**APPENDIX 12 MAV-1 APPLICATION CHECKLIST FOR CLASS 2 CELL, TISSUE OR GENE THERAPY PRODUCT (ICH CTD FORMAT)**

* This application checklist should be used to ensure the submission of a complete dataset in the ICH Common Technical Dossier (ICH CTD) 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 ICH technical guidance for explanatory notes on the preparation ofdocuments for a submission in ICH CTD format.

Legend:

|  |  |  |
| --- | --- | --- |
| Application type | **MAV-1** | Major Variation Application |
| Evaluation route | **F** | Full Dossier  |
| **A** | Abridged Dossier |

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**REVISION HISTORY**

Guidance Version (Publish Date)

ATPB-GN-012-000 (March 2021)

**Module 1 - Administrative Documentation**

| **Section** | **Documents** | **Evaluation Route** | **HSA Screening** |
| --- | --- | --- | --- |
|  |  | **F** | **A** | **Submitted?** | **Remarks** |
| 1.1 | **Cover letter** |[ ] [ ]   |  |
|  | * Include a cover letter accompanying the CD/DVD submission, stating the product name, and number of CD/DVDs submitted in support of the application.
 |  |  |  |  |
| 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** |[ ] [ ]   |  |
|  | * A concise and precise summary of the application should be provided.
* The absence/omission of certain documents and deviation(s) from guidelines should be justified.
 |  |  |  |  |
| 1.4 | **Labelling proposed and currently approved in Singapore** |  |  |  |  |
|  | * All proposed labels have to be submitted for registration in Singapore.
* For the proposed labels, a pristine and an annotated version (which highlights the changes made to the currently approved labelling) are 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/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)** |[ ] [ ]   |  |
|  | 1.4.4 | **Patient Information Leaflet (PIL)** |[ ] [ ]   |  |
| 1.5 | **Registration status in other countries** | [ ]  |[ ]   |  |
|  | 1.5.1 | **Tabulation of worldwide registration status** |  |  |  |  |
|  | 1.5.2 | **Approved SmPC/PI** |  |[ ]   |  |
|  |  | * Approved SmPC/ PI currently approved by each agency should be submitted.
 |  |  |  |  |
| 1.6 | **Description of Batch Numbering System** |  |  |  |  |
| 1.7 | **Proof of Approval** |  |[ ]   |  |
|  | * The proof of approval must come in the form of an official approval letter or equivalent document (e.g. CPP) issued by the National Medicine Regulatory Authority which certifies the registration status of the product (not provincial/ territory/ or state agencies). 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.
 |  |  |  |  |
| 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.
 |[ ] [ ]   |  |

**Module 2 - Common Technical Document Summaries**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section** | **Documents** | **Evaluation Route** | **HSA Screening** |
|  |  | **F** | **A** | **Submitted?** | **Remarks** |
| 2.1 | Overall CTD Table of Contents of Modules 2, 4 and 5 |[ ] [ ]   |  |
| 2.2 | Introduction |[ ] [ ]   |  |
| 2.3 | Quality Overall Summary |  |  |  |  |
| 2.4 | Non-clinical Overview | [ ] \* | [ ] \* |  |  |
| 2.5 | Clinical Overview |[ ] [ ]   |  |
| 2.6 | Non-clinical Summary |  |  |  |  |
|  | 2.6.1 | Introduction | [ ] \* | [ ] \* |  |  |
|  | 2.6.2 | Pharmacology Written Summary | [ ] \* | [ ] \* |  |  |
|  | 2.6.3 | Pharmacology Tabulated Summary | [ ] \* | [ ] \* |  |  |
|  | 2.6.4 | Pharmacokinetics Written Summary | [ ] \* | [ ] \* |  |  |
|  | 2.6.5 | Pharmacokinetics Tabulated Summary | [ ] \* | [ ] \* |  |  |
|  | 2.6.6 | Toxicology Written Summary | [ ] \* | [ ] \* |  |  |
|  | 2.6.7 | Toxicology Tabulated Summary | [ ] \* | [ ] \* |  |  |
| 2.7 | Clinical Summary |  |  |  |  |
|  | 2.7.1 | Summary of Biopharmaceutics Studies and Associated Analytical Methods | [ ] \* | [ ] \* |  |  |
|  | 2.7.2 | Summary of Clinical Pharmacology Studies | [ ] \* | [ ] \* |  |  |
|  | 2.7.3 | Summary of Clinical Efficacy | [ ]  | [ ]  |  |  |
|  | 2.7.4 | Summary of Clinical Safety | [ ]  | [ ]  |  |  |
|  | 2.7.5 | Literature References | [ ]  | [ ]  |  |  |
|  | 2.7.6 | Synopses of Individual Studies |[ ] [ ]   |  |

**Module 4 - Non-Clinical Study Reports**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section** | **Documents** | **Evaluation Route** | **HSA Screening** |
| **F** | **A** | **Submitted?** | **Remarks** |
| 4.1 | Table of Contents of Module 4 | [ ] \* | [ ] \* |  |  |
| 4.2 | Study Reports |  |  |  |  |
| 4.2.1 | Pharmacology | [ ] \* | [ ] \* |  |  |
| 4.2.2 | Pharmacokinetics | [ ] \* | [ ] \* |  |  |
| 4.2.3 | Toxicology | [ ] \* | [ ] \* |  |  |
| 4.3 | Literature References | [ ] \* | [ ] \* |  |  |

**Module 5 - Clinical Study Reports**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section** | **Documents** | **Evaluation Route** | **HSA Screening** |
|  |  | **F** | **A** | **Submitted?** | **Remarks** |
| 5.1 | Table of Contents of Module 5 |[ ] [ ]   |  |
| 5.2 | Tabular Listing of All Clinical Studies |[ ] [ ]   |  |
| 5.3 | Clinical Study Reports |  |  |  |  |
|  | 5.3.1 | Reports of Biopharmaceutic Studies | [ ] \* | [ ] \* |  |  |
|  |  | 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 comparability between the commercial product formulation and the clinical trial formulation used in pivotal studies should be submitted. |  |  |  |  |
|  | 5.3.2 | Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials | [ ] \* | [ ] \* |  |  |
|  | 5.3.3 | Reports of Human Pharmacokinetic Studies | [ ] \* | [ ] \* |  |  |
|  | 5.3.4 | Reports of Human Pharmacodynamic Studies | [ ] \* | [ ] \* |  |  |
|  | 5.3.5 | 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 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 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.
 |  |  |  |  |
|  | 5.3.6 | Reports of Post-marketing Experience | [ ] \* | [ ] \* |  |  |
|  | 5.3.7 | Case Report Forms and Individual Patient Listings (required upon request by HSA) |  |  |  |  |
| 5.4 | Literature References |[ ] [ ]   |  |
| 5.5 | Risk management plan (RMP) documents | [ ] \* | [ ] \* |  |  |
| 5.6 | Other Supporting Documents | [ ] \* | [ ] \* |  |  |