APPENDIX 11

REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

CONTENT:

1. INTRODUCTION

1.1. A significant part of the quality of a finished product is dependent on the quality of the Active Pharmaceutical Ingredient (API) used for its formulation. Thus, a proper system of qualification of suppliers is necessary to ensure a constant sourcing of API of appropriate quality and to safeguard the public health interests. This will be done through standardized quality assessment and inspection procedures.

1.2. The National Pharmaceutical Regulatory Agency (NPRA) under the purview of the Ministry of Health Malaysia has introduced mandatory control of API as part of the requirements in the product registration application.

1.3. The implementation began with voluntary submission for New Drug Product in April 2011 and followed by:

Phase 1	New Drug Products (January 2012)
Phase 2	Scheduled Poison a) New Application (Generic Product): - i. Parenteral Dosage Form : 1 July 2014 ii. Oral Dosage Form : 1 July 2016 iii. Others : 1 July 2018 b) Registered Product (Pharmaceutical products containing Scheduled Poison): All Dosage Form: Expire on 1 January 2020 onwards *refer to No. 7 of this document.
Phase 3	Generic Product NOT containing Scheduled Poison (to be determined)

References:

i) *Bil. (12) dlm. BPFK/PPP/01/03 Jld.1* (17 March 2011)
ii) *BPFK/PPP/07/25 (7)* (16 January 2014)
iii) *Bil. (11) dlm. BPFK/PPP/01/03 Jld.3* (27 June 2014)

1.4 The procedure for control of API established by the NPRA is based on the following principles:

- A general understanding of the production and quality control activities of the manufacturer;
- Assessment of API data and information, including changes and variations, submitted by the product registration holder (PRH)/API Manufacturer. These data should include the manufacturing process, material specifications and test data and results;

- Assessment of the manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key raw materials and API during and after purification through compliance with Good Manufacturing Practice (GMP);
- Random sampling and testing of API (post-marketing surveillance);
- Handling of complaints and recalls; and
- Monitoring of complaints from other agencies and countries.

1.5. This document is intended to provide guidance regarding the requirements to be included for API in the quality part of the product dossier (Part II-S).

2. DEFINITION

2.1 Definition of Active Pharmaceutical Ingredient (API)

API refers to any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body (*WHO Technical Report Series No. 970, 2012*).

2.2 Definition of Main API Manufacturer

Main API Manufacturer refers to the manufacturer involved in the final API manufacturing process and responsible for batch release.

3. SCOPE

3.1. This guideline encompasses the final API of new products for registration and current/existing registered products. This is applicable to all pharmaceutical products (excluding biologic products, traditional products, veterinary products, health supplement products and products for export only (FEO)) both locally manufactured and imported.

3.2. For biological active substances, refer to the relevant guidelines available for Biologics.

3.3. Premixing of API is part of the product manufacturing process; therefore, information on premixed API should be submitted under Part II-P. Submission for Part II-S solely includes information on API only.

3.4. Separate registration of the API is not a requirement for the purpose of product registration. However, the required technical documentation pertaining to each API should be submitted with the new product registration application.

4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION

The API information can be submitted to NPRA through one of the following three options:

- Option 1: Drug Master File (DMF) procedure; or
- Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP); or
- Option 3: Part II-S ACTD

4.1 Required Information

4.1.1 Document required for each option of API Information submission are summarized in table 1:

Table 1:
Summary of Document Required for API Information Submission:

Option	Documents required
Option 1 (DMF)	• Part II-S (Open Part) via the online system • DMF (both open and closed part) shall be submitted by DMF holder in electronic copy (CD/DVD) directly to the NPRA to maintain confidentiality of the contents. • Letter of Access (LOA) • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; • See Section 5 for details
Option 2 (CEP)	• Part II-S (Open Part) via the online system (as deemed appropriate) • CEP with written statement • See Section 6 for details
Option 3 (ACTD)	• Full details of Part II-S ACTD via the online system. • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; • See Section 7 for details

*For GMP requirement refer to No. 6.2 of this document.

4.1.2 Separate API information must be provided for each API for:

- Finished product containing more than one (1) API
- API from different manufacturing site
- API from different synthesis route

4.1.3 The NPRA reserves the right to request for **any** additional information about the API when deemed appropriate.

4.2 Online Submission

4.2.1 All Part II-S information should be submitted through the online QUEST system [except for Closed part of Drug Master File (DMF) for DMF option]. Refer to **'Help Button**' in QUEST for assistance during online submission.

4.2.2 Separate Part II-S information (in the same product registration application form) shall be submitted when:

- A finished product contains more than one (1) API
- An API is manufactured from more than one (1) manufacturing site
- An API is manufactured using more than one (1) synthesis route

4.2.3 Select the **correct API manufacturer** (with the exact name & address) from QUEST database and ascertain your selection. Changes to the name or address of an API manufacturer are NOT possible once a saved form is created.

4.2.4 There are three options for Part II-S information submission. Refer to No.5 of this document.

4.2.5 Change of submission option or change or addition of API manufacturer is NOT allowed once the screening approval is obtained.

4.2.6 The Administrative Procedure for Regulatory Control of Active Pharmaceutical Ingredient (API) is available on NPRA website (refer to 8.1).

4.3 Processing Fees

Fees are not required as the API application is already incorporated in the application for product registration.

4.4 Other Considerations

In the spirit of harmonisation of regulatory activities and optimisation of efficient assessment, NPRA may take into consideration the evaluation of relevant API by the regulatory authorities of reference countries (Australia, Japan, France, Switzerland, United Kingdom, Canada, Sweden, and the United State of America) and, other PIC/S countries and World Health Organization (WHO).

5. TYPES OF API SUBMISSION

5.1 Option 1: Drug Master File (DMF)

5.1.1 The Drug Master File (DMF) is a document that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more API.

5.1.2 DMF is generally created to allow an authorized party other than the holder of the DMF to refer the DMF without disclosing the contents of the file to any other party.

5.1.3 The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR)/ ACTD provide details on the information to be included in the API sections of an application dossier.

5.1.4 The DMF is divided into two parts, namely the Open (or PRH's) part and the Closed (or restricted) part.

5.1.5 The documents required for an online application making a reference to a DMF are as follows:

From the PRH: Open part of the DMF, as part of the submitted product dossier contains most of the information in Part II-S – (i.e. sections S1, S2.1 and S3 to S7 excluding S2.2 – S2.6):		
	S1	**General Information**
		1.1 Nomenclature 1.2 Structure 1.3 General Properties
	S2	**Manufacture**
		2.1 Manufacture(s)/Site of Manufacture ***ALL** manufacturers involved in manufacturing process of API, including intermediate manufacturers and milling/ micronisation sites.
	S3	**Characterisation**
		3.1 Elucidation of Structure and other Characteristics 3.2 Impurities
	S4	**Control of API/Drug Substance**
		From API manufacturer: 4.1 Specification of API 4.2 Analytical Procedures 4.3 Validation of Analytical Procedures 4.4 Batch Analysis-minimum three batches 4.4.1 Certificate of Analysis (COA)-minimum two batches. 4.5 Justification of Specification **From finished product manufacturer:** 4.1 Specification of API 4.4.1 Certificate of Analysis (COA)-minimum two batches
	S5	**Reference Standards or Materials**
		From API manufacturer and finished product manufacturer

	S6	**Container Closure System**
	S7	**Stability**
		Refer to No. 6 of this document
	S8	**Drug Master File (DMF)**
		8.1 Letter of Access 8.2.1 Name of DMF Holder 8.2.2 Address of DMF Holder 8.2.3 Phone No. of DMF Holder 8.2.4 Email address of Contact Person-DMF Holder
	S9	**Certificate of GMP for API Manufacturer**
		9.1 Attach a valid copy of GMP Certificate 9.2 GMP Issuing Body 9.3 Date of Issue of Certificate of GMP 9.4 Date of Expiry of Certificate of GMP
	S10	**Other Supporting Document** e.g. Attachment for S2.1 Manufacturer and compendial monograph
From the API Manufacturer: The Complete DMF (open part AND closed part); S1-S7. The closed part contains the confidential information in section Part II-S (i.e. section S2.2 -S2.6);		
	S2	**Manufacture** 2.1 Manufacture(s)/ Site of Manufacture 2.2 Description of Manufacturing Process and Process Controls 2.3 Control of Materials 2.4 Controls of Critical Steps and Intermediates 2.5 Process Validation and/or Evaluation 2.6 Manufacturing Process Development

5.1.6 Summary of Required Documents for API Information in Product Registration Application is available for download on NPRA website (refer to 8.1).

5.1.7 The PRH is responsible to ensure that the complete DMF (i.e. both the Open part and the Closed part) is submitted to NPRA via electronic copy (e.g. CD/DVD/e-DMF) together with a Letter of Access (LOA):
The Letter of Access from API Manufacturer/ holder of the DMF authorizes the NPRA to refer to the DMF, in support of the application for a finished product. Thus, the Letter of Access must state the following:

- The name of the finished product (product name, dosage form and product strength) to be registered
- DMF version number (Open part & Closed part)
- Contact person for DMF correspondence (name and email address)

- The PRH responsible for finished product registration
- A declaration that both the PRH and the NPRA shall be notified of any change in the API specification or in the manufacturing process that will likely affect the product's quality or safety.

5.1.8 The information contained in the closed part of the DMF will be regarded as confidential and will only be evaluated in support of the applications mentioned in the Letter of Access. The confidential information will not be disclosed to any third party without a written authorization from the API Manufacturer.

5.1.9 A BPFK/NPRA DMF number will be assigned to the DMF during product registration evaluation. For future correspondences, the PRH and the API Manufacturer should make a reference to the BPFK/NPRA DMF number. The NPRA will directly contact API Manufacturer for any correspondence pertaining to API information in closed part.

5.1.10 API Manufacturer is responsible to maintain and update the DMF. The PRH should file a variation once they are notified with the changes to the DMF.

- Any change or addition, including a change in authorization related to specific PRH, shall be submitted to the NPRA in duplicate and adequately cross-referenced to previous submission(s). The reference should include the date(s), volume(s), section(s), and/or page number(s) affected.
- Should any change to a DMF is necessary, the API Manufacturer shall notify each affected PRH who has referenced the DMF of the pertinent change. Such notice should be provided well before making the change in order to permit the PRH to supplement or amend any affected application(s) as needed.

5.2 Option 2: Certificates of Suitability (CEP)

5.2.1 CEP stands for certification of suitability of European Pharmacopoeia monographs/Certificate of Pharmacopoeia.

5.2.2 The CEP is a document that used to demonstrate the purity of a given API produced by a given manufacturer is suitably controlled by the relevant monograph(s) of the European Pharmacopoeia. By demonstrating grant a CEP for given API, the suppliers of the API can prove such suitability to their pharmaceutical industry clients and the NPRA.

5.2.3 The PRH should submit a copy of the most current CEP including all annexes, together with the following:

- A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision and;
- A declaration from the API Manufacturer that the PRH and the NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety.

Note: *All such written statements must state the name of the finished product (product name, dosage form and product strength) to be registered and the PRH shall responsible for finished product registration.*

5.2.4 The PRH should provide the following information in the online submission:

S(i-iii)	**Certificate of Suitability (CEP)**
	i) A copy of the most current CEP including all annexes ii) Written Statement** ** Written statement is: • A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision and; • A declaration from the API Manufacturer that the PRH and the NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety. • All such written statements must state the name of the drug product (product name, dosage form and product strength) to be registered and the PRH shall responsible for finished product registration.)
S1	**General Information**
	1.1 Nomenclature 1.2 Structure 1.3 General Properties Discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section
S2	**Manufacture**
	2.1 Manufacture(s)/Site of Manufacture ***ALL** manufacturers involved in manufacturing process of API, including intermediate manufacturers and milling/micronisation sites. 2.5 Process Validation and/or Evaluation In the case of sterile API, data on the sterilization process of the API, including validation data, should be included in the product dossier (S 2.5)
S3	**Characterisation**
	3.1 Elucidation of Structure and other Characteristics Studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section
S4	**Control of API/Drug Substance**
	From API manufacturer: 4.1 Specification of API

	Note: Specification should include all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that were not controlled in the CEP and Ph.Eur. monograph, such as polymorphs, impurities and/or particle size distribution. 4.2 Analytical Procedures* 4.3 Validation of Analytical Procedures* 4.4 Batch Analysis-minimum three batches 4.4.1 Certificate of Analysis (COA)-minimum two batches. 4.5 Justification of Specification *for any methods used by the API manufacturer and <u>in addition</u> to those in the CEP and Ph.Eur. monograph. **From finished product manufacturer:** 4.1 Specification of API 4.4.1 Certificate of Analysis (COA)-minimum two batches.
S5	**Reference Standards or Materials**
	From API manufacturer <u>AND</u> finished product manufacturer
S6	**Container Closure System** <u>Exception:</u> where the CEP specifies a container closure system and the PRH declares to use the same container closure system.
S7	**Stability**
	<u>Exception:</u> where the CEP specifies a **re-test period** that is the same as or of longer duration, and **storage conditions** which are the same or higher temperature and humidity as proposed by the PRH.
S10	**Other Supporting Document** e.g. Attachment for S2.1 Manufacturer and compendial monograph

5.2.5 Summary of Required Documents for API Information in Product Registration Application is available for download on NPRA website (refer to 8.1).

5.2.6 The NPRA reserves the right to request for **any** additional information about the API when deemed appropriate.

5.2.7 The PRH is responsible to submit the latest CEP updates, with annexes, as soon as it is available from the API Manufacturer.

5.3 Option 3: Part II-S ACTD

5.3.1 Information on the API sections (ACTD Part II-S: S1-S7), including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, shall be submitted in the product dossier.

5.3.2 The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR)/ ACTD provide details on the information to be included in the online submission:

S1	**General Information**
	1.1 Nomenclature 1.2 Structure 1.3 General Properties
S2	**Manufacture**
	2.1 Manufacture(s)/ Site of Manufacture ***ALL** manufacturers involved in manufacturing process of API, including intermediate manufacturers and milling/micronisation sites. 2.2 Description of Manufacturing Process and Process Controls 2.3 Control of Materials 2.4 Controls of Critical Steps and Intermediates 2.5 Process Validation and/or Evaluation 2.6 Manufacturing Process Development
S3	**Characterisation**
	3.1 Elucidation of Structure and other Characteristics 3.2 Impurities
S4	**Control of API/Drug Substance**
	From API manufacturer: 4.1 Specification of API 4.2 Analytical Procedures 4.3 Validation of Analytical Procedures 4.4 Batch Analysis-minimum three batches 4.4.1 Certificate of Analysis (COA)-minimum two batches. 4.5 Justification of Specification **From finished product manufacturer:** 4.1 Specification of API 4.4.1 Certificate of Analysis (COA)-minimum two batches.
S5	**Reference Standards or Materials**
	From API manufacturer AND finished product manufacturer

S6	**Container Closure System**
S7	**Stability**
	Refer to No. 6 of this document
S9	**Certificate of GMP for API Manufacturer**
	9.1 Attach a valid copy of GMP Certificate 9.2 GMP Issuing Body 9.3 Date of Issue of Certificate of GMP 9.4 Date of Expiry of Certificate of GMP
S10	**Other Supporting Document** e.g. Attachment for S2.1 Manufacturer and compendial monograph

5.3.3 Summary of Required Documents for API Information in Product Registration Application is available for download on the NPRA website (refer to 8.1).

6. OTHER RELATED INFORMATION

6.1 Stability Data

6.1.1 Current stability test data for an API shall be provided, for at least three (3) primary batches. These data shall include:

- The type of stability study and stability protocol
- API name, API manufacturer, packaging particular
- Batch details (e.g., batch number, date of manufacture, batch size)
- The general test methodology (e.g., duration of study, storage conditions of temperature and humidity, list of relevant testing, testing frequency, etc.);
- Proposed retest period or shelf-life;
- Proposed storage condition;
  A storage temperature must be specified, e.g.:
  - Do not store above 25 °C
  - Do not store above 30 °C
  - Store in a refrigerator (2 °C to 8 °C)
  - Store in freezer

  Other special storage condition, e.g.:
  - Protect from light
  - Protect from moisture
- The analytical test methods (e.g., assay method of quantitation, determination of degradation products, moisture etc.) with reference;
- Validation of test methods;
- Specification;
- Results of tests; and,
- Conclusions.

6.1.2 In circumstances where an API retest period has not been established and complete long-term stability data is not available at the time of submission, the minimum stability data required are as follows:

- At least twelve (12) months of long-term data and six (6) months of accelerated data on at least three (3) primary batches of the API;
- The batches should be at least pilot scale-sized and manufactured by a method that simulates the final commercial process.

  * In view of this, the re-test date may be extended beyond the end of long-term studies, which can be extrapolated not more than twelve (12) months covered by the long term data.

  A letter of commitment (to provide complete long-term stability data when study is completed/when requested) shall be submitted.

6.1.3 The submitted API stability data should be from batches manufactured at the API manufacturing site proposed for product registration in Malaysia. At the time of submission of the new product application, the API stability data requirements are summarized as follows:

Study	**Minimum time period covered by data at submission**	**Number of batches required**
Long term	12 months	A minimum of 3 primary batches of the API. The batches should be at least pilot scale, manufactured by the same manufacturing process and packaged in the same container closure system as declared in S6 Container Closure System.
Accelerated	6 months	

6.1.4 If API is sourced from multiple sites or from different route of synthesis (ROS) are proposed in product registration, stability data of 3 batches from each API site or from each ROS are required.

6.1.5 Where full long time data is not available from each API manufacturing site to support the proposed retest period, it (e.g., on-going 6 months long-time data) may be acceptable to extrapolate the full long time stability data from other site if it can be demonstrated that the submitted data is representative of the proposed site by fulfilled the following criteria:

- The quality to the API used in the stability batches are comparable (e.g., physical characteristics/attributes, established process validation, impurities profile, etc)
- Manufactured using the same route of synthetic and same manufacturing process. Scientific justification should be provided to demonstrate equivalence between the sites if differences exist

- Controlled by the same set of specifications
- Packaged in the same container closure system

If any of the above criteria are not met, full long time API site-specific stability data are required to support the application.

In addition, a commitment to provide full long stability data for the related on-going API stability studies once full data available. A process validation protocol and report from all related API manufacturers are required to support this scenario.

6.1.6 NPRA may request for additional stability data if deemed necessary for the evaluation of the application.

6.1.7 Stability data is not required where the CEP specifies a re-test period and storage condition that is the same as stated in the online submission.

6.2 Good Manufacturing Practice (GMP)

6.2.1 The GMP compliance evidence accepted for main API manufacturer (refer to definition at No. 2 of this document) are:

a) GMP Certificate or GMP Inspection Report issued by:
   i. Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Participating Authorities or;
   ii. World Health Organization (WHO) or;
   iii. Drug Regulatory Authority

6.2.2 Manufacturers involved in the manufacturing of **API intermediate** should be able to provide GMP compliance evidence below:

a) GMP Certificate or GMP Inspection Report issued by:
   i. PIC/S Participating Authorities or;
   ii. World Health Organization (WHO) or;
   iii. Drug Regulatory Authority or;
b) Self-declaration from competent person of API Intermediate Manufacturer (refer to *template letter GMP_CP_V1* at NPRA website) or;
c) Declaration from Qualified Person (QP) (for EU countries)

6.2.3 When an atypical API (e.g. excipient, food additive or cosmetic ingredient) is used as an active ingredient in pharmaceutical products, the GMP compliance evidence accepted are:

a) GMP Certificate or GMP Inspection Report issued by:
   i. PIC/S Participating Authorities or;
   ii. World Health Organization (WHO) or;
   iii. Drug Regulatory Authority or;

b) Self-declaration from competent person from Finished Product (FPP) Manufacturer whereby the supplier of atypical API is an approved supplier according to the FPP

manufacturer's quality management system [refer to *template Letter_AAPI_V1* at NPRA website (refer to 8.1)].

6.2.4 NPRA reserves the right to determine the acceptability of any GMP compliance evidence.

6.3 Atypical API

6.3.1 Atypical API is excipient, food additive or cosmetic ingredient used as an active ingredient in pharmaceutical products. These substances are known to have lower risk and widely used outside of the pharmaceutical industry, which have meet recognized quality standards, as atypical API for the purpose of this guidance.

6.3.2 A list of Atypical API and its regulatory requirement are outlined in *Guidance Notes for API Information* (refer to 8.1). This list is not meant to be exhaustive and will be reviewed by NPRA from time to time. Should a risk to health be identified, NPRA shall take appropriate compliance and enforcement action proportional to the risk.

6.3.3 It is important to note that each lot or batch of the atypical API shall be, prior to its use in manufacturing process of the finished pharmaceutical products, be tested against and comply with the specifications established by the finished product manufacturer for that atypical API.

6.3.4 Finished product manufacturer (and PRH) are responsible for ensuring products in domestic commerce are safe, suitable and of purported quality.

6.4 New Product Registration Application Using Same Source of Approved API

6.4.1 **Approved API** refers to an API (in a registered product) regulated and approved following the implementation of Directive on Regulatory Control of API in Malaysia dated 17 March 2011.

6.4.2 Same Source of Approved API means the new product registration application is using the same API, which is manufactured by the same API Manufacturer, with the same API synthetic route as the approved API. This new submission shall be made by the same PRH through the same Part II-S submission option.

6.4.3 The PRH should keep the content of their dossier updated with respect to the actual synthesis/manufacturing process. The quality control methods should be kept in line with the current regulatory and scientific requirements. Where there are changes affecting an approved API in a registered product that requires variation application, the variation application shall be made and approved for every affected registered product prior to submission of a new product registration containing an Approved API.

6.4.4 The PRH is required to declare that the quality of the API, with respect to the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress. The PRH shall also declare that no changes have been made to the API other than those approved by the NPRA.

6.4.5 In cases where some minor textual changes have been introduced, and without affecting the major content of the dossier, the PRH shall be able to provide a summary of changes made to previously approved dossier compared to current dossier. NPRA will review the changes introduced and may consider to accept or reject the dossier as an Approved API.

6.4.6 Template for Declaration Letter for An Approved API in New Product Registration Application is available on NPRA website.

6.5 Product Registration Application Referencing to a Drug Master File (DMF) Previously Submitted to NPRA

6.5.1 A Drug Master File (DMF) is a submission used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of an API, in support of a product registration application.

6.5.2 A complete DMF (containing both closed part & open part information) shall be submitted by DMF Holder to NPRA in an electronic copy (CD/DVD/USB/e-DMF) with a Letter of Access (LoA) permitting NPRA and local product registration holder (PRH) to reference the DMF.

6.5.3 DMF holders should send a copy of complete DMF in CD/DVD/USB together with a LoA directly to Head of New Drug Product Section / Generic Medicine Section, Centre of Product and Cosmetic Evaluation, NPRA.

6.5.4 The LoA should include the following:

a. Name of DMF holder
b. Name and address of API manufacturing facility
c. DMF version number (for Applicant's part and Restricted part)
d. Name of the finished product (product name, dosage form and product strength
e. Local product registration holder (PRH) responsible for product registration
f. A declaration that the local PRH and NPRA shall be notified of any changes in the API specification or in the manufacturing process that will likely affect the product's quality or safety
g. Name and email address of person(s) to be contacted for additional information
h. Signature of authorizing official

6.5.5 The DMF holder should send a copy of the **LoA and the open part of DMF** to the dedicated PRH, who is authorized to incorporate by reference the API information contained in the DMF. The PRH is required to upload the API information (open part) on QUEST3+ during registration application.

6.5.6 DMFs received will be kept safe at NPRA. The information in a DMF will only be reviewed when a PRH submit a product registration application referencing to the DMF (with a LoA). If there are deficiencies found in the confidential information provided in a DMF, NPRA will send a letter describing the deficiencies to the DMF holder. At the same time, NPRA will notify the PRH that additional closed part information is needed in the supporting DMF. Deficiencies related to open part of the DMF will be requested via QUEST3+.

6.5.7 In situations where the DMF holder has previously submitted a complete DMF to NPRA and wished to reference the **same version of DMF** with another PRH, DMF holder is **only** required to supplement with a **LoA**. The new LoA shall be sent to NPRA via email to apiscreening@npra.gov.my. Information below shall be provided as reference:

a. Indication for submission: new product application/ renewal/ variation
b. Name of Product
c. Name of API
d. Name of PRH
e. Name of DMF Holder
f. Name and Address of API Manufacturer
g. DMF Version Number (shall be the **same** as previously submitted and shall not more than **3 years** from last submission)

6.5.8 In situations where the DMF holder has previously submitted a complete DMF to NPRA and wished to reference an **updated version of the DMF**** with another PRH, DMF holders should provide information **in addition** to above:

a. Declaration of no change; or
b. Table of comparison to describe changes / differences between the previous and current version

**newer version of the DMF (with minor changes) for the same API salt/ form/ grade/ standard with the same API manufacturing process and synthesis route, at the same manufacturing site

6.5.9 The list of DMF received by NPRA will not be disclosed to PRH for confidentiality concerns. The action of **referencing a DMF** with more than one PRH **shall be initiated by the DMF holder** and as noted, the incorporation by reference must be accompanied by a copy LoA.

7. REGULATORY CONTROL OF API FOR REGISTERED PRODUCT

7.1 This section is applicable for registered products containing Scheduled Poison in ALL dosage forms with the expiration of the registration period starting 1 January 2020.

7.2 At the point of writing, NPRA has identified anti-infective API as the selected category for assessment purposes. This category was selected based on current public health needs and risk-based approach, which may be extended to other categories from time to time.

7.3 The PRH shall prepare all required Part II-S document. This information shall be uploaded to QUEST between 12 to 15 months prior to expiry of product registration.

a. Submission by DMF option- complete DMF (both open & closed part) shall be submitted in electronic copy (preferably in compact disc) together with a Letter of Access and Cover Letter. This document shall reach NPRA before submission of Form RegA2. Open part information shall also be uploaded to QUEST.
b. Submission by ACTD or CEP option- all documents shall be uploaded to QUEST.

7.4 Administrative Procedure for Regulatory Control of Active Pharmaceutical Ingredient (API) In Registered Product Containing Anti Infective API is available on NPRA website (refer to 8.1).

7.5 Once all required Part II-S document are ready for updating, PRH shall fill and submit *Application Form for Section S Revision for Products (Anti-Infectives) Registered Before the Implementation of Directive on Regulatory Control of API (Form RegA2).* Form RegA2 is an online form available on NPRA's website.

7.6 All submissions will be screened for eligibility based on product registration expiration date and category of API.

7.7 NPRA will enable "Product Editing" function in QUEST 3+ for the indicated product. PRH will be given strictly 30 calendar days to upload all required Part II-S document. Failure to update complete Part II-S information by the end of the given timeframe will affect product renewal status.

7.8 During assessment, additional information may be requested via email, if necessary.

7.9 For registered products not containing anti-infective API, Part II-S document shall be kept by the PRH. It is not necessary to upload to QUEST.

7.10 For non-anti-infective API, NPRA reserves the right to request for Part II-S documents for full assessment (if deemed necessary). If the outcome of the assessment is unsatisfactory or if there is any doubt in the submitted document, appropriate regulatory action may be taken against the relevant product and/or the status of the product registration will be reviewed for product recall, suspension or revoking of registration status.

8. REFERENCES AND GUIDELINES

8.1 Guidance Note for Active Pharmaceutical Ingredient (API) Information published on NPRA website: *https://npra.gov.my/index.php/en/active-pharmaceutical-ingredient-api-main-page.html*

8.2 Guidelines on the Technical Requirements Related to the Quality of API

The technical requirements related to the quality of API have already been addressed elsewhere, (such as in the ASEAN, WHO, ICH, EDQM and EMA guidelines), and the PRH are advised to refer to these guidelines available at the relevant website such as:

- Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part
- Guideline on Active Pharmaceutical Ingredient Master File (APIMF) Procedure.
- The ASEAN Common Technical Dossier (ACTD) For The Registration Of Pharmaceuticals For Human Use Organization Of The Dossier
- The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: Quality – M4Q(R1)
- ICH Q3A (R2) Impurities in new drug substances
- Impurities: Guideline for Residual Solvents Q3C (R6)
- Guideline for Elemental Impurities Q3D(R1)
- Guideline for Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk M7 (R1)
- Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7
- Guideline for Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11
- Certification database for information on Certificates of Suitability (CEPs) granted by the EDQM.