GUIDANCE NOTES

ACTIVE PHARMACEUTICAL INGREDIENT (API) INFORMATION (PART II S) FOR QUEST3+ PRODUCT REGISTRATION APPLICATION

CENTRE OF PRODUCT AND COSMETIC EVALUATION
NATIONAL PHARMACEUTICAL REGULATORY AGENCY (NPRA)

Please read *Drug Registration Guidance Document (DRGD): Appendix 6 : Guideline on Regulatory Control of Active Pharmaceutical Ingredients (APIs)* and these notes carefully before completing QUEST3+ product registration application form **Part II Section S.** An incomplete application form or dossier (with major deficiencies) is likely to be rejected during submission.

A. New Product Registration Application

1) All Part II Section S information should be submitted through QUEST3+ (except for Closed part of Drug Master File (DMF) for DMF option). Please refer to **'Help Button**' in QUEST3+ for assistance during online submission.

2) All Part II Section S information in mandatory field should be filled up according to the original dossier.

3) Original document should be uploaded to QUEST3+ for all API information (S1 to S10).

4) Separate Part II Section S information (in the same product registration application form) should be submitted when:
    i. A finished product contains more than one API
    ii. An API is manufactured from more than one manufacturing site
    iii. An API is manufactured using more than one synthesis route

5) Please select the **correct API manufacturer** (with the exact name & address) from QUEST3+ database and ascertain your selection. Changes to the name or address of an API manufacturer are NOT possible once a saved form is created.

6) There are three options for Part II Section S information submission. Requirements for each submission option are available in *Drug Registration Guidance Document (DRGD): Appendix 6: Guideline on Regulatory Control of Active Pharmaceutical Ingredients (APIs).* A summary of these requirements is provided in Appendix 1.

7) A change of submission option is NOT allowed once screening approval is obtained.

8) Change or addition of API manufacturer is not allowed once screening approval is obtained.

9) Please also refer to Appendix 2 for *API Administrative Procedure.*

B. Product Registration Application Using Same Source of an Approved API

1) This section outlines the requirements when preparing submissions, whereby the new finished product is manufactured using an approved API of a registered product. Both new and registered product shall use the same API, which is manufactured by the same API Manufacturer, by the same API synthetic route. This new submission shall be made by the same Product Registration Holder (PRH) through the same Part II Section S submission option.

2) **Approved API** refers to an API (in a registered product) which is regulated and approved following the implementation of Directive on Regulatory Control of API in Malaysia dated 17 Mar 2011, thus previously reviewed and approved by API Section, Centre for Product Registration, NPRA.

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 which 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.

4) PRH are required to declare that the quality of the API, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress. PRH should also declare that, no changes have been made to the API other than those approved by the NPRA.

5) In cases where some minor textual changes have been introduced, and not affecting the major content of the dossier, 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) Please refer to NPRA's website for template of '*Declaration Letter for An Approved API in New Product Registration Application*'.

C. Regulatory Control of API for Product Registered Before the Implementation of Directive on Regulatory Control of API in Malaysia

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.

2) At the point of writing, NPRA has identified anti-infective APIs 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.

3) The PRH shall prepare all required Part II S information. This information shall be uploaded to QUEST3+ 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 QUEST3+.
    b. Submission by ACTD or CEP option- all documents shall be uploaded to QUEST 3+.

4) Please refer to Appendix 3 for *Administrative Procedure for Regulatory Control of Active Pharmaceutical Ingredient (API) In Registered Product Containing Anti Infective API*; and Appendix 1 for *Active Pharmaceutical Ingredient (API) Submission Checklist For Product Registration.*

5) Once all required Part II S information 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.

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

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 information. Failure to update complete Part II S information by the end of the given timeframe will affect product renewal status.

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

9) For registered products not containing anti-infective APIs, part II S information shall be kept by the PRH. It is not necessary to upload to QUEST 3+. It is PRH's responsibility to ensure that the API used in the finished product fulfills NPRA's requirement.

10) For non-anti-infective APIs, 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.

D. Regulatory Control of Atypical APIs

1) Part D of this guidance note is focusing on the content of regulatory control of Atypical API in Malaysia and is applicable for product registration in Malaysia.

2) Atypical APIs are 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, that have meet recognized quality standards, as atypical APIs for the purpose of this guidance.

3) A list of Atypical APIs is available in Appendix 4. This list not meant to be exhaustive and will be reviewed by NPRA from time to time.

4) Regulatory requirement for Atypical APIs is outlined in Appendix 5. Should a risk to health be identified, NPRA will take appropriate compliance and enforcement action proportional to the risk.

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

E. Good Manufacturing Practice Compliance Evidence for Manufacturers Involved

1) This section outlines the level evidence required to support that the manufacturing of API (including intermediate manufacturing and milling sites) are complying to an appropriate Good Manufacturing Practices (GMP) quality system.

2) The term **Main API Manufacturer** refers to manufacturer involved in final API manufacturing process and responsible for batch release. The GMP compliance evidence accepted for main API manufacturer 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

3) Manufacturers involved in manufacturing of **API intermediate** should be able to provide GMP compliance evidence as 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 template letter GMP_CP_V1) or;

    c) Declaration from Qualified Person (QP) (for EU countries)

4) 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 template Letter_AAPI_V1).

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

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

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.

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) with a Letter of Access (LoA) permitting NPRA and local product registration holder (PRH) to reference the DMF.

3) DMF holders should send a copy of complete DMF in CD/DVD/USB together with a LoA directly to NPRA at address below:

   Head of *_____ Section
   Centre of Product and Cosmetic Evaluation
   National Pharmaceutical Regulatory Agency
   Ministry of Health Malaysia
   Lot 36, Jalan Universiti
   46200 Petaling Jaya
   Malaysia

   *indicated according to product category (e.g. New Drug Product or Generic)

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

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) 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+.

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)

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:
    h) Declaration of no change; or
    i) 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

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.

Appendix 1

SUMMARY OF REQUIRED DOCUMENTS FOR
ACTIVE PHARMACEUTICAL INGREDIENT (API) INFORMATION IN PRODUCT REGISTRATION

NO.	SECTIONS/ FIELDS	CONTENTS	MANDATORY INFORMATION (✓)			PRH (Please tick ✓)
			ACTD	DMF	CEP	
1.	**Submission Option**	i) Drug Master File (DMF) ii) Certificate of Suitability (CEP) iii) ASEAN Common Technical Dossier (ACTD) * Refer to DRGD Appendix 6 for description	✓	✓	✓	
2.	**Certificate of Suitability**	A copy of the most current CEP including all annexes			✓	
		CEP number			✓	
		Date of issue			✓	
		Date of expiry (By default: 5 years from date of issue)			✓	
		Written Statement			✓	
		i) Name of the finished product				
		ii) PRH responsible for the finished product				
		iii) 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				
		iv) 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				
3.	**Quality Overall Summary (QOS)**	i) Overall Summary ii) Table of Contents iii) Body of Data	✓	✓	✓	
4.	**S1. General information**					
	S1.1 Nomenclature	International non-proprietary names/ INN: Chemical names: Synonyms: CAS No: Chemical Abstracts Service	✓	✓	✓	
	S1.2 Structure formula	Structural formula (relative and absolute chemistry) Molecular formula Molecular weight Molecular weight (base)	✓	✓	✓	
	S1.3 General Properties	Physico-chemical properties: i) Colour, physical form (powder, amorphous, crystalline, liquid, etc) ii) Solubility: - Solubility in the <u>water</u>, acid, alkali, common solvent - Solubility (mg/ml) - over the physiological pH range (pH 1.2-6.8) in several buffered media - Solubility (mg/ml) - in 250mL water at pH 1.2, 4.5 and 6.8 performed at 37ºC iii) Pka, pH, partition coefficient (log P), Melting point, hygroscopicity, isomerism, chirality and polymorphism	✓	✓	**YES**, If there are any physicochemical & relevant API properties - not controlled by the CEP, e.g. solubilities and polymorphs	
5	**S2. Manufacture**					
	S2.1 API Manufacturer(s)	Name and address of manufacturer that produced the API (manufacturer responsible for release of the final API). - Attach GMP certificate in S9 - Attach S2.1 Manufacturer in S10	✓	✓	✓	
	S2.1.1 Other API Manufacture(s) involved	Manufacturers involved in each production steps, including intermediate manufacturer, milling and quality control testing sites. * GMP Compliance evidence is required for all manufacturer involved in API manufacturing process, including intermediate manufacturing and milling sites;	✓	✓	✓	
	S2.1.2 Name of Synthesis Route	State the name of synthesis route. (If no specific name was assigned, please state as "Only One Route").	✓	✓	✓	
	S2.2 Description of Manufacturing Process and Process Controls	i) Detailed Description of the Synthesis (step & process) from starting materials until purification step. ii) Proposed starting material iii) Manufacturing scheme that indicates molecular formula; molecular weights; chemical structures of starting materials, intermediates and the API including	✓	✓		

		stereochemistry; reagents, catalysts and solvents used in each step until purification step. iv) Catalyst & solvents used (ICH class & limit). v) Control strategy of solvents. (if skip testing, etc). vi) Quantities of materials used, operating conditions and yield ranges in the description of the process. vii) Recycling of filtrates/mother liquors (maximum holding time /maximum number of times the material may be recycled/Evidence / Data on the impurity levels). viii) Final Steps (eg. Purification procedure) ix) Commercial and Maximum batch size (batch range in kg) x) Alternatives steps (no changes in the impurity profile) xi) Re-processing; identified the process/step, method, frequency/limit of reprocess, same specification of the final API, no changes in the impurity profile, control of impurity levels, etc. xii) Reworking: equivalent quality as original process, impurity profile, etc xiii) Recovery of materials or solvents: step its introduced in the process, source, ratio (or range of mixtures) of fresh and recovered solvents, specifications (including justification of specification), impurity levels xiv) Blending of batches; each batch tested & comply to final API specification				
	S.2.2.1 Manufacturing Process Flowchart	Manufacturing Process Flow that indicates molecular formula; molecular weights; chemical structures of starting materials, intermediates and the final API, including its stereochemistry; reagents, catalysts and solvents used in each step until purification step.	✓	✓		
	S2.3 Control of Materials	i) Starting materials; Justification on selection of starting materials, Specification, Name & address of each supplier, CoA of starting material issued by each of suppliers, CoA of starting material issued by the API manufacturer (for each of suppliers), Preparation of starting materials (Brief description), characterisation. ii) All materials (solvent, catalyst or reagent) used during manufacturing process [Specification, function and control strategy]. iii) Others. e.g. benzene contamination, Quality of water etc.	✓	✓		
	S.2.3.1a TSE Risk Free Statement	i) Declaration; starting materials, reagents and all materials used to manufacture the API are of animal or human origin. ii) Document to demonstrate compliance on TSE/BSE requirement	✓	✓	✓	
	S2.4 Controls of Critical Steps and Intermediates	Controls of Critical Steps - critical steps & process control including tests and acceptance criteria (with justification including experimental data). Controls of Intermediates - List of Intermediates, specification, analytical procedure	✓	✓		
	S2.5Process validation and/or evaluation	Applicable to sterile API only	✓	✓	**YES**, If CEP did not specify asterile API	
	S2.6 Manufacturing Process Development	i) Description and discussion of significant changes made to the manufacturing process and/or manufacturing site of the API used in producing non-clinical, clinical, scale-up, pilot and if available, production scale batches. ii) The development history of the manufacturing process as described in S 2.2 iii) To state the date of changes.	✓	✓		
6	**S3. Characterisation and Impurities**					
	S3.1 Elucidation of Structure and other Characteristics	i) Pharmacopoeia API: - Comparison of spectral data between pharmacopoeia reference standard & API (If comparison is not available, assess as per non-pharmacopoeia API). ii) Non pharmacopoeia API: - Elemental analysis - Infrared Spectrophotometry (IR)	✓	✓	✓	

		- Ultraviolet absorption spectrum (UV) - Mass Spectrometry - Nuclear Magnetic Resonance Spectrometry (NMR) ; *^{1}H-NMR*, *^{13}C-NMR* - X-ray Diffraction - Differential Scanning Calorimetry (DSC) - Thermogravimetric analysis (TGA) - Others iii) Polymorphism - Description & characteristics of various polymorphic forms - Potential for formation of the polymorphic forms - Stability of the polymorphic forms - Evidence to prove the commercial scale process consistently produce desired polymorphic forms iv) Particle size distribution v) Isomerism				
	S3.2 Impurities	Organic Impurities, Inorganic Impurities, Residual solvents, Genotoxic Impurities - Possible carryover of impurities (during the synthesis and from the preparation of starting material and intermediates to the final API). - ll possible potential impurities that may arise from the starting materials, route of synthesis and possible degradation products should be listed with name, structure, origin, LOD and LOQ and ranges of results in at least 3 consecutive batches as well as the proposed limits taking into account the requirements of ICH guideline. - Any impurity greater than qualification threshold should be qualified and a rationale for establishing impurity limit/ acceptance criteria that includes safety considerations (eg. data from toxicology study, or batch analysis data of batches used in clinical trial with observed impurites content are equal or more than limit in the specification) should be provided. - discussion on impurities that stated in another pharmacopeia (if applicable)	✓	✓		
7	**S4. Control of Drug Substance/ API**					
	S.4.1 Specification	Table of Specification of API from both API Manufacturer & Product Manufacturer (with Specification version no. & effective date).	✓	✓	✓	
	S4.2 Analytical Procedures	i) The analytical procedures used for testing of API should be provided in sufficient details to enable reproducible testing by another laboratory ii) Compendial methods or appropriate information from the manufacturer	✓	✓		
	S4.3 Validation of Analytical Procedures	i) Analytical validation information, including experimental data for the analytical procedures used for testing the API ii) Typical validation characteristics to be considered: - Selectivity - Precision(repeatability, intermediate precision and reproducibility) - Accuracy - Linearity - Range - Limit of Quantitation - Limit of detection - Robustness - System suitability iii) Non-compendial methods	✓	✓		
	S4.4 Batch Analysis	i) Batch analysis results of at least 3 batches ii) Information in table form e.g.: batch number, batch size, manufacturing date, manufacturing site and batch use (validation, stability, commercial etc.)	✓	✓	✓	
	S.4.4.1 Certificates of Analysis(COA)	i) From API Manufacturer (2 Batches) ii) From Product Manufacturer (2 Batches)	✓	✓	✓	
	S.4.5 Justification of Specification	i) Discussion on inclusion/ omission of tests and analytical procedures	✓	✓	✓ (For non-	

		ii) Justification on range of acceptance criteria set for in-house tests			monograph tests)	
8	**S5. Reference Standards or Materials**					
	From API Manufacturer	i) Clearly stating: - Official reference standard used, with batch number - Primary reference standard used, with batch number - Working standard used, with batch number ii) For each Reference Standard should provide: - CoA of Reference Standard - IR spectra of reference standard - Overlaid IR spectra comparing the primary & working standards. - Reference standards available for impurities/related substances	✓	✓	✓	
	From Product Manufacturer	i) Clearly stating: - Official reference standard used, with batch number - Primary reference standard used, with batch number - Working standard used, with batch number ii) For each Reference Standard should provide: - CoA of Reference Standard - IR spectra of reference standard - Overlaid IR spectra comparing the primary & working standards. - Reference standards available for impurities/related substances	✓	✓	✓	
9	**S6.Container Closure System**					
	S.6 Container Closure System (CCS)	i) Description: primary packaging, secondary packaging, specifications,	✓	✓	✓	
		ii) IR spectra of primary packaging material, CoA, Functional secondary packaging components (If applicable), iii) Suitability: Moisture and light, compatibilty (e.g: Sorption or leeching)	✓	✓	**YES**, - If CEP did not specify a CCS or - CCS (in S.6) is different from CCS (in CEP)	
10	**S7. Stability**					
	Re-test Period or shelf life	Select (months) the proposed retest period based on stability study conclusion.	✓	✓	✓	
	Storage Condition	State API storage condition (including special label, if needed) based on study condition of stability data provided (eg: “Store below 25 °C, protect from light”).	✓	✓	✓	
	Stability Data	i) Stress Testing Study - API batch details (eg: moisture, light, acidic, basic, oxidative and thermal stress conditions).	✓	✓		
		ii) Long Term Stability Data - Minimum of 3 batches, (with recent results) - Batch information (manufacturing date, site, batch size, - Temperature/RH/Packaging iii) Accelerated Stability Data - Minimum of 3 batches, (with 6 months data) - Batch information (manufacturing date, site, batch size) - Temperature/RH/Packaging iv) Post-approval Stability Protocol and Stability Commitment	✓	✓	**YES**, If CEP did not specify a retest period with specific storage condition (CCS and specific temperature). or - CCS (in S.6 & S7) is different from CCS (in CEP)	
11	**S8.Drug Master File(DMF)**					
	General Note	i) The API manufacturer may submit the DMF (both open part & closed part) via electronic copy (CD) with a Cover Letter* & Letter of Access directly to **Head of New Drug Product/ **Head of Generic Medicine Section*, Centre of Product and Cosmetic Evaluation, NPRA to maintain confidentiality of the content. ii) The DMF should reach NPRA at the point of screening submission. Failure to do so may result in submission rejection. * Please refer to template of Cover Letter available on NPRA website ** refer to product category				

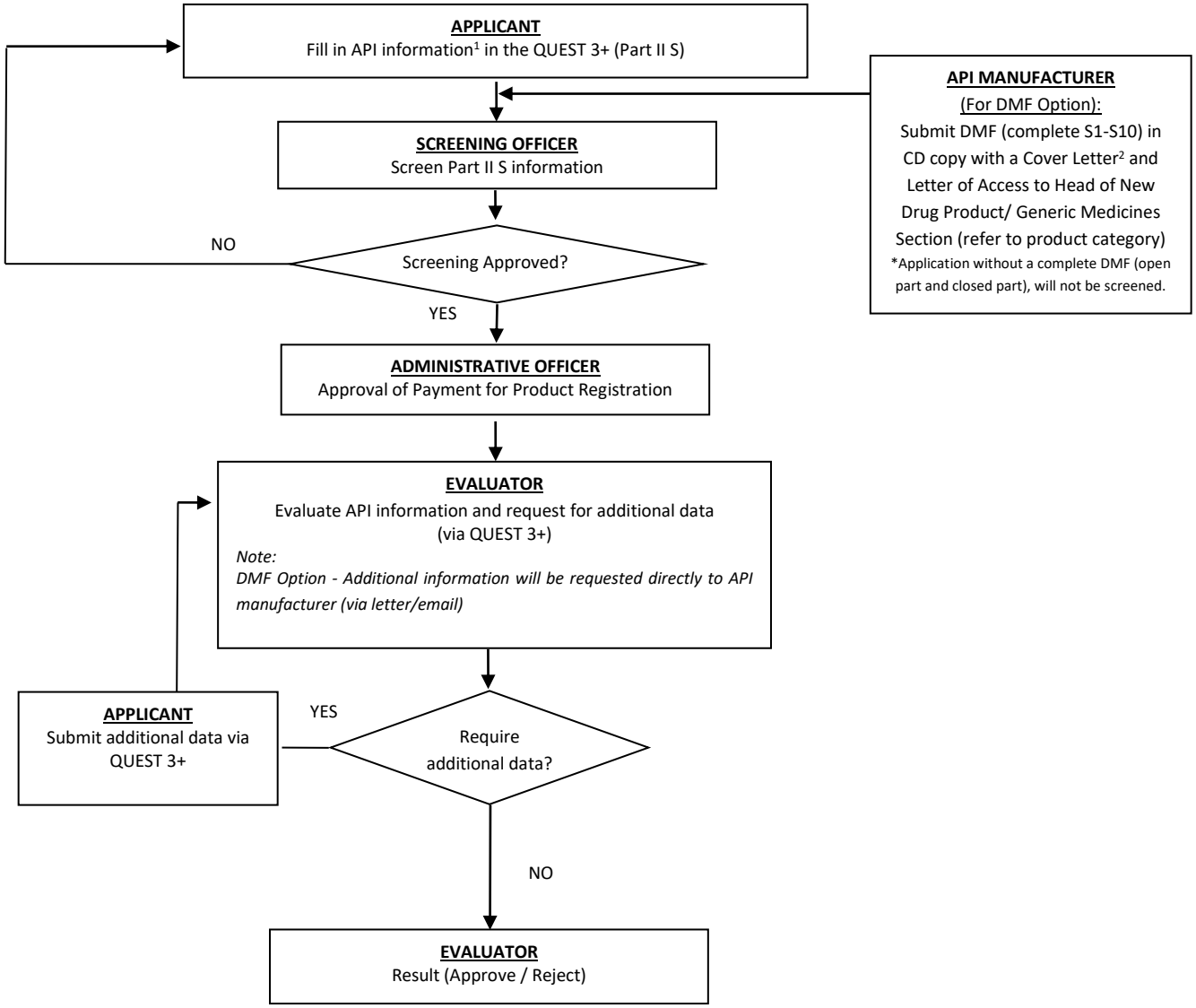
	DMF Version No.	Current DMF version number with effective date, &		✓		
	S.8.1 Letter of Access	The letter of Access authorizes NPRA to refer to the DMF, in support of the application for a finished product. Thus, the Letter of Access must state the following: - The name of the finished product (product name, dosage form and product strength to be registered; - The local applicant responsible for product registration; and - A declaration that the local applicant and NPRA shall be notified 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.		✓		
	S8.2 Name and complete address (including phone/fax no.) of DMF holder	S.8.2.1 Name of DMF Holder S.8.2.2 Address of DMF Holder S.8.2.3 Phone No. of DMF Holder S.8.2.4 Email address of Contact Person-DMF Holder		✓		
12	**S9. Certificate of Good Manufacturing Practice (GMP) for API Manufacturer**					
	S9. GMP Certificate	S.9. Attach a valid copy of GMP Certificate S.9.2 GMP Issuing Body S.9.3 Date of Issue of Certificate of GMP S.9.4 Date of Expiry of Certificate of GMP	✓	✓		
13	**S10. Other Supporting Document**					
	S10. Other Supporting Document	- Provide attachment for S2.1 Manufacturer in S10. - Official compendial monograph (if available) - Other supporting documents*	✓	✓	✓	
	Additional documents for Approved (API)	Declaration Letter from PRH (To state the changes if any) *(refer template letter)*	✓	✓	✓	
		Declaration Letter from API Manufacturer *(refer template letter)*	✓	✓		
		List of Additional Data - Provide all the additional data which has been requested during previous submission (approved API)	✓	✓	✓	
		List of Approved Variation Application - Provide list of all variation application which was approved	✓	✓	✓	
		Summary of other changes Table of comparison (Approved API & New submission)	✓	✓	✓	

* Additional information may be requested if deemed necessary

Appendix 2

API ADMINISTRATIVE PROCEDURE FOR NEW PRODUCT APPLICATION FOR NCE & GENERIC (CONTAINING *SCHEDULED POISONS*: *ALL DOSAGE FORMS*)

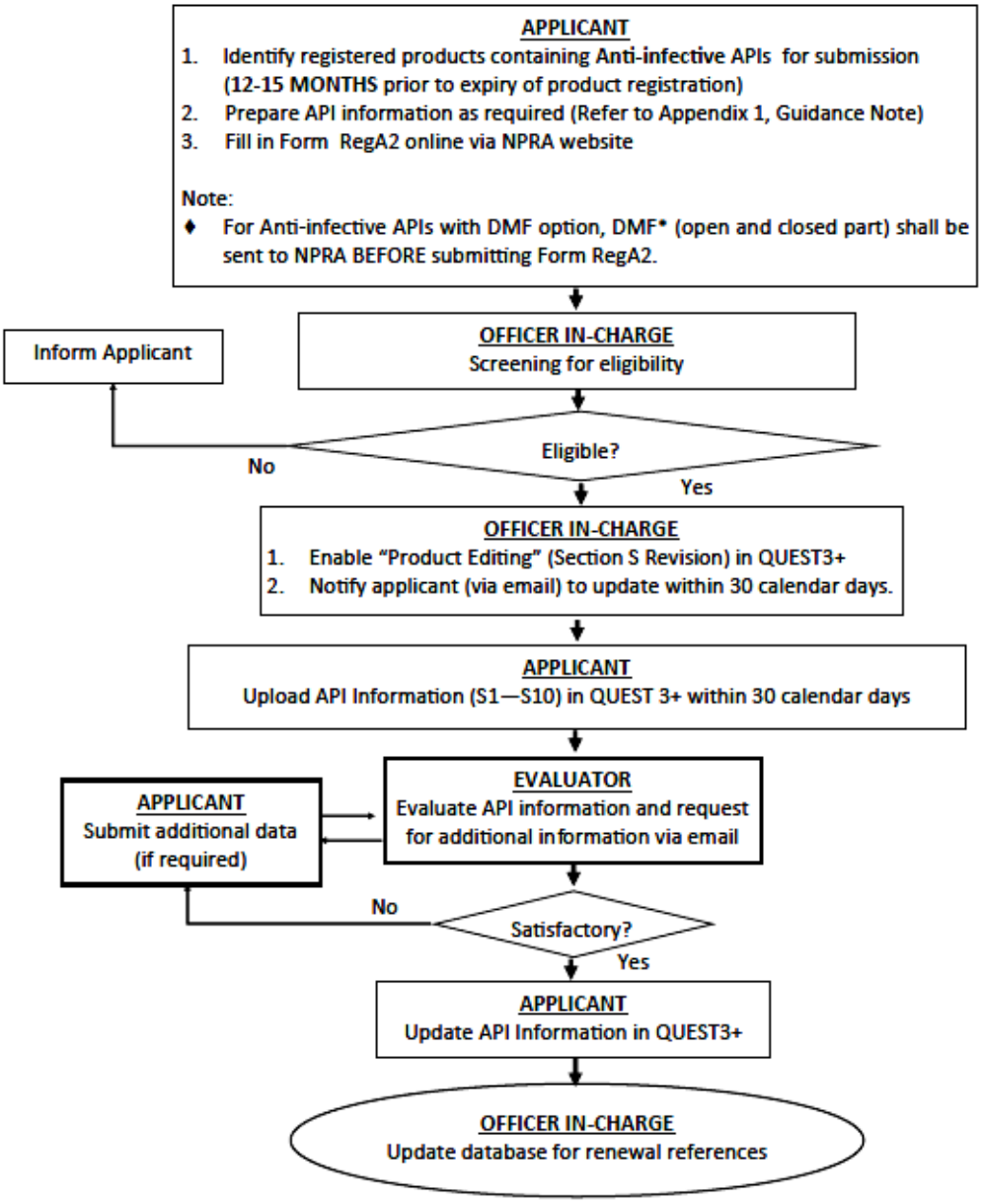
[Effective 2 Dec 2019]



Note:

1. Please Refer to Appendix 6: Guideline on Regulatory Control of API, from website www.npra.moh.gov.my (Guidelines Central→Active Pharmaceutical Ingredients (API))
2. Template of Cover Letter is available on NPRA website

ADMINISTRATIVE PROCEDURE FOR REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENT (API) IN REGISTERED PRODUCT CONTAINING ANTI INFECTIVE API



Footnote:

1. *CD copy of DMF (open and closed part) with a Letter of Access and Cover Letter should be sent to: *Head of New Drug Product Section/ *Head of Generic Medicines Section (*refer to product category)
2. **For registered products not containing anti-infective APIs, part II S information shall be kept by the PRH. It is not necessary to upload to Quest 3+ system.**

LIST OF ATYPICAL ACTIVE PHARMACEUTICAL INGREDIENT (API)

Examples of Atypical API:

No.	Substance Name
1	Aluminum Hydroxide
2	Ammonium Chloride
3	Ascorbic Acid
4	Calcium carbonate
5	Calcium chloride
6	Glucose / Dextrose
7	Glycerol / Glycerin
8	Glycine
9	L-Alanine
10	L-Alanyl-L-Glutamine
11	L-Arginine
12	L-Aspartic Acid
13	L-Cysteine
14	L-Glutamic Acid
15	L-Glutathione
16	L-Histidine
17	L-Isoleucine
18	L-Leucine
19	L-Lysine Acetate
20	L-Methionine
21	L-Phenylalanine
22	L-Proline
23	L-Serine
24	L-Threonine
25	L-Tyrosine
26	L-Valine
27	Magnesium Carbonate
28	Magnesium Chloride
29	Magnesium Hydroxide
30	Magnesium Oxide
31	Magnesium Sulphate
32	Medium Chain Triglyceride
33	Olive Oil
34	Potassium Chloride
35	Potassium Dihydrogen Phosphate
36	Potassium Phosphate
37	Sodium Acetate
38	Sodium Bicarbonate
39	Sodium Chloride
40	Sodium Glycerophosphate
41	Sodium Hydroxide
42	Sodium Lactate
43	Sodium Phosphate
44	Soybean Oil
45	Zinc Acetate
46	Zinc Carbonate

47	Zinc Chloride
48	Zinc Citrate
49	Zinc Gluconate
50	Zinc Oxide
51	Zinc Sulfate

Note: This list is not meant to be exhaustive and will be reviewed from time to time.

Appendix 5

SUMMARY OF REQUIRED DOCUMENTS FOR ATYPICAL ACTIVE PHARMACEUTICAL INGREDIENT (API) INFORMATION

Section S / Field		Mandatory (✓)	Remarks
S1.1	Nomenclature	✓	
S1.2	Structure formula	✓	
S1.3	General Properties	✓	
S2.1	API Manufacturer(s)	✓	
S2.1.1	Other API Manufacture(s) involved	✓ (if any)	
S2.1.2	Name of Synthesis Route	✓ (if any)	
S2.2	Description of Manufacturing Process and Process Controls	✓ (Brief description)	Brief description for: - Manufacturing process - Materials
S.2.2.1	Manufacturing Process Flowchart	✓	
S2.3	Control of Materials	Non-Mandatory	Should statement 'refer to restricted part' is given, information will be requested
S.2.3.1a	TSE Risk Free Statement	✓	
S2.4	Controls of Critical Steps and Intermediates	Non-Mandatory	
S2.5	Process validation and/or evaluation	Non-Mandatory	
S2.6	Manufacturing Process Development	Non-Mandatory	
S3.1	Elucidation of Structure and other Characteristics	Non-Mandatory	
S3.2	Impurities	Non-Mandatory	
S.4.1	API Specification from: i) API Manufacturer **and** ii) Finished Product Manufacturer	✓	
S4.2	Analytical Procedures	Non-Mandatory	
S4.3	Validation of Analytical Procedures	Non-Mandatory	
S4.4	Batch Analysis	Non-Mandatory	
S.4.4.1	Certificates of Analysis (COA) (2 batches each) from: i) API Manufacturer **and** ii) Finished Product Manufacturer	✓	
S.4.5	Justification of Specification from: i) API Manufacturer **and** ii) Finished Product Manufacturer	✓	
S5	Reference Standards or Materials from: i) API Manufacturer **and** ii) Finished Product Manufacturer	✓	If not available, please provide justification
S.6	Container Closure System (CCS)	✓	Description only
S7	Stability	Non-Mandatory	
S9	GMP Certificate	GMP Certificate Or Declaration on Quality Management System by Competent Person	Refer to template *Declaration on Quality of AAPI_V1* provided on NPRA Website
S10	Other information	✓	Additional information if deemed necessary