

**ACTIVE PHARMACEUTICAL INGREDIENT (API) SUBMISSION CHECKLIST
FOR UPDATING PART II S INFORMATION FOR PRODUCT REGISTERED
BEFORE THE IMPLEMENTATION OF DIRECTIVE ON REGULATORY CONTROL OF API**

Name of Product:	
MAL Number:	
Name of API:	
API Manufacturer:	

NO.	SECTIONS/ FIELDS	CONTENTS	MANDATORY INFORMATION (✓)			PRH (Please cross ☒)
			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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Certificate of Suitability	A copy of the most current CEP including all annexes			✓	<input type="checkbox"/>
		CEP number			✓	<input type="checkbox"/>
		Date of issue			✓	<input type="checkbox"/>
		Date of expiry (By default: 5 years from date of issue)			✓	<input type="checkbox"/>
		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			✓	<input type="checkbox"/>
3.	Quality Overall Summary (QOS)	i) Overall Summary ii) Table of Contents iii) Body of Data	✓	✓	✓	<input type="checkbox"/>
4.	S1. General information					
	S1.1 Nomenclature	International non-proprietary names/ INN: Chemical names: Synonyms: CAS No: Chemical Abstracts Service	✓	✓	✓	<input type="checkbox"/>
	S1.2 Structure formula	Structural formula (relative and absolute chemistry) Molecular formula Molecular weight Molecular weight (base)	✓	✓	✓	<input type="checkbox"/>
	S1.3 General Properties	Physico-chemical properties: (when applicable) i) Colour, Physical form (powder, amorphous, crystalline, liquid, etc) ii) Solubility: - Solubility in the <u>water</u> , acid, alkali, common solvent 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	<input type="checkbox"/>

5 S2. Manufacture					
S2.1 API Manufacture(s)	Name and address of manufacturer that produced the API (main manufacturer involved in synthesis steps). - Attach GMP certificate in S9	✓	✓	✓	<input type="checkbox"/>
S2.1.1 Other API Manufacture(s) involved	Manufacturers involved in each production steps, including intermediate manufacturer, micronization and milling. * GMP Compliance evidence is required for all manufacturer involved in API manufacturing process, including intermediate manufacturing, micronization and milling sites.	✓	✓	✓	<input type="checkbox"/>
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").	✓	✓	✓	<input type="checkbox"/>
S2.2 Description of Manufacturing Process and Process Controls	<ul style="list-style-type: none"> 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 	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY		<input type="checkbox"/>
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.	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY		<input type="checkbox"/>
S2.3 Control of Materials	<ul style="list-style-type: none"> 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. 	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY		<input type="checkbox"/>
S.2.3.1a TSE Risk Free Statement	<ul style="list-style-type: none"> 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 	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY		<input type="checkbox"/>

	S2.4 Controls of Critical Steps and Intermediates	<p>Controls of Critical Steps</p> <ul style="list-style-type: none"> - critical steps & process control including tests and acceptance criteria (with justification including experimental data). <p>Controls of Intermediates</p> <ul style="list-style-type: none"> - List of Intermediates, specification, analytical procedure 	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY		<input type="checkbox"/>	
	S2.5 Process validation and/or evaluation	Applicable to sterile API only	Required for Sterile anti-infective APIs ONLY	Required for Sterile anti-infective APIs ONLY	Required If CEP did not specify a sterile API	<input type="checkbox"/>	
	S2.6 Manufacturing Process Development	<p>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.</p> <p>ii) The development history of the manufacturing process as described in S 2.2</p> <p>iii) To state the date of changes.</p>	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY		<input type="checkbox"/>	
6	S3. Characterisation and Impurities						
	S3.1 Elucidation of Structure and other Characteristics	<p>i) Pharmacopoeial API:</p> <ul style="list-style-type: none"> - Comparison of spectral data between pharmacopoeial reference standard & API (If comparison is not available, assess as per non-pharmacopoeial API). <p>ii) Non pharmacopoeial API:</p> <ul style="list-style-type: none"> - Elemental analysis - Infrared Spectrophotometry (IR) - Ultraviolet absorption spectrum (UV) - Mass Spectrometry - Nuclear Magnetic Resonance Spectrometry (NMR); ¹H-NMR, ¹³C-NMR - X-ray Diffraction - Differential Scanning Calorimetry (DSC) - Thermogravimetric analysis (TGA) - Others <p>iii) Polymorphism</p> <ul style="list-style-type: none"> - 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 <p>iv) Particle size distribution</p> <p>v) Isomerism</p>	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	<input type="checkbox"/>	
	S3.2 Impurities	<p>Organic Impurities, Inorganic Impurities, Residual solvents, Genotoxic Impurities</p> <ul style="list-style-type: none"> - Possible carryover of impurities (during the synthesis and from the preparation of starting material and intermediates to the final API). - 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 impurities content are equal or more than limit in the specification) should be provided. - discussion on impurities that stated in another pharmacopeia (if applicable) 	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY		<input type="checkbox"/>	

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).	✓	✓	✓	<input type="checkbox"/>
	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	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY		<input type="checkbox"/>
	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				<input type="checkbox"/>
	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.)	✓	✓	✓	<input type="checkbox"/>
	S.4.4.1 Certificates of Analysis(COA)	i) From API Manufacturer (2 Batches) ii) From Product Manufacturer (2 Batches)	✓	✓	✓	<input type="checkbox"/>
	S.4.5 Justification of Specification	<u>From API Manufacturer</u> i) Discussion on inclusion/ omission of tests and analytical procedures ii) Justification on range of acceptance criteria set for in-house tests	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	<input type="checkbox"/>
		<u>From Product Manufacturer</u> i) Discussion on inclusion/ omission of tests and analytical procedures ii) Justification on range of acceptance criteria set for in-house tests	✓	✓	✓	<input type="checkbox"/>
8	S5. Reference Standards or Materials					
	From <u>API Manufacturer</u>	i) Clearly stating: - Official 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	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	<input type="checkbox"/>
From <u>Product Manufacturer</u>	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	✓	✓	✓	<input type="checkbox"/>	

9	S6.Container Closure System					
	S.6 Container Closure System (CCS)	<ul style="list-style-type: none"> 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, Compatibility (e.g: Sorption or leeching) 	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	<input type="checkbox"/>
10	S7. Stability					
	Re-test Period or shelf life	Select (months) the proposed retest period based on stability study conclusion.	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	Required for anti-infective APIs ONLY	<input type="checkbox"/>
	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").				<input type="checkbox"/>
	Stability Data	<ul style="list-style-type: none"> i) Stress Testing Study <ul style="list-style-type: none"> - API batch details (eg: moisture, light, acidic, basic, oxidative and thermal stress conditions). ii) Long Term Stability Data <ul style="list-style-type: none"> - Minimum of 3 batches, (with recent results) - Batch information (manufacturing date, site, batch size, - Temperature/RH/Packaging iii) Accelerated Stability Data <ul style="list-style-type: none"> - 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 				<input type="checkbox"/>
<input type="checkbox"/>						
11	S8.Drug Master File(DMF)					
	General Note	<ul style="list-style-type: none"> i) The API manufacturer may submit the DMF (both open part & closed part) via electronic copy (CD) directly to NPRA. The DMF (CD copy) shall accompany with a Cover Letter & Letter of Access to: <ul style="list-style-type: none"> **Head of New Drug Product Section/ **Head of Generic Medicine Section*, Centre Of Product Evaluation and Cosmetic, National Pharmaceutical Regulatory Agency Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor, Malaysia. ii) The DMF should reach NPRA before closure of "Product Editing Field". <p>* Please refer to template of Cover Letter available on NPRA website ** refer to product category</p>				<input type="checkbox"/>
	DMF Version No.	Current DMF version number with effective date				<input type="checkbox"/>
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: <ul style="list-style-type: none"> - 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. 	<input type="checkbox"/>				

	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				<input type="checkbox"/>
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	✓	✓		<input type="checkbox"/>
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	✓	✓	✓	<input type="checkbox"/>

* For **non-anti-infective** APIs, NPRA reserves the right to conduct assessment on the submitted Part II S documents and request for additional information (if 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