di kawasan hidung bayi dan kanak-kanak. Ia mungkin boleh menyebabkan masalah pernafasan / kesukaran bernafas.** b) English language:- **WARNING** **This product should not be applied to the facial area, in particular around the nose of infants and small children. It might cause breathing problem / shortness of breath.** **References: Directive No. 13, Year 2016 Ref. (44)dlm.BPFK/PPP/07/25** DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI BAHAN AKTIF MINYAK CAJEPUT (*MELALEUCA LEUCADENDRA*) DALAM BENTUK DOS TOPIKAL DENGAN MENAMBAH KENYATAAN AMARAN BERKAITAN RISIKO MASALAH PERNAFASAN/ KESUKARAN BERNAFAS
105.	**METHYL SALICYLATE** The following statements shall be included in the package inserts and product literature of topical preparations containing methyl salicylate ≥5%: **CAUTION** This product contains methyl salicylate and when applied or rub on to the skin, can be absorbed through the skin into the blood. For patients taking warfarin, excessive application on to the skin for muscle or joint pains may increase the chances of bleeding.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
106.	**METHYLPHENIDATE** The following boxed statement shall be included on the labels and in the package insert of products containing Methylphenidate HCl: **FOR SPECIALIST'S USE ONLY** The following statement shall be included in the package insert of products containing Methylphenidate: **WARNINGS AND PRECAUTIONS** **Priapism** Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention. ***Reference:* *Circular (19) dlm.BPFK/PPP/07/25* Directive No. 12 Year 2014 Direktif Untuk Semua Produk Yang Mengandungi Methylphenidate: Amaran Berkaitan Risiko *Priapism* (Kesan Ereksi Yang Berpanjangan) Di Kalangan Lelaki**
107.	**METOCLOPRAMIDE** The following statements shall be included in the package inserts of products containing Metoclopramide: **DOSAGE** Total daily dose of metoclopramide, especially for children and young adults, should not normally exceed 0.5mg/kg body weight. **WARNING** • Avoid doses exceeding 0.5mg/kg/day. • Extrapyramidal effects, especially dystonic reaction of metoclopramide

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	are more likely to occur in children shortly after initiation of therapy, and usually with doses higher than 0.5mg per kg of body weight per day. The following route of products containing Metoclopramide shall update its package inserts according to the directive (24)dlm.BPFK/PPP/07/25. As below: **1) PARENTERAL ROUTE** • **Indication** • **Dose and Administration** • **Contraindication** • **Special Warnings and Precautions For Use** **2) ORAL ROUTE (Tablet/ Syrup)** • **Indication** • **Dose and Administration** • **Contraindication** • **Special Warnings and Precautions For Use** **3) RECTAL ROUTE (Suppository)** • **Indication** • **Dose and Administration** • **Contraindication** • **Special Warnings and Precautions For Use** Reference Circular : (24)dlm.BPFK/PPP/07/25. Directive No. 17 Year 2014. **Direktif Untuk Semua Produk Metoclopramide: Memperketatkan Indikasi Dan Mengehadkan Dos Penggunaan Berikutan Risiko Kesan Advers Neurologik**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

108. **MICONAZOLE**

1. Intravaginal preparations

The following boxed warning shall be included on the labels and in the package inserts of intravaginal preparations containing Miconazole:

> Sila dapatkan nasihat doktor atau ahli farmasi sebelum menggunakan keluaran ini jika anda mengambil ubat warfarin, iaitu sejenis ubat antipembekuan darah, kerana lebam/ pendarahan pada gusi/ hidung boleh berlaku secara spontan.
>
> (Please consult your physician/ pharmacist before using this product if you are on the anticoagulant medicine warfarin, because bleeding from nose/ gums or bruising may accur spontaneously).

Reference: ***Circular (bil 45) dlm bpfkweb.bpkp.2.2001:*** *Keputusan Mesyuarat Pihak berkuasa Kawalan Dadah (PBKD) ke 122 Berhubung Amaran Berkaitan Interaksi Ubat Bagi Semua Keluaran ANTIFUNGAL INTRAVAGINAL Yang Mengandungi Miconazole*

2. Oral gel preparations

The following statements shall be included in the package insert and RiMUP of oral gel preparations containing Miconazole:

Package Insert

a) Contraindications

Use of miconazole oral gel in combination with the following drug that is subjected to metabolism by CYP2C9 (see Interactions):

- Warfarin

b) Interactions

Miconazole can inhibit the metabolism of drugs metabolized by the CYP2C9 enzyme system. This can result in an increase and/or prolongation of their effects, including adverse effects.

Miconazole oral gel is contraindicated with the co-administration of the following drug that is subjected to metabolism by CYP2C9 (see Contraindications):

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

- Warfarin

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]

When you must not use it

Do not use [product name] if you are on warfarin therapy.

3. Preparations other than oral gel

The following statements shall be included in the package insert and RiMUP of preparations (other than oral gel) containing Miconazole:

Package Insert

a) Warnings and Special Precautions

In patients on warfarin, caution should be exercised and the anticoagulant effect should be monitored (see Interactions).

b) Interactions

Miconazole administered systemically is known to inhibit CYP2C9 enzyme system. Due to the limited systemic availability after topical application, clinically relevant interactions occur very rarely. In patients on warfarin which is subjected to metabolism by CYP2C9, caution should be exercised and the anticoagulant effect should be monitored (see Warnings and Special Precautions).

Consumer Medication Information Leaflet (RiMUP)

a) Before You Use [Product Name]

Before you start to use it

You must tell your doctor if you:

- are on warfarin therapy

Reference : Directive No. 10 Year 2017. Ref. BPFK/PPP/07/25 (15) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi Miconazole : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
109.	**MIDAZOLAM** The following statements shall be included in the package inserts of IV preparations containing Midazolam: **WARNING** IV Midazolam has been associated with severe respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy resulted. IV Midazolam should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory and cardiac functions. Assure immediate availability of resuscitative drugs, equipments, appropriate antidote and personnel trained in their use. Dosage of IV Midazolam must be individualized for each patient. Lower doses are usually required for elderly, debilitated or higher risk surgical patients. When Midazolam is administered intravenously for conscious sedation, it should be injected slowly (over at least 2 minutes); it should not be administered by rapid or single bolus IV injection because of respiratory depression and/or arrest, especially in elderly or debilitated patients. The initial dose may be as little as 1mg, but should not exceed 2.5mg in a normal healthy adult; administer over at least 2 minutes and allow additional 2 or more minutes to fully evaluate sedative effect. If further titration is necessary, use small increments to the appropriate level of sedation, allowing an additional 2 or more minutes after each increment to fully evaluate sedative effect. See Dosage and Administration for complete dosing information. Please refer to SEDATIVE – HYPNOTIC products for additional information.
110.	**MINOXIDIL** The label and the package insert shall include the following statement: **To be supplied only on the prescription of a registered medical practitioner.** ***Note:*** The statement is exempted for external use preparation containing not more than 5% of Minoxidil; its salts; its derivatives *(Please refer latest Poison List: Preparations for external use containing not more than 5% of Minoxidil; its salts; its derivatives, which is under Group C)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
111.	**MOMORDICA CHARANTIA** For product containing Momordica Charantia, please state: - **"Shall not be used in pregnant and breast-feeding women."** - **"Be sure to tell your pharmacist, doctor, or other healthcare providers about any other supplements you are taking. There may be a potential for interactions or side effects."**
112.	**MONTELUKAST** The following statement shall be included in the package insert of product that contains Montelukast: Addition of this statement at **ADVERSE EFFECTS:** Postmarketing Experience Blood and lymphatic system disorders : thrombocytopenia ***Reference Directive : (31)dlm.bpfk/ppp/07/25 ;*** *Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 6 Year 2015 :* *Direktif Untuk Semua Produk Yang Mengandungi Montelukast : Pengemaskinian Sisip Bungkusan Dengan Maklumat Kesan Advers Berkaitan Thrombocytopenia*
113.	**MUCOLYTIC AGENT** The following warning shall be included in the package inserts of products containing: a) Acetylcysteine b) Carbocysteine c) Methylcarbocysteine (Mecysteine) **CONTRAINDICATIONS** Contraindicated in children below two (2) years of age. ***Reference: Circular Bil (7) dlm BPFK/PPP/01/03 Jld 1:*** *Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip Bungkusan Semua Produk Carbocysteine, Acetylcysteine Dan Methylcarbocysteine (Mecysteine)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
114.	**NEVIRAPINE** The following statement shall be included in the package insert of product that contains Nevirapine: Addition of this statement at approved Indication: "Avoid usage of Nevirapine in patient with CD4+cell count greater than 250cells/mm3". ***Reference: Circular Bil (43) dlm BPFK/02/5/1.3:*** *Pendaftaran Produk Yang Mengandungi Nevirapine*
115.	**NIFEDIPINE** The following statement shall be included in the package inserts of "short acting" Nifedipine products: **WARNING/ PRECAUTION** Several well documented studies have described profound hypotension, myocardial infarction and death when immediate release nifedipine capsules are used sublingually for acute reduction of blood pressure. **DOSAGE** • Lower doses may be required in elderly patients as a result of reduced drug clearance. • For hypertension, the dose used should not exceed 60mg daily.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
116.	**NITRATES** The following statements shall be included in the package inserts of all "**NITRATES FOR STABLE ANGINA PECTORIS**": • An appropriate statement concerning the development of tolerance (under **precaution** section). A suggested statement would be as follows: 'Development of tolerance may occur with all forms of nitrate therapy particularly with the long acting preparations that maintain continuously high plasma nitrate concentration'. • An appropriate recommendation on dosage regimens. The recommended dosage regimens should be one that is able to provide a low-nitrate period or a nitrate-free period of 8-12 hours every 24 hours to prevent the development of tolerance and thus maintain the antianginal effects.
117.	**NITRAZEPAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS
118.	**NORFLOXACIN** The following statement shall be included in the package inserts of products containing Norfloxacin: **PRECAUTION** i. Should not be used in children or pregnant women ii. Phototoxicity may occur
119.	**NORMAL GLOBULIN** **INTRAMUSCULAR (IM)** The following statement shall be included in the package inserts of Normal globulin IM preparations: **WARNING** Do not administer this preparation intravenously because of potential for serious hypersensitivity reactions.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
120.	**NOSCAPINE** 1. The following **contraindication** shall be included on the labels of products containing Noscapine: **Contraindicated in Women of Child-bearing Potential** 2. The following statement shall be included in the package inserts of products containing Noscapine: **WARNING** Experimental data now suggests that noscapine may exhibit a mutagenic effect in vitro. Because of the possible consequent risk to the developing foetus, the products containing noscapine is contraindicated in women of child bearing potential, therefore pregnancy should be excluded before treatment, and effective contraception maintained throughout treatment with such products. **PRECAUTION** In view of potential mutagenicity shown in vitro, potential risks should be balanced against anticipated benefits when treating children and neonates.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
121.	**NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)** The following statement shall be included in the package insert of products containing NSAID including COX-2 Inhibitors: **WARNING** Risk of GI Ulceration, Bleeding and Perforation with NSAID Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.
122.	**OLANZAPINE** (Please also refer to ANTIPSYCHOTIC AGENT) The following statements shall be included in the package insert and RiMUP of products containing Olanzapine: **Package Insert** **a) Special Warnings and Precautions for Use**: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if DRESS is suspected.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) Adverse Drug Reactions: **Skin and subcutaneous tissue disorders** Very rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects**: Very rare: Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia). **Reference : Directive No. 17 Year 2016. Ref. BPFK/PPP/07/25 (5) Jld 1.** DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI OLANZAPINE DENGAN MAKLUMAT KESELAMATAN BERKAITAN KESAN ADVERS DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)
123.	**ONDANSETRON** The following statements shall be included in the package inserts of injection products containing Ondansetron: **DOSAGE AND ADMINISTRATION:** **CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV AND RINV)** **CINV and RINV in Adults** …. IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes. …. **CINV and RINV in Elderly**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Ondansetron is well tolerated by patients over 65 years of age. In patients 65 years of age or older, all IV doses should be diluted and infused over 15 minutes and, if repeated, given no less than 4 hours apart. In patients 65 to 74 years of age, the initial IV dose of ondansetron 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart. In patients 75 years of age or older, the initial IV dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart. Reference: Zofran™ Injection package insert (June 2014 version)
124.	**PALIPERIDONE** The following statement shall be included in the package inserts of products containing Paliperidone: **Warnings and Precautions** **Intraoperative Floppy Iris Syndrome** Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone. IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy. **Undesirable Effects** **Postmarketing Data** Eye Disorders Frequency: Not known – Floppy iris syndrome (intraoperative) **References:** Circular (17)dlm.BPFK/PPP/01/03 Jld.3**:** Pekeliling untuk mengemaskini sisip bungkusan semula produk yang mengandungi Risperidone atau Paliperidone dengan amaran berkaitan risiko Intraoperative Floppy Iris Syndrome (IFIS) pada pesakit yang menjalani

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	pembedahan katarak
125.	**PARACETAMOL** The following statement shall be included on the labels, package inserts and RiMUP of ALL products containing Paracetamol: **WARNING** This preparation contains PARACETAMOL. Do not take any other paracetamol containing medicines at the same time. • **Allergy alert:** Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash. These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away. **ADVERSE EFFECT/UNDESIRABLE EFFECT** **(For product with package insert)** • Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported. Reference Directive : (29)dlm.bpfk/ppp/07/25 ; Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 5 Year 2015 : Direktif Untuk Produk Yang Mengandungi Paracetamol, Termasuk Produk Kombinasi : Pengemaskinian Label, Sisip Bungkusan, Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Kesan Advers Serius Pada Kulit

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
126.	**PARACETAMOL WITH CAFFEINE IN COMBINATION** The following statement shall be included on the labels and in the package inserts and RiMUP of products containing Paracetamol with Caffeine in combination: **WARNING** • Avoid other caffeine containing products. Too much caffeine may cause rapid heart rate, nervousness or sleeplessness. • Ask a doctor or pharmacist before use if you have high blood pressure, glaucoma, or overactive bladder syndrome. • **DO NOT exceed 8 tablets in 24 hours**. • **DO NOT** take more than the recommended dose unless advised by your doctor. Use the smallest effective dose. Taking more than the maximum daily dose may cause **severe or possibly fatal liver damage.** • **DO NOT** use with other drugs containing **paracetamol.** • **NOT recommended for children under 12 years** • **Allergy alert:** Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash. These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away. **ADVERSE EFFECT/UNDESIRABLE EFFECT** **(For product with package insert)** • Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported. Reference Directive : (29)dlm.bpfk/ppp/07/25 ; Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 5 Year 2015 : Direktif Untuk Produk Yang Mengandungi Paracetamol, Termasuk Produk Kombinasi : Pengemaskinian Label, Sisip Bungkusan, Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Kesan Advers Serius Pada Kulit

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
127.	**PEGFILGRASTIM** The following statement shall be included in the package inserts of ALL biosimilar products containing PEGFILGRASTIM **WARNINGS AND PRECAUTIONS** Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care. **UNDESIRABLE EFFECTS** Clinical Trials **In Cancer Patients** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥1/1000 to < 1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony stimulating factors. **In Normal Donors undergoing peripheral blood progenitor cell mobilization** Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported in healthy donors undergoing peripheral blood progenitor cell mobilization following administration of granulocyte colony stimulating factors. Post Marketing **Vascular disorders** Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony stimulating factor use. These have generally occurred in patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications or undergoing apheresis. **Reference: Circular Bil (20) dlm. BPFK/PPP/07/25. Directive No. 13 Year 2014. Direktif Untuk Semua Produk Yang Mengandungi Filgrastim Dan Pegfilgrastim : Amaran Berkaitan Risiko *Capillary Leak Syndrome (Cls)* Bagi Pesakit Kanser Dan *Healthy Donor* (Filgrastim) Dan Bagi Pesakit Kanser (Pegfilgrastim)**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
128.	***PELARGONIUM SIDOIDES*** The following warning shall be included on the labels and in the package inserts of products containing *Pelargonium Sidoides*: **WARNING** In very rare cases, *pelargonium sidoides* may cause hypersensitivity reactions.
129.	**PENICILLIN** The following statement shall be included on the labels of products containing penicillin: '**Not to be used in patients with known hypersensitivity to Penicillin**'
130.	**PHENIRAMINE** The following statement shall be included on the label and in the package inserts of liquid oral products containing Pheniramine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference:*** ***Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
131.	**PHENYLEPHRINE** The following statement shall be included on the labels and in the package insert of liquid oral products containing Phenylephrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference:*** ***Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
132.	**PIRIBEDIL** Please refer to DOPAMINERGIC INGREDIENT

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
133.	**PIROXICAM** The following additional information shall be included in the package inserts of products containing Piroxicam: **WARNING AND PRECAUTION** • Treatment should always be initiated by a physician experienced in the treatment of rheumatic diseases. • Use the lowest dose (no more than 20mg per day) and for the shortest duration possible. Treatment should be reviewed after 14 days. • Always consider prescribing a gastro-protective agent. **CONTRAINDICATION** • Piroxicam should not be prescribed to patient who is more likely to develop side effects, such as those with a history of gastro-intestinal disorders associated with bleeding, or those who have had skin reactions to other medicines. • Piroxicam should not be prescribed in association with any other NSAID or an anticoagulant. ***Reference:*** ***Circular Bil (80) dlm BPFK/02/5/1.3:*** *Menghadkan Indikasi bagi Produk untuk Kegunaan Systemic yang Mengandungi Piroxicam kepada 'For the symptomatic relief of pain and inflammation in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis' dan Tambahan Amaran dan Kontraindikasi terkini pada sisip bungkusan*
134.	**PRAMIPEXOLE** Please refer to DOPAMINERGIC INGREDIENT

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
135.	**PRAVASTATIN** The following additional information shall be included in the package insert of products containing Pravastatin. **DOSAGE AND ADMINISTRATION** Dosage in Patients Taking Cyclosporine In patients taking cyclosporine, with or without other immunosuppressive drugs, concomitantly with [Product Name], therapy should be initiated with 10mg/day and titration to higher doses should be performed with caution. Most patients treated with this combination received a maximum pravastatin dose of 20mg/day. **WARNINGS AND PRECAUTIONS** Skeletal Muscle Effects The use of fibrates alone may occasionally be associated with myopathy. The benefit of further alterations in lipid levels by the combined use of [Product Name] with fibrates should be carefully weighed against the potential risks of this combination. Cases of myopathy, including rhabdomyolysis, have been reported with pravastatin co-administered with colchicine, and caution should be exercised when prescribing pravastatin with colchicine. Pravastatin must not be co-administered with systemic fusidic acid. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Pravastatin therapy may be re-introduced seven days after the last dose of fusidic acid. **INTERACTIONS** Concomitant Therapy with Other Lipid Metabolism Regulators: Based on post-

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	marketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. Therefore, combined drug therapy should be approached with caution. Gemfibrozil and nicotinic acid: Gemfibrozil and nicotinic acid do not statistically significantly affect the bioavailability of pravastatin. However, in a limited size clinical trial, a trend toward CK elevations and musculoskeletal symptoms was seen in patients treated concurrently with pravastatin and gemfibrozil. Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency. Cyclosporine: In a multicentre study, the AUC values of pravastatin were shown to be five-fold higher in the presence of cyclosporine. There was no accumulation of pravastatin after multiple doses Clarithromycin, colchicine: The risk of myopathy/rhabdomyolysis is increased with concomitant administration of clarithromycin or colchicine with pravastatin. Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of pravastatin with systemic fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, pravastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. **Reference: Circular Bil (15) dlm. BPFK/PPP/07/25. Directive No. 8 Year 2014 Direktif Untuk Semua Produk Pravastatin: Mengehadkan Dos Penggunaan Pravastatin Untuk Mengurangkan Risiko Kecederaan Otot**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
136.	**PROMETHAZINE HCL** The following additional information shall be included on the label and in the package insert of liquid oral products containing Promethazine HCl: **WARNING** When used for treatment of cough and cold (a) "It (brand or generic names) should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression". (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference:*** ***Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
137.	**PROPAFENONE** The following warning shall be included in the package insert of products containing propafenone: **Propafenone is not recommended for treatment of less severe arrhythmias such as nonsustained ventricular tachycardias or frequent premature ventricular contractions even if the patients are symptomatic, because of recent evidence in the US of increase mortality in patients with non-lifethreatening arrhythmias who were treated with encainide and flecainide.**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
138.	**PROPOFOL** The following statement shall be included in the package inserts of products containing Propofol: **WARNING** Propofol is not recommended for paediatric general anaesthesia and sedation because its safety and effectiveness in these patients have not been established. There have been recent reports of adverse cardiac events and deaths associated with its use in paediatric intensive care. Although there is no evidence of a causal link of death with propofol in these cases, the drug could not be ruled out as a contributing factor. Until further data establishing its safety and delineating its appropriate dose range are available, propofol should not be used in paediatric intensive care. There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction orbemergence from anaesthesia induced by propofol.
139.	**PROPOLIS (ORAL)** For products containing Propolis (for oral use), please state: - **"This product contains propolis and may cause severe allergic reactions including fatal anaphylactic reaction in susceptible individuals."** - **"Asthma and allergy sufferers may be at a greater risk."**
140.	**PROPOLIS (TOPICAL)** The following information shall be included on the labels and/ or package inserts of products containing Propolis (for topical use): **WARNINGS** Propolis may cause allergic skin reaction. ***Reference:*** *a) **Circular Bil (48) dlm BPFK/02/5/1.3:** Pernyataan Amaran Pada Label Dan Sisip Bungkusan Produk Yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	b) ***Bil (56) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran pada Label dan Sisip Bungkusan Produk yang Mengandungi Propolis (topikal) dan Royal Jelly (Semua Bentuk)*
141.	**PROPYLTHIOURACIL** The following statement shall be included in the package inserts of products containing propylthiouracil: **[1]WARNING AND PRECAUTION** Potential risk of serious hepatoxicity or liver injury including liver failure and death. Patients who are initiated with propylthiourasil should be closely monitored for signs and symptoms of liver injury (e.g. fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising or yellowing of the eyes or skin) especially during the first six months. If liver injury is suspected, promptly discontinue propylthiouracil therapy. Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of the alternatives available. **[2]**The following boxed warning shall be included in the package inserts of products containing propylthiouracil: ***BOXED WARNING*** *Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.* *Propylthiouracil should be reserved to patients who cannot tolerate carbimazole/ methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for management of hyperthyroidism.* *Because of the risk of fetal abnormalities associated with carbimazole/ methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (See Warnings & Precautions).*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference: ***Circular [1]Bil (41) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berkaitan Dengan "Potential for an Increase in Risk of Hepatotoxicity" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Propylthiouracil* ***Circular [2]Bil (55) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Berbentuk "Boxed Warning" Yang Wajib Dimuatkan Pada Sisip Bungkusan Produk Propylthiouracil Dengan "Severe Liver Injury"*
142.	**PROTON PUMP INHIBITORS (PPI)** **(Products containing Pantoprazole, Omeprazole, Lansoprazole, Esomeprazole, Rabeprazole, Dexlansoprazole)** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Proton Pump Inhitors (PPI): **Package Insert** **1. Warnings and Precautions:** Regular Surveillance Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance. Subacute Cutaneous Lupus Erythematosus (SCLE) Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping {product name}. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors. Hypomagnesaemia Severe hypomagnesaemia has been reported in patients treated with PPI like {product name} for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics),

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment. Fracture Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium. Clostridium Difficile Diarrhea Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Vitamin B12 Deficiency Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed. **2. Undesirable Effects/Side Effects:** Subacute Cutaneous Lupus Erythematosus (SCLE) Skin and subcutaneous tissue disorders Frequency 'not known': Subacute cutaneous lupus erythematosus Interstitial Nephritis Renal and urinary disorders: Interstitial nephritis Hypomagnesaemia Metabolism and nutritional disorders Frequency “not known”: hypomagnesaemia. Fracture

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Musculoskeletal disorders Frequency "uncommon": Fracture of the hip, wrist or spine. <u>Clostridium Difficile Diarrhea</u> Infections & infestations: Clostridium difficile associated diarrhea. <u>Fundic Gland Polyps (Benign)</u> Gastrointestinal disorders Frequency "common": Fundic gland polyps (benign) <u>Vitamin B12 Deficiency</u> Metabolic/Nutritional: Vitamin B12 deficiency **3. Warnings & Precautions - Interference with laboratory tests** Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, [product name] treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment. **4. Pharmacodynamic** During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range. **<u>Consumer Medication Information Leaflet (RiMUP)</u>** **i. Side Effects:** When you are taking this medicine, your doctor will want to monitor you (especially if you are taking it for long term). Hence, you should report any new and exceptional symptoms and circumstances whenever you see your doctor. Please tell your doctor promptly if you get any of the symptoms below:

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

- Rash (especially in areas exposed to the sun), possibly with pain in the joints.(Subacute Cutaneous Lupus Erythematosus, SCLE)
- Fever, extreme tiredness, pus/blood in urine.
- Involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate
- Fracture in the hip, wrist or spine.
- Watery stool, stomach pain and fever that do not go away
- Anemic (pale skin, weakness, tiredness or lightheadedness), shortness of breath, a smooth tongue, nerver problems (numbness or tingling, muscle weakness and problems walking), vision loss and mental problems (depression, memory loss or behavioral changes).

a) Subacute Cutaneous Lupus Erythematosus (SCLE)
Frequency “not known”

b) Interstitial Nephritis
Kidney problems (interstitial nephritis)

c) Hypomagnesaemia
Frequency “not known”: Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood.

d) Fracture
Frequency “uncommon”: Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can ncrease the risk of osteoporosis).

e) Clostridium Difficile Diarrhea
Severe diarrhoea which may be caused by an infection (Clostridium difficile) in your intestines.

f) Fundic Gland Polyps (Benign)
Frequency “Common”: Benign polyps in the stomach

g) Vitamin B12 Deficiency
Proton pump inhibitors may cause vitamin B12 deficiency.

ii. Before you start to use it

Tell your doctor before taking this medicine, if you are due to have a specific blood test (Chromogranin A).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Reference : **1. Directive No. 16 Year 2017. Ref.** BPFK/PPP/07/25 (21) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi *Proton Pump Inhibitors (PPI)* : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Akibat Penggunaan Jangka Panjang (no. 1, 2, i) **2. Directive No. 15 Year 2017. Ref.** BPFK/PPP/07/25 (20) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi *Proton Pump Inhibitors (PPI)* : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan *Elevated Circulating Levels of Chromogranin A (CgA)* (no. 3, 4, ii)
143.	**PSEUDOEPHEDRINE** The following statement shall be included on the labels and in the package inserts of liquid oral products containing Pseudoephedrine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference:*** ***Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
144.	**PSYCHOTROPIC PRODUCTS** The following statement shall be included conspicuously on the labels of all psychotropic products: **CAUTION:** This preparation may be habit forming on prolonged use.
145.	**PSYLLIUM/ PLANTAGO (SEED/ HUSK)** For products containing Psyllium/ Plantago (Seed/ Husk), please state: - **"If the constipation does not resolve within 3 days or if abdominal pain occurs or in case of any irregularity of faeces, the use of psyllium should be discontinued and medical advice must be sought."** **"Please consume a large amount of fluid/ water when taking this**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	product."
146.	**QUETIAPINE** Please refer to ANTIPSYCHOTIC AGENT
147.	**QUINAGOLIDE** Please refer to DOPAMINERGIC INGREDIENT
148.	**RED YEAST RICE *(Monascus purpureus)*** "This product contains naturally occurring lovastatin. Please consult your doctor/ pharmacist before using this product." "Do not take this product if you are already on statin products (lovastatin, atorvastatin, fluvastatin, prasvastatin, simvastatin, rosuvastatin, etc). "If you experience any allergic reactions or side effects such as lethargy, body and muscle aches, please stop using this product" "Concurrent use of fibrates may cause severe myositis and myoglobinuria."
149.	**RISPERIDONE** Please refer to ANTIPSYCHOTIC AGENT The following statement shall be <u>included in the package inserts</u> of products containing Risperidone: **<u>Warnings and Precautions</u>** **Intraoperative Floppy Iris Syndrome** Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone. IFIS may increase the risk of eye

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy. **Undesirable Effects** **Postmarketing Data** Eye Disorders Frequency: Not known – Floppy iris syndrome (intraoperative) ***References:*** Circular (17)dlm.BPFK/PPP/01/03 Jld.3: *Pekeliling untuk mengemaskini sisip bungkusan semula produk yang mengandungi Risperidone atau Paliperidone dengan amaran berkaitan risiko Intraoperative Floppy Iris Syndrome (IFIS) pada pesakit yang menjalani pembedahan katarak*
150.	**ROPINIROLE** Please refer to DOPAMINERGIC INGREDIENT
151.	**ROSIGLITAZONE** 1. The following **black box warning** shall be included in the first part of package inserts of products containing Rosiglitazone as single ingredient or in combination with other active ingredients : • Rosiglitazone is contraindicated in patients with established NYHA Class I to IV heart failure and in patients with known ischaemic heart disease, particularly in those taking nitrates. • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Patients on rosiglitazone should be monitored carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	2. The following information shall be <u>included in the package inserts</u> of products containing Rosiglitazone as single ingredient or in combination with other active ingredients : **CONTRAINDICATIONS** Rosiglitazone is contraindicated in patients with NYHA Class I to IV heart failure or history of cardiac failure, patients with known ischaemic heart disease and patients with Acute Coronary Syndrome (unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction. **WARNING & PRECAUTIONS** Rosiglitazone has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short term clinical studies compared to combined active/placebo control (2.00% versus 1.53%). Death from myocardial ischaemic events occurred in 0.15% on rosiglitazone – containing regimens and 0.12% on comparator regimen. ***Reference:*** ***Circular Bil (6) dlm BPFK/PPP/01/03 Jld 1:*** *Direktif Memperketatkan Penggunaan Rosiglitazone dan Memperkukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Kardiovaskular Pada Sisip Bungkusan Semua Produk Rosiglitazone Termasuk Produk Kombinasi*
152.	**ROSUVASTATIN** The following <u>information</u> shall be <u>included on the labels and/or package inserts</u> of products containing Rosuvastatin: **DOSAGE AND ADMINISTRATION** <u>Dosage in patients with pre-disposing factors to myopathy</u> The recommended start dose is 5 mg in patients with pre-disposing factors to myopathy <u>Concomitant Therapy</u> Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when rosuvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir). Whenever possible, alternative medications should be considered, and if

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	necessary, consider temporarily discontinuing [Product Name] therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered. **CONTRAINDICATIONS** [Product Name] is contraindicated in patients receiving concomitant cyclosporine. **WARNINGS AND PRECAUTIONS** <u>Skeletal Muscle Effects</u> Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. All generic products containing Rosuvastatin should update their package inserts respectively according to the innovator's information such as parts for Interactions, Pharmacokinetics and other parts deemed relevant. *Reference: Circular (16)dlm. BPFK/PPP/07/25 Directive No. 9 Year 2014. Direktif Untuk Semua Produk Rosuvastatin: Mengehadkan Dos Penggunaan Rosuvastatin Untuk Mengurangkan Risiko Kecederaan Otot*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
153.	**ROYAL JELLY** The following information shall be included on the labels and/or package inserts of products containing Royal jelly: **WARNINGS** This product contains royal jelly and may cause severe allergic reactions including fatal anaphylactic reactions in susceptible individuals. Asthma and allergy sufferers may be at the greater risk. ***Reference:*** *a)* ***Circular Bil (48) dlm BPFK/02/5/1.3:*** *Pernyatan Amaran Pada Label Dan Sisip Bungkusan Produk Yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk)* *b)* ***Circular Bil (56) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran pada Label dan Sisip Bungkusan Produk yang Mengandungi Propolis (topikal) dan Royal Jelly (Semua Bentuk)* *c)* ***Circular Bil (12) dlm. BPFK/PPP/01/03:*** *Pernyataan amaran pada label dan sisip bungkusan produk yang mengandungi royal jelly (produk kosmetik)*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
154.	**SALBUTAMOL** 1. The following information shall be included in the <u>package inserts</u> of products containing Salbutamol in **<u>injection</u>** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. • Cautious use of salbutamol injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractibility. During IV infusion of salbutamol, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. 2. The following information shall be included in the <u>package inserts and product literature</u> of products containing Salbutamol in **<u>oral tablet/ capsule</u>** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	cardiovascular status should be made by a physician experienced in cardiology. 3. The following warning statement shall be included in the package inserts of products containing Salbutamol in **injection and oral** dosage form under section of **Warning & Precautions**: **Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.** **Reference:** *a)* ***Circular Bil (6) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Mengenai Insiden **Myocardial Ischaemia** pada Wanita Mengandung yang Menerima Rawatan **Beta Agonist** bagi Rawatan Melambatkan Kelahiran Pramatang pada Sisip Bungkusan Kumpulan Produk Ini* *b)* ***Circular Bil (18) dlm BPFK/PPP/01/03 Jld 1****: Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Risiko Kesan Advers Serius pada Jantung Termasuk Kematian dengan Penggunaan Produk Suntikan dan Oral Beta Agonis dalam Rawatan Kelahiran Pra-Matang*
155.	**SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)** Please state: “Individual allergic to aspirin/ other NSAID should avoid this product.”

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
156.	**SEDATIVE – HYPNOTIC PRODUCTS** The following statement shall be included in the package inserts under section on 'Warning' and 'Precaution' of products containing: a. Alprazolam b. Bromazepam c. Clobazam d. Diazepam e. Flurazepam hydrochloride f. Lorazepam g. Midazolam h. Nitrazepam i. Triazolam j. Zolpidem tartrate k. Zopiclone **WARNING/ PRECAUTION** • Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken • Complex sleep – related behaviors which may include sleep driving, making phone calls, preparing and eating food while asleep ***Reference:*** ***Circular Bil (75) dlm BPFK/02/5/1.3:*** *Pernyataan Amaran Pada Sisip Bungkusan Semua Produk Sedatif-Hipnotik Oral Berkaitan dengan Risiko* ***Complex Sleep - Related Behaviors Which May Include Sleep Driving, Making Phone Calls, Preparing and Eating Food (While Asleep)***

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
157.	**SELENIUM SULPHIDE** The following statement shall be included on the labels of products containing Selenium sulphide: **WARNING** Do not use on broken skin or inflamed. Avoid contact with eyes. (***AMARAN:*** *Selenium sulphide tidak boleh digunakan pada kulit yang pecah dan radang. Elakkan daripada terkena mata.*)
158.	**SENNA (CASSIA SPP.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part** The following statement shall be included on the labels of products containing senna (*cassia spp.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part:* • Do not use when abdominal pain, nausea or vomiting is present. • Frequent or prolonged use of this preparation may result in dependence towards the product and 'imbalanced electrolytes'. • Please consult a health care practitioner for use beyond 7 days.
159.	**SIMVASTATIN** The following statement shall be included in the package inserts of products containing Simvastatin: **1. Dosage and Administration** The 80mg dose is only recommended in patients at high risk for cardiovascular complications who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. Concomitant Therapy In patients taking fibrates (other than gemfibrozil and fenofibrate) concomitantly with [Product Name], the dose of [Product Name] should not exceed 10mg/day.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

In patients taking amiodarone, verapamil or diltiazem concomitantly with [Product Name], the dose of [Product Name] should not exceed 20mg/day.

In patients taking amlodipine or lipid-lowering dose of niacin (≥1g/day) concomitantly with [Product Name], the dose of [Product Name] should not exceed 40mg/day.

2. Contraindications

- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).
- Concomitant administration of gemfibrozil, cyclosporine, or danazol.

3. Interactions

Contraindicated Drugs

Potent inhibitors of CYP3A4: Concomitant use with medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g.: itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir or nefazodone) is contraindicated. If treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment.

Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with simvastatin is contraindicated.

Other Drugs

•Other fibrates: The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil or fenofibrate. When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small short-term clinical studies with careful monitoring.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	•Amiodarone: In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone. •Calcium channel blockers: -Verapamil or diltiazem: In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem. -Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine. -Niacin (≥1g/day): The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin. ***References:*** **Circular (18)dlm.BPFK/PPP/01/03 Jld.3:** *Pekeliling untuk mengemaskini sisip bungkusan semula produk yang mengandungi Simvastatin dengan memuatkan kontraindikasi dan had dos yang baru*
160.	**SODIUM METABISULPHITE (EXCIPIENT)** The following statement shall be included in the package inserts of products containing Sodium metabisulphite: **WARNING** This preparation contains Sodium metabisulphite that may cause serious allergic type reactions in certain susceptible patients. Do not use if known to be hypersensitive to bisulphites.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
161.	**SODIUM VALPROATE** a) The following <u>boxed warning</u> shall be <u>included in the package insert</u> of products containing Sodium valproate: **PANCREATITIS:** CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED. b) The following <u>statement</u> shall be <u>included in the package insert</u> of products containing Sodium Valproate: ***Posology and Method of administration* :** <u>*Female children, female adolescents, women of childbearing potential and pregnant women*</u> *[Product Name] should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably [Product Name] should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.* ***Special warnings and precautions for use* :** <u>*Female children/Female adolescents/ Women of childbearing potential/Pregnancy*</u> *[Product Name] should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	potential and risk of developmental disorders in infants exposed in utero to valproate. *The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with [Product Name] plans a pregnancy or if she becomes pregnant.* *Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of [Product Name] during pregnancy (see Fertility, Pregnancy and Lactation).* *The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.* *In particular the prescriber must ensure the patient understands:* • *The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.* • *The need to use effective contraception.* • *The need for regular review of treatment.* • *The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.* *In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible:* *Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.* ***Fertility, pregnancy and lactation*:** *[Product Name] should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.* *<u>Pregnancy Exposure Risk related to valproate</u>* *Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. *<u>Congenital malformations</u>* *Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.* *<u>Developmental disorders</u>* *Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.* *Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.* *Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.* *There are limited data on the long term outcomes.* *Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.* *Limited data suggests that children exposed to valproate in utero may be more*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). *<u>Female children, female adolescents and woman of childbearing potential (see above and Special Warnings and Precautions for use)</u>* *If a Woman wants to plan a Pregnancy* • *During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child.* • *In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed* • *In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.* *Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:* - *Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day.* - *The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.* - *Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.* - *To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.* **Reference :** **Directive No. 17 Year 2016. Rujukan BPFK/PPP/07/25 (3) Jld 1.** Direktif Bagi Semua Produk Yang Mengandungi Sodium Valproate Bagi Memperkukuhkan Amaran Berkaitan Risiko *Abnormal Pregnancy Outcomes*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
162.	**ST. JOHN'S WORT *(Hypericum perforatum)*** The following boxed statement shall be included on the labels of products containing St. John's Wort: Please consult your physician/ pharmacist before using this product if you are on any prescription medicines as there is possibility that interactions may occur with certain drugs. *(Sila dapatkan nasihat doktor/ ahli farmasi sebelum menggunakan produk ini, kerana kemungkinan berlakunya interaksi dengan penggunaan ubat preskripsi).*
163.	**STATINS** The following statement shall be included in the package inserts of ALL products containing statins (single active or in combination): a. Atorvastatin b. Fluvastatin c. Lovastatin d. Pravastatin e. Rosuvastatin f. Simvastatin g. etc. **DRUG INTERACTION**: Concurrent use of fibrates may cause severe myositis and myoglobinuria. **UNDESIRABLE EFFECTS**: There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins. ***References:*** **Circular (14) dlm.BPFK/PPP/07/25. Directive No. 7 Year 2014. Direktif Untuk Semua Produk Statin: Memperkukuhkan Amaran Berkaitan Risiko Kesan Advers Kognitif Dan Peningkatan Hba1c Serta *Fasting Blood Glucose (Fbg)***
164.	**STRONTIUM RANELATE** 1. The following **black boxed warning** shall be included in the first part of package inserts of products containing Strontium Ranelate: *[Brand Name]* should only be used for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. *[Brand Name]* is contraindicated in patients with: • established, current or past history of ischaemic heart disease; peripheral arterial disease and/or cerebrovascular disease; • uncontrolled hypertension; • current or previous venous thromboembolic events (VTE); • temporary or permanent immobilisation. 2. The following statement shall be included in the package inserts of products containing Strontium Ranelate: **Indication** • Treatment of **severe/established** osteoporosis in postmenopausal women **at high risk of fracture** to reduce the risk of vertebral and hip fractures • Treatment of **severe/established** osteoporosis in men at increased risk of fracture **[Brand Name] should only be used for whom treatment with**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. **<u>Contraindications</u>** • **Established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease** • **Uncontrolled hypertension** **<u>Special warnings and precautions for use</u>:** **<u>Cardiac ischaemic events</u>** **In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase in myocardial infarction has been observed in strontium ranelate treated patients compared to placebo.** **Before starting treatment, patients should be evaluated with respect to cardiovascular risk.** **Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with strontium ranelate after careful consideration.** **During [BRAND NAME] treatment, these cardiovascular risks should be monitored on a regular basis generally every 6 to 12 months.** **Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease or if hypertension is uncontrolled.** **<u>Undesirable effects</u>:** **SOC Cardiac disorders:** - **Common: Myocardial infarction** **<u>Myocardial infarction</u>** **In pooled randomised placebo-controlled studies of post-menopausal osteoporotic patients, a significant increase of myocardial infarction has been observed in strontium ranelate treated patients as compared to placebo (1.7% versus 1.1%), with a relative risk of 1.6**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	(95% CI = [1.07; 2.38]). ***References:*** **Circular (16)dlm.BPFK/PPP/01/03 Jld.3:** *Pekeliling tentang langkah-langkah pengurangan risiko bagi produk yang mengandungi Strontium Ranelate susulan risiko kesan advers kardiovaskular*
165.	**SULPHONAMIDES/ TRIMETHOPRIM** 1. The following statement shall be included on the labels of products containing Sulphonamides and Trimethoprim as single ingredient or in combination of both ingredients: Discontinue treatment with this drug immediately if skin rash or any sign of adverse reaction occurs. 2. The following statement shall be included in the package inserts of products containing Sulphonamides and Trimethoprim as single ingredient or in combination of both ingredients: Fatalities associated with the administration of sulphonamides and trimethoprim, either alone or in combination, have occurred due to severe reactions, including Steven-Johnson syndrome, toxic epidermal necrolysis and other reactions. The drug should be discontinued at the first appearance of skin rash or any sign of adverse reaction.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

166. **SYNTHETIC SALMON CALCITONIN**

1. Indication and duration of use for products containing synthetic salmon calcitonin (according to the stated dosage forms) are restricted as follows, and the package insert of the product shall be amended accordingly:

    a) For dosage form: Injection

    Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures.
    The duration of treatment should not be more than 4 weeks.

    For the treatment of Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment.
    The duration of treatment is limited to 3 months.

    Treatment of hypercalcaemia of malignancy.

    b) For dosage form: Nasal spray

    Prevention of osteoporosis: In acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures. Miacalcic should be supplemented with adequate doses of calcium and Vit D, as needed by the individual patient, to prevent further bone loss.
    The maximum duration of treatment is 3 months.

    Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable.
    The duration of treatment is normally 3 months.

    Algodystrophy or Sudeck's Disease (Neurodystrophic disorders) due to various causes and predisposing factors such as posttraumatic painful osteoporosis, reflex dystrophy, shoulder arm syndrome, causalgia and drug-induced neurotrophic disorders.
    ***The duration of treatment is up to 6 weeks**.*

2. Under "Dosage" in the package insert of products containing synthetic salmon calcitonin (injection and nasal spray), the following statement shall be stated:

    The treatment duration in all indications should be limited to the shortest period of time possible and using the lowest effective dose.

Reference: ***Directive (10)dlm.BPFK/PPP/07/25:*** *Direktif untuk mengehadkan indikasi dan tempoh penggunaan produk yang mengandungi Calcitonin Salmon sintetik dalam bentuk injeksi dan Intranasal 'Nasal Spray' berikutan risiko kanser*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
167.	**TABEBUIA SPP. (PAU D'ARCO)** The following warning statement shall be included on the labels of products containing Tabebuia spp. (Pau d'arco): "As the use of Tabebuia spp. (Pau d'arco) may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicine and before you undergo any surgical/ dental procedure." (Memandangkan pengambilan Tabebuia spp. (Pau d'arco) boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau akan menggunakan ubat lain dan sebelum prosedur pembedahan/ dental dijalankan)
168.	**TEMOZOLOMIDE** The following statement shall be included in the package inserts of products containing Temozolomide: **WARNINGS AND PRECAUTIONS** Hepatic injury, including fatal hepatic failure has been reported in patients receiving temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/ risks prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle, liver function test should be repeated midway during this cycle. For all patients, liver function test should be checked after treatment cycle. For patient with significant liver function abnormalities, physicians should assess the benefit/ risks of continuing treatment. Liver toxicity may occur several weeks or more after the last reatment of temozolomide. ***Reference: Circular Bil (18) dlm BPFK/PPP/07/25. Directive No. 11 Year 2014.*** **DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI TEMOZOLOMIDE: MAKLUMAT KESELAMATAN BARU BERKAITAN DENGAN RISIKO KECEDERAAN HATI**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
169.	**TERBUTALINE** 1. The following statement shall be included in the package inserts of products containing Terbutaline in **injection** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. • Cautious use of terbutaline injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractibility. During IV infusion of terbutaline, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. 2. The following information shall be included in the package insert and product literature of products containing Terbutaline in **oral tablet/ capsule** dosage form: • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	cardiovascular status should be made by a physician experienced in cardiology. 3. The following warning statement shall be included in the package inserts of products containing Salbutamol in **injection and oral** dosage form under section of **Warning & Precautions**: • **Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.** **Reference:** *a) **Circular Bil (6) dlm. BPFK/PPP/01/03:** Kenyataan Amaran Mengenai Insiden **Myocardial Ischaemia** pada Wanita Mengandung yang Menerima Rawatan **Beta Agonist** bagi Rawatan Melambatkan Kelahiran Pramatang pada Sisip Bungkusan Kumpulan Produk Ini* *b) **Circular Bil (18) dlm BPFK/PPP/01/03 Jld 1**: Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Risiko Kesan Advers Serius pada Jantung Termasuk Kematian dengan Penggunaan Produk Suntikan dan Oral Beta Agonis dalam Rawatan Kelahiran Pra-Matang*
170.	**TETRACYCLINE SYRUP** The following boxed warning shall be included on the label and in the package inserts of products containing Tetracycline (syrup) **NOT TO BE GIVEN TO CHILDREN UNDER 12 YEARS OF AGE**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
171.	**THIOMERSAL** ***Note:*** Thiomersal is not allowed in ophthalmic preparations as preservative**.** The following statement shall be included on the label and package inserts of products containing thiomersal for preparations other than ophthalmic preparation: **WARNING** **'RISK OF SENSITIZATION IN RELATION TO THIOMERSAL AND OTHER PRESERVATIVES'** ***Reference:*** ***Circular Bil (34)dlm BPFK/02/5/1.3:*** *Penggunaan Thiomersal Dalam Persediaan Vaksin*
172.	**THROMBOLYTIC AGENTS** The following caution shall be disclosed prominently in the package inserts of products containing "systemic thrombolytic agent" in particular "the tissue plasminogen activators": **WARNING** Severe bleeding such as intracranial haemorrhage may occur following administration of the drug, particularly in the elderly patients. The risk must be balanced against the potential benefit of thrombolysis. The following precautions need to be observed: Patients should be carefully observed for clinical signs during and following administration of the drug for early detection of bleeding. Frequent haematological tests such as blood coagulation tests are mandatory. To prevent bleeding at the site of centesis or other regions, caution must be exercised concerning procedures and management of arterial/ venus puncture. The use of heparin in conjunction with the thrombolytic agent for the purpose of prevention of reocclusion may increase the risk of intracranial haemorrhage. Close monitoring of patients is strongly recommended.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
173.	**TIAPROFENIC ACID** The following statement shall be included in the package inserts of products containing Tiaprofenic acid: **PRECAUTION** Urinary symptoms (bladder pain, dysuria, and frequency), haematuria or cystitis may occur. In certain exceptional cases, the symptoms have become severe on continued treatment. Should urinary symptoms occur, treatment with tiaprofenic acid must be stopped.
174.	**TOPIRAMATE** The following statement shall be included in the package inserts of products containing Topiramate: **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** **Visual field defects** Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible following topiramate discontinuation, however some cases were not. In a large proportion of postmarketing case reports reversibility was unknown, but in cases where an outcome was reported, the majority were reversible. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug. **Reference Circular : (22) BPFK/PPP/07/25. Directive No. 15 Year 2014 Direktif Untuk Semua Produk Yang Mengandungi Topiramate: Amaran Berkaitan Risiko Gangguan Penglihatan**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
175.	**TRETINOIN TOPICAL** The following statement shall be included in the package inserts of products containing Tretinoin used topically: **USE IN PREGNANCY:** Studies in animal have shown that oral tretinoin is fetotoxic in rats given 500 times the topical human dose and teratogenic in rats given 1,000 times the topical human dose. Topical tretinoin has caused delayed ossification in a number of bones in the offspring of rats and rabbits given 100 to 320 times the topical human dose, respectively. There has been increasing incidence of foetal malformation following topical administration of tretinoi. Use of topical tretinoin is not recommended during pregnancy, especially the first trimester.
176.	**TRIAZOLAM** Please refer to SEDATIVE – HYPNOTIC PRODUCTS
177.	**TRIMETAZIDINE** 146.1 Indication of products containing Trimetazidine shall be amended as follows: a) Indication of Trimetazidine for treatment of pectoris angina is limited to second-line add on therapy; and the indication in otology and ophthalmology field shall be removed. b) Permitted indication is ***trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.*** 146.2 The following warning statement shall be included in the package inserts of products containing Trimetazidine: a) At part of ***Dosage and method of administration*****:**

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	For products containing Trimetazidine 20mg: ***The dose is one tablet of 20mg of trimetazidine three times a day during meals.*** ***The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.*** ***Special populations*** ***Patients with renal impairment:*** ***In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals.*** ***Elderly patients:*** ***Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals. Dose titration in elderly patients should be exercised with caution.*** For products containing Trimetazidine 35mg: ***The dose is one tablet of 35mg of trimetazidine twice daily during meals.*** ***The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.*** ***Special populations*** ***Patients with renal impairment:*** ***In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast.*** ***Elderly patients:*** ***Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast. Dose titration in elderly patients should be exercised with caution.***

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)

b) At part of ***Contraindications*:**

- ***Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders***
- ***Severe renal impairment (creatinine clearance < 30ml/min).***

c) At part of ***Special warnings and precautions for use*:**

Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.

The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.

These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.

Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment.

Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:
- ***moderate renal impairment,***
- ***elderly patients older than 75 years old.***

d) At part of ***Side effects*:**

Nervous system disorders:

Frequency not known: ***Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation.***

Reference: Directive No. 5 Year 2013, (4)dlm.BPFK/PPP/07/25: *Direktif untuk menghadkan*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	penggunaan produk mengandungi Trimetazidine dan mengukuhkan amaran berkaitan dengan risiko kesan advers simptom parkinson pada sisip bungkusan semua produk Trimetazidine
178.	**TRIPROLIDINE** The following statement shall be included on the label and in the package inserts of liquid oral products containing Triprolidine: **WARNING** When used for treatment of cough and cold: (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. ***Reference:*** ***Circular Bil (34) dlm. BPFK/PPP/01/03:*** *Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)*
179.	**VARENICLINE** The following statement shall be included in the package inserts of products containing Varenicline: **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** Effect of smoking cessation: Smoking cessation, with or without pharmacotherapy has been associated with the exacerbation of underlying psychiatric illness (eg. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly. Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt. **UNDESIRABLE EFFECTS** Post marketing cases of MI, depression and suicidal ideation have been reported in patients taking varenicline. ***Reference:*** ***Circular Bil (83) dlm. BPFK/17/FV/28:*** *Maklumat daripada European Medicines Agency (EMEA) berkaitan penggunaan produk Champix (Varenicline) untuk rawatan berhenti merokok (smoking cessation).*

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
180.	**VITAMIN K** 149.1 The following statement shall be included in the label and package insert of health supplement products containing Vitamin K as combined ingredients with other vitamins and minerals in oral preparation: **'Consult a healthcare practitioner if you are on anticoagulant/ blood thinner products.** 149.2 The following statement shall be included in the package inserts of products containing Vitamin K1 (phytomenadione) as single ingredient used intravenously: **WARNING** Severe reactions, including fatalities, have occurred during and immediately after intravenous injection of Vitamin K1. Restrict intravenous use to emergency case. When intravenous administration is necessary, the rate of injection should not exceed 1mg per minute. **ADMINISTRATION**: In severe bleeding, or situations where other routes are not feasible, Vitamin K1 may be given by very slow intravenous injection, at a rate not exceeding 1mg per minute.
181.	**WARFARIN** a) The following statements shall be included in the package insert of products containing Warfarin: **Caution** Topical preparations containing methyl salicylate should be used with care in patients on **Warfarin** and excessive usage is to be avoided as potentially dangerous drug interaction can occur. **Contraindications** Co-administration with miconazole oral gel (see Interactions).

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Special Warnings and Precautions for Use: • Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphatemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin. • Co-administration with topical miconazole (see Interactions). **Interactions** The following drugs have been reported to potentiate the warfarin effect (increase INR): • Miconazole **Adverse Drug Reactions**: Skin and subcutaneous tissue disorders Frequency 'not known': Calciphylaxis b) The following <u>statements</u> shall be <u>included in the RiMUP</u> of products containing Warfarin: **Possible Side Effects**: Tell your doctor straight away if you have any of the following side effects : [...] A painful skin rash. On rare occasions warfarin can cause serious skin conditions, including one called calciphylaxis that can start with a painful skin rash but can lead to other serious complications. This adverse reaction occurs more frequently in patients with chronic kidney disease.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	Before You Use [Product Name] *When you must not use it* *Do not take [product name] together with miconazole oral gel* *Before you start to use it* *Some commonly used medicines and products that may interfere with [product name] include:* • *Miconazole* **Reference :** 1. Directive No. 15 Year 2016. Rujukan BPFK/PPP/07/25 (1) Jld 1**.** DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI WARFARIN DENGAN RISIKO KESAN ADVERS CALCIPHYLAXIS 2. **Directive No. 12 Year 2017. Ref.** BPFK/PPP/07/25 (17) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi Warfarin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat
182.	**ZIPRASIDONE** Please refer to ANTIPSYCHOTIC AGENT
183.	**ZOLPIDEM TARTRATE** Please refer to SEDATIVE – HYPNOTIC PRODUCTS
184.	**ZOPICLONE** Please refer to SEDATIVE – HYPNOTIC PRODUCTS

APPENDIX 10 : GUIDELINE ON PATIENT DISPENSING PACK FOR PHARMACEUTICAL PRODUCTS IN MALAYSIA

Outline:

10.1 PURPOSE

To provide guidance on the implementation of patient dispensing pack or original dispensing pack for pharmaceutical products in Malaysia.

10.2 OBJECTIVE

Improve patient's safety by:

- maintaining product integrity;
- prevent unnecessary exposure of the product;
- avoid product contamination due to handling especially in non-GMP premise; and
- Fewer steps in dispensing process hence less possibility for errors and improvement in efficiency.

10.3 DEFINITION

Patient dispensing pack or original dispensing pack is a ready-to-dispense pack with sufficient quantity equivalent to an amount not more than one month supply or per treatment for one patient's use.

10.4 BENEFITS

Key benefits identified:

- Ensuring patients on how to take medications and the importance of it, which will eventually increase patient's compliance.
- Clear identification of the medicine, by whom and where it was manufactured.
- Providing complete instructions on the use of the medicine.
- Original packing will maintain the integrity of the pack therefore ensuring the stability of the product.
- Original packing will carry batch number and expiry date.
- Prevent mix-ups (or contamination) during repacking and dispensing.
- Facilitate recall of products since the required information can only be found on the original pack.

10.5 CRITERIA FOR IMPLEMENTATION OF PATIENT DISPENSING PACK

- The patient dispensing pack size should be based on the medication, intended use, recommended dosage and dosage form sufficient for one month supply or per treatment for one patient's use.
- This requirement does not apply for blister or strip pack.
- Maximum permitted supply is one month but may be less depending on the intended use of the medication.
- The Product Registration Holder (PRH) is responsible to justify the proposed patient dispensing pack size based on these criteria as the dosing regimen for certain medication may equate to high numbers of tablets/ capsules. Justification should also address the definition of one month i.e. 28, 30 or 31 days.
- Blister or strip pack are strongly recommended for solid oral dosage forms (e.g. tablets and capsules) and bulk loose pack for supply more than one month are not permitted unless justified by the PRH.
- Oral chemotherapeutics in tablet or capsule must be packed in blister to reduce personnel exposure and presumably risk which can minimise the toxic effect of the chemotherapeutics.

10.6 PRODUCTS EXEMPTED FROM THIS REQUIREMENTS

The requirements do not apply to the following products:

- Injectables, eye, ear and nasal drops, suppositories and pessaries.
- Products for export only (FEO).
- Drug where the risk of issuing more than the amount required by the patient outweigh the benefits of the patient dispensing pack e.g. products containing substances with potential for abuse or cytotoxic agents where precise dosing are required.
- Drugs where the dosing needs to be tailored according to patient's body weight e.g. drugs used in oncology, HIV etc.
- Medically critical products and hospital packs for rare diseases with very low volumes where it is not viable to produce special packs for a single market.
- Products sold with devices with a fixed number of doses
- Situations where a patient dispensing pack is not appropriate will be considered on a case to case basis.

10.7 OTHER CONSIDERATIONS FOR IMPLEMENTATION

VARIATION APPLICATIONS

- Change in patient pack size with or without involving new pack type shall be submitted to Variation Section, Centre for Post Product Registration.

- Supporting documents required are:
  a. Justification for the new pack size and/or type;
  b. Accelerated stability data (3 or 6 months) and stability report for new pack types; and
  c. Commitment to provide complete real time stability data and report when available.

- List of products with recommended pack sizes for oral liquid preparations and dermatological are as in **Table 1** and **Table 2** respectively.

- For tablets and capsules in loose pack, the maximum packing size will depend on the highest dosage and frequency per patient's treatment or one month supply.

10.8 IMPLEMENTATION TIMELINE

- Implementation of patient dispensing pack has been conducted in a phased manner to ensure smooth transition while ensuring no supply disruption to patients. This implementation is effective since 1 March 2008 on a voluntary basis and mandated on 1 September 2008.

- All products manufactured from 1 September 2008 regardless whether it is imported or locally manufactured will need to conform to the principles of this guide.

10.9 CONCLUSION

Patient Dispensing Pack is convenient, safe and improves quality of dispensed medicines. It will increase efficiency in dispensing and improve safety by reducing the risk and possibility of error. It will also result in a reduction in drug waste and better use of resources.

TABLE 1:

Oral Liquid Preparation Maximum Pack Size Recommendations for Pharmaceutical Products

ATC Code	Recommended Pack sizes
R05 Cough & cold preparation R05A Cold preparation R05C Antitussives R05D Expectorants	Max 120ml (except for Pholcodine – Max 90ml)
R06A Antihistamines systemic	Max 120ml (except for Hydroxyzine HCl Syrup - 200ml)
R03 Anti-asthma & COPD products R03A Beta2 stimulants R03B Xanthines (theophyllines) R03C Non-steroidal respiratory anti-inflammatory (ketotifen)	Max 120ml (except for Procaterol - 250ml)
N02B Non-narcotic analgesics	Max 120ml
M01A Antirheumatics non-steroid	Max 120ml
H02 Systemic corticosteroids H02A Plain corticosteroids	Max 120ml
M06A Anti-inflammatory enzymes	Max 500ml
A02A Antacid antiflatulents **A02B Antiulcerants**	Max 250ml
A06A Laxatives	Max 120ml (except for Lactulose - 500ml)

A03 Functional GI disorder drugs A03A Antispasmodic A03E Other GI combinations (Colimix) A03F Gastroprokinetics (Metoclopramide, Motilium) A07 Antidiarrhoea	Max 120ml
A04A Antiemetic + Antinauseants **N07C Antivertigo products**	Max 120ml
N03A Antiepileptics	Max 250ml (Except for Sodium Valproate Syrup - 300ml)
N06A Antidepressant & Mood stabilizer **N06D Anti Dementia** **N07D Anti-Alzheimer products** **N05A Antipsychotics**	Max 250ml Max 20ml for drops
P01B Antihelmintics	Max 60ml
N05C Tranquillizers/ Anxiolytics	Max 250ml
A05B Hepatic protector – lipotropics	Max150ml
J05 Antivirals for systemic use **J05B Antivirals excluding Anti-HIV** **J05C HIV antivirals**	Max 250ml

J01 Antibiotics systemic J01A Tetracyclines & combination J01B Chloramphenicols + combinations J01C1 Oral broad spectrum Penicillins J01D1 Oral Cephalosporins J01E Trimethoprim combinations J01F Macrolides & similar type J01H Medium & narrow spectrum penicillins J01X Other antibiotics **J02A Systemic Antifungals Agents**	Max 120ml
N06D Nootropics **N06E Neurotonics & Miscellaneous**	Max 125 ml
G01A1 Trichomonacides	Max 120ml

TABLE 2:

DERMATOLOGICALS PREPARATION MAXIMUM PACK SIZE RECOMMENDATIONS FOR PHARMACEUTICAL PRODUCTS

ATC Code	Recommended Pack sizes
D01A Antifungals for topical use	Liquid preparation - max 250ml Others - max 60g
D02A Emollients and protectives	Non poisons (liquid preparation) - 250ml Others - 60g (max 500g for emollients) Except D02AC Soft paraffin and fat products and D02AX Other emollients and protectives (Aq. Cream) - max 500g
D03 Preparations for treatment of wounds and ulcers	Max 500ml to 1L ***Notes:*** ▪ Chlorhexidine gluconate aqueous 1L ▪ Povidon 10% 500ml ▪ Povidon-iodine 1L ▪ Dermacyn 500ml ▪ Hydrogen peroxide 1L ▪ Prontosan 500ml ▪ Octenisan 500ml ▪ Acetic acid 500ml ▪ Cetrimide 500ml

ATC Code	Recommended Pack sizes
D04A Antipruritics, anesthetics, etc. Except D04AA Antihistamines for topical use (not allowed for registration)	Liquid – max 250ml Others – 60g
D05A Antipsoriatics for topical use	Liquid – max 500ml (with a dispenser). Others – max *500g Bar – max 100g ***Notes:*** ▪ Tar Preparations ▪ Coal Tar Ointment/ Solution ▪ Liquor Picis Carbonis (LPC) 500g ▪ Dithranol Ointment 500g ▪ Cocois Co Lotion 500ml
D06A Antibiotics for topical use	Max 20g Except D06BB Antivirals - Max 10g D06B A 01 Silver Sulphadiazine for management of burns - 500g

ATC Code	Recommended Pack sizes
D07A Corticosteroids, plain	
D07AA Corticosteroids, weak (group I)	D07AA – Max 100g to **500g
D07AB Corticosteroids, moderately potent (group II)	D07AB – Max 50g to **500g
D07AC Corticosteroids, potent (group III)	D07AC – Max 15g to 100g
D07AD Corticosteroids, very potent (group IV)	D07AD – Max 15g to 100g
	** ***Note:*** Pack size of 500g is for hospitals and skin specialist clinics use.
D07C Corticosteroids, combinations with antibiotics	
D07CA Corticosteroids, weak, combinations with antibiotics	D07CA - Max 100g
D07CB Corticosteroids, moderately potent, combinations with antibiotics	D07CB - Max 50g
D07CC Corticosteroids, potent, combinations with antibiotics	D07CC - Max 15g
D07CD Corticosteroids, very potent, combinations with antibiotics	D07CD - Max 15g
D08A Antiseptics and disinfectants	Liquid antiseptics/ disinfectants - 1Litre Others - max 60g

ATC Code	Recommended Pack sizes
D10A Anti-acne preparations for topical use Except for D10AA Corticosteroids, combinations for treatment of acne	Liquid preparation - max 250ml (recommended to be used with a dispenser) Bar - max 100g All others - max 60g
D11AF Wart and anti-corn preparations	Max 15ml
M02A Topical products for joint and muscular pain	Liquid – 250ml Others, Max – 60g
D11AX11 Hyperpigmentation	Max 60g

Reference: Circulars

i) (Bil 16) dlm bpfk02/5/1.3.pdf
Kawalan Saiz Pek Persediaan Ubat Batuk Mengandungi Pholcodine (13 October 2003)

ii) Bil (22) dlm BPFK/02/5/1.3.pdf
Lanjutan Tempoh Untuk Menarik Balik Saiz Pek Persediaan Ubat Batuk Mengandungi Pholcodeine Yang Melebihi 90mL Dari Pasaran (07 November 2003)

iii) Bil (21) dlm.BPFK/02/5/1.3.pdf
Kawalan Penetapan Saiz Pek Maksima Bagi Semua Persediaan Ubat Batuk (07 November 2003)

iv) Bil (24) dlm BPFK/02/5/1.3.pdf
Pindaan Kepada Kawalan Penetapan Saiz Maksima Bagi Semua Persediaan Ubat Batuk (08 March 2004)

v) (1) dlm. BPFK/02/5/1.4
Perlaksanaan Konsep Pek Saiz Pesakit (Patient Pack Size) bagi Produk Farmaseutikal (20 February 2008)

vi) Bil (4) dlm BPFK/PPP/01/03 Jld 1
Direktif Justifikasi Untuk Perubahan Pek Saiz Pesakit Untuk Penyakit Kulit Tertentu Bagi Produk-produk Dermatologi (14 December 2010)

APPENDIX 11 : GUIDELINE ON FILLING THE ONLINE APPLICATION FORM FOR PRODUCT REGISTRATION VIA QUEST SYSTEM

IMPORTANT NOTES:

Online application forms are available for different product categories in the QUEST system:

a) Pharmaceuticals;
b) Health Supplements and Natural Products.

This appendix may not follow the sequence of the online registration forms.

Applicant shall follow and comply with all requirements in the online application forms as well as any supplementary documentation requested by the Authority, whichever it may deems fit.

Applicant shall ensure that you have clicked on the appropriate section of the display panel and fill the correct application form.

Applicants are advised to read the explanatory notes in this appendix, as well as relevant ASEAN or ICH guidelines and checklists, for full information on requirement for product registration. In order to facilitate the evaluation process the Authority, applicants shall conform to these guidelines as well as the main guidance document.

The Authority reserves the right to request for supplementary information in certain cases.

Outline:

11.1 Product Classification

11.1.1 Pharmaceuticals

11.1.2 Health Supplements and Natural Products

11.2 Submission of Application

11.2.1 Step 1: Product Validation

11.2.2 Step 2: New Registration Application Form

Part I – Administrative Data and Product Information

- **Section A: Product Particulars**
- **Section B: Product Formula**
- **Section C: Particulars of Packing**
- **Section D: Label (Mockup) for Immediate Container, Outer Carton and Proposed Package Insert**
  - Section E/ Section F: Supplementary Documentation

Part II, III & IV – Quality , Nonclinical Document & Clinical Document

11.1 PRODUCT CLASSIFICATION

Applicant shall ensure correct product category as listed below in order to determine the method of evaluation i.e. full evaluation (*) or abridged evaluation (**) in which available as separate modules for application.

11.1.1 Pharmaceuticals

i) New Drug Products *
ii) Biologicals *
iii) Generics (Scheduled Poison) *
iv) Generics (Non-Scheduled Poison) (or known as OTC/ non-prescription) - *other than listed at v)* *
v) Generics (Non-Scheduled Poison) **, which include, but not limited to the following:
   - Antiseptics/ skin disinfectants;
   - Locally-acting lozenges/ pastilles;
   - Topical analgesic/ counter-irritants;
   - Topical nasal decongestants;
   - Emollient/ demulcent/ skin protectants;
   - Keratolytics;
   - Anti-dandruff;
   - Oral care;
   - Anti-acne;
   - Medicated plasters/ patch/ pad; and
   - Topical antibacterial.

11.1.2 Health Supplements and Natural Products **

- Application form for registration for Health Supplements; and Natural Products (or termed as Traditional Products) are available under Abridged module.
- Do not use the pharmaceuticals module for these product categories.

11.2 SUBMISSION OF APPLICATION

Any application for a product registration shall follow a 2-step process i.e. Step 1 (Product Validation) and Step 2, as described below:

11.2.1 STEP 1: PRODUCT VALIDATION

- All fields are compulsory to be entered.
- Option is given either to accept the validation result and submit; or override and manually select.
- Once validation is verified and submitted, the related application form under Step 2 will be displayed.
- Information entered in Step 1 will be captured in the database and need not be re-entered at Step 2.

[1] Product Name

1) Product name, dosage form and strength shall be entered.
   (e.g. X Brand Paracetamol Tablet 500mg)

2) Product name is defined as a name given to a product which may be either a proprietary name (an invented name); or a generic name (common name) or scientific name, together with a trade mark or the name of the manufacturer.

3) Product name shall not imply the following:
   a. Tricky, confusive and against the law;
   b. Scandalous and offensive;
   c. Prejudicial;
   d. Notorious.

4) Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product or a product that has been revoked due to safety concerns is prohibited.

5) The invented name shall not be liable to confusion with the common name.

6) The generic name means the international non-proprietary name recommended by WHO (rINN), or if one does not exist, the usual approved name.

7) The product name shall be shown on the product labelling i.e. immediate label, outer unit carton, package insert and consumer medication information leaflet.

8) Dosage form and strength of product would need to be entered as part of product name to allow for multiple dosage forms (e.g. tablet, capsule) and strengths (e.g. 200mg and 400mg) for any particular named (proprietary or generic) product.

9) If a product name is found similar to another registered product or any other name which deemed inappropriate by the Authority, NPRA reserves the rights to request for the change of the product name.

10) The generic name cannot be used alone as product name but in combination with another name other than generic name.

[2] Dosage Form

- Please select dosage form and further select 'in the form of' from the drop-down list.

- For example, a tablet may be in the form of chewable, coated (enteric, film, or sugar), uncoated, dispersible, effervescent, extended release, subligual, etc.

- The form that correctly describes it in terms of its product quality control specifications and performance shall be selected.

- A separate application for registration is required for each dosage form.

[3] Active Ingredients

i) Name of Active Ingredient:

- Please refer Appendix 8.1 List of Prohibited and Restricted Active Ingredients and Combinations.

- Please select active ingredient from the search database by clicking button 'click here to search'. If an active ingredient is not listed in the database, please click button 'Not Listed Ingredient'. Automatic e-mail will be send to NPRA for verification. Please ensure that the spelling is accurate.

- The actual raw material that is employed in the manufacturing process shall be named. For example:

- Where the raw material used is the salt (e.g. ampicillin trihydrate) which will yield an equivalent effective component from its base content (i.e. ampicillin), the substance name is the salt and the equivalent base component should be indicated in remarks on substance (if any) field. ***
- Similarly where a chemical is a component in the ingredient (e.g. iron in ferrous sulfate; or EPA and DHA in fish oil), the component details shall be stated in the remarks field if a label claim of the component is made for the product, and the actual raw material used declared as the active ingredient.

- International Non-proprietary Names (INN), approved names, pharmacopoeia names of ingredients shall be used whenever possible.

- After each ingredient entry is correctly made, click the button 'add/ save'. The button 'remove' will allow for corrections to an entry under this heading. To remove item, please select item from the listing and click 'remove'.

ii) Strength of active ingredient:

- Please enter strength of active ingredient (numerical) and then select unit weights and measures from the drop-down list.

- Content of ingredients shall be expressed as appropriate in the following manner :
  a. quantity per dose unit
     (e.g. for unit dose formulations - tablet, capsule, lozenge, etc.)
  b. percentage composition - %w/w, %w/v, %v/v, etc.
     (e.g. for products without defined dose unit such as ointments, creams, solutions, etc.)
  c. weight per ml.
     (e.g. for solutions, injections, etc.)
  d. quantity (percentage or amount) per measured dose
     (e.g. oral liquids, metered aerosols, drops, etc.)

- Metric weights and measures shall be used.

- In cases where product contains active ingredient(s) that cannot be definitely identified (e.g. certain biological products) state the name of the material to which activity is ascribed and, where appropriate, the potency or activity of the product.

iii) Remarks on active ingredient (if any):***

- This field shall be used where the raw material in product formulation yields an equivalent active component.

After each ingredient entry is correctly made, click the 'add/ save' button. The remove button will allow for corrections to an entry under this heading. To remove item, select item from the listing and click remove.

[4] Excipient

- Please refer Appendix 8.2 List of Prohibited and Restricted Excipients; and Appendix 8.3 Lists of Permitted and Restricted Colouring Agents.

- Details are as for [3] Active Ingredients stated above.

- Please enter function of excipients, e.g. sweetener, preservative, thickening agent, etc. which can be selected from the drop-down list.

[5] Any Animal Origin

- Click the appropriate button 'Yes' or 'No'.

[6] Manufacturer

- Click button 'click here to search' to select manufacturer listed in the database. For a new manufacturer which is not listed in the database search, please click 'Not Listed Manufacturer' button. Automatic e-mail will be send to NPRA for verification.

[7] Is The Selected Manufacturer a Contract Manufacturer?

- Status as to whether the declared manufacturer is a contract manufacturer or otherwise, has to be entered. Click the appropriate button 'Yes' or 'No'.

[8] Is This Product Second Source?

- Click the appropriate button 'Yes' or 'No'.

- If yes, please attach letter of declaration stating that this product is a second source product; and provide registration number and product name of the first source.

[9] Does This Product Contain Any Premix?

- Click the appropriate button 'Yes' or 'No'.
- If yes, please provide the following details:
  i) State your premix form
  j) Manufacturer name
  k) Manufacturer address
  l) Certificate of Good Manufacturing Practice (GMP)
  m) Formulation
  n) Manufacturing Process
  o) Specification of Analysis
  p) Certificate of Analysis (CoA)

[10] Is This a Replacement Product?

- Click the appropriate button 'Yes' or 'No'.

- If yes, please attach letter of declaration stating that this product is a replacement product; and provide registration number and product name of the replaced product.

[11] Other Manufacturer (Repacker)

- Click the appropriate button 'Yes' or 'No'.

- Please enter name of company and click button 'search' to select other manufacturer (repacker) listed in the database. For a new other manufacturer (repacker) which is not listed in the database search, please click 'Not Listed Manufacturer' button. Automatic e-mail will be send to NPRA for verification.

- Select from processing type drop-down list, e.g. assembly, packing, production, labelling, fill and finish, others.

[12] Is This an Imported Product?

- Click the appropriate button ‘Yes’ or ‘No’.

11.2.2 STEP 2: NEW REGISTRATION APPLICATION FORM

Please click at 'Section List' button to display the application form at Step 2. The requirement displayed will depend on the category of product being selected for registration submission:

- Abridged Evaluation for certain **OTCs, health supplements and natural products;
- Generic Pharmaceutical Products - **Parts I & II;**
- Existing chemical or biological entity(s) in new dosage form - **Parts I & II together with pharmacokinetic data;**
- NDP and Biologics - **Parts I to Part IV:**
  - Part I - Administrative Data and Product Information
  - Part II - Quality
    (For details of Part II, please refer Section C: Quality Control in the main DRGD)
  - Part III - Nonclinical Document
  - Part IV - Clinical Document.

Please refer Glossary developed for the ACTD and ACTR. The definitions used in the glossary have been developed for the ASEAN Common Technical Dossier (ACTD) and Common Technical Requirements (ACTR). They are not necessarily meaningful outside the scope of the specific parts of ACTD and ACTR to which they refer.

PART I – ADMINISTRATIVE DATA AND PRODUCT INFORMATION

SECTION A: PRODUCT PARTICULARS

Details of the following as entered under Step 1 will appear automatically in the application form:

1. **Product name;**
2. **Name and Strength of Active Ingredients, Name and Strength of Excipients; and**
3. **Dosage form.**

Other fields as followed, shall be completed:

4. Product Description:

State, briefly on **visual and physical characteristics** of the product, including (where applicable):

- Shape, size, superficial markings for identification purposes, colour, odour, taste, consistency, type of tablet coating, type of capsule, etc.

- When describing liquids, state clearly whether it is in the form of a solution (clear), suspension, emulsion, etc.

5. Pharmacodynamics (for full evaluation only)

Please provide a concise and comprehensive summary of the pharmacological profile:

- Main and supplementary pharmacological effects (mechanism of action, actions other than the therapeutic effects);
- Relevant pharmacokinetics (absorption, plasma-protein binding, distribution, biotransformation, metabolism, excretion, etc);

- Bioavailability and bioequivalence studies in man.

6. Pharmacokinetics (for full evaluation only)

- Details are as for A5.1 Pharmacodynamics stated above.

7. Indication

- State briefly on the recommended clinical use(s) of product, indicating clearly whether curative, palliative, adjunctive, diagnostic, etc.

- Indications should be specific; phrases such as ‘associated conditions’ or ‘allied diseases’ would not normally be considered appropriate.

- Indications other than those specified and accepted at the time of registration must not be included in any product literature, data sheets, package inserts, labels, etc. without prior permission of the Authority.

- Should it be desired to include new indications, an application shall be filed to the Authority together with supporting clinical documentation on evidence of efficacy and safety for the additional uses (indications).

- In the case of products which are to be used as health supplements, no claims shall be made for the prevention and treatment of disease states.

- For natural products, please state briefly on recommended use(s) of the product, starting with the phrase "Traditionally used for...../ Homeopathyically used for.....".

8. Recommended Dose OR Dose/ Use Instruction

Recommended Dose (for full evaluation only):

- Please state the dose (normal dose, dose range) and dosage schedule (frequency, duration); and route of administration appropriate for each therapeutic indication.

- Dosage for adults, and, children (where appropriate) shall be stated.

- Dosage adjustments for special conditions, e.g. renal, hepatic, cardiac, nutritional insufficiencies (where relevant) shall be stated.

- Where appropriate, diluents and instructions for dilution, reconstitution and use or administration of the product shall be clearly stated.

- Distinction shall be made between therapeutic and prophylactic doses, and between dosages for different clinical uses, where applicable.

- Ensure that dosage recommendation is relevant and appropriate for the product.

Dose/ Use Instruction (for abridged evaluation only):

- State the dose (normal dose, dose range) and dosage schedule (frequency, duration) [and route of administration appropriate for each therapeutic indication]. Dosage for adults, and where appropriate children, should be stated.

- Dosage adjustments for special conditions e.g. renal, hepatic, cardiac, nutritional insufficiencies, where relevant, shall be stated.

9. Route of Administration (for full evaluation only)

- Details are as for Recommended Dose stated above.

- Please select route of administration from the drop-down list, e.g. intramuscular, oral, rectal, sublingual, etc.

10. Contraindication

- Please state conditions for which or under which the product shall not be used.

- Indicate clearly which conditions are :
  - absolutely contraindicated;
  - contraindicated but may be used under special circumstances and what precautions to be taken in such cases.

- Where there is likelihood that additives are added, especially for intravenous solutions, foreseeable contraindicated additives shall be mentioned (where applicable).

- Concurrent drug therapy which are contraindicated shall also be included where possible (where applicable).

11. Warnings and Precautions

- Please state briefly on warnings and precautions, where necessary to ensure safe use; and efficacious (where applicable) of the product;
  (e.g. caution against giving to children and elderly; against driving motor vehicles or manning heavy machinery after intake of product; use in pregnancy and lactation; in infants; etc.)

12. Interactions With Other Medicaments

- Please state interactions which are observed and/or for which there is potential clinical significance.

- Interactions may occur with:
  - medicinal products used for the same indication;

- medicinal products used for other indications;
- meals, or specific types of food.

13. Pregnancy and Lactation

Use in Pregnancy:

- The following shall be stated:
  a) conclusions from the animal reproduction/ fertility study and the human experience;
  b) the risk in humans at different stages of pregnancy, as assessed from a);
  c) information on the possibility of using the medical product in fertile and pregnant women.

Use in Lactation:

- When the active substance(s) or its metabolites are excreted in milk, recommendations as to whether to stop or continue breast feeding, and the likelihood and degree of adverse reaction in infant shall be stated.

For abridged evaluation, please state any effect on pregnancy and lactation, if applicable.

14. Side Effects/ Adverse Reactions

- Please state in order for severity and frequency, the side effects, adverse reactions, toxic effects, etc. (i.e. reactions, toxic effects, other than those desired therapeutically) including reactions such as allergy, hypersensitivity, drug dependence, addiction, carcinogenicity, tolerance, liver/ kidney toxicity etc.
- Indicate also symptoms and sites of effects/ reactions.
- Reactions, whether minor or serious shall be stated.
- Severity, reversible, frequency of occurrence shall be indicated, wherever possible.
- Clinical tests for detection of 'sensitive' patients, measure for management of adverse reactions developed shall be described wherever possible.

15. Signs and Symptoms of Overdose and Treatment

- Please state briefly symptoms of overdose/ poisoning, and where possible, recommended treatment and antidotes for overdose/ poisoning.

16. Storage Conditions

- Please state the recommended storage conditions (temperature, humidity, light etc.).

- Information include storage condition before first opening, after reconstitution and/or after opening and for all the listed pack types shall also be provided, where applicable. Stability data to support such storage condition shall be submitted.

17. Shelf Life

- Shelf life for all the listed pack types shall be supported by stability data.

- Information include shelf life before first opening, after reconstitution and/or after opening where applicable shall also be provided. Stability data to support such shelf life shall be submitted.

- Evidence is required to demonstrate that the product is stable which meets the finished product shelf life specifications throughout its proposed shelf-life and toxic decomposition products are not produced in significant amounts during this period; potency, sterility and efficacy of preservative, etc. are maintained.

18. Therapeutic Code

- Please indicate WHO assigned ATC code for each distinct therapeutic indication proposed for a product, if such a code is available. Click button 'click here to search' to search the code via database at http://www.whocc.no/atcddd/.

- For natural products, please select "Traditional/ Homeopathy" from the listed button.

After completion of Section A has been done, please click Section List for display of main page of application form and select Section B: Product Formula, or click button 'next' after saving the entered data.

SECTION B: PRODUCT FORMULA

a) For full evaluation requirement, B1.1 and B1.2 as described below is required under Section B: Product Formula. Data pertaining to quality of product is required to be submitted under Part II: Quality of Product.

B1.1 Batch Manufacturing Formula

- Please state batch size and actual batch manufacturing master formula.

- Data from validation step will be captured in terms of substance name, type (active or excipient ingredient), function and quantity per unit dose.
- Other information such as overage (where applicable) shall be entered.

B1.2 Attachment of the Batch Manufacturing Formula Documentation

- The attachment shall be submitted.

b) For abridged evaluation requirement, Batch Manufacturing Formula is required under B1.1 and Attachment of the Batch Manufacturing Formula documentation is required under B4 of the same section i.e. Section B.

Whereas B2.1, B3, B4 and B5 appear as below:

B2.1 Manufacturing process

- Please state a brief description of the manufacturing process.

- Essential points of each stage of manufacturing process and a description of the assembling of the product into final containers shall be covered. If the product is repacked/ assembled by another manufacturer, details of repacking/assembly and quality control shall be supplied.

- An **attachment** of the manufacturing process, in the form of a flow chart can be submitted under B2.2.

B3. In-Process Quality Control

- Please attach document for In-Process Quality Control to provide a summary of the tests performed, stages at which they are done, and the frequency of sampling and number of samples taken each time.

- Specifications for quality assurance of the product shall be supplied.

B4. Attachment of Finished Product Specification Documentation

- Please attach document for Finished Product Specification to provide details of quality control specifications, including a list of tests for both release and shelf life specifications (if they are different); and state the limits of acceptance.

B5. Attachment of Stability Data Documentation

- Reports of stability studies shall provide details of :
  - the batches placed under study (a minimum of 2 batches are required);
  - containers/ packaging type;
  - conditions of storage during study (temperature, humidity, etc);
  - duration of study and frequency (interval) of the tests/ observations;
  - the tests performed (including degradation products being monitored) and acceptance limits.

SECTION C: PARTICULARS OF PACKING

- This section is subjected to requirements as stated in Appendix 10: Guide for Implementation of Patient Dispensing Pack for Pharmaceutical Products in Malaysia. Please refer the appendix for details.

- Please enter particulars of packing in the following sub-sections:

C1 : Pack Size

- Please select pack size by weight or volume or quantity; and unit

C2 : Immediate Container Type

- Please select container type, e.g. aluminium, glass, metal, paper, plastic, others (if others, please specify)
- Please enter description of container type
- Please attach attachment of container type at table appeared after 'Add' button at the bottom page is clicked

C3 : Barcode/ Serial No.

- Please key in if any (optional)

C4 : Recommended Distributor's Price

- Please key in if any (optional)

C5 : Recommended Retail Price

- Please key in if any (optional)

and then click button 'Add' to save all the entered informations.

Note:
To add next particulars, repeat the same process until all packings are listed accordingly. To remove any item from the listing, select item from the listing and click the "Remove" button.

SECTION D: LABEL (MOCKUP) FOR IMMEDIATE CONTAINER, OUTER CARTON AND PROPOSED PACKAGE INSERT

- This section is subjected to requirements as stated in Appendix 9: Labelling Requirements and other appendices (where applicable). Please refer the appendices for details.

- Please attached label (mock-up) i.e. draft of the actual product label and proposed package insert at the following sub-sections:

  D1. Label (Mock-up) for Immediate Container

  D2. Label (Mock-up) for Outer Carton (Unit Carton)

  D3. Proposed Package Insert

SECTION E/ SECTION F: SUPPLEMENTARY DOCUMENTATION (AND PARTICULARS OF PRODUCT OWNER, MANUFACTURER, IMPORTER AND OTHER MANUFACTURER)

a) Product Owner

Please select one of the following for status of product owner:

- Manufacturer or
- Product registration holder or
- Product registration holder & manufacturer or
- Others (If the product owner is neither of the above status) – Please enter name and address of the product owner.

b) Letter of Authorization from Product Owner

- All applications for registration shall be accompanied with Letter of Authorization from product owner.
  (Not applicable if the Product Registration Holder is Product Owner).

- Letters of Authorization (LOA) shall be valid and current at the time of submission.

- The LOA shall be on the product owner's original letterhead and be dated and signed by the Managing Director, President, CEO or an equivalent person who has overall responsibility for the company or organization.

- The LOA shall state the name of the product concerned and also the name and actual plant address of the manufacturer(s) involved in the manufacture of the product.

c) Letter of Appointment of Contract Manufacturer from Product Owner

- Please attach (if applicable).

- Applicable for product which is contract manufactured by a manufacturer who is not the product owner.

d) Letter of Acceptance from Contract Manufacturer

- Please attach (if applicable).

- The letter of acceptance from the manufacturer shall be on the manufacturer's original letterhead and be dated and signed by the Managing Director, President, CEO or an equivalent person who has overall responsibility for the company or organization.

- The letter of acceptance shall state the name of the product concerned and also the name and actual plant address of the manufacturer(s) involved in the manufacture of the product.

e) Is the active ingredients patented in Malaysia?

- Click the appropriate button 'Yes' or 'No'.
- If yes, please attach the related document.
- Applicants who hold valid patents shall provide documentary evidence of the nature and extent of their patents.

f) Certificate of Pharmaceutical Product (CPP), Certificate of Free Sale (CFS) and Certificate of Good Manufacturing Practice (GMP)

- Please attach the certificates.

- Please key in issuing body, date of issue, date of expiry of the certificates. If the issuing body is not listed, please select 'Not Listed' button. Automatic email will be sent to NPRA for verification.

- The certificates shall be valid and current at the time of submission.

- For imported products, the following requirements shall be furnished, either a:
  i) CPP from the competent authority in the country of origin; OR
  *(**Note:** In the event a CPP is not available from the country manufacture, e.g. where a product is not licensed for sale in said country because its manufacturer is manufacturing under contract only for product owner from another country, the following alternatives may be considered: GMP Certification/ Manufacturing License for the manufacturer from the relevant competent authority, together with CPP from the country of the product owner; or CPP from country of release, if CPP from the country of the product owner is not available)*

  ii) CFS and GMP from the relevant competent authorities is deemed acceptable by the Authority for health supplements and natural products only.

- CPP shall be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce & be issued by the Health Authorities listed in the WHO Certification Scheme (*list is available from WHO website*: http://www.who.int).

- CPP which is issued by EMA for products registered through the centralized procedure in EU will be accepted.

- CPP issued by the manufacturer or other authorities are not acceptable.

- If more than one manufacturer is involved in the manufacture of a product, GMP certification shall be available for all the manufacturers.

- The Authority reserves the right to conduct an inspection on any manufacturing site.

- Unless otherwise supported by justifications acceptable to the Authority, the following products are unlikely to be registered:
  i) products not licensed/ certified for sale in the country of manufacture/ product owner;
  ii) products manufactured for export only (imported products).

g) <u>Is this product licensed to be placed on the market for use in the exporting country?</u>

If no, please state the reason.

h) Is the product on the market in the exporting country?

If no, please state the reason.

i) Summary of Product Characteristics (SPC)

Please attach (where applicable).

j) Consumer Medication Information Leaflet (RiMUP)

Please attach (where applicable).

k) Attachment of Protocol Analysis, Analytical Validation

Please attach (where applicable).

l) Certificate of Analysis (CoA) for Finished Product

- For two (2) batches.
- Compulsory for imported product.
- Please attach the certificate (which must be complete with the product specification and results).

m) Importer and Store Address

Please key in (where applicable).

n) Other Supporting Document

Please attach (if any).

PART II, III & IV – QUALITY , NONCLINICAL DOCUMENT & CLINICAL DOCUMENT

In order to complete these parts, please refer the main DRGD as well as ASEAN Common Technical Requirements Guidance Documents, and the following documents (where applicable):

a) Appendix 2: Requirements for Product Registration
b) Appendix 3: Guidelines on Registration of Biologics
c) Appendix 4: Guideline on Registration of Health Supplements
d) Appendix 5: Guideline on Registration of Natural Products
e) Appendix 6: Guideline on Regulatory Control of Active Pharmaceutical Ingredients (API)

APPENDIX 12 : CONDITIONS AND SUPPORTING DOCUMENTS REQUIRED FOR AN APPLICATION OF VARIATION

a) VARIATION TYPE I (MINOR VARIATION)

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
1.	Change in name of manufacturer and/or other manufacturers without any change in address of site.	• E13 (manufacturer) • E14 (other manufacturers) • D1 • D2 • D3 • E6 • E12	• E2 (manufacturer) • E3 (other manufacturers) • D1 • D2 • D3 • F6 • F12	<u>CONDITIONS</u> 1. The manufacturing/ other manufacturing site of the drug product remains unchanged. 2. No other changes to the label/ package insert except for the change of the name of a manufacturer/ other manufacturers of the drug product. 3. The manufacturing site remains the same. <u>SUPPORTING DOCUMENTS</u> 1. For local manufacturers/ other manufacturers: Certificate of name change i.e. Form 13 Company Act 1965. (Please attach the supporting document at E12/ F12). 2. For foreign manufacturers/ other manufacturers: A valid Good Manufacturing Practice (GMP) certificate. 3. Official letter from product owner authorizing the

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				manufacturer with new name to manufacture the drug product. 4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
2.	Replacement, addition or deletion of company logo on the packaging components (without any changes on graphic or label content)	• D1 • D2 • D3	• D1 • D2 • D3	<u>SUPPORTING DOCUMENT</u> Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
3.	Change in product owner	• E1.1 • E1.2 • E2.1 • E2.2 • E12 • D1 • D2 • D3 (if applicable)	• E1 • F1 • F2.1 • F2.2 • F12 • D1 • D2 • D3 (if applicable)	<u>CONDITIONS</u> 1. The Product Registration Holder remains the same. Submission shall be done by current PRH. 2. The manufacturing site remains the same. <u>SUPPORTING DOCUMENTS</u> 1. Letter of confirmation for change in product ownership countersigned by both old and new product owner. 2. Official letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 3. In the case of a contract manufacturer, new product owner to issue Letter Of Appointment to contract manufacturer and contract manufacturer to issue Letter Of Acceptance. 4. Revised labels and package insert (if applicable).
4.	Change in importer/ store address.	• E13.1 (importer) • E15 (store address)	• E2.1 (importer) • E4 (store address)	

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
5.	Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking.	• A4 • P1 • P5.1 • P5.2 • D3 • E8 (if applicable) • E9	• A2 • D3 • F8 (if applicable) • B4 • F9	<u>CONDITIONS</u> 1. Any new ink must be of oral pharmaceutical/ food grade and not a listed banned substance. 2. Release and end-of-shelf life specifications of the drug product remain unchanged except for appearance. 3. New markings do not cause confusion with other registered products. <u>SUPPORTING DOCUMENTS</u> 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Release and end-of-shelf life specifications of the drug product with the new product description. 3. Certificate of analysis (CoA) of new ink. 4. Details of the proposed new inks (where applicable) 5. Detailed drawing or written description of the current and proposed imprint/ bossing/ markings.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
6.	Change in shape or dimensions of the container or closure without any other changes.	• P7 • C (if applicable)	• C (if applicable)	CONDITIONS 1. The primary packaging material of container or closure remains the same. 2. Not applicable for sterile products. 3. No change is made to the product shelf life and/or storage conditions. 4. No change in the qualitative or quantitative composition of the container and/or closure and the change do not affect the delivery, use, safety or stability of the drug product. SUPPORTING DOCUMENTS Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
7.	• Change in pack size of the drug product (Finished product), without change in primary packaging material. (including pack size meant as samples) • Change in the number or units (e.g. tablets,	• C • D1 • D2 • D3 • E8 (if applicable) • P7	• C • D1 • D2 • D3 • F8 (if applicable)	CONDITIONS 1. The primary packaging material of container or closure remains the same. Primary packaging material is the material that is in contact with the finished product and may affect the delivery, use, safety or stability. 2. No other changes to the label/ package insert except for the pack size. 3. The new size is consistent with the dosage regimen and duration of use as approved in the package insert.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
	ampoules) in a pack. • Change in volume of non sterile preparations			*The sentence 'Sample not for sale' can be added in the product label without going through variation approval. <u>SUPPORTING DOCUMENTS</u> Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
8.	Tightening of specification limits of drug product (finished product) and/or drug substance (active ingredient)	• E9 • E10 • E11 • P5.1 • P5.2 • P5.4 • S4.1 • S4.2 • S 4.4	• B4 • F9 • F10 (finished product) • F11 (active ingredient)	<u>CONDITION</u> 1. Any change should be within the range of currently approved limits. <u>SUPPORTING DOCUMENTS</u> 1. Tabulation of the current and revised release and shelf life specifications of the drug product/drug substance with changes highlighted. 2. Certificate of Analysis (CoA) for drug product or drug substance. 3. Protocol analysis for drug product/ drug substance. 4. Revised specification of drug substance. 5. Specifications of drug product. 6. Batch analysis of drug product.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
9.	Change in particular of manufacturer of drug substance (active ingredient) without any change in specification a. Change in manufacturer of drug substance b. Addition of manufacturer of drug substance c. Change in name and/or rephrasing of address of a manufacturer of drug substance.	• S2.1 • S4.4	• F11	<u>CONDITIONS</u> 1. Finished product release and end of shelf life specification remains the same. 2. Method of preparation and route of synthesis remain the same. 3. For (c), the manufacturing site of the drug substance remains the same. <u>SUPPORTING DOCUMENTS</u> **For (a) & (b):** 1. Certificate of Analysis (CoA) for drug substance (Also include CoA from all of the drug substance manufacturers proposed to be retained) or batch analysis of drug substance. 2. Certificate of Suitability (CEP) for the drug substance or Drug Master File; or reference to DMF by USFDA, TGA or JFDA (if applicable). 3. Tabulation of the differences compared with the registered manufacture information (if applicable). **For (c)**: 1. Updated information of the manufacturer of the drug substance. 2. Official document/ evidence when required.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
10.	Change in secondary packaging material (or change in any part of the primary packaging material that is not in contact with the finished product (e.g. colour of flip off caps, colour code rings on ampoules, change of needle shields i.e. different plastic used).	• C • D2 • D3 • P7	• C • D2 • D3	CONDITIONS 1. The primary packaging material of container or closure remains the same. 2. The change does not affect the delivery, use, safety or stability of the finished product SUPPORTING DOCUMENT Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
11.	Change in testing procedure of an excipient	• P4.2 • P4.3	Not applicable	CONDITION Specifications of the excipient and drug product (finished product) remain the same.

b) VARIATION TYPE II (MAJOR VARIATION)

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
1.	Change of product name.	• A1 • D1 • D2 • D3 • E4 (if applicable) • E8 (if applicable)	• A1 • D1 • D2 • D3 (if applicable) • F4 (if applicable) • F8 (if applicable)	CONDITIONS 1. No change to product (formulation, specification etc) except for the product name 2. No confusion with other already registered product's name. 3. The new name does not (1) suggest greater safety or efficacy than supported by clinical data (2) imply a therapeutic use (3) imply superiority over another similar product (4) imply the presence of substance(s) not present in the product. 4. Health Supplements & Natural Products - Please refer Appendix 4 and Appendix 5, respectively. SUPPORTING DOCUMENTS 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter confirming change in name only issued by the product owner or PRH. 3. A declaration from the applicant that there is no change to the product/ label except name. 4. Updated CPP if applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
2.	Change in content of leaflet or prescribing information/ PIL/ SPC.	• A1 – A17 • D1 • D2 • D3 • E7 • E8 (if applicable)	• A1 – A13 • D1 • D2 • D3 • F7 • F8 • F12	<u>CONDITION</u> As a subsequent change due to revision of datasheet approved by regulatory authority e.g. Summary of Product Characteristics (SPC), or US Package Insert (USPI) or equivalent document. For natural products: Proposed indication shall be within those listed under Appendix 5. <u>SUPPORTING DOCUMENTS</u> 1. For all types of product please provide revised drafts of the package insert and labeling incorporating the proposed variation with: a. Copy with amendments clearly marked. b. Clean copy of the proposed new package insert. 2. For innovator product please provide: a. Datasheet approved by regulatory authority e.g. Summary of Product Characteristics (SPC), or US Package Insert (USPI) or equivalent document. b. Conclusion or abstract of recent Periodic Safety Update Report where applicable. c. Expert Clinical Report (if applicable) d. Company Core Datasheet where applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				3. For generic product please provide supporting documents e.g. Martindale or equivalent document to support the change. 4. For natural products, please provide: a) Justification for the proposed change. b) Supporting documents from the clinical papers, Chinese Pharmacopoeia and/or herbal monograph/ compendium on the therapeutic uses and safety aspect of the relevant active ingredient/s.
3.	Change in content of label inclusive of change in graphics/ artwork.	• D1 • D2 • D3	• D1 • D2 • D3	<u>CONDITIONS</u> For Natural Products Please refer to (List of Prohibited Visuals/ Graphics On Label of Natural Products in Appendix 5) <u>SUPPORTING DOCUMENT</u> Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
4.	Change in manufacturing process of the finished product	• E11 • P3.2 • P3.2.1 • P3.3 • P3.4 • P5.1 • P5.4 • P8	• B2.1 • B2.2 • B3 • B4 • B5 • F10 (CoA of finished product)	CONDITIONS 1. The same currently approved manufacturing site. 2. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 3. Finished product specification is not adversely affected. SUPPORTING DOCUMENTS 1. Description of the proposed change in manufacturing process. 2. Comparative batch analysis data between the currently approved and proposed manufacturing processes OR Certificate of Analysis (CoA), where applicable. 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Comparative dissolution profile data between the products manufactured in the currently approved and proposed manufacturing process for oral solid dosage forms as per compendium and validation batches, where applicable. 5. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies, where applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				For abridged-products, only supporting documents (1), (2) and (3) are required. Process validation report may be requested when deemed necessary.
5.	Change in overage of active ingredient	• B1.2 • E11 • P5.4 • E12 • P8	• B1.2 • F10 • F12 • B5	<u>CONDITION</u> Finished product release and end of shelf life specification remains the same. <u>SUPPORTING DOCUMENTS</u> 1. Certificate of Analysis (CoA) of drug product. 2. Justification for the change. 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Batch manufacturing formula. 5. Comparative batch analysis data of drug product. 6. Table of comparison of proposed and current batch manufacturing formula. 7. Letter of commitment to undertake the proposed change under real time stability study.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	**ABRIDGED EVALUATION**	
6.	Replacement of an excipient with a comparable excipient and/or change in content of excipient.	• A2.1 • B1.2 • P1 • P4.1 • P4.2 • P3.2 • P3.2.1 • E11 • P5.4 • P8 • E12 • D1 • D2 • D3 (if applicable)	• A4.2 • B1.2 • B2.1 • B2.2 • B3 • B4 • B5 • F10 • F12 • D1 • D2 • D3 (if applicable)	<u>CONDITIONS</u> 1. Finished product release and end of shelf life specification remains the same. 2. There is no change in dissolution profile for oral solid dosage forms (where applicable). 3. Replacement of an excipient with a comparable excipient of the same functional characteristics. 4. No changes on the specification of the excipient for product specific requirements (e.g. particle size profiles, polymorphic form, etc.), if applicable. 5. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. <u>SUPPORTING DOCUMENTS</u> 1. Comparison of new and existing formula. 2. Batch Manufacturing Formula. 3. Excipient specification (if applicable). 4. Manufacturing process with amendments. 5. Certificate of Analysis (CoA) of drug product. 6. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 7. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and proposed solid dosage forms formulation (where

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				applicable). 8. Stability data of drug product (please refer to ASEAN Guideline On Stability Study of Drug Product) 9. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 10. Batch analysis data. 11. Product interchangeability/ equivalent evidence (if any). 12. Justification for the change supported by appropriate development of pharmaceutics. 13. New unit formula for coating agent (where applicable).
7.	Change in batch size	• B1.2 • E11 • P5.4 • P3.4 • E12 • P3.2 • P3.2.1 (if applicable)	• B1.2 • F10 • F12 • B2.1 • B2.2 (if applicable)	<u>CONDITIONS</u> 1. The change does not affect the reproducibility and/or consistency of the product. 2. No change to the manufacturing method nor to the in-process controls other that those necessitated by the change in batch-size, e.g. use of different size equipment. 3. Finished product release and end of shelf life specification remains the same. <u>SUPPORTING DOCUMENTS</u> 1. Comparative tabulated format of the proposed and current manufacturing formula.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				2. New batch manufacturing formula. 3. Batch analysis data (in a comparative table). 4. Certificate of analysis for 2 batches of drug product. 5. Process validation report (may be requested when deemed necessary). 6. Justification for the change. 7. Letter of commitment to undertake the proposed batch size under real time stability studies. 8. Description of the manufacturing process (if applicable).
8.	Change in hard capsule shell (colour, size or source)	• A4 • P1 • P8 • E11 • P4.5 • P5.4 • E12 • P5.1 • E9 • D1 • D2 • D3 (if applicable)	• A2 • A3.2 • B4 • B5 • F9 • F10 • D1 • D2 • D3 (if applicable)	<u>CONDITIONS</u> 1. Includes change of hard gelatin capsule to vegetable capsule but does not apply change from hard gelatin capsule to soft gel capsule. 2. Any new coloring agent used must be of oral pharmaceutical/ food grade and not a listed banned substance. 3. Same functional characteristics, no change in dissolution profile for solid dosage forms 4. Finished product release and shelf life specifications remain the same except for the product description. <u>SUPPORTING DOCUMENTS</u> 1. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				Product) where applicable. 2. Certificate of analysis (CoA) of drug product with the new description. 3. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate issued from relevant veterinary authority of the issuing country. 4. Certificate of analysis of the new capsule shell. 5. Revised specifications of drug product. 6. Batch analysis data. 7. Comparative dissolution profile data of drug product. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
9.	Change in finished product or active ingredient specification (includes addition of a new test parameter)	• E9 • E10 • E11 • P5.1 • P5.4 • P5.6 • S4.1 • S4.2 • S4.3 • S4.4	• B4 • F9 • F10 • F11	CONDITIONS The change should not be the result of unexpected events arising during manufacture or because of stability concerns. SUPPORTING DOCUMENTS 1. For change in finished product specifications: a. Certificate of analysis of drug product as per the new specifications: b. Comparative table of approved and proposed specifications with justification c. Appropriate analytical validation data d. Revised specifications of drug product. e. Revised analytical procedures. f. Batch analysis data of drug product. 2. For change in active ingredient/ drug substance specifications: a. Comparative table of approved and proposed specifications with justification b. Specification of drug substance, c. Analytical procedures of drug substance, d. Validation of analytical procedures, e. Batch analysis of drug substance

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
10.	Change to in-process tests or limits applied during manufacture of the product.	• P3.3 • P3.4 • E9 • E10	• B3 • F9	<u>CONDITIONS</u> 1. Includes tightening of in-process limits and addition of new tests 2. Release and shelf-life specifications of drug product remain unchanged <u>SUPPORTING DOCUMENTS</u> 1. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 2. Revised in-process specifications together with justification and relevant process validation data.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
11.	Change or addition in primary packaging material	• C • D1 • D2 • D3 • P3.2 • P3.2.1 • P7 • P8 • E8 (if applicable), • E12	• C • D1 • D2 • D3 (if applicable), • B5, • F8 (if applicable) • F12	<u>CONDITIONS</u> Release and shelf life specification remains the same. <u>SUPPORTING DOCUMENTS</u> 1. Assembly process for the new packaging material/ revised manufacturing process and revised flow chart (if any) 2. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Justification for the change in packaging material and appropriate scientific studies on the new packaging. 5. For semisolid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs. (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). 6. Container closure system (if applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
12.	Change in shelf life of finished product:- a) As packaged for sale b) After first opening c) After dilution/ reconstitution	• A16 • P8 • E12 • D1 • D2 • D3	• A13 • B5 • F12 • D1 • D2 • D3	<u>CONDITIONS</u> 1. **For (a) & (b)** - The studies must show conformance to the current shelf life specification. 2. **For (c)** - Studies must show conformance to the current shelf life specification for the reconstituted product. <u>SUPPORTING DOCUMENTS</u> 1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least 2 pilot/ production scale batches of the product in the authorized packaging material • as a package for sale and/or • after first opening and/or • after the dilution/ reconstitution In accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf life of the drug product (if applicable).
13.	Change in storage	• A15	• A12	<u>CONDITION</u>

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
	conditions	• P8 • D1 • D2 • D3	• B5 • D1 • D2 • D3	The studies must show conformance to the current shelf life specification. <u>SUPPORTING DOCUMENTS</u> 1. Results of appropriate real time stability studies covering the duration of currently approved end-of-shelf life (at proposed storage condition) of at least 2 pilot/ production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (if applicable).
14.	Appointment, deletion or change of other manufacturers	• D1 • D2 • D3 • E14 • E12	• E3 • F12 • D1 • D2 • D3	<u>SUPPORTING DOCUMENTS</u> 1. GMP certificates of the proposed other manufacturers. 2. Description of the manufacturing activity of all other manufacturers involved (including assembling process). 3. Letter of appointment and acceptance for contract of other manufacturers. 4. Revised drafts of the labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
15.	Addition or deletion of scoring/ break line on tablet	• A4 • P1 • D1 • D2 (if applicable) • D3 • E9 • E11 • P5.1 • P5.4 • E12	• A2 • B4 • F9 • F10 • F12 • D1 • D2 • D3 (if applicable)	CONDITIONS Finished product release and shelf life specifications remain the same except for the product description. SUPPORTING DOCUMENTS 1. Certificate of analysis (CoA) FPQC X 1 batch (shall include data on the test of uniformity of content of the subdivided parts of tablets at release). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Release and end-of-shelf life specifications of the drug product with the new product description.
16.	Change in test procedure or analytical protocols of finished product.	• E9 • E10 • E11 • P5.4	• B4 • F9 • F10	CONDITIONS 1. Finished product specifications are not adversely affected. 2. Appropriate analytical validation or re-validation studies have been performed in accordance with relevant guidelines. 3. Results of method validation show new test procedure to be at least equivalent to the former procedure.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	**ABRIDGED EVALUATION**	
				SUPPORTING DOCUMENTS 1. Appropriate verification/ validation data and comparative analytical results between the currently approved and proposed test. 2. Revised protocol of analysis. 3. Certificate of analysis of drug product.
17.	Change or addition of fill volume and/or change of shape or dimension of container or closure for a sterile solid and liquid drug product	• P3.4 • P8 • E12 • C • D1 • D2 • D3 (if applicable)	Not applicable	CONDITIONS 1. Release and end-of-shelf life specifications of the drug product are not affected. 2. The packaging material remains the same. SUPPORTING DOCUMENTS 1. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2. Validation data of the manufacturing process, sterilization and container closure system (if applicable). 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Revised drafts of the package insert and labeling incorporating the proposed variation, where applicable.

APPENDIX 13 : SUPPORTING DOCUMENTS REQUIRED FOR CHANGE OF MANUFACTURING SITE (COS) APPLICATION

a) Supporting documents required for change of manufacturing site (COS) application

No	Document To Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
1.	Letter of authorisation/ appointment from the product owner to authorise Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.	√	√	√	√	√
2.	Letter from the manufacturer/ product owner to clarify/ explain the need to change site of manufacture.	√	√	√	√	√
3.	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry (check) specifications of the product as the same as already approved. *OR* If there are minor changes, to declare the 'minor changes' & justify the need for such changes.	√	√	√	√	√
4.	'Release' and 'end-of-shelf life' specifications from proposed site.	√	√	√	√	√

No	Document To Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
5.	Original copy of the Certificate of Free Sale (CFS) / Certificate of Pharmaceutical Product (CPP) and notarised Good Manufacturing Practice (GMP) from the source country of the new manufacturing site in the case of an imported product *OR* Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site.	√	√	√	√	√
6.	Specification of the drug substance	√	√	√	√	√
7.	Product formula/ Batch Manufacturing Formula	√	√	√	√	√
8.	Original copy of Certificate of Analysis (CoA) from the new manufacturing site.	√	√	√	√	
9.	Comparative batch analysis data of drug product of at least two production batches (or one production batch and two pilot batch) from the proposed site and last three batches from the current site; batch analysis data on the next two full production batches should be available upon request or reported if outside specifications (with proposed action).	√	√	√	√	
10.	"Accelerated" and on-going stability data as per ASEAN Guideline on Stability Study of Drug Product and a letter of commitment to submit real time stability data.	√	√	√	√	
11.	Amended immediate label, outer label and package insert for the product from the proposed site.	√	√	√	√	√
12.	Process validation report as per ASEAN Guideline On Submission Of Manufacturing Process Validation Data For Drug Registration.	√	√	√	√	

No	Document To Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
13.	Holding time studies testing of bulk pack during storage and transportation between the bulk production site and primary packager (where applicable).	√	√	√	√	
14.	Letter of commitment to submit stability data, certificate of analysis, process validation report (where applicable) and sample for laboratory testing within 6 months of approval of site change.					√
15.	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.	√	√		√	
16.	Comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for "biowaiver". *For further information, please refer circular:* Bil (31) dlm. BPFK/PPP/01/03 *OR* Report of bioavailability and bioequivalence studies for generic products. *OR* Comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable. (*Please refer to ASEAN Guidelines and list of products requiring BA and BE study).*	√	√	√		

No	Document To Be Submitted	Type I *(Except Natural Product)*	Type II	Type III	Type IV	Type V
17.	Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for "biowaiver". *For further information, please refer circular:* Bil (31) dlm. BPFK/PPP/01/03 *OR* Letter of commitment to submit report of bioavailability and bioequivalence studies for generic products. *OR* Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable. *(Please Refer to ASEAN Guidelines and list of products requiring BA and BE study).*					√

b) Supporting documents required for Type I change of manufacturing site (COS) application for natural products

No.	Documents To Be Submitted
1.	Letter of authorisation/ appointment from the product owner to authorise Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.
2.	Letter of declaration stating the reason(s) for change of manufacturing site and clearly state the proposed and current name and address of manufacturer
3.	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry specifications of the product as the same as already approved. *OR* If there are minor changes, to declare the 'minor changes' & justify the need for such changes.
4.	'Release' and 'end-of-shelf life' specifications from proposed site.
5.	Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site.
6.	Product formula / Batch Manufacturing Formula
7.	Amended immediate label, outer label and package insert for the product from the proposed site.
8.	Declaration and commitment that the manufacturer will carry out continuous quality monitoring on the post change products
9.	Letter of commitment to submit stability data and certificate of analysis after approval of site change.
10.	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.

APPENDIX 14 : GUIDELINES ON SAFETY DATA REQUIREMENTS FOR COMPLEMENTARY MEDICINE PRODUCTS

Contents

1. Introduction

Consumer interest in health and self-care has expanded the market for a wide range of health supplements and traditional products. These categories of products have been used since the earliest history of humanity and have formed one of the foundations for healthcare in cultures throughout the world. With the increased use of such products and the broad spectrum of products classified under this category, it is important to ensure that the products consumed are safe for consumers.

Evaluation of the safety of complementary medicine products (health supplements, herbal products and traditional medicine) must be done in a manner that is cost effective and science-based within the regulatory environment.

Most ingredients might be considered as safe, considering the experience or history of long use. When an ingredient is well known for a specific use, the assessment will be limited to published data (including traditional references). However, under certain conditions, additional data will be required to prove the safety of the product, e.g. for a new active ingredient or a new combination of ingredients. Even if a product has been in use over a long period of time, chronic toxicology risks may have occurred but not recognized.

2. Objectives

This Guideline aims to provide guidance in submitting safety data requirements for assessment to facilitate registration of complementary medicine.

3. Safety Data

Proof that a product is of quality, safe and as efficacious as claimed is a pre-condition for marketing of a complementary medicine product. Safety is dependent upon the overall product formulation, its intended use, dosage, route of administration, duration of use and targeted group where applicable.

Each active ingredient shall make a relevant and reasonable contribution to the overall therapy and the quantity of each active ingredient shall be safe for the recommended use and range of dosage.

3.1 Safety data shall be required to substantiate the safety profile for the following complementary medicine product to be marketed but not limited to:

a. New ingredients
b. Existing active ingredients/products with new combination, new dosage, new delivery system, new methods of manufacturing or for use in a special target population (e.g. pregnant, lactating women, children, etc).
c. Existing ingredients/products with safety concern. Safety concerns may be newly emerging or established, and in some cases may need additional information to support safe usage in complementary medicine. These safety concerns may be addressed by including additional cautionary statements.

3.2 Safety substantiation might not be required for complementary medicine products that do not fall under items a. - c. as mentioned above. Traditional medicines with documented data; health supplements which have been consumed as food or is a food constituent within the normal usage limit or for those containing ingredients with well documented and established safety profile may also not require further safety substantiation.

Further examples would include:

i) Product containing the same combination (same number of active ingredients) as with another previously registered product with the active ingredients within limits previously registered.
ii) Combination of vitamins and minerals within permissible limits
iii) Formulary products

3.3 Some general principles on assessing product safety shall be as follows:

a) Single ingredient

For well-known ingredients such as vitamins or minerals and herbal ingredients, documented data will be accepted to demonstrate safety of use.

If an ingredient has been used traditionally and documented that it had no safety concerns, the submission of toxicology studies will not be required. However, if history of use is used to support safety, then the details of use must be consistent with its traditional use.

If toxic effects have been reported or there is insufficient documented safety evidence and there are doubts concerning the product/active ingredient, submission of toxicological reports will be required.

In a case when the anticipated intake of this ingredient is significantly higher than the estimated historical intake, or for which the historical intake cannot be assessed, additional safety data/studies will be required.

b) Combination products

There are no special requirements for combinations of well-known ingredients such as vitamins or minerals. Each active ingredient and dosage will be assessed independently and according to documented data.

The intended use/function of each ingredient must support a logical use of the combination in question and if for traditional use must prescribe to the philosophy of that culture. Like acting herbal ingredients are considered to have an additive effect.

Therefore, the dosage of each active substance may be reduced as compared to its single use. The counteracting by one active ingredient to the adverse reaction produced by

another must be explained. Illogical combination of herbs or ingredients having widely different therapeutic uses will require justification.

However, for a combination consisting of new active ingredients, toxicological and clinical data for finished product may be requested. This will also apply to new combinations of well-known ingredients. Safety data will have to be on the product with information on individual ingredients as supportive references.

c) <u>Target population</u>

It cannot be assumed that an ingredient is suitable for pregnant or lactating women unless evidence is provided to the contrary. If required, the product should carry the following statement:

"Pregnancy and breastfeeding: Insufficient reliable data"

or

"If you are pregnant /breastfeeding, please consult your doctor/pharmacist before taking this product."

A product will also be generally assumed not safe for children unless proven otherwise. If the product has children dosage instructions, there must be evidence to fully demonstrate safety in children of that age.

4. Overview

Information that will be required to substantiate the safe use of a product may include but is not limited to:

4.1 Literature search

A comprehensive literature search which would include both positive and negative reports must be submitted. The search criteria used should also be mentioned and references cited. Certified translated copies by the recognised bodies must also be provided if the original articles are not in the English or Malay language.

4.2 Extent of use

Information on extent of use in other countries may provide insight into the safety profile. The maximum amount of the ingredient that is recommended or suggested for use as food may be provided as proof of safe use. However, the amount in the product should not exceed the recommended level.

If evidence is to be based on traditional use, it must be clearly stated that the ingredient under review is equivalent to that used traditionally. Knowledge of chemical components of an ingredient will aid in safety evaluation by identifying potentially toxic constituents or constituents known to mimic or modulate endogenous intermediates. Modern extraction methods used may in some instances produce a substance that is compositionally different from those produced using traditional methodology.

The industry should be able to capture the safety data of any abnormalities and or untoward adverse reaction that might be occurred or derived from animal and or human study. Efficacy data will also often include information on adverse events that will be useful in safety evaluation.

Evidence of the regulatory status of the product in other countries may also be provided as supportive evidence to justify safe use of the product.

4.3 Pharmacological properties

This would include pharmacodynamic and pharmacokinetic studies for medicinal use except for traditional products which will be based on the philosophy of its traditional use.

4.4 Toxicology data

The intended use and the duration of use whether it is for short or long term use will also determine the type of toxicity data needed, e.g acute and/or chronic toxicity. Other toxicity data which should be identified would include teratogenicity, carcinogenicity and mutagenicity data, where necessary. All evidence, both favorable and unfavorable should be included.

Toxicity data could be derived from sources such as authoritative reference test or from animal and/or human study. The Organisation for Economic Co-operation and Development (OECD) Guidelines shall be used as a guide to conduct toxicity study on animals.

4.5 Human data

Safety profile of an ingredient may be obtained from sufficiently powered prospective observational studies, clinical trials, dose-escalation studies, systematic reviews, retrospective meta-analysis studies or even observation of adverse events under controlled studies.

4.6 Post marketing surveillance

Premarket safety studies are sometimes limited by the number of study subjects. When products are in wide use, detection of adverse events provides a strong surrogate for safety monitoring in the general population and in consumers who have chronic conditions. Post marketing surveillance also provides valuable information about a product's safety profile in vulnerable populations e.g. in pregnancy, lactation, the elderly etc.

Interaction with other medications/ supplementation or even food has significant safety implications because of their effects on bioavailability or induction/inhibition of metabolizing enzymes. Such interaction may lead to synergism or antagonism of intended effects.

Safety concerns from existing products may come from the reporting of the adverse reaction monitoring mechanism in the market or through post market control.

The industry and regulator may collect those data from post-market reporting and should assess the causality between the emerging safety concern and the product.

5. Glossary

5.1 New ingredient

New ingredient refers to complementary medicine active ingredient/excipient that has never been listed in the Quest database.

5.2 New delivery system

New delivery system involves a change in the method of administration and/or the physical dosage form of a complementary medicine product.

5.3 New combination

A combination product, even if it consists of only existing ingredients, is regarded as a *New Combination*, when no product of the same composition (in terms of the constituent ingredients and their relative quantities if higher than documented limits) had been approved for marketing in Malaysia before.

5.4 New dosage

New dosage refers to the quantity of ingredients/ substances to be used in a daily dose as well as single dose basis, if higher than documented limits.

5.5 Recognised bodies (with reference to translation of documents)

Certified translators, embassies, Malaysia Pharmaceutical Society (MPS), Malaysian Organisation of Pharmaceutical Industries (MOPI), Pharmaceutical Association of Malaysia (PhAMA), Malaysian Dietary Supplement Association (MADSA), Federation of Chinese Physicians & Medicine-Dealers Association of Malaysia (FCPMDAM), Federation of Chinese Physicians & Acupuncturists Association of Malaysia (FCPAAM), Malaysian Chinese Medical Association (MCMA), Direct Selling Association of Malaysia (DSAM), Malaysian Direct Distribution Association (MDDA), Persatuan Pengeluar Ubat Tradisional Malaysia (PURBATAMA), Gabungan Pertubuhan Pengamal Perubatan Tradisional Melayu Malaysia (GAPERA), Malaysian Homeopathic Medical Council (MPHM), Malaysian

Association of Traditional Indian Medicine (PEPTIM), and related industry associations of the country of origin recognized by the local authority.

6. References

1. World Health Organization. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine, 2000.
2. World Health Organization. Guidelines for the regulation of herbal medicines in the South-East Asia Region, 2003.
3. WHO Research Guideline for The Evaluation of Safety and Efficacy of Herbal Medicine 1993.
4. Organization for Economic Cooperation and Development (OECD) Guideline for toxicity studies in animals. Webpage: www.oecd.org
5. Therapeutic Goods Administration, Australia; Webpage: www.tga.gov.au
6. Health Canada; Webpage: www.hc-sc.gc.ca/index-eng.php
7. European Medicines Agency; Webpage: www.emea.eu
8. Medicines and Healthcare Products Regulatory Agency (MHRA); Webpage: www.mhra.gov.uk
9. ASEAN Traditional medicine and Health supplement Product Working Group (TMHS PWG) Meeting minutes