GUIDANCE NOTES

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

CENTRE FOR PRODUCT REGISTRATION
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 screening process.

General Points

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:
   a. A finished product contains more than one API
   b. An API is manufactured from more than one manufacturing site
   c. 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) A change of submission option is NOT allowed once screening approval is obtained.

7) 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.

8) Please also refer to subsidiary guidance documents available at NPRA's website, http://npra.moh.gov.my/:

   QUEST3+ API Administrative Procedure

   Important Note: Once screening approval is obtained, applicants are required to submit API information (in electronic copy) to API Section, Centre of Product Registration (PPP) and Laboratory Services Section, Centre of Quality Control (PKK) within 5 working days from the approved payment date.
   Refer to template letter in NPRA's website:
   - Template Letter for API Submission to PPP
   - Template Letter for API Submission to PKK

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. The new submission 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 subsidiary guidance documents available at NPRA's website for 'Declaration Letter for An Approved API in New Product Registration Application'.

Good Manufacturing Practice Evidence for Manufacturers Involved

1) This section outlines the level of 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 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 evidence accepted are:

    a) GMP Certificate or GMP Inspection Report issued by:

        i. PIC/S Participating Authorities or;
        ii. Drug Regulatory Authority or;
        iii. World Health Organization or;

    b) Self-declaration from competent person from Finished Pharmaceutical Product (FPP) Manufacturer whereby the supplier of atypical API is an approved supplier according to the FPP manufacturer's quality system.

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

Appendix 1

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

NO.	SECTIONS/ FIELDS	CONTENTS	MANDATORY INFORMATION (✓)		
			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, odour, taste, Physical form (powder, amorphous, crystalline, liquid, etc) ii) Solubility: - Solubility in the water, 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 (main manufacturer[1] involved in synthesis steps). - Attach GMP certificate in S9	✓	✓	✓
	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	i) Detailed Description of the Synthesis (step & process) from	✓	✓	

	Manufacturing Process and Process Controls	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	✓	✓	
	S2.5 Process validation and/or evaluation	Applicable to sterile API only	✓	✓	**YES**, If CEP did not specify a sterile 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) Pharmacopoeial API: - Comparison of spectral data between pharmacopoeial reference standard & API (If comparison is not available, assess as per non-pharmacopoeial API). ii) Non pharmacopoeial 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). - Il 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 ii) Justification on range of acceptance criteria set for in-house tests	✓	✓	✓ (For non-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) directly to Head of API Section, Centre of Product Registration, 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.			
	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