REGISTRATION GUIDELINE OF VETERINARY PRODUCTS (REGOVP)

National Pharmaceutical Control Bureau
Ministry of Health, Malaysia

Version 3

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

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

PREAMBLE

This "**REGISTRATION GUIDELINE OF VETERINARY PRODUCTS (REGOVP)**" will serve as the reference guide for registration of pharmaceutical products for animal use.

The contents of this version include:

- Information relating to administrative requirements and procedures.
- Information on Drug Control Authority (DCA) policies currently applicable.
- Guidelines on the online application process and requirements which will incorporate the ASEAN technical requirements and standards for pharmaceuticals (where applicable).

An on-going review of policy matters will continue, taking into account the global regulatory environment, to allow for timely and pertinent changes.

Please visit the National Pharmaceutical Control Bureau (NPCB) website at http://www.bpfk.gov.my for updates in regulatory information.

GUIDELINE HISTORY

No.	Guideline	Description of Amendment	Effective date
1.	Registration Guideline of Veterinary Products (REGOVP) First Version – August 2007	Initial Publication	August 2007
2.	Registration Guideline of Veterinary Products (REGOVP) Second Version – December 2009	Revision of REGOVP August 2007	December 2009
3.	Registration Guideline of Veterinary Products (REGOVP) Third Version – July 2014	Revision of REGOVP December 2009	July 2014

TABLE OF CONTENTS

SECTION 1
GENERAL OVERVIEW OF THE DRUG REGISTRATION SYSTEM IN MALAYSIA (INCLUDING ADMINISTRATIVE PROCEDURES)

SECTION 1

SECTION A: GENERAL OVERVIEW

1. INTRODUCTION

1.1 The Control of Drugs and Cosmetics Regulations 1984 was gazetted in June 1984, with the establishment of the Drug Control Authority (DCA) as the licensing authority. The daily operations of drug and cosmetic registration, together with the attendant monitoring and surveillance activities have been delegated to the National Pharmaceutical Control Bureau (NPCB).

1.2 The guidelines outlined in this document are primarily drawn up in accordance to the legal requirements of the **Sale of Drugs Act 1952** and the **Control of Drugs and Cosmetics Regulations 1984.** While every effort has been made to include the legal requirements of other related legislation, wherever possible, applicants are reminded that it is still their responsibility to ensure that their products duly comply with the requirements of these legislation, namely:-

(i) **Dangerous Drugs Act 1952**;

(ii) **Poisons Act 1952**;

(iii) **Medicine (Advertisement & Sale) Act 1956**;

(iv) **Patent Act 1983**; and also

(v) Any **other relevant Acts.**

1.3 Paragraph 7(1)*(a)* of the **Control of Drugs and Cosmetics (Amendment) Regulations 2006** requires all products to be registered with the DCA prior to being manufactured, sold, supplied, imported, possessed or administered, unless the product is exempted under the specific provisions of the Regulations.

A 'product' as defined in the Regulations means

(a) a drug 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;

(b) a drug to be used as an ingredient of a preparation for a medicinal purpose; or

(c) a cosmetic"

Any change to the above defined parameters may result in the need to apply for a new product registration or an application for approval of an amendment (variation) to the existing product registration.

1.4 Applicants are encouraged to be familiar with the contents of these guidelines and the governing legislation before they submit applications for product registration.

2. DRUG REGISTRATION

2.1 Any ***drug*** which 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 animals*, whether internally or externally, for a *medicinal purpose* is required to be registered with the DCA.

Medicinal purpose means any of the following purposes:

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

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

(iii) contraception;

(iv) inducing anaesthesia;

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

(vi) controlling body weight;

(vii) general maintenance or promotion of health or well-being.

A SEPARATE REGISTRATION GUIDANCE DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICAL PRODUCTS FOR HUMAN USE IS AVAILABLE.

2.2 The Regulations do not apply to the following products :-

(i) diagnostic agents and test kits for laboratory use;

Diagnostic agents/test kits for laboratory use must be labelled **'FOR LABORATORY USE ONLY'**. Products which are not labelled as such shall be deemed to be for human or animal use and need to be registered with the DCA.

(ii) non-medicated medical and contraceptive devices;

(iii) non-medicated bandages, surgical dressings, plaster, dental fillings;

(iv) instruments, apparatus, syringes, needles, sutures, catheters;

(v) **Food** - as defined under the Food Act 1983 and Food Regulations 1985.

(vi) **Pesticides applied externally**

"pest" includes bacteria, virus, fungi, weeds, insects, rodents, birds, or any other plant or animal that adversely affects or attacks animals, plants, fruits or property

(vii) **Feed and Feed Additive** as defined under the Feed Act 2009.

"Feed additive" means any added ingredient including microorganism and enzyme not normally consumed as feed by itself, whether or not it has nutritive value, which affects the characteristics of feed or animal products.

(viii) **Cosmetics for animals**

A cosmetic product shall mean "any substance or preparation intended to be placed in contact with various external parts of the animal body or with teeth and the mucous membranes of the oral cavity, with a view exclusively or mainly to cleaning them, perfuming them,changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition

(ix) **Disinfectant**

"Disinfectant" means a substance:

a) that is recommended by its manufacturer for application to an **inanimate object** to kill a range of micro-organisms; and

b) that is not represented by the manufacturer to be suitable or internal use

(x) **Health/Dietary Supplement and Herbal/Natural Products** for oral use.

Health/Dietary Supplement and Herbal/Natural products for oral use which are currently controlled under the Feed Act 2009.

(xi) **Antibiotics** for growth stimulation and prevention of diseases as defined under the Feed Act 2009.

2.3 The implementation of the Regulations on veterinary products shall be on all products containing Scheduled poison(s) as defined in the Poisons Act 1952 and which do not contain scheduled poison, intended to be administered to animals for **medicinal purpose.**

2.4 Premixes for medicinal purpose

Premixes are defined as:

Mixtures of one or more active ingredients, usually in suitable bases, that are prepared to facilitate feeding the active ingredients to animals. They are used exclusively in the preparation of animal feed for medicinal purpose.

Premixes occur in granulated, powdered, semi-solid or liquid form.

May occur in pelleted form.

Premixes for medicinal purpose are registrable.

2.5 Dietary /health supplements and herbal/natural products making a therapeutic claim/indication are considered as Non-Poison (OTC) product. Scientific evidence and efficacy data will be required for the registration of any therapeutic claim.

2.6 Scheduled Poison and OTC substance in soluble powder to be added to drinking water and/or animal feed which may contain one or more active ingredients **with excipients** intended for medicinal purpose need to be registered.

The directions for use are a mandatory labelling requirement.

However, raw material containing scheduled poison and OTC substance shall not be considered for registration, and such raw material is not allowed to be used by the end user

End user include in-farm (Cattle, Poultry, Swine etc) self-mixers or home mixers of animal feed and feed millers.

2.7 **Combination Products**

(For list of combination not allowed to be registered by the DCA see Appendix 6)

A combination product must provide advantage over and above that which can be obtained by the use of monosubstance preparations. Information and data to demonstrate that the combination of active ingredients provides a benefit that cannot be obtained by the use of each of the active ingredients individually (i.e., each active ingredient has made a contribution) is required.

When 3 or more active ingredients are used in the same combination, the resulting benefit from the use of the combination must be a benefit that cannot be obtained from combinations involving a lesser number of active components than the number contained in the full combination (e.g., a 3-way combination must be better than all possible 2-way combinations of the same 3 actives).

This demonstration of benefit is satisfied when it is proven that each active ingredient has made a meaningful contribution to the overall effect (safety and/or efficacy) of the combination.
There should not be any adverse interaction between the active ingredients (e.g. in the case of pharmaceutical incompatibilities or in case an active ingredient masks toxic effects of the other ingredients).

2.7.1 **Products containing Glucosamine and Chondroitin**

a) Products containing Glucosamine as single active ingredient are registrable as non-prescription product with indication as 'Adjuvant therapy for osteoarthritis'. Products containing Glucosamine in

combination with Chondroitin are also registrable as non-prescription product with similar indication. Products containing Glucosamine either as single ingredient or in combination with other supplement/herbal ingredients are not allowed to be registered as dietary supplements.

3. PROCEDURE FOR PROCESSING APPLICATIONS

3.1 Application Type

An application for a product registration may be sub-divided into one of the following:

(i) Application for an innovator product/new chemical entity

- containing a new chemical entity;
- containing a new combination of existing chemical entity(s);
- containing existing chemical entity(s) for use by a different route of administration;

(ii) Application for a generic[1] product (products containing Scheduled Poisons & products not containing Scheduled Poisons)

[1a generic product is a product that is essentially similar to a so called reference product/innovator product.]

3.2 Data Requirements

The data required to support an application is divided into:

a) Administrative documentation (Part I);

b) Quality documentation (Part II);

c) Safety and residues documentation (Part III); and

d) Efficacy documentation (Part IV).

Data to be submitted will be based on each application type as follows:

Innovator product – Parts I to IV

Generic product – Parts I & II

Applicants are advised to read the explanatory notes in ***Section 2*** of this registration guideline, and also the relevant ASEAN or VICH guidelines, for full information on product data requirement. In order to facilitate the evaluation process, applicants should conform to these guidelines. The authority may in certain cases request for supplementary information. The applicant should make available the requested information within the specified period. Failure to do so may result in the rejection of the application for product registration.

4. APPLICATION FORMALITIES

4.1 Who Can Apply For Product Registration

The authority accepts only web-based **online submissions** via http://www.bpfk.gov.my.

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.

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);

The applicant (if said company is not the product owner) should be authorized in writing by the product owner to be the holder of the product registration certificate and be responsible for all matters pertaining to the registration of the product.

4.2 Responsibility of Product Registration Holder (i.e. the applicant for product registration)

a) To ensure that all transactions with NPCB 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;

4.3 How to Apply

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

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

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

5. 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.

5.1 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; and

e) Fee for Certificates.

5.2 **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.

6. TYPES OF APPLICATION

6.1 Registration of Products

6.1.1 Application for product registration for the following categories:

a) Innovator Products;
b) Generic;

6.1.2 Products for export only

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 to be exported, new registration for export only is NOT necessary if there is no change in the formulation or appearance of the registered product. In this case, 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) Applications for registration of FEO products are processed based on abridged evaluation.

f) Applications shall be submitted by using an application form BPFK 438.1 (V).

Note: The applicant must first register membership for QUEST system with NPCB and subsequently purchase a USB Token that contains a User Digital Certificate, from Digicert Sdn. Bhd. This is to enable the applicant to access the system for product updating once the application for registration is approved.

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

7.1 Registration Number

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

Registration number appears as MALYYMM$$$$@##, e.g. MAL11070001HACERS:

- 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.HA/ HX and
- ## refers to administrative code used by NPCB i.e. C/ E/ R/ S.
- The symbols @ and ## refer to:
  a) HA= Scheduled Poison
  b) HX= Non-scheduled Poisons
  c) C= Contract Manufactured (the product is manufactured by a GMP certified contract manufacturer)
  d) E= For Export Only (FEO) (the product is to be sold for export only and not for sale in the local market)
  e) R= Repacked (the product is repacked by an approved GMP certified repacker)
  f) S= Second source (the product from a second source/ approved second manufacturer)

7.2 Product Particulars

The holder of the registration certificate 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, labelling, package

insert, product literature or any relevant particulars of the registered product shall be made without prior approval of the authority.

7.3 Labelling

The registered product shall be labelled with the Registration Number. The labels for the registered product shall comply with all other labelling requirements specified by the authority.

7.4 Product Authentication

The registered product shall be affixed with the security device approved by the authority. The said security device, 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 **Appendix 1.1** for Product Identification Chart which indicates where the security device may be affixed on the product label*)

7.5 Indication, 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.

7.6 Bioequivalence

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, will be established by the authority.

7.7 Adverse Reactions, Complaints

The holder of the registration certificate shall inform the authority of any adverse reactions of or complaints on the registered product immediately after he receives notice of such adverse reactions or complaints.

7.8 Holder of Registration Certificate

The holder of the registration certificate shall inform the authority of any change in his name or address.

7.9 Withdrawal From Registration

The holder of the registration certificate shall notify the authority of any decision to withdraw the registration of the product and shall state the reasons for the decision.

The holder shall also notify the authority when he is no longer authorized to be the holder of the registration certificate.

The onus is on the holder to inform the manufacturer/contract giver.

Upon withdrawal, the registration certificate is no longer valid.

7.10 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 to which such registration is subject.

The holder of the registration certificate shall immediately surrender to the authority the registration certificate upon cancellation or suspension of the registration of the product.

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, upon which the registration certificate is no longer valid.

7.11 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

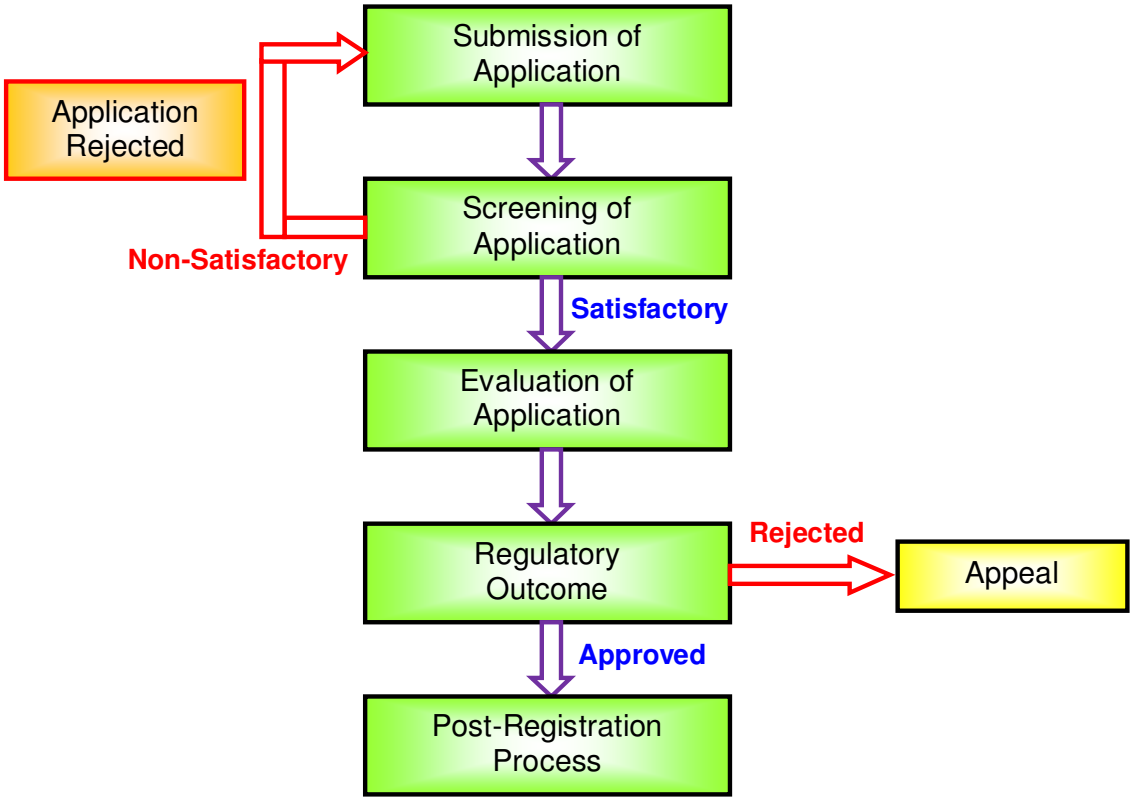
m) Records and statistics pertaining to manufacture, sale, supply, import or export of any products.

SECTION B: PRODUCT REGISTRATION PROCESS

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

8. FLOW OF REGISTRATION PROCESS

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) Multiple applications;

d) Variants; and

e) 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.

The authority will register product with specific brand/proprietary name for only one Product registration holder.
The same brand/proprietary name is not allowed for other product registration holder.

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 Centre for Product Registration, NPCB for verification.

8.1.2 Method of Evaluation

Method of Evaluation According to Product Categories

No.	Product Category	Method of Evaluation
		Full Evaluation
1.	Innovator Products	√
2.	Generics (Scheduled Poison)	√
4.	Generics (Non-Scheduled Poison) [or known as OTC]	√

8.1.3 Multiple of 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 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.

8.1.4 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, 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 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.

Proprietary products manufactured under licence by different manufacturers, or different subsidiaries, or in different countries under the same parent firm shall require separate registration.

8.1.5 Variants for a Given Product

Applications for variants (different colour/flavours) for veterinary products will be considered on a case by case basis.

8.1.6 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 www.bpfk.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 Section 2: Guide On How To Fill The Online Application Form For A 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).

For payment, applicant shall submit two (2) copies of printed payment voucher together with appropriate fees to the Finance Department, NPCB 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 Processing of Applications

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.

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 NPCB 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

8.5 **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. 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.

8.6 Post-Registration Process

Registration status of a product shall be valid for **five (5) years** or such period as specified in the registration certificate (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 D: Post-Registration Process.

8.7 Rejection, Suspension or Cancellation of Registration [Reg. 11]

The authority may reject, suspend or cancel 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.

Such products may not be imported, manufactured, sold, supplied, possessed for sale or administered.

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.

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, upon which the registration is no longer valid.

8.7.1 Appeal Against Authority Decisions [Reg. 18]

8.7.1.1 Any applicant/product registration holder aggrieved by The decisions of the authority may make a written appeal to the Minister of Health. **All notice of appeals MUST** be made within **fourteen (14) days** from the date of the authority notification.

8.7.1.2 A period of 180 days from the date of notice of appeal is given for submission of any supporting data or documents for innovator products/NCE. A period of 90

days is allowed for other products. The appeal is considered closed if all the required information is not submitted within the stated time given. **Any request for extension of this period will not be entertained.**

8.7.2 Decision of The Minister [Reg. 18]

The decision of the Minister made on any appeal is final.

Refer to Appendix 11

SECTION C: QUALITY CONTROL

9. PROTOCOL OF ANALYSIS

The Protocol of Analysis for a product is a requirement for the registration of the product and must be submitted with the initial data submission for product registration. This protocol of analysis must be in the manufacturer's official format and must comply with NPCB's requirements as mentioned in Appendix 8. Evaluation of the protocol of analysis will be conducted together with the analysis of the product after the said product is registered. The onus is on the applicant to ensure that the testing methods in the protocol of analysis are validated and suitable under actual conditions of use. If the protocol of analysis is found to be unsatisfactory or unavailable or if the test method submitted in the protocol is not reproducible/ workable, action will be taken to cancel the registration of the said product.

Analytical method validation data can be submitted if available. This data must comply with the requirements of the relevant International/ASEAN guidelines for analytical method validation.

SECTION D: POST- REGISTRATION PROCESS

10. MAINTENANCE OF REGISTRATION

10.1 Conditions for Registration [Reg. 8(1)]

The authority may specify certain special conditions for registration for a particular product or group of products, and may amend any conditions for registration.

Specific product labeling requirements, for label and/or package insert, may also be laid down.

The authority may cancel the registration of any product if the conditions for registration are not complied with.

10.2 Validity Period of Registration [Reg. 8(6)]

The registration of a product shall be valid for **5 years** or such period as specified by the authority (unless sooner suspended or cancelled by the authority).

10.3 Renewal of Product Registration

Renewal of product registration can be done **six (6) months prior to the expiry** of the validity period of product registration. After the expiry date, status of product registration shall change to status of expired, and application for renewal of the product registration can no longer be submitted.

Applicant shall submit the application to the Center for Product Registration, NPCB.

11. 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.

11.1 Variation

11.1.1 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 of NPCB.

The registration of a product may be cancelled if changes are made without the prior approval of NPCB.

11.1.2 All necessary documents in accordance to the specified conditions laid down for each type of variation (amendment) should be submitted. The product registration holder is responsible for ensuring that all the necessary validation has been conducted to demonstrate that the change does not reduce the quality, safety or efficacy of the product.

11.1.3 Any change which affects the composition or characteristics of the product shall require a new application for registration.

(Please refer **Appendix 2** for details of the types of variations allowed and the conditions and/or supporting documents necessary for each type of variation defined.)

11.1.4 Applicant shall submit the application to the Center for Product Registration, NPCB.

11.2 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).

11.2.1 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. 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:

d) 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.

11.2.2 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 NPCB 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 the related circulars and directives at www.bpfk.gov.my

11.2.3 Types of Manufacturing Site Changes (COS)

No	Type 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.
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.

11.2.4 Mode of Submission

a) Complete application for COS with supporting documents shall be submitted to the Veterinary Medicine Section in Center for Product Registration, NPCB.

b) For submission of COS Type II to Type V, applicant can download Form BPFK 415.3 from NPCB's website www.bpfk.gov.my under Industry - Forms. Submission of completed application form with supporting documents shall be made together with processing fees, according to category of product, as stipulated in the form.

11.2.5 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 3: Supporting Documents Required for Change of Manufacturing Site Application.

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

d) For further information pertaining to COS, please refer to the related circulars and directives at www.bpfk.gov.my

11.3 Change of 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 Appendix 4: Change of Product Registration Holder.

12. POST-MARKETING ACTIVITIES

12.1 Pharmacovigilance

12.1.1 Adverse Drug Reaction Reporting And Safety Updates

The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC), Sub-committee of the Drug Control Authority (DCA), reviews Malaysian reports of suspected drug reactions.

12.1.1.1 MADRAC encourages animal health care professionals, farmers, public and other users of veterinary medicines to report all suspected adverse reactions but it is a compulsory requirement that the product registration holder of a product should inform the authority of any adverse reactions to the target animal, non-target animal and to the person handling the product.

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

12.1.1.3 All labels and package inserts must be amended to include any new adverse reactions, warning, precautions etc. within the time frame given by the authority.

12.2 Post-Market Surveillance

12.2.1 Market Surveillance of registered products

a) Samples of products registered by the authority may be taken and tested for compliance with official or pharmacopoeia standards or specifications agreed by the manufacturer.

b) If a sample fails to meet adequate specifications, the product registration holder will be issued a warning. Unless the failure is serious enough to justify recall of the product, the product registration holder has up to 30 days to identify the source/cause of quality defect and actions to be taken to improve quality.

12.2.2 Product Complaints

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

b) It is also the responsibility of the prescribers, the pharmacists, as well as all other animal health professionals who come into contact with the drug to report.

12.2.3 Product Recalls

a) Recalls of defective or unsafe products are instituted by the authority, supported by the 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.

SECTION E: INSPECTION, LICENSING AND RELEVANT DOCUMENTS

13. INSPECTION, LICENSING AND RELEVANT DOCUMENTS

Inspection and licensing of manufacturing premises or facilities, importers and wholesalers of registered products 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 is a prerequisite for the application of a manufacturing license as well as product registration whereas compliance to GDP is a prerequisite for the application of a wholesale license or import license.

13.1 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 that are put in the market are safe, efficacious and of quality.

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

Guidelines	Product Type/ Category
PIC/S Guide to Good Manufacturing Practice for Medicinal Products *	Pharmaceuticals (Poison and Non-Poison) Veterinary Products
Guideline on Good Manufacturing Practice (GMP) for Veterinary Premixes; 1st Edition, January 2015	Veterinary Premixes
Guidelines on Good Distribution Practice (GDP); 2nd Edition 2013	For activities related to the storage and distribution by manufacturers, importers and wholesalers (where applicable)

Additional Information:

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.

13.1.1 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 is taken into consideration before the products are registered with the Authority. NPCB as the secretariat to the DCA is responsible to ensure 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 details and forms, please refer Guidance Document on Foreign GMP Inspection.

13.2. 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.

13.2.1 Types of Licenses

Type of Licenses	Activity
Manufacturer's License	Licensed Premises is allowed to: Manufacture registered products and to sell by wholesale or supply their products
Import License	Licensed Premises is allowed to: Import and sell by wholesale or supply registered products
Wholesaler's License	Licensed Premises is allowed to: Sell by wholesale or supply registered products

13.2.2 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. Application form must be submitted with the following supporting documents.

   a) Company's Organization Chart
   b) Location Map of Premise
   c) Layout Plan of Premise
   d) List of Storage Equipments
   e) Details of other products (Non-medicinal) stored at the same premise
   f) A copy of Business License (Local Authority) for business premise or store (if any)
   g) A copy of Applicant's/License Holder's Identity Card
   h) 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)
   i) 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.**

13.2.3 Additional List of License For Registered Products

1. Additional list of License are issued based on the application submitted when the products are newly registered, changing of manufacturer or importer or any

registered left out products from the products list of Manufacturer's License and Import License.

2. When submitting the application form for Additional 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.

13.3 **GMP Certificate**

1. GMP certificates are issued for the purpose of exportation of locally manufactured registered products. It endorses that the local manufacturer complies with the current GMP requirements. These certificates 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 by filling Borang BPFK-420 *Permohonan Sijil Amalan Perkilangan Baik (APB).*

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

13.4 **Relevant Documents**

Certificates and relevant documents should be valid at the time of submission.

13.4.1 All applications for registration must be accompanied with the following:

(i) Letter of authorisation from the product owner. (NOT APPLICABLE IF THE APPLICANT IS THE PRODUCT OWNER);

(ii) Where a product is contract manufactured, letters of authorisation of contract manufacture and acceptance to

and from the manufacturer and also each sub-contractor, if applicable (e.g. repacker).

The letter of authorisation should 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 letter of acceptance from the manufacturer shall comply with similar requirements as stated above.

The letters of authorisation and acceptance should 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.

13.4.2 Imported products will also need to furnish either a:

(i) Certificate of Pharmaceutical Product (CPP) from the competent authority in the country of origin[2]; ***OR***

(ii) Certification for Free Sale (CFS) and Good Manufacturing Practice (GMP)[3] from the relevant competent authorities as deemed acceptable by the DCA.

CPPs shall be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce if issued by the Health Authorities listed in the WHO Certification Scheme (*list available from the WHO website*: http://www.who.int).

CPPs issued by EMA for products registered through the centralized procedure in EU will be accepted.

CPPs 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 should be available for all the manufacturers.

The Drug Control Authority reserves the right to conduct an inspection on any manufacturing site.

[2 In the event a CPP is not available from the country of 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 Licence for the manufacturer from the relevant competent authority, together with

(1) CPP from the country of the product owner; OR

(2) CPP from country of release, if (1) is not available]

[[3] Authority will usually recognize GMP Certification/Manufacturing Licence issued by the relevant national or regional Veterinary Service or Department of Animal Health or Department of Agriculture.]

14. APPENDICES

Appendix 1:	Fees
Appendix 1.1:	Product Identification Chart - for security device labelling
Appendix 2:	Guidelines on Application for Variation of Registered Products
Appendix 3:	Change in Manufacturing Site Application
Appendix 4:	Change of Product Registration Holder
Appendix 5:	Permitted colouring agents in pharmaceutical and traditional products
Appendix 6:	List of ingredients (active) not allowed to be registered by the Drug Control Authority
Appendix 7:	Guideline for Stability Data
Appendix 8:	Guidelines for the Submission of Protocol of Analysis and Analytical Method Validation Documents
Appendix 9:	Allowable Maximum Residual Limit (MRL)
Appendix 10 :	Regulation of Veterinary Products in Malaysia

APPENDIX 1: FEES

1.1 Charges for USB Token of Quest Membership

Application category	Charges
First-time User	**Package A** (USB Token of 2-years validity + Guide Manual) : COST RM335 **Package B** (USB Token of 1-year validity + Guide Manual) : COST RM320
Supplementary User	**Package A** (USB Token of 2-years validity + Guide Manual) : COST RM335 **Package B** (USB Token of 1-year validity + Guide Manual) : COST RM320
Renewal of USB token	**Package C1** (New USB Token of 2-years validity) : COST RM280 **Package C2** (Utilized old USB Token of 2-years validity) : COST RM100

1.2 Processing And Analysis Fee For Product Registration

Every application for registration shall be accompanied with a processing as specified below:

No.	Category of Product	Processing Fees	Renewal Fees
1.	Innovator/New Chemical Entity	RM 1,500.00	RM 1,000.00
2.	Pharmaceutical a) Generic (Scheduled Poison) b) Generic (Non-Scheduled Poison)	RM 1,500.00	RM 1,000.00
3.	For Export Only (FEO) a) Generic (Scheduled Poison) b) Generic (Non-Scheduled Poison)	RM 500.00	RM 500.00

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	Not more than 1 month	1 year
2. Import	RM 500.00	Not more than 1 month	1 year
3. Wholesale	RM 500.00	Not more than 1 month	1 year

1.4 Charges For Amendments To Particulars of A Registered Product

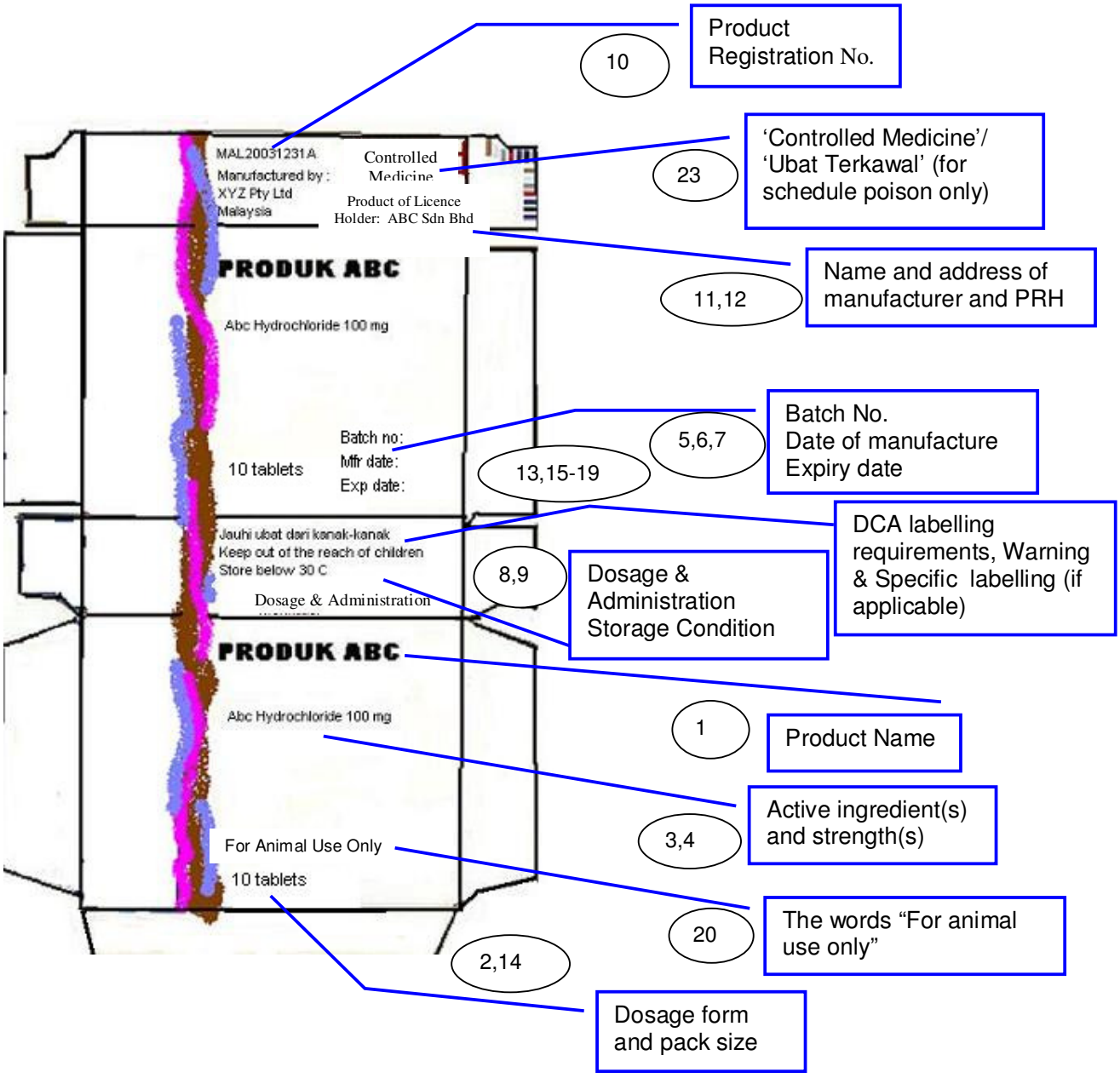
Types of Amendment	Processing fee
	Pharmaceutical
1. Change of Manufacturing Site (Type II, III, IV, V)	RM 1,000.00
2. Change of Product Registration Holder	RM 1,000.00

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

APPENDIX 1.1: **PRODUCT IDENTIFICATION CHART**
(to identify where the security device may be affixed on the product label)



APPENDIX 2: GUIDELINES ON APPLICATION FOR VARIATION OF REGISTERED PRODUCTS

The purpose of these guidelines are to provide guidance to product registration holders (PRH)/applicants who intend to apply to vary the registered information of a registered product. The guideline defines the type of variations and outlines the supporting documents necessary for each type of variation:

Type I: Minor variation with a 14 days validation period

The product registration holders (PRH) may proceed to implement the change after a 14 days validation period upon the date of receiving the documents by variation unit.
Minor variations are subject to the conditions specified.

FOR INTERIM PERIOD:

An applicant may submit Type I variation manually together with the required documents by using the form specified. The manual submission must be submitted together with variation online application. The approval will only be notified via online submission.

Type II: Major Variation

Type II variation is considered a major change and approval is required prior to implementation.

The Marketing Authorization Holder is responsible for ensuring that all the necessary validation has been conducted to demonstrate that the change does not reduce the quality, safety or efficacy of the product.

ATTACHMENT 1

TYPE I

No.	TITLE OF VARIATION	AFFECTED FIELDS PHARMACEUTICAL	SUPPORTING DOCUMENTS REQUIRED OR CONDITIONS TO BE FULFILLED
1.	Change in name of manufacturer and/or repacker without any change in address of site.	Can be made through **VIEW & EDIT VALIDATION**	a) Certificate of name change i.e. Form 13 Company Act 1965. → please attach the supporting document at **E12**.
2.	Change in company logo on the packaging components (without any changes on graphic or label content)	D1, D2, D3	a) Draft packaging components with the amended information.
3.	Change in product owner	E1.1, E1.2, E2.1, E2.2, E12 D1, D2, D3	CONDITIONS a) The Product Registration Holder remains the same. Submission shall be done by current PRH. b) The manufacturing site remains the same. SUPPORTING DOCUMENTS a) Letter of confirmation for change in product ownership countersigned by both old and new product owner. b) Official letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license. c) 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. d) Revised labels and package insert (if applicable).
3.	Change in importer or distributor	E13.1	
4.	Replacement, 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**)**	a) Finished product release and shelf life specification have not been changed except for the description b) Any new ink must comply with the relevant pharmaceutical legislation. - New description of the product.
5.	Change in shape or dimensions of the container or closure.	P7	a) No change in the type of container or closure. b) The product is not intended to be sterile. c) No change is made to the product shelf life

			and/or storage conditions.
6.	Change in pack size of the finished product. Change in the number or units (e.g. tablets, ampoules) in a pack. Change in volume of non sterile preparations. Change in volume of parenteral preparations and peritoneal dialysis with similar characteristics.	C1, D3, E8(if applicable)	a) The primary packaging materials remains the same.
7.	Tightening of specification limits of finished product or active ingredient.	E9,E10 P5.1, P5.2,P 5.4 S4.1, S4.2,S 4.4	a) New specifications b) **Certificate of analysis (CoA) FPQC (P5.4) or active ingredient X 1 batch (S4.4)**
8.	Change in source or addition of source of active ingredient **without any change in specification** (except direct compressed granules/ pellets).	S2.1	a) Finished product release and end of shelf life specification remains the same.
9.	Change in secondary packaging material	C2, D1, D2, D3 P7	a) The primary packaging material remains the same. b) Draft packaging components.
10.	Change in test procedure or analytical protocols of finished product.	E9, E10	a) Appropriate (re-)validation studies have been performed in accordance with relevant guidelines. b) Results of method validation show new test procedure to be at least equivalent to the former procedure. c) Finished product specifications are not adversely affected.
11.	Change in name and/or address of a manufacturer of the active substance	S2.1	
12.	Change in testing procedure of an excipient	P4.2, P4.3	Specifications of the excipient / finished product remain the same.

TYPE II

1.	Change in product name only.	Can be made through **VIEW & EDIT VALIDATION**	a) Draft label and leaflet. b) Letter confirming change in name only issued by the PRH or manufacturer.
2.	Change in content of leaflet or prescribing information/PIL/SPC.	A1 – A17, C1 D3, E7 (Summary of Product Characteristics from manufacturer) E8 (if applicable)	a) For all types of product provide:- - Copy with amendments clearly marked. - Clean copy of the proposed new leaflet. → please note that only clean copy of package insert is to be attached at D3 in addition to the supporting documents. b) Provide the following (innovator product only):- - Company Core Data sheet - Conclusion or abstract of recent Periodic Safety Update Report where relevant. - Expert Clinical Report (if applicable) For generic product please provide a copy of reference to support the change
3.	Change in content of label inclusive of change in graphics.	D1, D2	a) Draft label with changes marked clearly. b) Clean copy of label
4.	Change in manufacturing process of the finished product	E11, P 3.2, P3.2.1, P3.3, P3.4, P5.1, P 5.4, P8	a) Finished product specification is not adversely affected. b) The new process must lead to an identical product regarding all aspect of quality, safety and efficacy. c) The product does not contain a biological active substance. ⊕ **Certificate of analysis (CoA) FPQC (P5.4)** - **Requirement :** **2 batches for imported products** **1 batch for locally manufactured products**
5.	Change in **overage of active ingredient or excipient**	B1.1, B1.2	Finished product release and end of shelf life specification remains the same
6.	Replacement of an excipient with a comparable excipient and/or change in content of excipient. (Including colouring and or flavouring agent).	Can be made through **VIEW & EDIT VALIDATION**	a) No changes on the specification of the excipient for product specific requirements (e.g. particle size profiles, polymorphic form, etc.), if applicable. b) Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. c) Provide the following:- 1. Comparison of new and existing formula 2. Batch Manufacturing Formula 3. Excipient specification 4. Manufacturing process 5. Stability data of finished product (refer to Malaysian Guidelines for Stability Studies of

			Drug Product for data required) -} new formula 6. To amend label (If applicable, i.e. if the variations involve the addition of preservative /alcohol) (D1 & D2) 7. Certificate of analysis (CoA) FPQC X 1 batch (P5.4) } of the new formula
7.	Change in batch size.	B 1.1, B1.2	a) The change does not affect the reproducibility and/or consistency of the product. b) 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. c) Finished product specification is not adversely affected. d) To provide Batch manufacturing formula e) batch comparative analysis - imported product/s : 3 batch for each old and new batch size - locally manufactured product/s: 3 batch for old and 1 new batch → to attach the batch analysis at P5.4
8.	Change in capsule shell or film coated agent.	Can be made through **VIEW & EDIT VALIDATION**	a) Includes change of hard gelatin capsule to vegetable capsule but does not apply change from hard gelatin capsule to soft gel capsule. b) Provide the following :- - New unit formula for coating agent - Batch manufacturing formula - New manufacturing process c) Stability data of finished product (refer to Malaysian Guidelines for Stability Studies of Drug Product for data required) d) To include the function for each and every excipient used.
9.	Change in finished product or active ingredient specification	E9, E10, P5.1, S4.1	a) Includes addition of a new test parameter. Certificate of analysis for one batch (for locally manufactured product/s) or two batches (for imported product/s) as per the new specification to be provided upon approval and when change is affected.
10.	Change to in-process tests or limits applied during manufacture of the product.	P3.3	a) Includes tightening of in-process limits and addition of new tests b) Any change should be within the range of the currently approved limits.
11.	Change/ addition in primary packaging material.	C2, D1, D2, D3 P3.2, P8	a) Provide the following:- - Assembly process for the new packaging material - Stability data (refer to Malaysian Guidelines for Stability Studies of Drug Product for data required) - Draft label
12.	Change in shelf life of finished product:-	A15, A16, P8	a) Provide stability data (refer to Malaysian Guidelines for Stability Studies of Drug

	As packaged for sale After first opening After reconstitution	D1,D2, D3	Product for data required)
13.	Change in storage conditions	A15, P8 D1,D2, D3	a) Provide stability data (refer to Malaysian Guidelines for Stability Studies of Drug Product for data required)
14.	Appointment or change in repacker.	D1, D2, D3 , E14, *E12 (for other supportive documents)	a) Provide the following:- - *GMP certificate of the new packer - *Assembling process - ***Letter of appointment and acceptance for contract repacker** - Draft label
15.	Change in target species	A6.2	a) Addition of a non-food producing species:- - Pharmacokinetics and metabolism in target species, or comment on adequacy of the justification for not providing such data - Efficacy in the additional target species - Tolerance in the additional target species - Likely increase in operator exposure - Likely increase in environmental load or pattern of exposure b) Extension to include new target group (subset of target species):- - Pharmacokinetics and metabolism in target group, or comment on adequacy of the justification for not providing such data - Efficacy in the new target group - Tolerance in the new target group - Likely increase in operator exposure - Relevance of original residue studies and stability of existing withdrawal periods in the case of food producing species - Change to environmental load
16.	Change in withdrawal period	A18.1	Provide safety and residues data which are supported by evidence
17.	Change in maximum residual limit (MRL)	A18.2	Provide safety and residues data which are supported by evidence

NOTE:

1. **Other supportive documents can be attached at E12 where such documents are necessary.**

2. **Please note that for every variations made, reason for changing/remarks should be clearly written and explained.**

3. **Please note that there will be no correspondence with the applicant for variation module. For any rejection made for certain field, only the main field will be rejected (i.e. the supportive documents will be kept until the main field is resubmitted). However, if the main field is not resubmitted without any reason for a certain period of time, the supportive documents will be rejected and a new application must be submitted.**

APPENDIX 3: SUPPORTING DOCUMENTS REQUIRED FOR CHANGE OF MANUFACTURING SITE (COS) APPLICATION

Supporting documents required for change of manufacturing site (COS) application

No.	Document to be submitted	Type I	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.	√	√	√	√	√
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.	√	√	√	√	
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.	√	√		√	

APPENDIX 4: CHANGE OF PRODUCT REGISTRATION HOLDER

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.

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 Control Bureau (NPCB).
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 authority 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 authority 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.

APPLICATION

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

1. Application Form
2. *Borang Penyerahan Permohonan*
3. Processing Fee
4. Original Supporting Documents

PROCESSING FEE

1. NON-REFUNDABLE processing fee.
   - 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.

SUPPORTING DOCUMENTS

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

   LIST OF REQUIRED 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 (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, 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.

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 Control Bureau 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

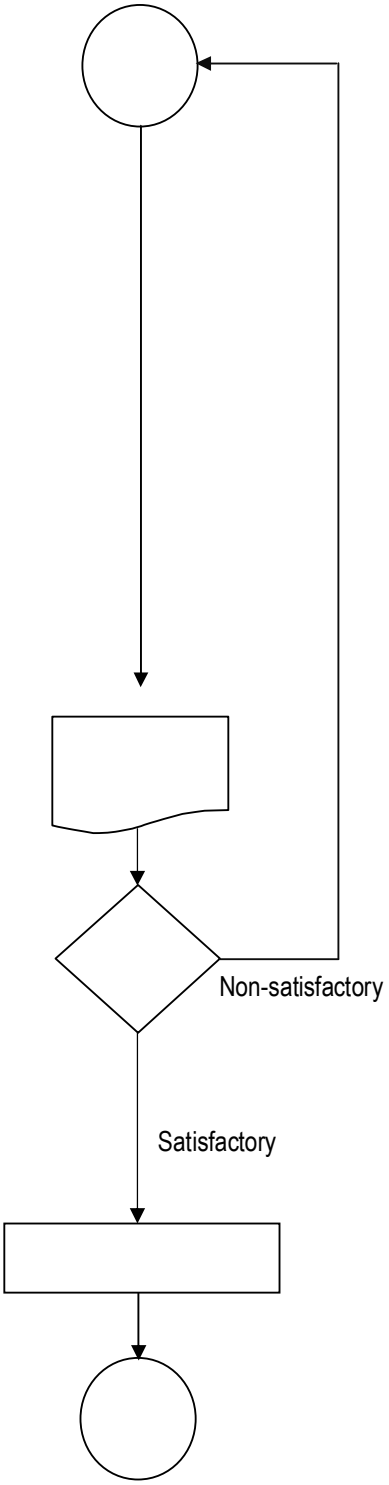
***Certified by Notary Public/ Commissioner for Oath*

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.*

FLOWCHART FOR THE CHANGE OF PRODUCT REGISTRATION HOLDER



Company (Existing PRH)

Submit completed application to NPCB 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

APPENDIX 5: LIST OF PERMITTED AND RESTRICTED COLOURING AGENTS

5.1 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
11.	Cochineal or Carminic Acid, Carmine from Cochineal	75470

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
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
22.	Bole or Iron Oxide, Carbon Black (or Vegetable Origin), Titanium Dioxide	77891

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
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

5.2 **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

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
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
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

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
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 6: LIST OF INGREDIENTS (ACTIVE) NOT ALLOWED TO BE REGISTERED BY THE DRUG CONTROL AUTHORITY

This is not an exhaustive list, it will be reviewed when necessary.

A. Ingredients not allowed in veterinary products

1. Avoparcin

B. Ingredients not allowed for food-producing animals and aquacultures

1. Chloramphenicol

2. Nitrofurans such as :
   i) Nitrofurantoin
   ii) Nitrofurazone
   iii) Furazolidone
   iv) Furaltadone

3. Beta agonists such as :
   i) Salbutamol
   ii) Terbutaline
   iii) Clenbuterol
   iv) Fenoterol
   v) Salmeterol
   vi) Bambuterol HCl
   vii) Bitolterol Mesilate
   viii) Broxaterol
   ix) Eformoterol fumarate
   x) Pirbuterol HCl
   xi) Procaterol HCl
   xii) Reproterol HCl
   xiii) Rimiterol HBr
   xiv) Tretoquinol HCl
   xv) Tulobuterol HCl

4. Chlorpromazine

5. Carbadox

6. Olaquindox

7. Chloroform

8. Colchicine

9. Dapsone

10. Nitroimidazole such as :
    i) Dimetridazole

ii) Ipronidazole
iii) Metronidazole
iv) Ronidazole

1. Teicoplanin
2. Vancomycin

B. Any products containing Chlorofluorocarbon

C. Combinations not allowed in veterinary products

1. Herbal + Scheduled poison
2. Herbal + OTC

APPENDIX 7: GUIDELINE FOR STABILITY DATA

The purpose of stability testing is to provide evidence on how the quality of a product, in its proposed marketing packaging, varies with time under the influence of a variety of environmental factors, such as temperature, humidity and light, and enables recommended storage conditions and shelf lives to be established.

1. Size and number of batches tested

The overall quality of the product batches of the formulation used in stability testing should be representative of the quality of the formulation to be made on a production scale.

Stability data from 2 current batches (preferably pilot and/or production scale) is considered by the DCA to be the statistical minimum necessary to establish a shelf life for a product.

Therefore when data from less than the minimum two batches are provided the applicant should include a valid scientific argument justifying the suitability of the data provided for establishing the proposed shelf life.

The batch identity, date of manufacture and batch size should be reported with the stability data.

2. Containers

The product should be packaged in the same containers (materials and size) that are proposed for the marketing of the final product.

If the product will be marketed in containers of differing materials, then all proposed containers should be trialled.

If the product is to be marketed in containers in which stability testing would be impractical (e.g., too large), then stability trials in smaller containers of the same materials and construction may be used to extrapolate to the larger containers.

3. Bracketing

Bracketing design may be used if the product strengths are very closely related in composition, such as,

1. a tablet range made with different compression weights of a similar basic granulation, or
2. a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells, or
3. bottles containing 100 tablets and bottles containing 1000 tablets, or
4. bottles containing 100 mL of a product and bottles containing 500 mL of the product.

Bracketing can be applied to different container sizes or different fills in the same container closure system. For example, where the same strength and exact container/closure system is used for three or more fill contents, the manufacturer may elect to place only the smallest and largest container closure system into the stability program.

An example of bracketing design is given in the table below:

Table 1-1 Bracketing design

Strength		**50 mg**			**75 mg**			**100 mg**		
Batch		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Container size	**100 mL**	√	√	√				√	√	√
	250 mL									
	500 mL	√	√	√				√	√	√

4. Storage condition

Storage stability programmes should include real time studies or a combination of real time and accelerated conditions. Recommended storage conditions from the labeling of Veterinary Products are listed below:

Store below –18℃ (deep freeze);

Store below –5℃ (freeze);

Store between 2℃ and 8℃ (refrigerate. Do not freeze);

Store below 8℃ (refrigerate);

Store below 25℃ (air conditioning);

Store below 30℃ (room temperature).

The temperature at which samples are stored at (e.g., real time and/or accelerated conditions) will impact on how the stability data are interpreted and the length of shelf life that can be recommended. Recommended storage conditions are as follows:

Table 1-2 Recommended storage conditions (temperatures and relative humidities)

Proposed storage temperature (product label)	Real time testing (Minimum 2 batches)	Accelerated testing (Minimum 2 batches)
Products intended for Storage in a freezer	-20℃±5℃	Accelerated trial probably not appropriate
Products intended for Storage in a refrigerator	5℃ ±3℃	25℃ ±2℃ and 60% RH ±5% RH

25℃ (air conditioning)	25℃ ±2℃ and 60% RH ±5% RH	35 - 40℃ ±2℃ and 75% RH ±5% RH
30℃ (room temperature)	30℃ ±2℃ and 75% RH ±5% RH	40 - 45℃ ±2℃ and 75% RH ±5% RH

5. Testing intervals

Samples should be tested as soon as practicable following manufacture, and then every 3 months over the first year, every 6 months over the second year and at 12-month intervals thereafter. The dates of product testing should be recorded and reported with the stability data.

6. Test parameters

The stability study should cover those features susceptible to change during storage and likely to influence the quality, safety and efficacy of the product. Test parameters to be measured in a stability trial are determined by the dosage form/formulation type and may include:

- Physical properties of the product;
- Organoleptic properties (taste, odour, etc.);
- Active ingredient content and formation of toxic degradation products;
- The content of other important components of the formulation (e.g., antimicrobial preservatives);
- Microbial properties (where appropriate); and

Relevant test parameters for each type of dosage form are given in Attachment C. It is expected that all relevant parameters will be addressed in a stability trial. If certain parameters are not addressed relevant scientific argument should be provided as to why testing was not required.

7. Expiry specification

An expiry specification is the combination of physical, chemical, biological and microbiological test requirements that a veterinary chemical product must meet throughout its shelf life. The range of values that each test parameter must fall within throughout the shelf life of the product should be provided. These are often referred to as “check specifications” or “expiry specifications”.

8. Duration of stability trials

(i) Locally manufactured product

At point of submission, 3 months accelerated data (45-50℃/75% RH ±5% RH) or 6 months accelerated data (40℃/75% RH ±5% RH) and a commitment letter to submit real time stability data once available is required to claim for 3 years shelf life.

(ii) Imported product

A minimum of 12 months real time stability data with a complete accelerated data are required during submission to claim for 2 years shelf life

9. Testing requirements for specific veterinary chemical product types

(i) Controlled-release dosage forms

In addition to the specific stability tests that are required for the particular dosage form, the stability study should include the dissolution test to determine the rate of release of the active substance.

(ii) Intramammary products

Intramammary products are solutions, emulsions, suspensions or semi-solid preparations containing one or more active substances in a suitable vehicle. In addition to the parameters relevant to particular dosage forms, a test for sterility must be performed.

(iii) Oral drenches

Drenches for oral administration are available as powders or concentrated solutions or suspensions. They are also available as solutions or suspensions ready for use. Parameters relevant to particular dosage forms should be monitored in the stability study.

(iv) Veterinary liquid products for cutaneous applications

Veterinary liquid products for cutaneous applications are liquid preparations intended to be applied to the skin to obtain a local and/or a systemic effect. Veterinary liquid products for cutaneous applications include dip concentrates, pour-on, spot-on, sprays, teat dips, teat sprays and udder-washers. These preparations may be supplied as concentrates or ready-to-use products. They are solutions, emulsions or suspensions containing one or more active substance in a suitable vehicle. In addition to the parameters relevant to particular dosage forms, stability data on diluted dipping/jetting and teat sprays products are required.

10. Additional Tests

i) Parenteral products

(a) Stability of reconstituted products

The in-use stability of parenteral veterinary products that are reconstituted prior to administration, or diluted prior to use, or claimed to be stable when mixed with other products, or where the product may be labile once the container is opened, must be demonstrated,

Note: the in-use stability data for reconstituted products and for parenteral products supplied in multi-dose containers is not required if the product label contains a disposal statement to the effect “To avoid microbial contamination, unused portions

of the product must be discarded within 24 hours after reconstitution or first broaching of the container".

(b) In-use stability testing

The in-use stability test should be designed to simulate the use of the product in practice. The product should be stored as recommended on the product label throughout the duration of the test. A storage condition recommendation for the product after first use may be specified on the label that is different to the unopened container storage conditions.

ii) Sterile eye and ear preparations in multiple dose containers

For sterile eye and ear preparations packaged in multi-dose containers, in-use (broached container) testing is required if the product is not used within four weeks after opening the container.

Note: the in-use testing is not required if the product label states that the product be used within 4 weeks of opening the container.

iii) Sterility requirements for product stated to be sterile

Sterility should be considered as part of the shelf life of a veterinary chemical product stated to be sterile. The samples should be tested on the initial date and at the proposed expiration date.

- **Injectables**

Sterility testing should be demonstrated for all injectable veterinary chemical products (including intra-mammary products) except euthanasia products and ear implants for bovine and ovine species.

- **Ophthalmic products**

Sterility should be demonstrated for all ophthalmic products.

- **Ampoules**

Sterility should be demonstrated on sealed ampoules only on the date of manufacture. Since the ampoules are hermetically sealed, this type of seal prevents microbial contamination.

- **Sterile products with microbial inhibitors**

Veterinary chemical products containing preservatives (microbial inhibitors) to control microbial contamination should be tested for preservative contents at reasonable intervals in the stability trial. This may be accomplished by microbial challenge test (e.g., Efficacy of Antimicrobial Preservation of the BP or Antimicrobial Preservative Effectiveness Test of the USP) and by performing chemical assays for the preservatives during the regular stability testing schedules. If a lack of or low levels are found, testing for sterility should be carried out.

iv) Dissolution testing

The dissolution test for solid dosage forms is a physical quality control test designed to ensure the consistency of active substance release from the dosage form and

assure consistent batch-to-batch behaviour. Dissolution data should be generated on at least 6 individual units at each test station.

11. Interpretation of stability data and recommendation of product shelf life

This section clearly defines the maximum shelf life that can be recommended on the basis of a given stability data set. The information will be of benefit to applicants developing stability testing programs for veterinary chemical products and it will give added transparency and consistency to the assignment of product shelf lives.
Real time studies, or a combination of real time and accelerated studies, should be provided to support the proposed shelf life.

i) Real time stability data

The real time stability data should be generated by storing the product under the proposed (label) storage conditions for the product. The maximum shelf life that will be recommended based on evaluation of real time data is as follows: Where product samples exhibit adequate stability when stored for Y months at temperature X℃, then a shelf life of Y months may be recommended where the normal (label) storage conditions of the product specify storage at or below X℃.

ii) Accelerated stability data

Accelerated stability testing studies are designed to increase the rate of chemical degradation or physical change of a veterinary chemical product by using exaggerated storage conditions. In general, accelerated stability trials should be conducted at a storage temperature 10 – 15℃ above the proposed storage temperature. The accelerated data should be supported by real time data of the same stability trial duration. Where no significant change occurs at the accelerated condition, the maximum shelf life that will be recommended based on evaluation of real time plus accelerated data is as follows:

Table 1-4 Shelf life based on accelerated stability data

Stability data type	Duration of stability trial	Maximum shelf life
Real time + accelerated	Up to 12 months	Twice the duration of the trial
Real time + accelerated	X* months	X + 12 months

X* = GREATER THAN 12 MONTHS

Example 1: The proposed storage condition for a product is 'store below 30℃ (room temperature)'. Stability data for 3 batches stored for 12 months at 30℃ and 40 - 45℃ are provided in the application. The maximum shelf life that the NPCB will recommend for the product on the basis of the submitted data is 24 months when stored below 30℃ (room temperature).

Example 2: The proposed storage condition for a product is store 'below 30℃ (room temperature)'. Stability data for 3 batches stored for 18 months at 30℃ and 40 - 45℃ are provided in the application. The maximum shelf life that the NPCB will

recommend for the product on the basis of the submitted data is 30 months (i.e., 18 + 12 months) when stored below 30℃ (room temperature).

PARAMETERS/CHARACTERISTICS OF THE PRODUCT TO BE TESTED IN STABILITY TRIALS

Veterinary products that are the subject of an individual monograph in a recognized pharmacopoeia [BP, BP (Vet), Ph Eur and USP] are required to comply with the requirements stated in the monograph. The following list of parameters for each dosage form is presented as a guide for the type of tests to be included in a stability study. In general, appearance and assay tests should be performed for all dosage forms.

The list of test parameters presented for each dosage form is not intended to be exhaustive, nor it is expected that every listed test be included in the design of a stability protocol for a particular veterinary chemical product (for example, a test for odour should be performed only when necessary and with consideration for safety of the analyst).

Dosage form	Recommended Test Parameters
Aerosols (pressurised pharmaceutical preparations)	Identification of the Active substance Active substance assay Preservative content (where appropriate) Delivered dose or dose per actuation Particle size distribution (suspensions only) Number of metered doses
Capsules	Appearance Identification of the active substance Uniformity of content/mass Active substance assay Impurities (where appropriate) Disintegration time Dissolution profile (where appropriate)
Collars/ear tags	Appearance Identification of the active substance Uniformity of content/mass Active substance assay Dissolution profile (release of active substance from the inert matrix)
Emulsions	Appearance (including phase separation) Identification of the active substance Active substance assay Preservative content (where appropriate) pH Viscosity Microbial Limit (where appropriate)

Dosage form	Recommended Test Parameters
Granules	Appearance Identification of the active substance Active substance assay Moisture content Uniformity of content/mass (for single dose preparations only) Dissolution profile (where appropriate)
Implants (sub-cutaneous, intravaginal)	Appearance Identification of the active substance Active substance assay Uniformity of content/mass Hardness Friability Moisture content (where appropriate) Dissolution profile (release of the active substance from the inert matrix)
Injectables	Appearance, colour, clarity Identification of the active substance Particulate matter Active substance assay Impurities (where appropriate) Preservative content (where appropriate) Sterility (where appropriate) Bacterial endotoxins -Pyrogens pH (aqueous preparations only)
Oral powders	Appearance Identification of the active substance Active substance assay Moisture content (where appropriate) Microbial Limit (where appropriate)
Paste	Appearance Identification of the active substance Active substance assay Viscosity Microbial Limit (where appropriate)
Powders for injection	Appearance Identification of the active substance Active substance assay Impurities (where appropriate) pH of reconstituted solution Sterility testing for reconstituted solutions (where appropriate) **Note: In-use shelf life of reconstituted product should not exceed 24 hours unless justified by providing stability data to show that the reconstituted product is stable for the length of time stated on the label.**

Dosage form	Recommended Test Parameters
Soluble powders in drinking water	Appearance Identification of the active substance Active substance assay pH of solution **Note: In-use shelf life of medicated drinking water should not exceed 24 hours unless justified by providing stability data to show that the active substance is stable for the length of time stated on the label**
Solutions	Appearance (e.g. cloudiness, precipitation, clarity of solution) Identification of the active substance pH (aqueous solutions only) Active substance assay Impurity content (where appropriate) Preservative content (where appropriate) Sterility (where appropriate) Viscosity (where appropriate) Specific gravity (where appropriate) Microbial Limit (where appropriate)
Suppositories	Appearance Identification of the active substance Active substance assay Microbial Limit (where appropriate) Dissolution
Suspensions	Appearance Identification of the active substance pH (aqueous suspensions only) Viscosity (where appropriate) Active substance assay Particle size distribution (where appropriate) Preservative content (where appropriate) Microbial Limit (where appropriate)
Tablets	Appearance Identification of the active substance Active substance assay Impurities (where appropriate) Tablet hardness Friability (uncoated tablets) Disintegration time Dissolution profile (where appropriate) Uniformity of content/mass Uniformity of weight **Note: For chewable tablets, testing for disintegration time and dissolution profile is not required.**

Dosage form	Recommended Test Parameters
Topical, ophthalmic and otic products (e.g., powders, ointments, creams, lotions, gels and pastes)	Appearance, colour, clarity and odour Identification of the active substance Active substance assay Preservative content (where appropriate) pH Microbial limits/sterility (where appropriate) **Note: For ophthalmic products (creams, solutions, suspension and ointments), testing for sterility is required.**

Reference: Guidelines For The Generation of Storage Stability Data of Veterinary Chemical Products, Veterinary Guideline No 68, APVMA

APPENDIX 8: GUIDELINES FOR THE SUBMISSION OF PROTOCOL OF ANALYSIS AND ANALYTICAL METHOD VALIDATION DOCUMENTS

8.1 Guidelines for The Submission of Protocol of Analysis

I. General Requirements

1. The Protocol of analysis must be in a standard format that contains information as stated below:-
   a. Product name
   b. Name and address of manufacturer
   c. Name, signature and designation of authorized person
   d. Effective date
   e. Review date

2. Protocol of analysis must consist of all test methods and specifications that are carried out by the manufacturer. Standard pharmacopoeias, for example, BP/USP can be used as references. The tests and specifications in the pharmacopeias are the minimum requirements.

3. Photocopies of methods/ methods directly copied from pharmacopoeias are not acceptable. Manufacturers can use methods from those standard references but must have their own written and detailed procedure.

4. Manufacturers must confirm that all test methods in their protocol of analysis perform as expected. Copies of chromatograms (HPLC/GC/TLC), UV spectrum etc must be submitted together with the protocol of analysis.

5. Protocol of analysis must be properly ordered with proper numbering for all tests and specifications.

6. All references stated in the protocol of analysis must be submitted and clearly labeled.

7. Protocol of analysis submitted must be in either Bahasa Malaysia or English. Protocol of analysis in other languages will be rejected.

8. An authorized copy of latest certificate of analysis for the product concern must be submitted with the protocol of analysis.

II. Specific Requirements

1. Identification test
   a. List of equipment and apparatus required.
   b. List of chemical / reagents
   c. Preparation of sample and standard solutions.
   d. Details of method and procedures.
   e. Specification and acceptance criteria

2. Physical test (friability, uniformity of weight, pH, viscosity, etc).
   a. List of equipment required together with test parameters.
   b. Sample preparation (if any).
   c. Specification and acceptance criteria

3. Disintegration test
    a. Equipment required
    b. Test parameters
    c. Test medium
    d. Specification

4. Dissolution test
    a. Equipment and apparatus required.
    b. List of chemical / reagents required
    c. Test parameters i.e. type and volume of dissolution medium, rotation rate, temperature of solution and time.
    d. Preparation of dissolution medium, preparation of sample and standard solution (if any), etc.
    e. Type and method of analysis (HPLC, UV, etc) and test procedures. For example, if HPLC method is used, test method has to include the preparation of mobile phase, brand and type of column used, run time, detector used (UV, RI, etc), injection volume, system suitability test and other parameters.
    f. Typical chromatograms / UV spectrum for sample & standard solution, system suitability etc.
    g. Complete formula for calculation. For example, 'slow release' products calculation must include quantity of active substance in the medium volume which have been taken out for analysis.
    h. Test specification

5. Impurities / degradation / purity test
    a. List of equipment and apparatus required,
    b. List of chemical and reagents required.
    c. Preparation of sample and standard solutions.
    d. Detailed method and procedures
    e. Complete formula for calculation.
    f. Typical chromatogram of system suitability test, sample & standard solutions if applicable.
    g. Specification / acceptance criteria.

6. Assay and uniformity of content
    a. List of equipment and apparatus required,
    b. List of chemical and reagents required.
    c. Preparation of sample and standard solution
    d. Detailed method and procedures
    e. Complete formula for calculation.
    f. Typical chromatogram/spectrum of system suitability test, sample & standard solutions if applicable.
    g. Specification / acceptance criteria.

7. Pyrogen / abnormal toxicity test
    a. List of equipment, apparatus, glassware and reagents required.
    b. Preparation of sample solution and injection dose.
    c. Test method & procedure.
    d. Test interpretation
    e. Test specification

8. Bacterial Endotoxins Test (LAL)
    a. List of apparatus, glassware and reagents required.
    b. Preparation of standard solution, LAL reagent/substrate and sample.

c. Determination of MVD (Maximum Valid Dilution) and endotoxin limit.
d. Detailed test procedure.
e. Calculation and interpretation of test result
f. Test specifications.

9. Microbial Limit Test

9.1 Determination of microbial contamination test
   i. List of apparatus and culture required.
   ii. Preparation of test medium and growth promotion test.
   iii. Sample preparation including method for neutralizing of preservatives for samples that contain preservatives.
   iv. Complete test procedure by 'surface spread' for bacteria and 'pour plate' for fungi.
   v. Colony counting
   vi. Specification and acceptance criteria

9.2 Test for specified microorganisms and total viable aerobic count
   i. List of apparatus and culture required.
   ii. Preparation of test medium and growth promotion test.
   iii. Sample preparation including method for neutralizing of preservatives for samples that contain preservatives.
   iv. Complete test procedure for each of specific microorganism involved.
   v. Observation on colonies presence.
   vi. Specifications and acceptance criteria.

10. Sterility test
   a. List of apparatus required.
   b. List of biological and chemical substance required:-
      i. Culture medium
      ii. List of rinsing solution, buffer solution and diluent
      iii. Neutralizing agent (if any)
      iv. List of specific type cultures required
   c. Method used (e.g. membrane filtration method, direct inoculation, etc)
   d. Method of preparation of the following solutions/materials:-
      i. Culture medium (e.g. Fluid Thioglycollate Medium and Soyabean Casein Digest Medium).
      ii. Rinsing solution, buffer solution and diluents.
      iii. Neutralizing agent (if any).
      iv. Microorganism culture
   e. Growth promotion test for medium used in sterility testing (specific aerobes, anaerobes and fungi).
   f. Preparation of sample solution (including neutralizing procedure of antimicrobial agent for antibiotic samples and samples which contain preservatives).
   g. Complete test procedure for sterility test.
   h. Specifications and acceptance criteria.
   i. Validation procedure & validation data (if applicable).

11. Microbiology assay
   a. List of apparatus required.
   b. List of biological and chemical substances required.
   c. Procedure for the preparation of following solutions/substances:-

i, Culture mediums
ii. Rinsing solutions.
iii. Buffer solutions
iv. Diluents
v. Microorganism culture used in assay

d. Test method (e.g. agar diffusion, turbidimetric, randomized block, dose, etc)
e. Test procedure
   i. Preparations of solutions containing antimicrobial agents which may be present in the sample to be tested (if applicable).
   ii. Preparation of standard solutions (including any steps to counteract the antimicrobial properties of any preservatives, etc present in the sample)
   iii. Preparation of test solutions (including any steps to neutralize the antimicrobial properties of any preservatives, etc present in the sample)
   iv. Dilution schemes for test and standard solutions.
   v. Application of test & standard solutions (volume, latin squares, etc)
   vi. Incubation temperature & time
   vii. Procurement of test data.
f. Complete calculation for the test including ANOVA tablet and other data showing validity of test results.
g. Specifications and acceptance criteria.

8.2 Guideline for submission of analytical method validation documents.

1. Introduction

The requirements for the submission of the analytical method validation data and documents by the industry to the Drug Analysis Division, National Pharmaceutical Control Bureau (NPCB) are presented in this guide.

All the analytical validation done by the industry should be in accordance to ASEAN and ICH Technical Requirements Guidance Documents specifically:-

Q2A: Text on validation of analytical procedures, 1994
Q2B: Validation of analytical procedure: methodology, 1996

2. Requirements

The industry is required to submit the following documents for evaluation by NPCB:-

a. Analytical method protocol for the testing of the raw materials (only the active pharmaceutical ingredients (API) and preservatives if any). This should include the specifications and certificate of analysis. All analytical test procedures where possible should be in accordance with the official monograph of that ingredient in the latest edition of the official pharmacopoeia such as British Pharmacopoeia, United States Pharmacopoeia and WHO.

b. Analytical method validation protocol for the finished product. The protocol of analysis should be in accordance with NPCB's guidelines for the submission of protocol of analysis.

c. Protocol for the analytical method validation procedure carried out on the finished product. This procedure should include all details about the validation process including preparation of all solutions used – standards, samples,

placebo etc, detection methods, test conditions, equipment used, statistical analysis & evaluation, calculations etc.

Types of analytical procedures to be validated includes:-

i. Identification tests
ii. Quantitative tests for impurities' content
iii. Limit tests for control of impurities
iv. Quantitative tests of the active ingredient in the sample
v. Pyrogen / Bacterial endotoxin test
vi. Sterility test

A brief description of the type of tests considered in this document is provided below:-

Identification tests are intended to ensure the identity of an active ingredient in the sample. This is normally achieved by comparison of a property of the sample e.g. spectrum, chromatographic behavior, chemical reactivity, etc) to that of a reference standard.

Testing for impurities can be either a quantitative test or a limit test for the impurity in the sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test.
Assay procedures are intended to measure the content of active pharmaceutical ingredient present in a given sample. The analytical data submitted must be able to support the claim that the analytical method employed has been validated.

Pyrogen Test and Limulus Amebocyte Lysate Test -
Relevant validation data for pyrogen test and Limulus Amebocyte Lysate Test include product independent data such as equipment validation, validation of temperature system, lysate sensitivity and product dependent validation data such as inhibition / enhancement studies and validation for routine LAL tests according to the type of LAL test method employed eg. Gel Clot method, quantitative end point method or quantitative kinetic method.

Sterility testing applied to products that are required to be sterile. A satisfactory result indicates that no contaminating microorganism has been found in the sample examined in the condition of the test. For sterility testing it is imperative that the testing procedure adopted by the manufacturers include all aspects of validation of the testing method including the precautions against microbial contamination.

d. Complete set of data obtained from the validation process. These include all raw data such as weights used, chromatograms, tabulated sets of value as well as graphs, statistical analysis & evaluation, calculations & formulae etc. Summary of data will not be accepted. Acceptance criteria for each characteristic/ parameter should also be submitted. For products tested using analytical methods described in official pharmacopeias, users are not required to validate accuracy and reliability of these methods, but must submit data verifying their suitability under actual conditions of use.

1. Certificate of analysis of three (3) recent batches of the finished product.
2. Certificate of analysis for one batch of API used in the product.
3. Summary on the validation process together with conclusion reached.

APPENDIX 9: ALLOWABLE MAXIMUM RESIDUAL LIMIT (MRL)

This is not an exhaustive list. MRL not in the list but available in MRL list of Codex alimentarius, EMEA, Canada, USFDA, Japan NDA & Australia is allowed. Product containing ingredient not listed in MRL list from the countries mentioned will not be considered to be registered.

A) MAXIMUM PERMITTED PROPORTION OF DRUG RESIDUES IN FOOD

The food specified in column (2) of the Table below shall not contain the drug specified in column (1) thereof in proportions greater than the maximum permitted proportions specified opposite and in relation to that food in column (3) thereof.

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
Albendazole	2-Aminosulfone metabolite	Muscle, fat (cattle and other species), milk (cattle)	100
		Liver, kidney (cattle and other species)	5000
Amoxicillin	Amoxicillin	Milk (cattle)	4
		Muscle, liver, kidney, fat (all food producing species)	50
Ampicillin	Ampicillin	Milk (cattle)	4
		Muscle, liver, kidney, fat (all food producing species)	50
Amprolium	1-4 amino-2-n-propyl-5-(pyrimidinylmethyl)-2-picolinium chloride hydrochloride	Muscle (chicken, turkey, pheasant and calf), liver (calf), kidney (calf)	500
		Liver (chicken, turkey and pheasant), kidney (chicken and turkey)	1000
		Fat (calf)	2000
		Egg (chicken and turkey)	4000
Azaperone	Sum of azaperone and azaperol	Muscle, fat (pig)	60
		Liver, kidney (pig)	100
Benzylpenicillin	Benzylpenicillin	Milk (cattle)	4
		Liver, kidney, muscle (cattle and pig)	50
Carazolol	Carazolol	Muscle, fat (pig)	5
		Liver, kidney (pig)	25
Carprofen	Carprofen	Muscle (horse)	50
		Fat (horse)	100
		Muscle, fat (cattle)	500
		Liver, kidney (cattle and horse)	1000

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
Cefquinome	Cefquinome	Milk (cattle)	20
		Muscle, fat (cattle)	50
		Liver (cattle)	100
		Kidney (cattle)	200
Ceftiofur sodium	Desfuroylceftiofur	Milk (cattle)	100
		Muscle (pig and cattle)	200
		Fat (pig and cattle)	600
		Liver (pig and cattle)	2000
		Kidney (pig and cattle)	4000
Clorsulon	Clorsulon	Muscle (cattle)	100
		Liver (cattle)	200
		Kidney (cattle)	300
		Fat (cattle)	400
Closantel	Closantel	Muscle, liver (cattle)	1000
		Muscle, liver (sheep)	1500
		Fat (sheep)	2000
		Kidney, fat (cattle)	3000
		Kidney (sheep)	5000
Cloxacillin	Cloxacillin	Milk (cattle)	30
		Muscle, liver, kidney, fat (all food producing species)	300
Colistin	Colistin	Milk (cattle)	50
		Muscle, liver, fat (cattle, chicken, pig, rabbit and sheep)	150
		Kidney (cattle, chicken, pig, rabbit and sheep)	200
		Egg (chicken)	300
Danofloxacin	Danofloxacin	Fat (cattle)	200
		Muscle (cattle and chicken)	300
		Kidney (cattle)	500
		Fat (chicken)	600
		Liver (cattle)	900
		Liver, kidney (chicken)	1200
Decoquinate	Decoquinate	Muscle, liver, kidney, fat (cattle and sheep)	500
Dexamethazone	Dexamethazone	Milk (cattle)	0.3
		Muscle, kidney (cattle, horse and pig)	0.5
		Liver (cattle and pig)	2.5
Dicloxacillin	Dicloxacillin	Milk (cattle)	30

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
		Muscle, liver, kidney, fat (all food producing species)	300
Dihydrostreptomycin	Dihydrostreptomycin	Milk (cattle)	200
		Muscle, liver, fat (cattle, chicken, pig and sheep)	500
		Kidney (cattle, chicken, pig and sheep)	1000
Diminazene	Diminazene	Milk (cattle)	150
		Muscle (‘cattle)	500
		Kidney (cattle)	6000
		Liver (cattle)	12000
Doramectin	Doramectin	Muscle (cattle)	10
		Kidney (cattle)	30
		Liver (cattle)	100
		Fat (cattle)	150
Doxycycline	Doxycycline	Muscle (cattle, pig and poultry)	100
		Liver (cattle, pig and poultry), fat (pig and poultry)	300
		Kidney (cattle, pig and poultry)	600
Enrofloxacin	Sum of enrofloxacin and ciprofloxacin	Muscle, liver, kidney (cattle, chicken and pig)	30
Erythromycin	Erythromycin	Milk (mammalian)	40
		Edible offal, muscle, egg (mammalian and poultry)	300
Estradiol-l7β	Estradiol-17β	Food of bovine origin	GAHP*
Ethopabate	Ethopabate	Muscle (chicken)	500
		Liver, kidney (chicken)	1500
Febantel	Sum of febandazole, oxfendazole and oxfendazole sulfone	Milk (cattle) muscle, kidney, fat (cattle, pig and sheep)	100
		Liver (cattle, pig and sheep)	500
Fenbendazole	Sum of febandazole, oxfendazole and oxfendazole sulfone	Milk (cattle), muscle, kidney, fat (cattle, pig and sheep)	100
		Liver (cattle, pig and sheep)	500
Florfenicol	Sum of florfenicol and its metabolites	Muscle (cattle)	200
		Kidney (cattle)	300

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
	measured as florfenicol-amine	Liver (cattle)	3000
Flubendazole	Flubendazole	Muscle, liver (pig)	10
		Fat (pig)	20
		Fat (cattle)	40
		Liver (cattle)	100
		Muscle (poultry)	200
		Egg (poultry)	400
		Liver (poultry)	500
Flumequine	Flumequine	Muscle, fat (cattle, pig, poultry and sheep)	50
		Liver (cattle, pig, poultry and sheep)	100
		Kidney (cattle, pig, poultry and sheep)	300
Flumethrin	Flumethrin	Edible offal, muscle and milk (cattle)	50
Gentamicin	Gentamicin	Milk (cattle), muscle, fat (cattle and pig)	100
		Liver (cattle and pig)	200
		Kidney (cattle and pig)	1000
Isometamidium	Isometamidium	Muscle, fat, milk (cattle)	100
		Liver (cattle)	500
		Kidney (cattle)	1000
Ivermectin	22, 23 Dihydroavermectin B1a	Liver (pig and sheep)	15
		Fat (pig and sheep)	20
		Fat (cattle)	40
		Liver (cattle)	100
Levamisole	Levamisole	Muscle, kidney ,fat (cattle, pig, poultry and sheep)	10
		Liver (poultry)	100
Lincomycin	Lincomycin	Edible tissue (pig)	100
Maduramicin	Maduramicin	Edible tissue, muscle, (chicken)	240
		Fat (chicken)	480
		Liver (chicken)	720
Moxidectin	Moxidectin	Muscle (deer), liver (cattle)	20
		Liver (sheep), kidney (deer), fat (cattle and sheep)	50

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
		Liver (deer), kidney (cattle and sheep)	100
		Fat (deer), milk (cattle and sheep)	500
Neomycin	Neomycin	Muscle, liver, fat (chicken, turkey, duck, cattle, goat, sheep and pig), egg (chicken), milk (cattle)	500
		Kidney (chicken, turkey, duck, cattle, goat, sheep and pig)	1000
Nicarbazin	Nicarbazin	Muscle, liver, kidney (chicken)	4000
Nystatin	Nystatin	Edible tissue (pig and poultry), egg (poultry)	0
Oxacillin	Oxacillin	Milk (all food producing species)	30
		Muscle, liver, kidney, fat (all food producing Species)	300
Oxfendazole	Sum of fenbendazole, oxfendazole and oxfendazole sulfone	Muscle, kidney, fat (cattle, pig and sheep), milk (cattle)	100
		Liver (cattle, pig and sheep)	500
Oxibendazole	Oxibendazole	Milk (cattle and sheep)	50
		Muscle, liver, kidney, fat (cattle, horse, pig and sheep)	100
Oxytetracycline	Oxytetracyline	Fat (cattle, sheep, pig, chicken and turkey)	10
		Milk (cattle), muscle (cattle, sheep, pig, chicken and turkey)	100
		Egg (chicken)	200
		Liver (cattle, sheep, pig, chicken and turkey)	300
		Kidney (cattle, sheep, pig, chicken and turkey)	600
Penicillin	Penicillin	Edible tissue (chicken, quail, pig and sheep), egg (chicken and quail), milk (cattle)	0
		Edible tissue (turkey)	10
		Edible tissue (cattle)	50

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
Phoxim	Phoxim	Edible offal, muscle (pig)	10
		Fat (pig)	50
Progesterone	Progesterone	Food of bovine origin	GAHP*
Ractopamine	Ractopamine	Muscle (pig)	10
		Fat (pig)	10
		Liver (pig)	40
		Kidney (pig)	90
Robenidine hydrochloride	Robenidine Hydrochloride	Edible tissue (poultry)	100
		Fat (poultry)	200
Salinomycin	Salinomycin	Egg (poultry)	20
		Muscle (cattle)	50
		Edible offal (pig), muscle (pig and poultry)	100
		Edible offal (cattle and poultry)	500
Sarafloxacin	Sarafloxacin	Fat (chicken)	10
		Liver (chicken)	100
Spectinomycin	Spectinomycin	Milk (cattle)	200
		Muscle (cattle, chicken and pig)	300
		Fat (cattle, chicken and pig)	500
		Liver (cattle, chicken and pig)	2000
		Kidney (cattle, chicken and pig)	5000
Spiramycin	Expressed as spiramycin equivalents antimicrobially active residues Sum of spiramycin and neospiramycin	Muscle (pig)	200
		Kidney, fat (pig)	300
		Liver (pig)	600
		Muscle (cattle and chicken), milk (cattle)	200
		Kidney (cattle), fat (cattle and chicken)	300
		Liver (cattle and chicken)	600
		Kidney (chicken)	800
Streptomycin	Streptomycin	Milk (cattle)	200
		Muscle, liver, fat (cattle, chicken, pig and sheep)	500
		Kidney (cattle, chicken, pig and sheep)	1000
Sulphadiazine	Sulphadiazine	Edible offal (mammalian), muscle (mammalian), milk (cattle)	100

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
Sulphadimethoxine	Suiphadimethoxine	Milk (cattle)	10
		Edible offal, muscle (cattle and chicken)	100
Sulphadimidine	Sulphadimidine	Milk (cattle)	25
		Edible offal (chicken and mammalian), muscle (chicken and mammalian), liver, kidney, fat (cattle)	100
Suiphamethazine	Sulphamethazine	Edible tissue (cattle, turkey, chicken and pig)	100
Sulphaquinoxaline	Sulphaquinoxaline	Edible offal, muscle (poultry)	100
Sulphonamide	Sulphonamide	Muscle, liver, kidney, fat (all food producing species), milk (cattle)	100
Testoterone	Testoterone	Food of bovine origin	GAHP*
Tetracycline	Sum of parent drug and its 4-epimer	Muscle (cattle, poultry, pig and sheep), milk (cattle)	100
		Egg (poultry)	200
		Liver (cattle, poultry, pig and sheep)	300
		Kidney (cattle, poultry, pig and sheep)	600
Thiabendazole	Sum of thiabendazole and 5-hydroxy-thiabendazole	Muscle, liver, kidney and fat (cattle, pig, goat and sheep), milk (cattle and goat)	100
Tiamulin	8-alpha-hydroxymutilin	Muscle (pig)	3600
		Liver (pig)	10800
		Kidney, fat (pig)	14400
Tilmicosin	Tilmicosin	Milk (sheep)	50
		Muscle, fat (cattle, poultry, pig and sheep)	100
		Kidney (cattle and sheep)	300
		Liver (cattle and sheep),	1000
		Kidney (pig)	1000
		Liver (pig)	1500
Trenbolone acetate	β-Trenbolone ά-Trenbolone	Muscle (cattle)	2
		Liver (cattle)	10
Triclabendazole	5-chloro-6-(2',3'-dichloro-phenoxy) benzimidazole-2-one	Fat (cattle and sheep)	100

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
Trimethoprim	Trimethoprim	Edible offal, muscle (mammalian and chicken), egg (chicken), milk (cattle)	50
Tylosin	Tylosin	Milk (cattle)	50
		Muscle, liver, kidney (chicken and cattle), edible tissue (cattle), fat (chicken), egg (chicken)	200
Virginiamycin	Virginiamycin	Muscle, liver, kidney, fat (cattle)	0
		Muscle (pig and poultry)	100
		Fat (poultry)	200
		Liver (pig and poultry)	300
		Kidney, fat (pig)	400
		Kidney (poultry)	500
Zeranol	Zeranol	Muscle (cattle)	2
		Liver (cattle)	10

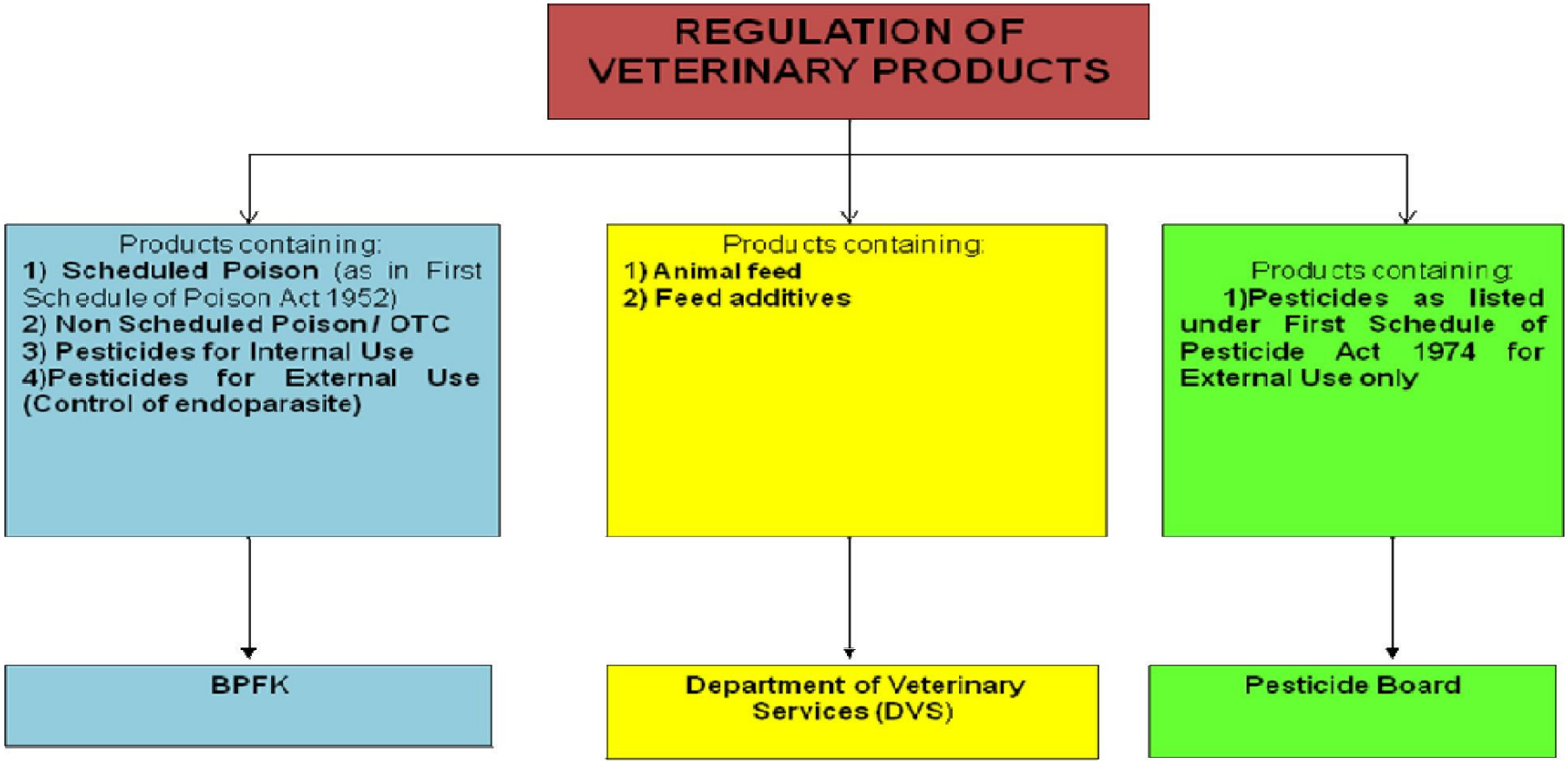
** Good animal husbandry practice*

Reference: Adopted list from Fifteenth A Schedule, [Regulation 40], Food Act 1985

B) MAXIMUM PERMITTED PROPORTION OF DRUG RESIDUES IN AQUACULTURE AND ALLOWABLE WITHDRAWAL PERIOD

BIL	PHARMACOLOGICALLY ACTIVE SUBSTANCES				MRLs µg/kg (ppb)	WITH DRAWAL PERIOD
1	Anti-infectious agents	Antibioticss	Sulfonamides	Sulfonamide	100	30 days
2			Diamino pyrimidine derivatives	Trimethoprim	50	30 days
3			Penicilin	Amoxicyllin	50	30 days
4				Ampicillin	50	30 days
5				Benzylpenicillin	50	30 days
6				Cloxacillin	300	30 days
7				Dicloxacillin	300	30 days
8				Oxacillin	300	30 days
9			Quinolones	Danofloxacin	100	30 days
10				Difloxacin	300	30 days
11				Enrofloxacin	100	30 days
12				Flumequine	600	30 days
13				Oxolonic acid	100	30 days
14			Macrolides	Erythomicyin A	200	30 days
15				Tilmicosin	50	30 days
16				Tylosin	100	30 days
17			Florfenicol	Florfenicol	1000	30 days
18			Tetracyclines	Chlortetracycline	100	30 days
19				Oxytetracycline	100	30 days
20				Tetracycline	100	30 days
21			Lincosamides	Lincomycin	100	30 days
22				Neomycin	500	30 days
23				Paromomycin	500	30 days
24				Spectinomycin	300	30 days
25			Polymyxins	Colistin	150	30 days
26	Antiparasitic Agents	Agents acting against ectoparasites	Organophosphates	Deltamethrin	10	30 days
27		Agents acting against endo- and ectoparasites	Avermectins	Emamectin	100	30 days
28		Dyes		Malachite green	2	30 days

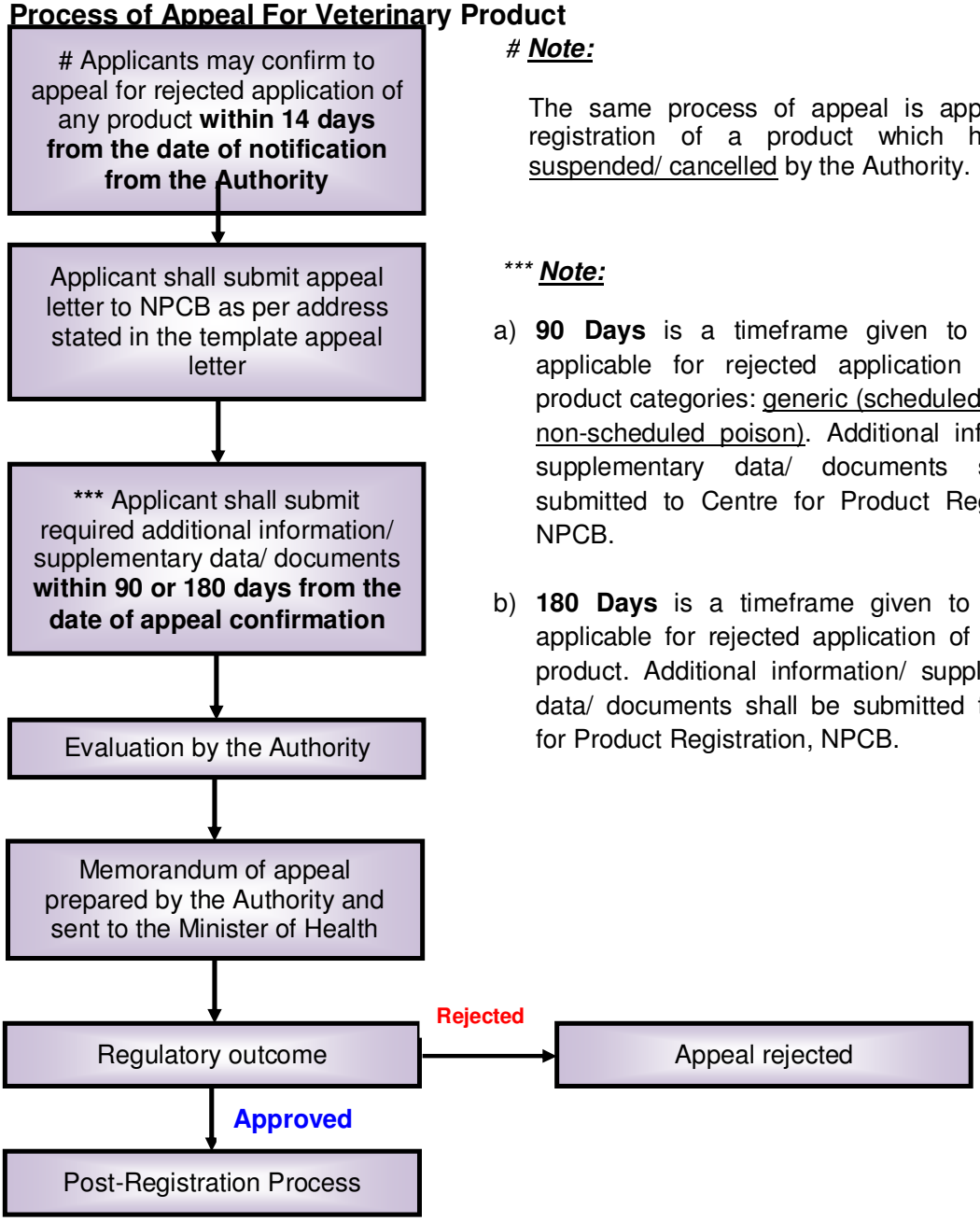
APPENDIX 10: REGULATION OF VETERINARY PRODUCTS IN MALAYSIA



- Products containing feed additives in combination with scheduled poisons will be regulated by the DCA
- Products containing pesticide ingredients in combination with scheduled poisons will be regulated by the DCA.

APPENDIX 11: APPEAL

Process of Appeal For Veterinary Product



*# **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). Additional information/ supplementary data/ documents shall be submitted to Centre for Product Registration, NPCB.

b) **180 Days** is a timeframe given to applicant applicable for rejected application of innovator product. Additional information/ supplementary data/ documents shall be submitted to Centre for Product Registration, NPCB.

TEMPLATE FOR AN APPEAL LETTER

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

Tarikh:

Y. B. Menteri Kesihatan Malaysia
d/a Biro Pengawalan Farmaseutikal Kebangsaan
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 2

GUIDE ON HOW TO FILL THE ONLINE APPLICATION FORM FOR A PRODUCT REGISTRATION

Separate modules are available for pharmaceuticals for human use and veterinary use. Please ensure that you click on the appropriate section of the display panel and fill the correct application form.

{NOTE: THE PROCESSING FEE, ONCE PAYMENT HAS BEEN CONFIRMED, CANNOT BE REFUNDED}

This appendix may not follow the sequence of the online registration forms.

Applicants who are attempting to fill up this form for the first time are advised to familiarise themselves with the drug registration system in Malaysia by reading Section 1 of this guidance document.

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.

Applicants are advised to read the explanatory notes in this appendix, as well as relevant ASEAN or VICH 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.

15. CHECK LIST OF PRODUCT REGISTRATION FORM ENTRY

Indicator

X : Non-Poison (OTC)
A : Scheduled Poison
√ : Mandatory
* : Not mandatory
N/A : Not Applicable

√* For OTC product, not mandatory if all information is already in the mock-up label

Product Validation

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) i) Is the selected manufacturer a contract manufacturer? (Yes/ No)
7.	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

No.	Step I: Product Validation
8.	Is this a replacement product? (Yes/ No) If yes, please provide: a) Letter of Declaration stating that this product is a replacement product Registration number and product name of the replaced product
9.	Is this an imported product? (Yes/ No)

Step II:			
Part I: Administrative Data And Product Information			
No.	**Section A: Product Particulars**	**Innovator**	**Generic A/X**
1.	Product Name	√	√
2.	Name & Strength of Active Substance and Excipient	√	√
3.	Dosage Form	√	√
4.	Product Description	√	√
5.	Pharmacodynamics	√	√
6.	Pharmacokinetics	√	√
7.	Environmental Properties	√	√
8.	Indication	√	√
9.	Target Species	√	√
10.	Recommended Dose	√	√
11.	Route of Administration	√	√
12.	Contraindication	√	√
13.	Warning and Precautions	√	√
14.	Interaction of Other Medicaments	√	√
15.	Pregnancy and Lactation	√	√
16.	Side Effects	√	√
17.	Symptoms and Treatment of Overdose	√	√
18.	Storage Condition	√	√
19.	Shelf Life	√	√
20.	Therapeutic Code/ ATCVet Code	√	√

Step II:			
21.	Withdrawal Period	√	√
22.	Maximum Residual Limit (MRL)	√	√
No.	**Section B: Product Formula**		
1.	Batch Manufacturing Formula	√	√
	Does the product contain or consist of genetically modified organisms (GMO)	√	√
2.	Attachment of Batch Manufacturing Formula Documentation	√	√
No.	**Section C: Particulars of Packing**		
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**		
1.	Proposed Label Mock-up for Immediate Container	√	√
2.	Proposed Label Mock-up for Outer Carton (if applicable)	√	√
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)	*	√
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)	√	√

Step II:			
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.	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)	*	*
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	√	√

Step II:			
30.	Worldwide registration status (For Imported product ONLY)	√	√
PART II: QUALITY OF PRODUCT			
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	√	NA
	c) Controls of Materials	√	NA
	d) Controls of Critical Steps and Intermediates	√	NA
	e) Process Validation and/or Evaluation	√	NA
	f) Manufacturing Process Development	√	NA
3.	Characterisation		
	a) Elucidation of Structure and Characteristics	√	NA
	b) Impurities	√	NA
4.	Control of Drug Substances		
	a) Specifications	√	√
	b) Analytical Procedures	√	NA
	c) Validation of Analytical Procedures	√	NA
	d) Batch Analysis	√	√
	e) Justification of Specifications	√	NA
5.	Reference Standards or Materials	√	NA
6.	Container Closure System	√	NA
7.	Stability	√	*
No.	**Section P: Drug Product (Finished Product)**		

Step II:			
1.	Description and Composition	√	√
2.	Pharmaceutical Development		
	a) Information on Development Studies	√	NA
	b) Components of the Drug Product	√	NA
	c) Finished Products	√	√
	d) Manufacturing Process Development	√	NA
	e) Container Closure System	√	√
	f) Microbiological Attributes	√	*
	g) Compatibility	√	NA
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	√	NA
	e) Excipient of Human or Animal Origin	√	√
	f) Novel Excipients	√	NA
5.	Control of Finished Products		
	a) Specifications	√	√
	b) Analytical Procedures	√	√
	c) Validation of Analytical Procedures	√	*
	d) Batch Analysis	√	√
	e) Characterization of impurities	√	NA
	f) Justification of Specifications	√	NA

Step II:			
6.	Reference Standards or Materials	√	NA
7.	Container Closure System	√	√
8.	Stability	√	√
9.	Product Interchangeability/Equivalence Evidence	√	NA
PART III: NONCLINICAL DOCUMENT			
	Section A: Table of Contents		
	Section B: Nonclinical Overview		
	III A: SAFETY DOCUMENTATION		
	1.1 Pharmacodynamics	√	NA
	1.2 Pharmacokinetics 1.2.1 Absorption 1.2.2 Distribution 1.2.3 Metabolism (inter-species comparison) 1.2.4 Excretion 1.2.5 Other Pharmacokinetics Studies	√	NA
	Toxicology		
	2.1 Single Dose Toxicity 2.2 Repeat Dose Toxicity 2.3 Tolerance in the target species of animal – Target animal safety 2.4 Reproductive Toxicity 2.4.1 Studies of the effects on reproduction 2.4.2. Embryotoxicity/foetotoxicity,including tetarogenicity 2.5 Mutagenicity 2.6 Carcinogenicity (if necessary)	√	NA
	Studies of Other effects		
	3.1 Special studies (e.g. neurotoxicity, sensitisation etc.) 3.2 Microbiological studies 3.3 Studies on metabolites, impurities, other substances & formulation	√	NA
	User Safety		
	4.1 Inherent toxicity or other harmful effects 4.2 Route and degree of exposure 4.3 Risk management proposal	√	NA
	Environmental Risk Assessment		

Step II:			
	(Environmental Safety)		
	5.1 Extent of exposure of the product to the environment 5.2 Specific investigations of the following, as appropriate : - fate and degradation in soil, fate and behaviour in water and air, effects on aquatic organisms, effects on other non-target organisms	√	NA
7	**Key Literature**		
	III B : RESIDUE DOCUMENTATION (Human Food Safety) (For a product intended for use in food-producing animal species)		
	Formulation used in residue studies	√	NA
	Residue Studies		
	2.1 Pharmacokinetics 2.2 Depletion of residues 2.3 MRLs 2.4 Withdrawal periods	√	NA
	Analytical Method(s)		
	3.1 Description of the method	√	NA
	3.2 Validation of the method 3.2.1 Specificity 3.2.2 Accuracy, including sensitivity 3.2.3 Precision 3.2.4 Limit of detection 3.2.5 Limit of quantitation 3.2.6 Practicability and applicability under normal laboratory conditions 3.2.7 Susceptibility to interference 3.2.8 Storage stability	√	NA
PART IV: CLINICAL (EFFICACY DOCUMENTATION)			
	Part III and IV are adopted and adapted from EMEA Guidelines and APVMA Guidelines. Please also refer to the relevant VICH Guidelines		NA

Step II:			
	IV A : PRE-CLINICAL DOCUMENTATION		
1	1.1 Pharmacodynamics 1.2 Pharmacokinetics	√	NA
2	Target Species Tolerance	√	NA
3	Resistance	√	NA
	IV B: CLINICAL DOCUMENTATION		
	Summary of the results and critical evaluations of dose determination and dose confirmation studies and clinical trials Tabular presentation of all clinical trials and studies Individual Summary of the most important and significant studies Summary of Clinical Safety etc		

15.1 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

- Product name, dosage form and strength shall be entered.
  (e.g. X Brand Paracetamol Tablet 500mg)

- 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.

- Product name shall not imply the following:
  a. Tricky, confusive and against the law;

b. Scandalous and offensive;
c. Prejudicial;
d. Notorious.

- 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.
- The invented name shall not be liable to confusion with the common 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 product name shall be shown on the product labelling i.e. immediate label, outer unit carton, package insert and patient information leaflet (PIL).
- 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.
- If a product name is found similar to another registered product or any other name which deemed inappropriate by the Authority, NPCB reserves the rights to request for the change of the product 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 6 List of Ingredients (active) Not Allowed to be Registered by the Drug Control Authority.
- 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 NPCB 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, 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) <u>Strength of active ingredient</u>:

- 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 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 5 List 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

- **Definition of Manufacturer:** A company that carries out at least one step of production as well as the final release of the finished product.
- 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 NPCB for verification.

[6.1] 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'.

[7] 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.

[8] 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

[9] Is This an Imported Product?

- Click the appropriate button 'Yes' or 'No'.

16.2 **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:

- Generic Pharmaceutical Products - **Parts I & II;**
- Innovator/NCE Products - **Parts I to Part IV:**

- Part I - Administrative Data and Product Information
- Part II - Quality *
- 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.

[*Please refer also to the following guidelines which have been prepared to facilitate submission of relevant documents for PART II (attached as **Appendix 8**)*

- *Guidelines for submission of protocol of analysis*
- *Guidelines for submission of analytical method validation documents**]***

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

No.	Product Category	Part I	Part II	Part III	Part IV
1.	Innovator/NCE Products	√	√	√	√
2.	Generics (Scheduled Poison)	√	√	Not Applicable	Not Applicable
3.	Generics (Non-Scheduled Poison)	√	√	Not Applicable	Not Applicable

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 follows, 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

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);

6. Pharmacokinetics

- Relevant pharmacokinetics (absorption, plasma-protein binding, distribution, biotransformation, metabolism, excretion, etc);

7. Environmental properties (for products used directly in the environment e.g. medicines for fish, it may be appropriate to provide general information on environmental effects).

8. Indication

State briefly recommended clinical use(s) of product, indicating clearly also whether curative, palliative, adjunctive, diagnostic, etc.

Note 1: Indications should be specific; phrases such as 'associated conditions' or 'allied diseases' would not normally be considered appropriate.

Note 2: 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 the prior permission of the DCA.

Note 3: Should it be desired to include new indications, an application shall be filed with the DCA together with supporting clinical documentation on evidence of efficacy and safety for the additional uses (indications).

9. Target Species

State the target species and sub-group, when appropriate.

10. Recommended Dose OR Dose/ Use Instruction

State the dose (normal dose, dose range) and dosage schedule (frequency, duration) and route of administration appropriate for each therapeutic indication and target species, including direction for proper use of the product by the veterinarian, farmer or owner.
Any special equipment needed for administration of the product should be mentioned. Where the product is to be administered via the feed or water, any dosage adjustment for inappetent animals should be specified, if justified from the data available.

Note 1:Where appropriate, diluents and instructions for dilution, reconstitution and use or administration of the product should be clearly stated.

Note 2: Distinction should be made between therapeutic and prophylactic doses, and between dosages for different clinical uses where applicable.

Note 3: Ensure that dosage recommendation is relevant and appropriate for the product.

Note 4: In the case of premixes for inclusion in the feeding-stuffs: any restriction on the range or type of feed which may be used for the preparation should be indicated. If specific mixing instructions are needed, it should be clearly stated.

11. Route of Administration

- 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.

12. 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).

13. Warnings and Precautions

State briefly precautions and warnings necessary to ensure safe and efficacious use of the drug, including special precautions for use, special warnings for each target species, and special precautions to be taken by the person administering the products to animals.
Where necessary, recommendations to minimise exposure of the product user during administration and, where relevant, during preparation of the product for administration should also be given in this section.
Guidance on remedial action to be taken following accidental contact should also be given, where necessary.
Any measures which can be taken to identify animals at risk and prevent the occurrence, or detect early the onset or worsening of conditions should be stated. If there is a need for awareness of clinical signs representing early warning of a serious ADR, a statement should be included. Any need for specific clinical or laboratory monitoring should be stated.

14. 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.

15. Pregnancy and Lactation

In order to ensure the safe use of the product, the practitioner must be informed of the recommendations regarding the use of the product in pregnant/lactating animals or laying birds.

The following should be mentioned;
a) conclusions from the animal reproductive toxicity/fertility study;
b) the risk in animals at different times of pregnancy, as assessed from a);
c) information on the possibility of using the product in breeding animals/laying birds.

Use in lactation:
When the active substance(s) or its metabolites are excreted in the milk, a recommendation as to whether to stop or continue to feed (new-born) animals, and the likelihood and degree of adverse reaction should be given.

16. 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, carcinogenicity, tolerance, liver/kidney toxicity etc.

Indicate also symptoms and sites of effects/reactions. In addition, it should be indicated whether certain species or breeds or types of individual are more susceptible to the undesirable effect concerned, or whether it is more frequent under certain types of husbandry conditions.

Note 1: Reactions, whether minor or serious, should be stated.

Note 2: Severity, reversible, frequency of occurrence should be indicated wherever possible.

Note 3: Clinical tests for detection of 'sensitive' animals, measure for management of adverse reactions developed shall be described wherever possible.

17. Signs and Symptoms of Overdose and Treatment

- Please state briefly symptoms of overdose/ poisoning, and where possible, recommended treatment and antidotes for overdose/ poisoning.

18. 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.

19. 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.

20. Therapeutic Code

Applicants should indicate the WHO assigned ATCvet code for each distinct therapeutic indication proposed for a product, if such a code is available. Click to search database.

If the product is for food producing animals

21. Withdrawal Period(s)

The withdrawal period is defined as the period between the last administration of the veterinary product to animals under normal conditions of use and the production of foodstuffs from such animals.

If necessary different withdrawal periods should be stated for meat and offal, milk, eggs and honey. Withdrawal periods should be indicated in days, except for milk withdrawal periods, which may be more appropriately expressed in hours.

A zero withdrawal period should be expressed as *'Zero hours/days'*.

However, for fish meat, the withdrawal period should be stated in degree days. The number of degree days is divided by the average water temperature, in ℃, to give the withdrawal period in days.

Please state the source of reference for information supplied.

22. Maximum Residual Limit (MRL)

A Maximum Residual Limit (MRL) is defined as *the maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg*

or g/kg on a fresh weight basis) which may be accepted to be legally permitted or recognised as acceptable in or on a food.

In order to protect the health of the consumer of foodstuffs of animal origin, one of the most important principles is that foodstuffs obtained from animals treated with veterinary products must not contain residues of the drug or its metabolites which might constitute a health hazard for the consumer.

Please refer to Appendix 9 to see Allowable Maximum Residual Limit food. For substances not in the list, source of reference for the limit has to be provided.

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

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 If the product contains or consist of Genetically Modified organism (GMO), please state the ingredient/organism used.

B1.3 Attachment of the Batch Manufacturing Formula Documentation

- The attachment shall be submitted.

SECTION C: PARTICULARS OF PACKING

- 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 : <u>Barcode/ Serial No.</u>

- Please key in if any (optional)

C4 : <u>Recommended Distributor's Price</u>

- Please key in if any (optional)

C5 : <u>Recommended Retail Price</u>

- Please key in if any (optional)

and then click button 'Add' to save all the entered informations.

<u>Note:</u>
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.

<u>SECTION D: LABEL (MOCKUP) FOR IMMEDIATE CONTAINER, OUTER CARTON AND PROPOSED PACKAGE INSERT</u>

- 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

Outer(Carton), Inner & Blister/Strips Labels

The following information should be present on the labeling of the product:

	Parameters	Unit Carton	Inner/ 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.	Expiration Date	✓	✓	✓
8.	Dosage and Administration	✓	✓	NA
9.	Storage Condition	✓	✓*	NA
10.	Country's Registration Number	✓	✓*	NA
11.	Name & Address of Manufacturer	✓	✓*	NA
12.	Name & Address of Registration Holder	✓	✓*	NA
13.	Warnings/Precautions (if applicable)	✓	✓*	NA
14.	Pack Sizes (unit/volume.)	✓	✓	NA
15.	Direction for Use	✓	✓*	NA
16.	Withdrawal Period (product for food producing animal)	✓	✓*	NA
17.	Name & content of preservative(s) where present	✓	✓	NA
18.	To declare source of ingredients derived from animal origin, including gelatin (active, excipient, and /or capsule shell)	✓	✓*	NA
19.	The words "Keep out of reach of children" or words bearing similar meaning in B.M. and English	✓	✓	NA
20.	The words " For animal use only" or words bearing similar meaning	✓	✓	✓
21.	Disposal of containers	✓	✓*	NA
22.	Other specific labelling requirements (if applicable)	✓	✓*	NA
23.	Statement on Controlled Medicines/Ubat Terkawal for product containing Scheduled Poison only	✓	✓*	NA

NA - Not applicable

* Exempted for <u>small</u> labels such as used in ampoules and vials

** For multi-vitamins and minerals preparations it is suggested to label as multi-vitamins and minerals

\# Where inner label is too small, this statement may be printed on the outer label

If the product is without an outer carton, the inner label should bear all the information that is required

Package inserts are required for products classified as Scheduled Poisons. They may also be submitted for OTC products. The draft copy of the package insert should be submitted for evaluation. The following information is required to be included in the package insert:

i) Brand or Product Name
ii) Name and Strength of Active Substance(s)
iii) Product Description
iv) Pharmacodynamics/Pharmacokinetics/Environmental Properties
v) Indication
vi) Recommended Dosage
vii) Mode of Administration
viii) Contraindications
ix) Warnings and Precautions
x) Interactions with Other Medicaments
xi) Statement on usage during pregnancy and lactation
xii) Adverse Effects/Undesirable Effects
xiii) Overdose and Treatment
xiv) Incompatibilities (for injections only)
xv) Withdrawal Period(s)
xvi) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
xvii) Dosage Forms and packaging available
xviii) Name and Address of manufacturer and marketing authorisation holder
xix) Date of Revision of Package Insert

Product Information Leaflet can be submitted in place of a package insert for an OTC product. The draft copy of the PIL should be submitted for evaluation. A PIL may also be submitted as additional information for scheduled poison products. The following information is required to be included in the PIL:

i) Name of Product
ii) Description of Product
iii) What is the medicine?
iv) Strength of the medicine
v) What is this medicine used for?
vi) How much and how often should you give this medicine to animal?
vii) When should you not give this medicine to animal?
viii) Undesirable effects/side effects
ix) What other medicine or food should be avoided whilst giving this medicine to animal?
x) What should you do if you miss a dose for the animal?
xi) How should you keep this medicine?
xii) Signs & symptoms of overdose
xiii) What to do when you have given more than the recommended dosage to the animal?
xiv) Name/logo of manufacturer/importer/marketing authorisation holder
xv) Care that should be taken when giving this medicine to animal?
xvi) When should you consult your veterinarian?

SECTION E: SUPPLEMENTARY DOCUMENTATION (AND PARTICULARS OF PRODUCT OWNER, MANUFACTURER, IMPORTER AND OTHER MANUFACTURER)

1. 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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 NPCB for verification.

- The certificates shall be valid and current at the time of submission.

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. Summary of Product Characteristics (SPC)

Please attach (where applicable).

10. Patient Information Leaflet (PIL)

Please attach (where applicable).

11. Attachment of Protocol Analysis, Analytical Validation

Please attach (where applicable).

12. Certificate of Analysis (CoA) for Finished Product

- For two (2) recent batches.
- Please attach the certificates (which must be completed with the product specification and results).

13. Importer and Store Address

Please key in (where applicable).

14. Other Supporting Document

Please attach (if any).

PART II

Please refer to ASEAN Technical Requirements Guidance Documents listed below:

ASEAN Guideline for Validation of Analytical procedures

ASEAN Guidelines on Process Validation

ASEAN Guideline for Drug Product Stability Study

Glossary of terms used in the ACTD/ACTR

Please also refer to the relevant VICH Guidelines.

For innovator/NCE products, complete documents for Part II (Substance and Product) need to be submitted. For other categories of products, only the indicated documents should be submitted.

Requirements for Innovator/NCE Product

Part I
Part II
Part III
Part IV

PART III and PART IV

For innovator/NCE products, complete documents for Part III and Part IV should be submitted immediately after online submission of Part I and II. Please submit the documents in hard copy (printed) as well as soft copy (preferably in CD's) to NPCB.

Part III and IV are adopted and adapted from EMEA Guidelines and APVMA Guidelines. Please also refer to the relevant VICH Guidelines.

PART III: Non Clinical (Safety and Residues Documentation)

III A : SAFETY DOCUMENTATION	
1	**Pharmacology**
	1.1 Pharmacodynamics
	1.2 Pharmacokinetics 1.2.1 Absorption 1.2.2 Distribution 1.2.3 Metabolism (inter-species comparison) 1.2.4 Excretion 1.2.5 Other Pharmacokinetics Studies
2	**Toxicology**
	2.1 Single Dose Toxicity
	2.2 Repeat Dose Toxicity
	2.3 Tolerance in the target species of animal – Target animal safety

	2.4 Reproductive Toxicity 2.4.1 Studies of the effects on reproduction 2.4.2. Embryotoxicity/foetotoxicity, including tetarogenicity
	2.5 Mutagenicity
	2.6 Carcinogenicity (if necessary)
3	**Studies of Other effects**
	3.1 Special studies (e.g. neurotoxicity, sensitisation etc.)
	3.2 Microbiological studies
	3.3 Studies on metabolites, impurities, other substances & formulation
4	**User Safety**
	4.1 Inherent toxicity or other harmful effects
	4.2 Route and degree of exposure
	4.3 Risk management proposal
5	**Environmental Risk Assessment (Environmental Safety)**
	5.1 Extent of exposure of the product to the environment
	5.2 Specific investigations of the following, as appropriate : - fate and degradation in soil, fate and behaviour in water and air, effects on aquatic organisms, effects on other non-target organisms
6	**Key Literature**

III B : RESIDUE DOCUMENTATION (Human Food Safety) (For a product intended for use in food-producing animal species)	
1	Formulation used in residue studies
2	**Residue Studies**
	2.1 Pharmacokinetics
	2.2 Depletion of residues
	2.3 MRLs
	2.4 Withdrawal periods
3	**Analytical Method(s)**
	3.1 Description of the method
	3.2 Validation of the method 3.2.1 Specificity 3.2.2 Accuracy, including sensitivity 3.2.3 Precision 3.2.4 Limit of detection 3.2.5 Limit of quantitation 3.2.6 Practicability and applicability under normal laboratory conditions 3.2.7 Susceptibility to interference 3.2.8 Storage stability

PART IV : Clinical (Efficacy Documentation)

Part III and IV are adopted and adapted from EMEA Guidelines and APVMA Guidelines. Please also refer to the relevant VICH Guidelines.

IV A : PRE-CLINICAL DOCUMENTATION	
1	1.1 Pharmacodynamics 1.2 Pharmacokinetics
2	Target Species Tolerance
3	Resistance

IV B : CLINICAL DOCUMENTATION
Summary of the results and critical evaluations of dose determination and dose confirmation studies and clinical trials Tabular presentation of all clinical trials and studies Individual Summary of the most important and significant studies Summary of Clinical Safety etc

New/additional indication

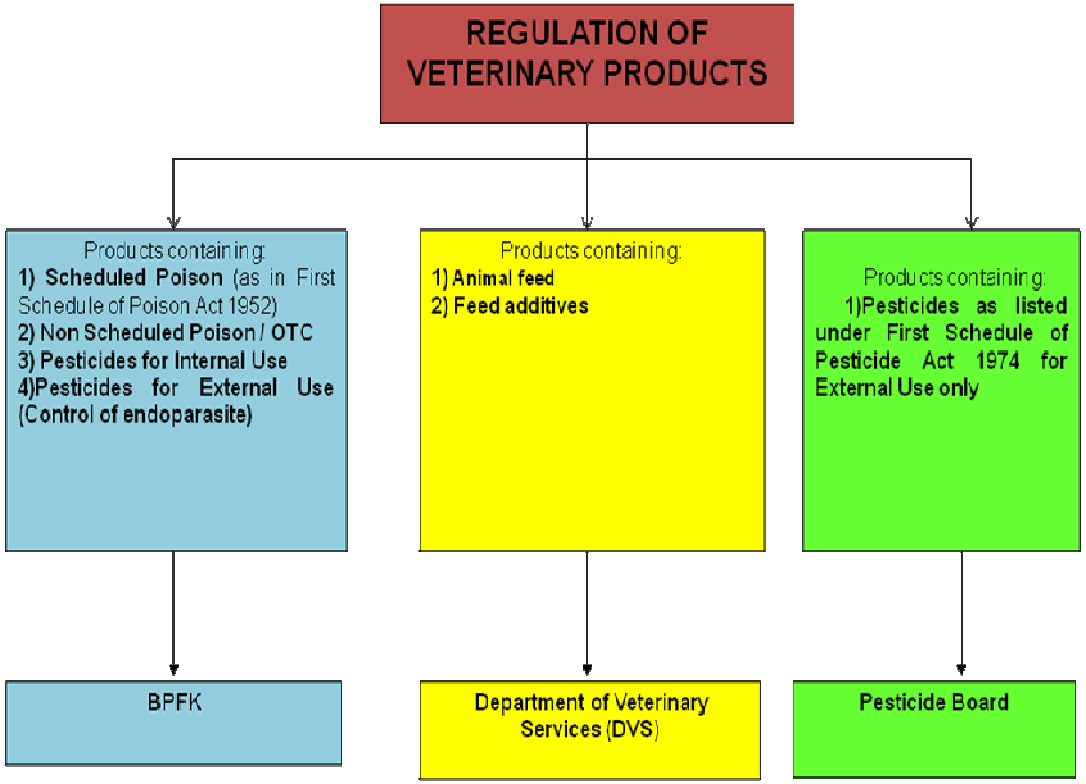
New/additional indication is defined as an indication which is not previously approved for a registered product. This includes a new therapeutic indication and does not include changing/ rephrasing of sentence.

LIST OF UPDATES

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>1.</td><td>February 2015</td><td>Section E, Inspection, Licensing and Relevant Documents</td><td><u>Amendment at Section E: Inspection, Licensing and Relevant Documents Subsection 13.1: Inspection</u>
<table>
<tr><th>Guidelines</th><th>Product Type/ Category</th></tr>
<tr><td>PIC/S Guide to Good Manufacturing Practice for Medicinal Products *</td><td>Pharmaceuticals (Poison and Non-Poison) Veterinary Products</td></tr>
<tr><td>Guideline on Good Manufacturing Practice (GMP) for Veterinary Premixes; 1st Edition, January 2015</td><td>Veterinary Premixes</td></tr>
<tr><td>Guidelines on Good Distribution Practice (GDP); 2nd Edition 2013</td><td>For activities related to the storage and distribution by manufacturers, importers and wholesalers (where applicable)</td></tr>
</table></td><td>Memo from PKP. Ref: (37)dlm.BPFK/30/06/1 Bhgn 7</td></tr>
<tr><td>2.</td><td>April 2015</td><td>Section A: General Overview</td><td><u>Deletion of Section A: General Overview, Subsection 2.2: (vi)</u></td><td></td></tr>
</table>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
3.	April 2015	Section A: General Overview	**Amendment of Section A: General Overview, Subsection 2.2: (vii) and (viii)**	
4.	April 2015	Appendix 10: Regulation of Veterinary Products in Malaysia	**Amendment of Appendix 10: Regulation of Veterinary Products in Malaysia**	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	



NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
5.	July 2015	Section A: General Overview	**Addition of Section A: General Overview, Subsection 2.4**	
6.	July 2015	Section A: General Overview	**Amendment of Section A: General Overview, Subsection 2.6**	
7.	July 2015	Section A: General Overview	**Addition of Section A: General Overview, Subsection 2.2: (x) and (xi)**	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
8.	October 2015	Section A: General Overview Appendix 1: Fees	**Amendment of Section A: General Overview, Subsection 2.5** **Amendment of Appendix 1: Fees, Subsection 1.2**	