APPENDIX 3A *APPLICATION CHECKLIST (ASEAN CTD – NDA and GDA)*

This Application Checklist should be used to ensure submission of a complete dataset in the ASEAN Common Technical Dossier (ACTD) format for NDA and GDA applications only.

All documents required under Part I must be submitted in softcopy in PRISM.

Colour scanned copies of the original documents should be submitted and original hard copies of documents are not required.

However, HSA reserves the rights to request for the original or certified true copy of submitted documents if there is any doubt that a submitted scanned document is not an accurate reflection of the original document.

The acceptance of the application after screening does not preclude requests by HSA for additional documents or changes to the information/documents during evaluation.

This Checklist should be completed by checking each item against the dossier according to the application type relevant for your submission.

The Application Checklist should be submitted in MS WORD format.

**Note**:

* Cells with  indicate that the documents are mandatory for the selected application type and evaluation route.
* Cells with \* indicate that the documents may be optional depending on the application type/product/change.
* Cells without  indicate that the documents are not required for the selected application type and evaluation route.
* If a mandatory document is not included in the submission (i.e. applicant is unable to select any of the cells with  for a particular document), justifications for the omission must be provided in the cover letter.

Please refer to the *Guidance on Therapeutic Product Registration in Singapore* and the ASEAN Guidance on ACTD for explanatory notes on the preparation ofdocuments for a submission in ACTD format.

Legend:

|  |  |  |
| --- | --- | --- |
| Application type | NDA | New Drug Application |
| GDA | Generic Drug Application |
| Evaluation route | F | Full Dossier |
| A | Abridged Dossier |
| V | Verification Dossier   * Includes Verification CECA Dossier for GDA |

**REVISION HISTORY**

Form Version (Publish Date)

TPB-SUB-005-007 (Version 7; Updated 29 September 2023)

Part I – PRISM Application Form and Administrative Documentation

| Section | Documents | | | Application Type & Evaluation Route | | | | | HSA Screening | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NDA** | | | **GDA** | |
| F | A | V | A | V | Submitted? | Remarks |
| 1.0 | **PRISM Application Form** | | |  |  |  |  |  |  |  |
|  | 1.0.1 | Section 1: Company Particulars | |  |  |  |  |  |  |  |
|  |  | * The Company is based and registered in Singapore. | |
|  | 1.0.2 | Section 2: Applicant Particulars | |  |  |  |  |  |  |  |
|  |  | * The applicant of a product registration refers to the local company that is applying for the product registration. The applicant company may authorise officers, permanent employees, or designated external parties, all of whom are referred to as the “applicant representative”, to submit the application for product registration in Singapore. * The NRIC/FIN of the applicant representative entered must be the same as that used to access the PRISM application. * Note: Section 2.4.5 of the PRISM application form does not support the entry of multiple email addresses. | |
|  |  |
|  | 1.0.3 | Section 3: Application Details | |  |  |  |  |  |  |  |
|  |  | * A separate product registration, and therefore a separate application, is required for each pharmaceutical dosage form, strength, and presentation of the therapeutic product, for example: * Powders for solution for injection containing different amounts of drug substance per container; * Solution for injection presented in vials/ampoules versus single-use pre-filled syringe; * Solution for injection presented with different labelled strengths in the product names; * Concentrates labelled with the total amount of drug substance in the container closure system; and * All single-use pre-filled syringes containing different amounts of drug substance in each syringe. | |  |  |  |  |  |  |  |
|  |
|  |  | 3.1 | Type of Application |  |  |  |  |  |  |  |
|  | 3.2 | Type of Product |  |  |  |  |  |  |  |
|  | 3.3 | Reference Product | **\*** | **\*** | **\*** |  |  |  |  |
|  |  | * All GDA applications – the Singapore reference product’s SIN number must be specified. |  |  |
|  |  |  | * If a GDA-2 application is not submitted at the same time as the related GDA-1 application, both the Singapore reference product’s and the GDA-1 product’s SIN numbers should be specified. |  |  |
|  |  |  | * \*: For NDA-3 applications not submitted at the same time as the NDA-1/2 application – the NDA-1/2’s SIN number should be specified. |  |  |
|  | 3.4 | Product Intended for Export (non-mandatory field) – to either leave blank or indicate as “No” |  |  |  |  |  |  |  |
|  | 3.5 | Type of Dossier |  |  |  |  |  |  |  |
|  | 3.6 | Type of Format |  |  |  |  |  |  |  |
|  | * The dossier format selected must be the same as that of the actual submitted dossier. |
|  | * **Note:** Once the format type has been set in PRISM, it cannot be changed throughout the entire life cycle of the product. |
|  | 1.0.4 | Section 4: Product Information | |  |  |  |  |  |  |  |
|  |  | 4.1 | Product Name |  |  |  |  |  |  |  |
|  |  |  | * Refer to Guidance document, Appendix 17, Section 1.1.4 for details. |  |  |
|  |  |  | * The product name is entered in the following format:   Product Name - Dosage Form – Product Strength |  |  |
|  |  |  | * The strength of the active ingredient (drug substance) is included as part of the product name to allow differentiation between different strengths of the products |  |  |
|  |  |  | * For products that are for single-use (e.g. pre-flled syringes) or presented as powder for solution for injection, the strength of the product reflected in the product name should be in “xx mg/CCS” and not “per ml”. |  |  |
|  |  |  | * The pharmaceutical dosage form should be as specific as possible with respect to the product’s actual dosage form (e.g. “Film-coated Tablet” instead of “Tablet”). |  |  |
|  |  |  | * Proposed product names comprising of the international non-proprietary name (INN) includes a differentiator (e.g. name of the product owner) to allow better product differentiation from currently registered products. |  |  |
|  |  |  | * The product names of generic products should generally follow the naming format of the relevant innovator product, unless it can be justified that the different naming format does not result in confusion and there is minimal risk for medication errors. |  |  |
| 4.2 | Product Formula |  |  |  |  |  |  |  |
|  |  | * Refer to Guidance document, Appendix 17, Section 1.1.4 for details. |  |  |
|  |  |  | * The full composition of the drug product, i.e. a listing of all active ingredient and excipients (including water) that are present in the final pharmaceutical dosage form is stated. |  |  |
|  |  | * For products that are for single-use (e.g. pre-filled syringes) or presented as powder for solution for injection, the amount of active ingredient and excipient in the product is reflected as “xx mg/CCS” and not “per ml”. |  |  |
|  |  | * The quantities of active ingredients presenting in the form of salts and chelates should be clearly stated, , e.g. ABC phosphate eqv ABC |  |  |
|  |  | * The functions of the excipients should be differentiated in the product formula using parentheses before the ingredient name, e.g. (Film coating) Ingredient Z. |  |  |
|  |  | * The full compositions of all proprietary ingredients (e.g. colourants, flavouring agents, etc.) used in the product is stated in the Product Formula, and their uses differentiated as stated in the following sections. |  |  |
|  |  |  | * Information on residual amounts of certain materials, such as antibiotics, thiomersal and materials of biological origin (e.g. human serum albumin), added or present in the product must be declared. |  |  |
|  |  | 4.3 | Ingredients Derived From Human Blood or Animal Sources | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | \*: Only applicable for products containing ingredient(s) derived from human blood or animal sources. |  |  |
|  |  | * The information should be provided in the following format: (Species & product) – (In manufacturing/drug substance/excipient) – (Country) |  |  |
|  |  | * The TSE checklist (Annex 1 of Appendix 19) should be submitted if applicable. |  |  |
|  |  | 4.4 | Pharmacotherapeutic Group (ATC Code) |  |  |  |  |  |  |  |
|  |  |  | * The WHO ATC code should be provided for each distinct therapeutic indication proposed for a product, if available. |  |  |
|  | * If the WHO ATC code is not available at the time of the application submission, **“Pending”** should be stated in this field. |  |  |
|  |  |  | * There is no spacing in-between the characters entered. |  |  |
|  |  | 4.5 | Dosage Form |  |  |  |  |  |  |  |
|  |  | * The dosage form is as specific as possible as each form is distinctly identified, e.g. “Tablet, Film-coated, Extended Release” instead of “Tablet”. |  |  |
|  |  | * In certain cases, the dosage form may also include information about the container closure system, e.g. pre-filled syringe, spray pump and pressurised container. |  |  |
|  |  | * If the physical form supplied is different from that which is to be administered to/used by the patient, i.e., if transformation of the product is required before it can administered/used, both forms need to be conveyed within the term. |  |  |
|  |  | 4.6 | Route of Administration |  |  |  |  |  |  |  |
|  |  |  | * All routes of administration proposed for the product is included. |
|  |  | 4.7 | Packaging, Shelf Life & Storage Condition |  |  |  |  |  |  |  |
|  |  |  | * The description of the container closure system (CCS) includes the capacity and type of glass used in injectable vials, ampoule. |  |  |  |  |  |  |  |
|  |  |  | * All proposed pack sizes for the application are included (should match against the proposed outer cartons) |  |  |  |  |  |  |  |
|  |  |  | * The “Pack Size” refers to the quantity of container closure systems in each commercial pack of the product (e.g., for a commercial box of 50 tablets packed as 5 blister strips of 10 tablets in each strip, the pack size is 5 blister strips). |  |  |  |  |  |  |  |
| * If a medical device (e.g. vial adaptor, syringe and needle) is packed together with the drug product, information of the medical device and its description is included as a single entry with the drug product or diluent. |  |  |  |  |  |  |  |
|  |  |  | * If there is more than one component in a drug product (e.g. powder for injection and diluent as a composite pack) and each component has a different shelf life, the shorter shelf life is used as the shelf life of the composite pack. |  |  |  |  |  |  |  |
|  |  | 4.8 | Forensic Classification |  |  |  |  |  |  |  |
|  |  | * Refer to Guidance document, Section 1.2 for details. |
|  |  | 4.9 | Registration Status in Other Countries |  |  |  |  |  |  |  |
|  |  | * For each country, state the application status, status date and forensic classification (if applicable). |  |  |
|  |  | * For all of HSA’s reference agencies, state the application status, status date, application details and forensic classification. |  |  |
|  |  | * If an application is pending or not submitted to any of HSA’s reference agencies, state that the application is pending (including the submission and expected outcome dates), or not submitted (date not required). |  |  |
|  |  |  | * For products approved via an appeal process, following either a negative opinion/rejection/non-approvable decision or an approvable/conditional approvable decision, the reasons for the initial regulatory decision should be provided, along with the subsequent approval. |  |  |
| * For applications submitted to the European Union agencies, the type of authorisation procedure, i.e. centralised, decentralised, mutual recognition or national, should be identified; for decentralised and mutual recognition procedures, the reference member state should be indicated. |  |  |
|  |  |  | * For applications approved by the UK MHRA, indicate whether approval was granted through a national procedure or whether MHRA acted as RMS or CMS for the decentralised and mutual recognition procedures on or prior to 31 January 2020 when the UK has formally left the European Union. |  |  |
|  |  |  | * For approved indication(s) and dosing regimen(s) for an approved application, applicants can make reference to the approved PI of the reference agency instead of typing out the information under Application Details (e.g. “Refer to approved PI attached in PRISM 1.5.1 for indication and dosing regimen”). |  |  |
|  |  | 4.10 | Product Owner Information |  |  |  |  |  |  |  |
|  | * Input the full name and address of the legally registered owner of the product formulation, i.e. the drug product. |  |  |
|  | 1.0.5 | Section 5: Manufacturer’s Particulars | |  |  |  |  |  |  |  |
|  |  | * Particulars are to be provided for manufacturing sites for all active drug substance(s), drug product, drug product intermediate and diluent used to reconstitute drug product (if packed and sold together with drug product), and quality control testing sites for the drug product. * For drug product manufacturing and quality control testing sites, enter the full name and address of the manufacturer, and select the applicable manufacturing operation as listed below, to reflect the manufacturing activities performed at the site: * Bulk Production * Bulk Production (Solvent/Diluent) * Bulk Production (Drug Product Intermediate) * Primary Packaging * Secondary Packaging * Quality Control Testing * Bulk Production/Primary Packaging * Bulk Production/Secondary Packaging * Bulk Production/Primary Packaging/Secondary Packaging * Primary Packaging/Secondary Packaging | |  |  |  |  |  |  |  |
|  |  | * For local finished product manufacturer, enter the Manufacturer’s Licence No. instead of the GMP Certificate No. | |  |  |
|  | * All manufacturers’ names and addresses should be consistent throughout all the documents submitted in the application, such as GMP certificates, CPPs, Letters of authorisation and Part II of the CTD. | |  |  |
|  | 1.0.6 | Section 6: Information on Company Responsible for Batch Release | |  |  |  |  |  |  |  |
|  |  | * If there are multiple companies responsible for batch release, the applicant must declare all of the sites. | |  |  |
| * The finished product manufacturer(s) from which the batch releaser is releasing the product must be specified. | |  |  |
|  | 1.0.7 | Supporting Attachments | |  |  |  |  |  |  |  |
|  |  | * All documents relating to Part I of the CTD must be attached. | |  |  |
|  |  | * The risk management plan must be attached (for NDA-1 and biosimilar product applications only). | |  |  |
|  |  | * Other Parts of the CTD should either be attached in full in this PRISM section or submitted as soft copies in a CD/DVD. | |  |  |
|  |  | | |  |  |  |  |  |  |  |

| Section | Documents | | | Application Type & Evaluation Route | | | | | HSA Screening | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NDA** | | | **GDA** | |
| F | A | V | A | V | Submitted? | Remarks |
|  | **Important Note:** All documents submitted in support of an application to HSA must be in English. For documents in their original language which is not English, a certified translation or a verified translation may be acceptable. Please refer to Guidance document, Section 6.2.2 (Language and Translation) for more information. | | | | | | | | | |
|  | **Administrative Documentation** | | | | | | | | | |
| 1.1 | Cover Letter | | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  | * The cover letter should state the product name and the number of CD/DVDs submitted in the application dossier. * A concise and precise summary of the application should be provided. * Applicants should ensure that the application dossier is complete. * The omission of any documents within the dossier or any deviation from the guidelines must be appropriately justified. * Request for priority review should be stated with the justification document appended. | | |
| 1.2 | Comprehensive Table of Contents | | |  |  |  |  |  |  |  |
|  | * A complete list of all documents, organised by Part, should be provided in the application dossier. | | |
|  | * The location of each document should be identified by the Part number. | | |
| 1.3 | Introduction *(refer to 1.1 Cover Letter)* | | |  |  |  |  |  |  |  |
| 1.4 | Labelling and PI/PIL **proposed** in Singapore. | | |  |  |  |  |  |  |  |
|  | * All proposed labels have to be submitted for registration in Singapore. | | |  |  |
|  | * The product name to be stated on the labels should be the same as that in PRISM | | |  |  |
|  | * One PI and/or PIL should be registered for each product application.   + Multiple PI/PILs per product application (e.g. for multiple manufacturing sites) should be avoided.   + If there are different strengths or dosage forms, applicants are encouraged to submit one common PI/PIL for all strengths or dosage forms.   + If separate PI/PILs are to be registered for different strengths or dosage forms, the content should be consistent across the PI/PILs, except for strength/dosage form-specific information. | | |  |  |
|  | * Labelling must be in English. Any non-English country-specific labelling requirements on the artwork/drafts should be highlighted if the labelling is shared with other countries. | | |  |  |
|  | * \*: If non-English text is included in the labelling, applicants must provide an official statement to declare that the non-English text is complete, accurate and unbiased information and is consistent with the English text. | | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  | 1.4.1 | Outer Carton Labels   * The draft artwork of the outer carton labels should be in the actual format, design and colour that are to be printed. * Separate labels must be submitted for each pack size of the product. | |  |  |  |  |  |  |  |
|  | 1.4.2 | Inner/Blister Labels   * The draft artwork of the inner/blister labels should be in the actual format, design and colour that are to be printed * Separate labels must be submitted for each pack size of the product. | |  |  |  |  |  |  |  |
|  | 1.4.3 | Package Insert (PI)   * A PI is required for TPs registered with a Prescription Only Medicines (POM) forensic classification. | |  |  |  |  |  |  |  |
|  | 1.4.4 | Patient Information Leaflet (PIL)   * A PIL is required for TPs registered with a Pharmacy Only (P) or General Sale List (GSL) forensic classification. * The PIL should be written in a language easily understood by consumers/patients. | |  |  |  |  |  |  |  |
| 1.5 | Approved SmPC/PI/PIL | | |  |  |  |  |  |  |  |
|  | 1.5.1 | SmPC/PI/PIL approved by HSA’s reference regulatory agencies | |  |  |  |  |  |  |  |
|  |  | * The approved SmPC/PI/PIL currently approved by each of HSA’s reference agencies should be submitted, where applicable. | |
|  | * The submitted SmPC, PI and/or PIL should state the country that the document originated from. | |  |  |
| 1.5.2 | SmPC/PI/PIL approved by Country of Origin/Country of Manufacture | |  | **\*** | **\*** | **\*** | **\*** |  |  |
| 1.5.3 | PI / SmPC / PIL approved by other regulatory agency | |  |  |  |  | **\*** |  |  |
|  |  | * The approved SmPC / PI / PIL from the drug regulatory agency that issued the proof of approval, should be submitted if it is not from the Country of Origin. | |  |  |
|  |  | * The submitted SPC, PI and/or PIL should state the country that the document originated from. | |  |  |
|  | 1.5.4 | If applicable, a declaration that the translation of the SmPC/PI/PIL conforms to the SmPC/PI/PIL currently approved should be submitted. | |  | **\*** | **\*** | **\*** | **\*** |  |  |
| 1.6 | Assessment report issued by HSA’s reference regulatory agency: | | (Please specify) |  |  |  |  |  |  |  |
| * The submitted Assessment reports and supporting documents must be unredacted and unedited. Refer to Guidance document, Section 15.6.3 or 18.5.2 for details. | | |  |  |
| 1.7 | Description of batch numbering system | | |  |  |  |  |  |  |  |
| 1.8 | Proof of Approval from:  Competent Drug Regulatory Agency  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | | |  |  |  | **\*** |  |  |  |
| * The proof of approval must come in the form of a Certificate of Pharmaceutical Product (CPP) that is valid at the time of submission, or an official approval letter that certifies the product’s registration status in the country at the point of submission to HSA; and * the SPC, PI and/or PIL approved by the drug regulatory agency that issued the proof of approval. | | |  |  |
| * CPPs that indicate that the product is not licensed in the exporting country (including the scenario where the product is licensed “solely for export only”) are not acceptable proof of approval. | | |  |  |
| * The approval letter should be a colour scanned copy of either the original copy or a certified true copy of the original document (certified by the drug agency that issued the approval letter) and in English. | | |  |  |
| * Reference to drug regulatory authority websites in the form of website screenshots and URLs (for the website) as proof of the approval status of the products by that regulatory authority are acceptable, provided that the product’s identity and product’s ownership can be confirmed from the websites. | | |  |  |
| * All aspects of the product’s quality and intended direction(s) for use in Singapore should be the same as those approved by the drug regulatory agency that issued the approval letter. | | |  |  |
| * If the brand name (trade name) of the product registered in the country which issued the proof of approval is different from that proposed in Singapore, a declaration letter from the product owner should be submitted, declaring that both products marketed under the different brand names are identical in all aspects of quality, safety and efficacy except for the brand name. | | |  |  |
| * The following are **not** acceptable as Proof of Approval:   + WHO Prequalified Products Listing   + Free Sale Certificates   + Statements of Licensing Status of Pharmaceutical Product   + EU Decentralised/MRP procedure outcome letters/documents | | |  |  |
| * Proof of approval must be accompanied by the PI/PIL as approved in the country that issued the proof of approval. | | |  |  |
| \*: Proof of approval is not required for GDAs for finished products manufactured (up to primary packaging) in Singapore undergoing abridged evaluation. | | |  |  |
| 1.9 | Proof of Approval from HSA’s reference regulatory agencies  (NDA: 2 reference regulatory agencies; GDA: 1 reference regulatory agency)  Please specify the issuing agencies: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | | |  |  |  |  |  |  |  |
| * For a verification evaluation of an NDA, proof of approval from at least two (or at least one or two for NDA-3, depending on the eligibility criteria stated in section 14.3.1) of HSA’s reference drug regulatory agencies, including the chosen primary reference agency, is required. Proof of approval must come in the form of:   + an official approval letter, or equivalent document (e.g. Certificate of Pharmaceutical Product; CPP), which certifies the registration status of the drug product; and   + the SPC, PI and/or PIL approved by the drug regulatory agency that issued the approval letter. | | |  |  |
| * The validity period of the approval from the chosen (primary) reference agency for the verification route is not more than 3 years for NDA and 2 years for GDA. | | |  |  |
| 1.10 | Authorisation Letters | | |  |  |  |  |  |  |  |
|  | * All scanned copies of the authorisation letters shall be on the authorising company’s (i.e. Product Owner’s) letterhead, dated and signed by the designated authorised person in the company. | | |  |  |
|  | * The company names and addresses, and product name stated in the letters should be consistent with the information provided in the PRISM application form and dossier. | | |  |  |
|  | 1.10.1 | Authorisation Letter from Product Owner to the Applicant company | |  |  |  |  |  |  |  |
|  |  | * This letter authorises the local applicant company to apply for and be the Product Registrant for a specific product and be responsible for all matters pertaining to the registration of this product in Singapore. | |
|  | 1.10.2 | Authorisation Letter from Product Owner to the Manufacturer(s) | |  |  |  |  |  |  |  |
|  |  | * This letter authorises the specified manufacturer to produce, pack and/or label the **drug product** intended for Singapore. | |  |  |
|  |  | * If there are multiple drug product manufacturers, the applicant may opt to submit one authorisation letter which clearly states all of the manufacturers (names and addresses) and their responsibilities related to the product. | |  |  |
|  |  | * For biologic drug products, an additional authorisation letter from the Product Owner to the Drug Substance Manufacturer is required. | |  |  |
| 1.10.3 | Authorisation Letter from Product Owner to the Batch Releaser | |  |  |  |  |  |  |  |
|  |  | * This letter authorises the specified company to test and batch release the product. | |  |  |
|  | * If there are multiple sites responsible for the batch release of the product, then the applicant may opt to submit one authorisation letter which clearly states all of the batch releasers (names and addresses) and their responsibilities. | |  |  |
|  | 1.10.4 | Authorisation Letter from Product Registrant to Secondary Packager located in Singapore | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | * This letter authorises the specified company to pack and/or label the product. | |
| 1.11 | GMP certification/proof of GMP compliance for each finished product manufacturer performing bulk production (including solvent/diluent and drug product intermediate), primary and secondary packaging activities, and batch releaser. | | |  |  |  |  |  |  |  |
|  | * A colour scanned copy of the original or certified true copy of GMP certification or an equivalent document issued by the relevant drug regulatory agency should be submitted, certifying that the manufacturer concerned complies with current applicable GMP standards. | | |  |  |
|  | * Examples of Acceptable Proof of GMP Compliance (other than GMP Certificate): * EU:   + Screenshots of EUDRA GMP Database website   + Certificate printed from EUDRA GMP website which includes the EUDRA GMP watermark * US/FDA:   + EIR report **(Complete set)**   + Covering letter (stating the status of the audit) * Health Canada:   + Drug Establishment Licences (DEL) **AND**   + Inspection Exit Notice * SwissMedic:   + For manufacturers located in Switzerland, a Manufacturer’s Licence issued by SwissMedic is an acceptable documentary GMP evidence. | | |  |  |
|  | * Certain accreditation documents/certificates issued by other drug regulatory agencies (for example, Japan/PMDA Accreditation Certificate of Foreign Drug Manufacturer), the US/FDA Establishment Licence and the Canada/Health Canada Establishment Licence are **not** acceptable proof of GMP compliance. | | |  |  |
|  | * Validity period of Proof of GMP Compliance: * The submitted Proof of GMP compliance must be valid at the time of submission to HSA.   + If the validity period/expiry date is not stated on the GMP Certificate, HSA will consider the certificate valid for a period of 3 years from the date of the last inspection or from the date of issuance of the certificate. | | |  |  |
|  | * The names and addresses of manufacturer(s) and batch releaser(s) should be consistent with the information provided in the Proof of GMP Compliance submitted, the PRISM application form and CTD sections S2.1 and P3.1. | | |  |  |
|  | * Diluents used for reconstituting the therapeutic product which are packaged together with the therapeutic product will be considered as part of the final therapeutic product. Manufacturer(s) of the supplied diluent(s) will follow the same requirements applicable to the therapeutic product, e.g. proof of GMP compliance. | | |  |  |
|  | * For **biologic** products: Evidence of GMP compliance for each drug substance manufacturer must be provided.   Acceptable GMP evidence for DS manufacturers:   1. A **valid GMP certificate** issued by any PIC/S authority. For PIC/S authorities which do not issue GMP certificates, either the **GMP inspection report** together with the **close-out letter** where applicable, or other evidence from the authority such as the manufacturing licence to demonstrate that the site complies with PIC/S GMP requirements can be submitted.   The GMP evidence provided must cover the DS of interest. Examples of such evidence include:   * A GMP certificate with the DS of interest stated * A GMP inspection report or manufacturing licence with the DS of interest included in the scope * A Written Confirmation for the DS of interest from the PIC/S authority which issued the GMP certificate * GMP evidence specifying the category of DS (e.g., recombinant DNA derived protein) or describing the manufacturing operations specific to the category of DS (e.g., fractionation and purification of plasma-derived products, virus inactivation of vaccines)  1. A valid **Active Pharmaceutical Ingredient (API) Registration Certificate** covering the DS of interest listed on EUDRAGMP. | | |  |  |  |  |  |  |  |
|  | * For **chemical** products: Evidence of GMP compliance for each drug substance manufacturer is to be provided, i**f available**. This is optional until the official implementation of the requirement on 1 Oct 2024.   Acceptable GMP evidence for DS manufacturers:   1. A **valid GMP certificate** issued by any PIC/S authority. For PIC/S authorities which do not issue GMP certificates, either the **GMP inspection report** together with the **close-out letter** where applicable, or other evidence from the authority such as the manufacturing licence to demonstrate that the site complies with PIC/S GMP requirements can be submitted.   The GMP evidence provided must cover the DS of interest. Examples of such evidence include:   * A GMP certificate with the DS of interest stated * A GMP inspection report or manufacturing licence with the DS of interest included in the scope * A Written Confirmation for the DS of interest from the PIC/S authority which issued the GMP certificate  1. A valid **Active Pharmaceutical Ingredient (API) Registration Certificate** covering the DS of interest listed on EUDRAGMP. 2. A valid **Certificate of Suitability** to the monographs of the European Pharmacopoeia **(CEP)** for the DS of interest issued by EDQM. | | |  |  |  |  |  |  |  |
|  | * For drug product manufacturing sites that use parametric release, a GMP Conformity Assessment is required for overseas drug product manufacturers. Refer to Guidance document, Sections 15.1 (NDA) and 18.1 (GDA) for eligibility criteria and the relevant supporting documents | | |  |  |  |  |  |  |  |
|  | * For **GDA Verification CECA**: a GMP certificate/proof of GMP compliance and the latest inspection report issued by the chosen reference agency should be submitted. | | |  |  |  |  |  |  |  |
|  | * If applicable, either the Application for GMP Evidence Evaluation or the Application Form for Requesting An Overseas GMP Audit should be submitted for finished product manufacturing sites which are new to Singapore. | | |  |  |  |  |  |  |  |
| 1.12 | Patent Declaration Form | | |  |  |  |  |  |  |  |
|  | * A colour scanned copy of the signed and dated patent declaration form is required for each NDA and GDA. | | |  |  |
|  | * The information stated on the form must be same as that in the PRISM application form. | | |  |  |
|  | * Under “Declaration”, the patent declaration must be signed by the Company Director, Company Secretary as registered with ACRA, or equivalent. * Alternatively, submit a letter of authorisation (on original letterhead) signed by any of the above to authorise the specific person (such as company legal representative, regulatory affairs personnel) to make the declaration. | | |  |  |
|  | * Evidence of authorisation (e.g. ACRA printout from BizFile) should be submitted together with the declaration. | | |  |  |
| * Declaration forms must bear the signature of the authorised person. | | |  |  |  |  |  |  |  |
| 1.13 | Declaration on rejection, withdrawal and deferral | | |  |  |  |  |  |  |  |
| * The product name that is stated on the declaration letter must be same as that in the PRISM application form. | | |
| * The declaration letter should be issued by the product owner or local registrant, and state that the application as submitted to HSA and directions of use including indication(s), dosing regimen(s) and patient population(s) have not been rejected or withdrawn, have not been approved via an appeal process, and are not pending deferral, by any drug regulatory agency. * If any of the above applies, details and reasons must be provided. | | |  |  |  |  |  |  |  |
| 1.14 | Declaration for NDA/GDA Verification or GDA Verification-CECA | | |  |  |  |  |  |  |  |
|  | * A declaration letter should be submitted stating that all aspects of the Singapore product’s quality are identical to that currently approved by the chosen (primary) reference regulatory agency at the time of submission. | | |  |  |  |  |  |  |  |
|  | * A separate declaration letter stating that the Drug Master File provided is the same as that submitted to the primary reference agency, if applicable. | | |  |  |  |  |  |  |  |
| 1.15 | Registration Status in Other Countries | | |  |  |  |  |  |  |  |
|  | * For NDAs and GDAs, the registration status should be entered into PRISM section 4.9. In the event that the PRISM text space does not allow input of the full details of the indication(s) and/or reason(s), a brief description may be entered. The full details should then be attached in softcopy (PDF) in this PRISM under [7] “Supporting Attachments”) | | |
| 1.16 | Confirmation of Reference Agency’s Approval of Chemistry & Manufacturing Control (CMC) Aspects | | |  | **\*** |  | **\*** |  |  |  |
|  | * For NDAs and GDAs submitted under the abridged evaluation route and for which approval has been obtained from at least one of HSA’s reference agencies not more than 5 years before the date of submission to HSA, a colour scanned copy of the completed Dossier Clarification Supplement should be submitted in PRISM under “Other Supporting Documents” (refer to Appendix 18). | | |

|  |  |  |
| --- | --- | --- |
| **Consent to Disclosure of Information** | **Yes** | **No** |
| The applicant hereby consents to the disclosure of information submitted in this application, including information provided in response to an Input Request, by the HSA to partner regulatory authorities within the Access Consortium. Such disclosure, if made, will be in accordance with the [Terms of Reference](https://www.hsa.gov.sg/therapeutic-products/international-collaboration/access) of the Access; in particular, for the purpose of information exchange and enabling work-sharing. The HSA will notify the applicant in writing if such disclosure of information submitted in this application is made. |  |  |

Part II – Quality

| Section | Documents | | | Application Type & Evaluation Route | | | | | HSA Screening | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NDA** | | | **GDA** | |
| F | A | V | A | V | Submitted? | Remarks |
| Important notes for PART II   * For **verification dossier** – The submission should include Part II dossier as originally submitted to the chosen (primary) reference agency, and any documentation submitted to the same reference agency in subsequent variations to the quality aspects of the product.   + Complete assessment report (unredacted) and other relevant supporting documents from the chosen (primary) reference agency must be submitted in Part I (1.6 Assessment Report).   + Application(s) without complete assessment reports (unredacted) and other relevant supporting documents from the chosen (primary) reference agency will not be accepted for screening.   + Refer to Guidance document, Section 15.6.3 or 18.5.2 for the documents required to be submitted for verification or verification-CECA applications. * For information that is required but not available in the submission dossier, applicants can provide the information separately as attachments in PRISM.   + Multiple pieces of information can be included in a single attachment. | | | | | | | | | | |
| A | Part II Table of Contents | | |  |  |  |  |  |  |  |
| B | Quality Overall Summary (QOS) either in Word or PDF format | | |  |  |  |  |  |  |  |
| C | Body of Data | | | | | | | | | |
|  | **Drug Substance (Active Substance)** | | | | | | | | | |
|  | * If a Drug Master File (DMF) or Plasma Master File (PMF) or Certificate of Suitability of Monographs of the European Pharmacopoeia (CEP) is submitted, refer to Guidance document, Section 15.3.1 or 18.3.1 * If a drug product contains more than one drug substance, the information within Part II.S must be provided in its entirety for each drug substance. The S section checklist should be duplicated accordingly for each additional drug substance. | | | | | | | | | |
|  | S | Drug Substance dossier type:  CEP  DMF [015:      ]  In-house  PMF   * For application(s) supported by DMF(s),   + The electronic format of the DMF(s) from the DMF holder(s) must be received by HSA prior to the submission of the application(s).   + To specify the assigned DMF number in the field above.   + To include a copy of the email acknowledgment from HSA on the receipt of the Letter of Access. | | | | | | |  |  |
|  | S.1 | General Information   * For application(s) supported by CEP(s), section S1 is optional. | | | | | | | | |
|  |  | S.1.1 | Nomenclature | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | S.1.2 | Structure | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | S.1.3 | General Properties | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  | S.2 | Manufacture   * For application(s) supported by DMF(s), section S2.2, S2.3, S2.4, S2.5 and S2.6 must be included in the closed part of the DMF. * For application(s) supported by CEP(s), section S2.2 (except information for ‘Typical production batch size’), S2.3, S2.4, S2.5 and S2.6 are optional. | | | | | | | | |
|  |  | S.2.1 | Manufacturer(s) |  |  |  |  |  |  |  |
|  |  | S.2.2 | Description of Manufacturing Process and Process Controls | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * The typical production batch size should be stated. * Optional if the retest period/ shelf life is stated on the CEP | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | S.2.3 | Control of Materials | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | S.2.4 | Controls of Critical Steps and Intermediates | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | S.2.5 | Process Validation and/or Evaluation | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This section must be submitted for sterile APIs and NBEs (in accordance to the ICH M4Q guidelines). |  |  |  |  |  |
|  |  | S.2.6 | Manufacturing Process Development | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * Refer to ICH Q11 for the documentary requirements regarding development and manufacturing processes (drug substance) that adopt the principles of enhanced approach (QbD) |  |  |  |  |  |
|  | S.3 | Characterisation   * For application(s) supported by CEP(s), section S3 is optional. | | | | | | | | |
|  |  | S.3.1 | Elucidation of Structure and other Characteristics | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | S.3.2 | Impurities | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  | * Discussion on the presence of potential mutagenic impurities | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  | S.4 | Control of Drug Substance   * Refer to Guidance document, Section 15.3.1 or 18.3.1 for details | | | | | | | | |
|  |  | S.4.1 | 1. Specification of Drug Substance from drug product manufacturer (DP-DS specification) |  |  |  |  |  |  |  |
|  |  |  | * A common DP-DS specification should be submitted if multiple drug substance sites are proposed for registration, unless otherwise justified. * The specification document number, version number and/or effective date should be stated. |  |  |  |  |  |
|  |  |  | 1. Specification of Drug Substance from drug substance manufacturer | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * To indicate if the drug substance specification is the same as the DP-DS specification.   Yes  No   * This is optional if the drug substance specification is exactly the same as the DP-DS specification. * The specification document number, version number and/or effective date should be stated. |  |  |  |  |  |
|  |  | S.4.2 | 1. Analytical Procedures from drug product manufacturer | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional for compendial test methods. A copy of the compendial monograph (as claimed) should be submitted |  |  |  |  |  |
|  |  |  | 1. Analytical Procedures from drug substance manufacturer | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional for compendial test methods. A copy of the compendial monograph (as claimed) should be submitted * This is optional if the analytical procedures are exactly the same as those from the drug product manufacturer * This is optional for application(s) supported by CEP(s) and the same dossier as that approved by EDQM |  |  |  |  |  |
|  |  | S.4.3 | 1. Validation of Analytical Procedures from drug product manufacturer | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional for compendial test methods. |  |  |  |  |  |
|  |  |  | 1. Validation of Analytical Procedures from drug substance manufacturer | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional for compendial test methods. * This is optional if the test methods are exactly the same as those from the drug product manufacturer. * This is optional for application(s) supported by CEP(s) and the same dossier as that approved by EDQM |  |  |  |  |  |
|  |  | S.4.4 | 1. Batch Analyses data from drug product manufacturer |  |  |  |  |  |  |  |
|  |  |  | * Batch analyses data from a minimum of 2 batches should be submitted. * One set (i.e. from at least 2 batches) from each DP-DS specification should be submitted if a common DP-DS specification is not submitted and justified in S.4.1. |  |  |  |  |  |
|  |  |  | 1. Batch Analyses data from drug substance manufacturer |  |  |  |  |  |  |  |
|  |  |  | * Batch analyses data from a minimum of 2 batches (preferably production scale or at least pilot scale) from each proposed drug substance manufacturer should be submitted. |  |  |  |  |  |
|  |  | S.4.5 | 1. Justification of Specification from drug product manufacturer | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional if the specification is set according to BP/JP/Ph. Eur./USP |  |  |  |  |  |
|  |  |  | 1. Justification of Specification from drug substance manufacturer | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional if the specification is set according to BP/JP/Ph. Eur./USP. * This is optional if the specification is exactly the same as that from the drug product manufacturer. * This is optional for application(s) supported by CEP(s) and the same dossier as that approved by EDQM. |  |  |  |  |  |
|  | S.5 | Reference Standards or Materials   * This is optional if the reference standards or materials used by drug substance manufacturer are exactly the same as those used by the drug product manufacturer. * This is optional for application(s) supported by CEP(s) and the same dossier as that approved by EDQM. | | | | | | | | |
|  |  | The source of reference standard (in house or official with reference to compendial standard) used for the testing of the drug substance should be stated. | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | For in house reference standards, the specifications of reference standard should be submitted from both the drug product manufacturer and drug substance manufacturer. | | **\*** | **\*** | **\*** | **\*** | **\*** |
|  |  | Evidence of characterisation for in-house / working standards (e.g. tests of NMR, MS are documented in the CoA will suffice) is required. | | **\*** | **\*** | **\*** | **\*** | **\*** |
|  | S.6 | Container Closure System   * This is optional for applications where the CCS is stated in the CEP. | | | | | | | | |
|  |  | Complete technical information should be provided on the type of container closure used. | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  | A declaration of compliance to the appropriate international standards or pharmacopoeia is to be provided, e.g. food contact EC/10/2011, Ph. Eur. Chapter 3. | | **\*** | **\*** | **\*** | **\*** | **\*** |
|  |  | For drug substance(s) in solution(s), the suitability of the CCS should be demonstrated (e.g. extractable and leachable studies, CCS integrity study). | | **\*** | **\*** | **\*** | **\*** | **\*** |
|  | S.7 | Stability   * Refer to Guidance document, Section 15.3.1 or 18.3.1 for details. * This is optional for applications where the retest period is stated in the CEP. | | | | | | | | |
|  |  | S.7.1 | Stability Summary and Conclusions | | | | | | | |
|  |  |  | The conclusion of the stability studies, stress studies, storage condition and proposed re-test/shelf life period should be stated in the summary. | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | Information such as the batch size, date of manufacture, site of manufacture and container closure system should be stated | **\*** | **\*** | **\*** | **\*** | **\*** |
|  |  |  | * The stability batches should be manufactured by the same process and packaged in the same container closure system as that proposed for Singapore. |  |  |  |  |  |
|  |  | S.7.2 | Post-approval Stability Protocol and Stability Commitment | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This should be submitted as per ICH Q7 Section 11.54, based on the proposed storage condition. If any results fall outside of the retest / shelf-life specifications, these should be reported together with the proposed action. |  |  |  |  |  |
|  |  | S.7.3 | Stability Data   * Refer to ICH Q1 for the relevant requirements. | | | | | | | |
|  |  |  | Data from at least three primary batches (one tenth of production scale) or two pilot scale batches and one small scale batch should be submitted. | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | If the drug substance is sourced from multiple sites, stability data from each site should be provided, unless otherwise justified. | **\*** | **\*** | **\*** | **\*** | **\*** |
|  |  |  | Results from Stress Testing (including Photostability testing) should be submitted, unless otherwise justified. | **\*** | **\*** | **\*** | **\*** | **\*** |
|  | Drug Product   * P Section checklist should be duplicated accordingly for   + Each Drug Product Intermediate site; and   + Each final drug product, e.g. drug product (powder) supplied with a diluent (solution). | | | | | | | | | |
|  | P.1 | Description and Composition of the Drug Product | |  |  |  |  |  |  |  |
|  |  | The composition of proprietary materials (e.g. capsule shells, colouring blends, imprinting inks) should be submitted, if applicable. | | **\*** | **\*** | **\*** | **\*** | **\*** |
|  | P.2 | Pharmaceutical Development   * Refer to ICH Q8 Part II – Annex for the documentary requirements for development and manufacturing processes that adopt the principles of enhanced approach (QbD) * Refer to Guidance document Section 15.3.2 or 18.3.2 for details. | | | | | | | | |
|  |  | P.2.1 | Information on Development Studies |  |  |  |  |  |  |  |
|  |  | P.2.2 | Components of the Drug Product | | | | | | | |
|  |  | P.2.2.1 | Active Ingredients |  |  |  |  |  |  |  |
|  |  | P.2.2.2 | Excipients | | | | | | | |
|  |  |  | * The choice of excipients listed in 3.2.P.1, their concentration and characteristics that can influence the drug product performance should be discussed and submitted. |  |  |  |  |  |  |  |
|  |  |  | * The use of antioxidant(s) and/or preservative(s), and their concentration(s) should be explained, fully justified and submitted, if applicable. |  |  |  |  |  |
|  |  | P.2.3 | Finished Product | | | | | | | |
|  |  | P.2.3.1 | Formulation Development |  |  |  |  |  |  |  |
|  |  |  | * Elemental impurity risk assessment as per ICH Q3D should be provided. |  |  |  |  |  |
|  |  | P.2.3.2 | Overages |  |  |  |  |  |  |  |
|  |  |  | * The use of overages should be explained, fully justified and submitted, if applicable. |  |  |  |  |  |
|  |  | P.2.3.3 | Physicochemical and Biological Properties |  |  |  |  |  |  |  |
|  |  | P.2.4 | Manufacturing Process Development |  |  |  |  |  |  |  |
|  |  | P.2.5 | Container Closure System | | | | | | | |
|  |  |  | * For sterile products, container closure integrity data should be submitted. |  |  |  |  |  |  |  |
|  |  |  | * For liquid preparations, the suitability of Container Closure System should be demonstrated (e.g. extractable and leachable studies). |  |  |  |  |  |
|  |  |  | * For Container Closure Systems which are also a delivery device e.g. nasal sprays, inhalers, prefilled syringes, the technical properties of the container closure system with respect to patient use should be considered and submitted. |  |  |  |  |  |
|  |  | P.2.6 | Microbiological Attributes |  |  |  |  |  |  |  |
|  |  | P.2.7 | Compatibility | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is applicable for drug products which have reconstitution diluents or dosage device (e.g. infusion bags, tubings). |  |  |  |  |  |
|  | P.3 | Manufacture | | | | | | | | |
|  |  | * For parametric release product, GMP DEVA for parametric release is product specific. Refer to Guidance document, Section 15.1 and 18.1 (GMP Certification/Proof of GMP Compliance) for details. | |  |  |  |  |  |  |  |
|  |  | * The site involved in sterilising the drug product is required to be registered and should be listed in PRISM. GMP or ISO 13485 is required for the sterilising site. | |  | **☐** |  |  |  |
|  |  | * Refer to Appendix 17, Section 1.1.5 for guidance on entering information in PRISM Section 5. | |  |  |  |  |  |
|  |  | P.3.1 | Batch Formula |  |  |  |  |  |  |  |
|  |  |  | * For multiple batch sizes, the batch formula for each batch size is to be provided. |  |  |  |  |  |
|  |  | P.3.2 | Description of Manufacturing Process And Process Controls | | | | | | | |
|  |  |  | * The flow chart and IPC should be submitted. |  |  |  |  |  |  |  |
|  |  |  | * Any proposed holding time(s) should be stated for each process and accompanied by relevant supportive data. |  |  |  |  |  |
|  |  | P.3.3 | Controls of Critical Steps and Intermediates |  |  |  |  |  |
|  |  | P.3.4 | Process Validation and/or Evaluation   * Refer to ASEAN Guidelines on Submission of Manufacturing Process Validation Data for Drug Registration for regulatory submission requirements. * Refer to Guidance document, Section 15.3.2 or 18.3.2 for details, including details for parametric release application(s). * Refer to “FDA Process Validation: General Principles and Practises” for process validation that adopts an enhanced life cycle approach. | | | | | | | |
|  |  |  | Option 1  Option 2  Option 3 |  |  |  |  |  |  |  |
|  |  |  | * Option 1: Submission of three consecutively manufactured validation batches |  |  |  |  |  |
|  |  |  | * Option 2: Submission of development pharmaceutics report and validation data from one pilot batch with validation scheme on production scale batches.   NOTE: This option is not recommended for biological/biotechnological product(s), product(s) manufactured using non-standard manufacturing process and other specialised product(s). Refer to ASEAN Guidelines on Submission of Manufacturing Process Validation Data for Drug Registration for details. |  |  |  |  |  |
|  |  |  | * Option 3: Submission of declaration letter that the same pre-approval dossiers pertaining to process validation submitted have been submitted to the reference agency are submitted to HSA. In addition, a letter of undertaking to conduct three consecutive full production batches and to submit the report to HSA upon request. |  |  |  |  |  |
|  |  |  | * The manufacturing site at which the validation is carried out should be stated and be the same as that proposed for Singapore. |  |  |  |  |  |
|  |  |  | * The product formula of the validation batches should be the same as that proposed for Singapore, unless otherwise justified. |  |  |  |  |  |
|  |  |  | * Information such as the batch number, date of production, batch size and batch type should be stated. |  |  |  |  |  |
|  |  |  | * For concurrent validation, prior concurrence from HSA is required before the application submission. A copy of the written correspondence should be submitted together with the dossier. |  |  |  |  |  |
|  |  |  | * The bracketing/matrixing approach should be stated and fully justified. |  |  |  |  |  |
|  |  |  | Annex A1  Annex A2  Annex A3 |  |  |  |  |  |  |  |
|  |  |  | * For solid oral drug products, refer to Annex A1 for registration requirements. |  |  |  |  |  |
|  |  |  | * For aseptically processed drug products, refer to Annex A2 for registration requirements. |  |  |  |  |  |
|  |  |  | * For terminal sterilised drug products, refer to Annex A3 for registration requirements. |  |  |  |  |  |
|  | P.4 | Control of Excipients   * Refer to Guidance document, Section 15.3.2 or 18.3.2 for details. * State if each excipient is compendial or non-compendial * Information on proprietary ingredients, should be as detailed as possible. In cases where the formula of the proprietary ingredient is confidential, the formula should then be provided by the ingredient manufacturer directly to HSA. | | | | | | | | |
|  |  | P.4.1 | Specifications or Certificate of Analyses |  |  |  |  |  |  |  |
|  |  | P.4.2 | Analytical Procedures | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional for compendial test methods and specifications set according to BP/JP/Ph. Eur./USP. |  |  |  |  |  |
|  |  | P.4.3 | Excipients of Human or Animal Origin | | | | | | | |
|  |  |  | * For human plasma-derived products, please refer to Appendix 8 for registration requirements. | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * For animal-derived excipients, please refer to Appendix 9 for registration requirements. | **\*** | **\*** | **\*** | **\*** | **\*** |
|  |  | P.4.4 | Novel Excipients |  |  |  |  |  |  |  |
|  |  |  | * The information provided should be as per the full drug substance section and submitted in section Q4A.3. |  |  |  |  |  |
|  | P.5 | Control of Drug Product (Finished Product)   * For parametric release applications, refer to Guidance document, Sections 15.3.2 or 18.3.2 for details. | | | | | | | | |
|  |  | P.5.1 | Specification(s) of Drug Product | | | | | | | |
|  |  |  | * The specification document number, version number and/or effective date should be stated. |  |  |  |  |  |  |  |
|  |  |  | * The release and stability indicating parameters should be clearly defined or differentiated. |  |  |  |  |  |
|  |  | P.5.2 | Analytical Procedures | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional for compendial test methods. A copy of the compendial monograph (as claimed) should be submitted. |  |  |  |  |  |
|  |  | P.5.3 | Validation of Analytical Procedures | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional for compendial test methods. |  |  |  |  |  |
|  |  | P.5.4 | Batch Analyses |  |  |  |  |  |  |  |
|  |  |  | * Batch analyses data from a minimum of 3 batches (preferably production scale) should be submitted. |  |  |  |  |  |
|  |  | P.5.5 | Characterisation of Impurities |  |  |  |  |  |  |  |
|  |  | P.5.6 | Justification of Specification(s) | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  |  |  | * This is optional if the specifications are set according to BP/JP/USP. |  |  |  |  |  |
|  | P.6 | Reference Standards or Materials | | | | | | | | |
|  |  | * The source of the reference standard (in house or official with reference to compendial standard) used for the testing of the drug product should be stated. | |  |  |  |  |  |  |  |
|  |  | * For in house reference standards, the specifications of the reference standard should be submitted. | |  |  |  |  |  |
|  |  | * Evidence of characterisation for in-house / working standards (e.g. tests of NMR, MS are documented in the CoA will suffice) should be submitted. | |  |  |  |  |  |
|  | P.7 | Container Closure System | | | | | | | | |
|  |  | * Complete technical information on the type of container closure used should be submitted. | |  |  |  |  |  |  |  |
|  |  | * A declaration of compliance to the appropriate international standards or pharmacopoeia, e.g. food contact EC/10/2011, Ph. Eur. Chapter 3, should be submitted. | |  |  |  |  |  |
|  | P.8 | Stability | | | | | | | | |
|  |  | P.8.1 | Stability Summary and Conclusions | | | | | | | |
|  |  |  | * The conclusion of the stability studies, stress studies, storage condition and proposed shelf life period should be stated in the summary. |  |  |  |  |  |  |  |
|  |  |  | * Information such as the batch size, date of manufacture, site of manufacture, container closure system, and source and batch number of drug substance used for each drug product stability batch should be stated. |  |  |  |  |  |
|  |  |  | * The stability batches should be manufactured by the same process and packaged in the same container closure system as that proposed for Singapore. |  |  |  |  |  |
|  |  | P.8.2 | Post-approval Stability Protocol and Stability Commitment |  |  |  |  |  |  |  |
|  |  |  | * This should be submitted as per WHO Annex 2 and based on the proposed storage condition. If any results fall outside of the retest / shelf-life specifications, these should be reported together with the proposed action. |  |  |  |  |  |
|  |  | P.8.3 | Stability Data   * Refer to Guidance document, Section 15.3.2 or 18.3.2 for the regulatory submission requirements. * Refer to ASEAN Guideline on Stability Study of Drug Product for the regulatory submission requirements for chemical drug substance(s).   Refer to ICH Q5C for Biotechnological/Biological products for the regulatory submission requirements. | | | | | | | |
|  |  |  | For NDA: stability data from at least three primary batches (one set) under ASEAN storage conditions and accelerated storage conditions should be submitted.  **OR**  For GDA critical dosage forms or unstable drug substances: stability data from at least three primary batches (one set) under ASEAN storage conditions and accelerated storage conditions should be submitted.  **OR**  For GDA conventional dosage forms and stable drug substances: stability data from at least two primary batches (one set) under ASEAN storage conditions and accelerated storage conditions should be submitted. |  |  |  |  |  |  |  |
|  |  |  | * Zone IVb long term storage condition stability data should be submitted unless fully justified with supporting data (such as Out-of-Specification data under 30°C storage condition and investigation reports, to demonstrate an unstable drug product stability profile). |  |  |  |  |  |
|  |  |  | * A ‘30oC ± 2oC/RH not specified’ long term storage condition is permissible for products in primary containers impermeable to water vapour. |  |  |  |  |  |
|  |  |  | * A ‘30oC ± 2oC/35% RH ± 5% RH’ long term storage condition is permissible for aqueous-based products packed in semi-permeable containers. Potential water loss should be evaluated in addition to physical, chemical, biological and microbiological stability. |  |  |  |  |  |
|  |  |  | * One set of stability data (both long term and accelerated storage conditions) should be submitted for each batch size, strength and/or container closure system, unless otherwise justified. The use of reduced designs should also be fully justified. |  |  |  |  |  |
|  |  |  | Please refer to Guidance document, Section 15.3.2 or 18.3.2 for the regulatory submission requirements and additional documentary requirements for the following scenarios:   1. Multiple drug substance manufacturers:   Yes  No   1. Multiple drug product manufacturers:   Yes  No   1. Multiple drug substance and drug product manufacturers:   Yes  No   1. Multiple primary packagers:   Yes  No   1. Drug product stability batch(es) using development or pilot drug substance batches:   Yes  No |  |  |  |  |  |  |  |
|  |  |  | For in-use stability studies, refer to ASEAN Guideline on Stability Study of Drug Product for regulatory submission requirements. |  |  |  |  |  |  |  |
|  |  |  | * Information such as the batch number, in-use storage condition(s), length of storage prior to start of in-use stability testing and completed in-use test intervals should be stated. |  |  |  |  |  |
|  | P.9 | Product Interchangeability (Bioequivalence Study Reports)   * Refer to Guidance document, Section 18.3.2 and Appendix 10 for the registration and documentary requirements. | |  |  |  |  |  |  |  |
|  | * The complete bioequivalence study report (including all appendices and data) should be provided. | |  |  |  | **\*** | **\*** |  |  |
| * The bioanalytical study report and description of the bioanalytical method validation should be provided. | |  |  |  | **\*** | **\*** |  |  |
| * BE inspection reports (for the clinical facility where the BE study was conducted) from national drug regulatory agencies or WHO should be provided (where available). | |  |  |  | **\*** | **\*** |  |  |
|  | * Relevant information on the test product used in the BE study should be provided: | |  |  |  | **\*** | **\*** |  |  |
| * The product name, strength, dosage form, batch number, expiry date and batch size should be provided. * The test product used in the BE study should be from a batch of at least 100,000 units or 1/10 of production scale, whichever is greater. If the maximum production scale batch size of the BE test product strength is not stated in the dossier, this information should be provided here. | |  |  |
| * The name and full address of the drug substance and drug product manufacturing sites together with relevant supporting documents, e.g. active ingredient Certificate of Analysis, batch manufacturing records, should be provided. | |  |  |
| * The Certificate of Analysis of the test product used in the BE study should be submitted. | |  |  |
| * A signed statement confirming that the test product used in the BE study is the same formulation and is manufactured by the same process as that submitted for registration should be submitted. * If the test product used in the BE study is of a different strength from that proposed for registration, a signed statement confirming that the test product used in the BE study has the same qualitative composition and quantitatively proportional composition and is manufactured by the same process as that proposed for registration should be submitted. | |  |  |
|  | * Relevant information on the reference product used in the BE study should be provided: | |  |  |  | **\*** | **\*** |  |  |
| * The product name, strength, dosage form, batch number and expiry date should be provided. | |  |  |
| * The name and full address of the drug product manufacturing site together with product labels (e.g. outer carton, package insert/patient information leaflet) should be provided. The product labels should contain the BE reference product’s batch number and its full address of the drug product manufacturing site for verification that the BE reference product is manufactured by the Singapore-registered drug product manufacturing site. If the BE reference product was manufactured by a non-Singapore-registered manufacturer, please refer to Guidance document, Section 18.3.2 and Appendix 10 Section 2.3 for the relevant criteria and documentary requirements. | |  |  |
| * The Certificate of Analysis of the reference product should be submitted. | |  |  |  |  |  |  |  |
|  | * **Comparative Dissolution Profile (CDP) testing** * The dissolution profiles should be determined in at least 3 pH media within the physiological range, such as 0.1N HCl, a pH 4.5 buffer and a pH 6.8 buffer. * The following data should be submitted:   + Individual dissolution data;   + Mean, range and RSD of dissolution data from 12 units; and   + Statistical comparison using a procedure described in international guidelines, e.g. f2 calculations | | | | | | | | |
|  | * **For applications of a solid oral dosage form with a BE study**, CDP testing data should be provided between BE test and reference products | |  |  |  | **\*** | **\*** |  |  |
| * If the reference product used in BE study (BE RP) is not the Singapore reference product (SRP), refer to Appendix 10, Section 2.3 for the criteria to be fulfilled. * The following additional documents are to be provided:   + Comparative table that lists the qualitative composition of the BE RP and SRP;   + CDP between BE RP and SRP; and   + CDP between generic product and SRP. | |  |  |  | **\*** | **\*** |  |  |
| * If the test product used in BE study is manufactured at a DS manufacturing site other than that proposed for registration, refer to Appendix 10, Section 2.2.1 for the documents to be submitted. | |  |  |  | **\*** | **\*** |  |  |
| * If the test product used in BE study is manufactured at a DP manufacturing site other than that proposed for registration, refer to Appendix 10, Section 2.2.2 for the documents to be submitted. | |  |  |  | **\*** | **\*** |  |  |
| * **For P & GSL medicines of oral solid modified-release dosage forms**, CDP should be provided between the generic product and SRP. | |  |  |  | **\*** | **\*** |  |  |
| * If a biowaiver is requested for subsequent strength(s), CDPs between generic product of the strength used in the BE study and its subsequent strength(s) are to be provided. | |  |  |  | **\*** | **\*** |  |  |
|  | * Relevant supporting documents should be provided if the generic product contains a different salt, ester, ether, isomer, mixture of isomer, complex or derivative of the active substance compared to the Singapore reference product. | |  |  |  | **\*** | **\*** |  |  |
|  | * Justifications and relevant supporting documents for biowaiver requests should be submitted (where applicable): * Biowaiver based on dosage forms * Biowaiver for multiple strengths * BCS-based biowaiver | |  |  |  | **\*** | **\*** |  |  |
| D | Key Literature References | | |  |  |  |  |  |  |  |
| Q | Country-specific Quality Requirements | | | | | | | | | |
|  | Q1 | Checklist for Human Blood Product with the required supporting documents | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  | Q2 | TSE Checklist with the required supporting documents | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  | Q3 | Blank Production Batch Record | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
|  | Q4 | Appendices | | | | | | | | |
|  |  | A.1 | Facilities and Equipment |  |  |  |  |  |  |  |
|  |  | A.2 | Adventitious Agents Safety Evaluation |  |  |  | **\*** | **\*** |  |  |
| A.3 | Novel Excipients |  |  |  | **\*** | **\*** |  |  |

Part III – Non-clinical Data

| Section | Documents | | | | | Application Type & Evaluation Route | | | | | HSA Screening | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NDA** | | | **GDA** | |
| F | A | V | A | V | Submitted? | Remarks |
| A | Table of Contents of Part III | | | | |  |  |  |  |  |  |  |
| B | Non-clinical Overview | | | | |  |  |  |  |  |  |  |
| B1 | General Aspect | | | |  |  |  |  |  |  |  |
| B2 | Content and Structural Format | | | |  |  |  |  |  |  |  |
| C | Non-clinical Summary (Written and Tabulated) | | | | |  |  |  |  |  |  |  |
|  | C1 | Non-clinical Written Summary | | | |  |  |  |  |  |  |  |
|  |  | C1.1 | | | Pharmacology |  |  |  |  |  |  |  |
|  |  | C1.2 | | | Pharmacokinetics |  |  |  |  |  |  |  |
|  |  | C1.3 | | | Toxicology |  |  |  |  |  |  |  |
|  | C2 | Non-clinical Tabulated Summaries | | | |  |  |  |  |  |  |  |
| D | Non-clinical Study Report | | | | |  |  |  |  |  |  |  |
|  | D1 | | Table of Contents | | |  |  |  |  |  |  |  |
|  | D2 | | Pharmacology | | |  |  |  |  |  |  |  |
|  |  | | D2.1 | Primary Pharmacodynamics | |  |  |  |  |  |  |  |
|  |  | | D2.2 | Secondary Pharmacodynamics | |  |  |  |  |  |  |  |
|  |  | | D2.3 | Safety Pharmacology | |  |  |  |  |  |  |  |
|  |  | | D2.4 | Pharmacodynamic Drug Interactions | |  |  |  |  |  |  |  |
|  | D3 | | Pharmacokinetics | | |  |  |  |  |  |  |  |
|  |  | | D3.1 | Analytical Methods and Validation Reports | |  |  |  |  |  |  |  |
|  |  | | D3.2 | Absorption | |  |  |  |  |  |  |  |
|  |  | | D3.3 | Distribution | |  |  |  |  |  |  |  |
|  |  | | D3.4 | Metabolism | |  |  |  |  |  |  |  |
|  |  | | D3.5 | Excretion | |  |  |  |  |  |  |  |
|  |  | | D3.6 | Pharmacokinetic Drug Interactions (non-clinical) | |  |  |  |  |  |  |  |
|  |  | | D3.7 | Other Pharmacokinetic Studies | |  |  |  |  |  |  |  |
|  | D4 | | Toxicology | | |  |  |  |  |  |  |  |
|  |  | | D4.1 | Single-Dose Toxicity | |  |  |  |  |  |  |  |
|  |  | | D4.2 | Multiple-Dose Toxicity | |  |  |  |  |  |  |  |
|  |  | | D4.3 | Genotoxicity | |  |  |  |  |  |  |  |
|  |  | | D4.4 | Carcinogenicity | |  |  |  |  |  |  |  |
|  | | D4.5 | Reproductive and Developmental Toxicity | |  |  |  |  |  |  |  |
|  |  | | D4.6 | Local Tolerance | |  |  |  |  |  |  |  |
|  |  | | D4.7 | Other Toxicity Studies | |  |  |  |  |  |  |  |
| E | List of Key Literature References | | | | |  |  |  |  |  |  |  |

Part IV – Clinical Data

| Section | Documents | | | Application Type & Evaluation Route | | | | | HSA Screening | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **NDA** | | | **GDA** | |
| F | A | V | A | V | Submitted? | Remarks |
| A | Table of Contents of Part IV | | |  |  |  |  |  |  |  |
| B | Clinical Overview | | |  |  |  |  |  |  |  |
| C | Clinical Summary | | |  |  |  |  |  |  |  |
|  | C1 | Summary of Biopharmaceutic Studies and Associated Analytical Methods | |  |  |  |  |  |  |  |
|  | C2 | Summary of Clinical Pharmacology Studies | |  |  |  |  |  |  |  |
|  | C3 | Summary of Clinical Efficacy | |  |  |  |  |  |  |  |
|  | C4 | Summary of Clinical Safety | |  |  |  |  |  |  |  |
|  | C5 | Synopses of Individual Studies | |  |  |  |  |  |  |  |
| D | Tabular Listing of All Clinical Studies | | |  |  |  |  |  |  |  |
| E | Clinical Study Reports | | |  |  |  |  |  |  |  |
|  | E1 | | Reports of Biopharmaceutic Studies |  | **\*** | **\*** |  |  |  |  |
|  |  | | * For Abridged and Verification Dossiers, information on the comparability between clinical trial (pivotal studies) and commercial formulations should be available in the Clinical Overview/Summary. If the commercial formulation for the Singapore market differs from the clinical trial formulation used in the pivotal studies, the final study report(s) of biopharmaceutic studies to establish bioequivalence between the commercial product formulation and the clinical trial formulation used in pivotal studies should be submitted. * For Full Dossiers, all biopharmaceutic study reports are required. |
| E2 | | Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials |  |  |  |  |  |  |  |
| E3 | | Reports of Human Pharmacokinetic (PK) Studies |  |  |  |  |  |  |  |
| E4 | | Reports of Human Pharmacodynamic (PD) Studies |  |  |  |  |  |  |  |
| E5 | | Reports of Clinical Efficacy and Safety Studies |  |  |  |  |  |  |  |
| * For Full Dossiers, study reports of ALL clinical trials (including the appendices and tables) should be submitted. |  |  |
| * For Abridged and Verification Dossiers, study reports of pivotal or relevant clinical trials should be submitted (appendices and tables are required only upon request by HSA). |  |  |
| * The clinical trials should be conducted using the drug product formulation submitted in the application and in the appropriate patient population for the indication(s) and/or dosing regimen(s) as requested in the application. |  |  |
| * If the commercial formulation for the Singapore market differs from the clinical trial formulation used in the pivotal studies, biopharmaceutic study reports are required (see section E1). |  |  |
| * If the information on the comparability between the clinical trial formulation and the proposed commercial formulation is not available in the clinical study reports or the Clinical Overview/Summaries, a separate declaration letter should be submitted to confirm that the clinical trial formulation is the same as the commercial formulation proposed for registration in Singapore. |  |  |
| * Phase III, confirmatory, randomised, controlled pivotal trials conducted in compliance with Good Clinical Practice (GCP) are required to support each requested indication and dosing regimen, unless adequately justified. Active-controlled studies should use relevant active comparators that are locally registered, unless adequately justified. |  |  |
| E6 | | Reports of Post-marketing Experience | **\*** | **\*** | **\*** |  |  |  |  |
| E7 | | Case Report Forms and Individual Patient Listings (required upon request by HSA) |  |  |  |  |  |  |  |
| F | List of Key Literature References | | |  |  |  |  |  |  |  |
| G | Risk management plan (RMP) documents as separate attachment in PRISM under [7] “Supporting Attachments” | | | **\*** | **\*** | **\*** | **\*** | **\*** |  |  |
| H | Other Supporting Documents | | |  |  |  |  |  |  |  |