**MAV-1 CHECKLIST FOR CLASS 2 CELL, TISSUE AND GENE THERAPY PRODUCT (ACTD FORMAT)**

* This application checklist should be used to ensure the submission of a complete dataset in the ASEAN Common Technical Dossier (ACTD) format for MAV-1 application.
* Colour scanned copies of the original documents should be submitted and hard copies of original 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 the evaluation.
* This checklist should be completed by checking each item against the dossier according to the application relevant for your submission.

**Note:**

* Cells with [ ]  indicate that the documents shown are mandatory for the selected application type and evaluation route.
* Cells with [ ] \* indicate that the documents shown may be optional depending on the application type/product/change.
* Cells without [ ]  indicate that the documents shown 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 Cell, Tissue and Gene Therapy Products 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 | **MAV-1** | Major Variation Application |
| Evaluation route | **F** | Full Dossier  |
| **A** | Abridged Dossier |

**Part I - Administrative Documentation**

| **Section** | **Documents** | **Evaluation Route** | **HSA Screening** |
| --- | --- | --- | --- |
|  |  | **F** | **A** | **Submitted?** | **Remarks** |
| 1.1 | **Cover letter** |[ ] [ ]   |  |
|  | * Include a cover letter stating the product name, the proposed evaluation route, the referenced drug regulatory authority (for Abridged route), the proposed indication.
* A concise summary of the application and justification for the need for the application should be provided.
* The absence/omission of certain documents and deviation(s) from guidelines should be justified.
 |  |  |  |  |
| 1.2 | **Comprehensive Table of Contents** |[ ] [ ]   |  |
|  | * A complete list of all documents organised by Module should be provided in the application dossier.
* The location of each document should be identified by the Module number.
 |  |  |  |  |
| 1.3 | **Introduction** *(refer to 1.1 Cover Letter)*  | [ ] \* | [ ] \* |  |  |
| 1.4 | **Labelling proposed and currently approved in Singapore** |  |  |  |  |
|  | * All proposed labels have to be submitted for registration in Singapore.
* Handwritten information is not acceptable.
* Movable text boxes/pictures placed over other hidden information/text are not acceptable.
* If the proposed labels contain QR code, the website and information that will be provided by the QR code should be submitted.
* For the proposed labels, a pristine and an annotated version (which highlights the changes made to the currently approved labelling) is required.
* Annotations should be made on the proposed labelling materials based on the actual text to be added, and on current approved labelling materials.
* Any current approved text proposed for deletion should be struck through, whereas newly added and proposed text should be underlined or highlighted.
* Current approved text that is not intended to be deleted should not be annotated.
* The translocation of current approved text from one section to another in its entirety can be allowed.
* 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 Label** | [ ] \* | [ ] \* |  |  |
|  |  | * 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 different pack size of the product.
 |  |  |  |  |
|  | 1.4.2 | **Inner Label** | [ ] \* | [ ] \* |  |  |
|  |  | * The draft artwork of the inner 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 all CTGT product registration.
* The submission of one common PI for all strengths or dosage forms is encouraged.
 |  |  |  |  |
|  | 1.4.4 | **Patient Information Leaflet (PIL)** | [ ] \* | [ ] \* |  |  |
|  |  | * The PIL is optional for Class 2 CTGTP.
* The PIL should be written in a language easily understood by consumers/patients and be consistent with the CTGTP labels and/or PI.
 |  |  |  |  |
| 1.5 | **Registration status in other countries** | [ ]  |[ ]   |  |
|  | 1.5.1 | **Tabulation of worldwide registration status** |  |  |  |  |
|  | 1.5.2 | **Approved SmPC/PI** |  |[ ]   |  |
|  |  | * The approved SmPC/ PI currently approved by each of HSA’s reference agencies should be submitted, where applicable.
 |  |  |  |  |
|  |  | * The submitted SmPC / PI should state the country that the document originated from.
 |  |  |  |  |
|  |  | * SmPC/PI approved by Country of Origin/Country of Manufacture. Please provide justification if the document is not available.
 |[ ]  [ ] \* |  |  |
|  |  | * The approved SmPC / PI from the drug regulatory agency that issued the proof of approval, should be submitted if it is not from the Country of Origin. Please provide justification if the document is not available.
 |[ ]  [ ] \* |  |  |
|  |  | * The submitted SmPC / PI should state the country that the document originated from.
 |  |  |  |  |
|  | 1.5.3 | **Assessment report issued by HSA’s reference regulatory agency, where applicable** |  | [ ] \* |  |  |
|  |  | * The submitted assessment reports and supporting documents must be unredacted and unedited.
 |  |  |  |  |
| 1.6 | **Description of Batch Numbering System** | [ ] \* | [ ] \* |  |  |
|  | * Required if there are changes to the batch numbering system.
* Examples of batch numbering system should be included to illustrate how the batch number enables identification, where applicable.
 |  |  |  |  |
| 1.7 | **Proof of Approval** |  |[ ]   |  |
|  | * 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.
* 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.
* Proof of approval must be accompanied by the SmPC/PI and/or PIL as approved in the country that issued the proof of approval.
 |  |  |  |  |
| 1.8 | **Authorisation Letters** |  |  |  |  |
| 1.9 | **GMP certification/proof of GMP compliance for each manufacturer inclusive of secondary packer(s)** |  |  |  |  |
| 1.10 | **Relevant accreditation certificates or licences for sites responsible for donor starting material procurement (e.g. apheresis site, tissue bank), quality control testing (e.g. sterility testing laboratory) and storage** |  |  |  |  |
| 1.11 | **Declaration on rejection, withdrawal and deferral** |  |  |  |  |
|  | * The product name that is stated on the declaration letter must be same as that in the 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.
 |[ ] [ ]   |  |

**Part III - Non-Clinical Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section** | **Documents** | **Evaluation Route** | **HSA Screening** |
| **F** | **A** | **Submitted?** | **Remarks** |
| A | Table of Contents of Part III | [ ] \* | [ ] \* |  |  |
| B | Non-Clinical Overview | [ ] \* | [ ] \* |  |  |
| C | Non-clinical Summary |  |  |  |  |
| 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 (Primary Pharmacodynamics, Secondary Pharmacodynamics, Safety Pharmacology) | [ ] \* | [ ] \* |  |  |
| D3 | Pharmacokinetics (Analytical Methods and Validation Reports, Biodistribution) | [ ] \* | [ ] \* |  |  |
| D4 | Toxicology (Single-Dose Toxicity, Repeated-Dose Toxicity, Genotoxicity, Carcinogenicity, Reproductive and Developmental Toxicity, Local Tolerance) | [ ] \* | [ ] \* |  |  |
|  |  D5 | Additional Supporting Studies | [ ] \* | [ ] \* |  |  |
| E | Literature References | [ ] \* | [ ] \* |  |  |

**Part IV - Clinical Data**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section** | **Documents** | **Evaluation Route** | **HSA Screening** |
|  |  | **F** | **A** | **Submitted?** | **Remarks** |
| A | Table of Contents of Part IV |[ ] [ ]   |  |
| B | Clinical Overview |[ ] [ ]   |  |
| C | Clinical Summary |  |  |  |  |
|  | C1 | Summary of Biopharmaceutics 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 | [ ] \* | [ ] \* |  |  |
|  |  | * Information on the comparability between clinical trial (pivotal studies) and commercial formulations should be available in the Clinical Overview/Summary.
* A declaration letter is to be provided to HSA to indicate whether the clinical trial formulation or the manufacturing process used in the pivotal studies is the same as the commercial formulation proposed for registration in Singapore.
* 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 comparability between the commercial product formulation and the clinical trial formulation used in pivotal studies should be submitted.
 | [ ] \* | [ ] \* |  |  |
|  | E2 | Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials | [ ] \* | [ ] \* |  |  |
|  | E3 | Reports of Human Pharmacokinetic Studies | [ ] \* | [ ] \* |  |  |
|  | E4 | Reports of Human Pharmacodynamic Studies | [ ] \* | [ ] \* |  |  |
|  | E5 | Reports of Efficacy and Safety Studies |[ ] [ ]   |  |
|  |  | * Study reports of ALL clinical trials (including the appendices and tables) should be submitted.
* The clinical trials should be conducted using the CTGT 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 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.
* Pivotal trials conducted in compliance with Good Clinical Practice (GCP) are required to support each requested indication and dosing regimen, unless adequately justified.
 |  |  |  |  |
|  | E6 | Reports of Post-marketing Experience | [ ] \* | [ ] \* |  |  |
|  | E7 | Case Report Forms and Individual Patient Listings (required upon request by HSA) |  |  |  |  |
| F | Literature References |[ ] [ ]   |  |
| G | Risk management plan (RMP) documents | [ ] \* | [ ] \* |  |  |
| H | Other Supporting Documents | [ ] \* | [ ] \* |  |  |