APPENDIX 13:
DRUG MASTER FILES AND CERTIFICATES OF SUITABILITY

1. GENERAL OVERVIEW

1.1. **Who should submit the document?**
- The applicant of the product registration shall submit the DMF or the Certificate of Suitability (CEP) with the product registration dossier.
- The DMF holder may submit the DMF via electronic copy (CD) and hardcopy (optional) directly to NPCB to maintain confidentiality of the contents.

1.2. **Classification of Active Pharmaceutical Ingredient (API)**
- Any substance or combination of substances used in a finished product, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings. (Ref: WHO)
- API can be classified into:
  - New API, used for the first time in a medicinal product either for human or veterinary use
  - Existing API not described in the European Pharmacopoeia (Ph.Eur.) or the pharmacopoeia of an EU Member State
  - Existing API described in the Ph.Eur. or in the pharmacopoeia of an EU Member State
- API can further be divided into:
  - Inorganic substances
  - Organic substances (isolated from material of animal or human origin)
  - Organic substances (synthetic or semi-synthetic or isolated from herbal sources or micro-organisms)

1.3. **Scope**
- API for new application for product registration. It is applicable to all pharmaceutical products (excluding traditional products) locally manufactured or imported. API used in product for export only (FEO) is exempted from submitting the DMF and CEP in product application.
- Separate registration of the API is not a requirement for the purpose of product registration. However, the required technical documentation pertaining to each API should be submitted with the product application.
• An API is assessed once an application using the related API is submitted for registration of a product by a Marketing Authorisation Holder (MAH).

1.4. Required Information
• Drug Master File
  o A Drug Master File (DMF) is a submission to the National Pharmaceutical Control Bureau (NPCB) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.

  o Technical contents of a DMF are reviewed only in connection with the review of a new application for product registration.

  o DMF’s are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file.

  o See section 2 for details (page 3).

• Certificates of Suitability (CEP)
  o CEP stands for Certification of suitability of European Pharmacopoeia monographs. COS (“Certificate of Suitability”) means the same and, even if often used, is not the official acronym.

  o The role of the CEP is to demonstrate that the purity of a given substance produced by a given manufacturer is suitably controlled by the relevant monograph(s) of the European Pharmacopoeia. By demonstrating that they have been granted a CEP for their substance, suppliers of raw materials can prove this suitability to their pharmaceutical industry clients and/or the NPCB.

  o Note that technical information (such as functionality tests, stability data when a retest period is not mentioned on the Certificate) is optional. However when it is not covered by the CEP and it may be required by NPCB and Marketing Authorisation Holder (MAH), it should be part of the application for product registration.

  o Where a CEP for an API is available or the API is listed on the list of APIs prequalified by WHO, Drug Master File (DMF) of such API may not be required by NPCB. However, the NPCB may request any additional information about the API if it is deemed appropriate.

  o See section 3 for details (page 5).
2. DRUG MASTER FILE (DMF)

2.1. The ICH M4Q technical guideline and ASEAN Common Technical Requirements (ACTR) provide details on the information to be included in the API sections of an application dossier.

2.2. If drug product contains more than one API, the information within Module 3.2.S (ICH CTD) or part 2.S (ACTD) must be provided in its entirety for each API.

2.3. If an API is manufactured by a manufacturer different from the product owner, data on its manufacture, quality control and stability shall be submitted via a DMF.

2.4. Where the API and drug product are manufactured by the same manufacturer, data on its manufacture, quality control and stability shall be submitted via a DMF.

2.5. The DMF is divided into two parts: an open (or applicant’s) part and a closed (or restricted) part.

2.6. The documentary requirements for an application making a reference to a DMF are as follows:

- From Applicant:
  - The open part of the DMF from the applicant, as part of the submitted dossier (the open part contains most of the information in Module 3.2S (ICH CTD) or Part 2.S (ACTD) - i.e. S1, S2.1 and S3 to S7 sections);
    - S1 General Information
      - 1.1 Nomenclature
      - 1.2 Structure
      - 1.3 General Properties
    - S2 Manufacture
      - 2.1 Manufacturer (s)
    - S3 Characterisation
      - 3.1 Elucidation of Structure and other Characteristics
      - 3.2 Impurities
    - S4 Control of Drug Substance
      - 4.1 Specification
      - 4.2 Analytical Procedures
      - 4.3 Validation of Analytical Procedures
      - 4.4 Batch Analysis
      - 4.5 Justification of Specification
    - S5 Reference Standards or Materials
    - S6 Container Closure System
    - S7 Stability
• From DMF Holder:
  o The complete (open and closed parts) DMF from the API manufacturer – i.e. the DMF holder (the closed part contains the confidential information in section 3.2.S.2.) and,
    ▪ S2 Manufacture
      – 2.1 Manufacturer (s)
      – 2.2 Description of Manufacturing Process and Process Controls
      – 2.3 Control of Materials
      – 2.4 Controls of Critical Steps and intermediates
      – 2.5 Process Validation and/or Evaluation
      – 2.6 Manufacturing Process Development
  o An original Letter of Authorisation (see below).

2.7. The Letter of Authorisation authorises NPCB to refer to the DMF in support of the application for a drug product. Thus, the Letter of Authorisation must state the following:

• The name of the drug product (product name, dosage form and product strength) to be registered;
• The local applicant responsible for product registration; and,
• A declaration that the local applicant and NPCB will be notified of any change in the API specification or in the manufacturing process that will likely affect the product’s quality or safety.

2.8. If a Letter of Authorisation does not fulfill these requirements, NPCB reserves the right to return the DMF to the DMF holder.

2.9. The DMF holder may submit the DMF via electronic copy (CD) or hardcopy (optional) directly to NPCB to maintain confidentiality of the contents. The information contained in the restricted part of the DMF will be regarded as confidential and will only be evaluated in support of the applications mentioned in the letter of authorisation. The confidential information will not be disclosed to any third party without a written authorisation from the DMF Holder.

2.10. Upon receipt of the DMF or CEP or any certification recognized by the NPCB, a DMF number or reference number will be assigned. For future correspondence, the applicant and the DMF holder should make a reference to the assigned DMF number or reference number. Should there be deficiencies within the restricted part of the DMF, NPCB will raise queries directly with the DMF holder. The applicant referencing a DMF is required to include a copy of the DMF holder’s letter of authorisation in the application.
2.11. Applicants are responsible to maintain and update the DMF. Applicants should file a variation if there are changes to the DMF. Please refer Annex A for Type I & Type II variations for DMF.

2.12. DMF Holder Obligations:
   • Any change or addition, including a change in authorisation related to specific applicants, should be submitted in duplicate and adequately cross referenced to previous submission(s). The reference should include the date(s), volume(s), section(s), and/or page number(s) affected.
   • A DMF holder must notify each affected applicant who has referenced its DMF of any pertinent change in the DMF. Notice should be provided well before making the change in order to permit the applicant to supplement or amend any affected application(s) as needed.

2.13. A DMF is not required for common inorganic salts (for example, sodium chloride, and other common electrolytes) used and regarded as API drug substances in products such as injections and dialysis solutions, and simple organic compounds available commercially in high purity (for example, natural occurring organic acids and their salts, including ascorbic acid and sodium citrate, and simple mono- and disaccharides such as glucose and sucrose). Although a DMF is not required for these active ingredients, evidence needs to be submitted by the finished product manufacturer that the substance is obtained from a reliable source and consistently comply with the applicable pharmacopoeial specifications. Any non-pharmacopoeial specifications need to be assessed by the NPCB to determine their appropriateness and adequacy to ensure the quality of the substance.

2.14. Where a DMF is submitted for an API controlled according to a pharmacopoeial monograph, the DMF should include a discussion of the potential impurities most likely to arise during synthesis using the actual manufacturing process described in the DMF together with evidence that these impurities are adequately controlled by the test procedures described in the pharmacopoeial monograph. Where particular impurities found in the substance are not listed in the monograph, but are proposed to be allowed at certain level, a justification (including toxicological data, if appropriate) should be provided.

3. CERTIFICATES OF SUITABILITY (CEP)

3.1. If reference is made to a CEP, the applicant should submit a copy of the valid CEP, including all annexes, in lieu of a DMF or Section S of the CTD. However, the following documents must accompany the CEP (and inserted into its corresponding CTD S section):
   • Results of batch analysis (S4.4) from the API manufacturer* demonstrating compliance with the Ph. Eur. monograph and including any additional tests/limits listed on the CEP; and,
• Additional data to address any relevant parameter(s) not addressed in the CEP, such as stability data (S7), if a re-test period is not stated on the CEP and physico-chemical characteristics (e.g. particle size, polymorphism, etc), if applicable.

3.2. NPCB reserves the right to request for any additional information about the API if it deemed appropriate.

3.3. If there is a CEP for animal-derived material used in the drug product, the applicant may submit the CEP in lieu of the documents stipulated in DRGD.

3.4. It is the applicant’s responsibility to submit the latest CEP updates, with annexes, as soon as it is available from the European Directorate for the Quality of Medicines and Healthcare (EDQM).

3.5. NPCB will recognize the evaluation of relevant APIs by the regulatory authorities of the reference countries (Australia, Japan, France, Switzerland, United Kingdom, Canada, Sweden, United State of America), WHO (prequalified list of pharmaceutical) and the European Directorate for the Quality of Medicines & Healthcare (EDQM).

* If the API manufacturer is CEP certified and drug product manufacturer claims otherwise (USP, JP, In-House etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted instead.

4. STABILITY DATA OF API (3.2.S.7)

4.1 Stability test data should be provided for at least 3 production batches and should include:
• batch details (batch number, date of manufacture);
• the general test methodology (duration of study, storage conditions of temperature and humidity, time points when samples were removed for analysis etc.);
• the analytical test methods (assay method of quantitation, determination of degradation products, moisture etc);
• validation of test methods;
• results of tests;
• conclusions.

4.2 In circumstances where complete real time stability data is not available at the time of submission, the minimum stability data required are as follows:
• At least 12 months of real time data and 6 months of accelerated data on at least three primary batches of the API;
• The batches should be at least pilot scale-sized and manufactured by a method that simulates the final commercial process.
In view of this, the shelf life may be extended beyond the end of real time studies which can be extrapolated not more than 12 months covered by the real time data.

4.3 If the API is sourced from multiple sites, stability data from each site should be provided.

4.4 NPCB may request for additional stability data if deemed necessary for the evaluation of the application.

5. SITE INSPECTION

5.1. Dependent on the outcome of the evaluation of the API dossier, a risk-based approach will be used in planning of inspections, taking into account the type of APIs and the outcome, results and reports of inspections conducted by other regulatory authorities or competent organizations.

5.2. NPCB will plan and coordinate the performance of inspections at the manufacturing site(s) of APIs and that of the key intermediate (if relevant) to assess compliance with the relevant sections of relevant GMP Guidelines, and will compare the technical information on the manufacturing process given in the API dossier submitted with the manufacturing process actually carried out on the site.

5.3. The inspections will be performed by auditors who have the relevant qualifications and experience to perform such inspections, be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in GMP. Auditors will perform the inspections and report on its findings in accordance with established SOPs so as to ensure a standard harmonized approach.

6. MAINTENANCE OF APPROVAL STATUS

6.1. Manufacturers of finished products should establish a mechanism by which manufacturers/suppliers of API will provide information on any changes (variations) in manufacture and control that may have impact on the safety, efficacy and quality of the API. It is the applicant's responsibility to provide NPCB with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have an impact on the quality of the API that has been previously approved. For those APIs approved by NPCB, an evaluation of variations according to the established guidelines will need to be done.

6.2. Random samples of APIs supplied to manufacturers of finished pharmaceutical products may be taken for independent testing if there is a need. Certificates of Analysis released by the manufacturer and specifications for test methods should be provided by the manufacturer or applicant to NPCB for review upon request. In the event of failure to meet the established criteria for testing, NPCB will investigate the problem and communicate this to the manufacturer concerned.
6.3. NPCB may conduct a re-evaluation of the APIs at a 5 year interval. If, as a result of this re-evaluation, it is found that a API and/or specified manufacturing site no longer complies with the recommended standards, such APIs and manufacturing sites will be removed from the approved list.

6.4. Re-evaluation, including re-inspections, may also be performed:
- if any fraud or omissions by the applicant or manufacturer(s) of APIs in the initial assessment procedure or during the follow-up activities, becomes evident; and
- if NPCB or other parties as user of the procedure consider(s) that a batch or batches of supplied prequalified APIs are not in compliance with the specifications which were found to be applicable upon prequalification.
ANNEX A – TYPE I & TYPE II VARIATION ON DMF

**Type I:** Minor variation with a 14 days validation period. The applicant may proceed to implement the change after a 14 days validation period upon the date of receiving the documents by variation unit.

Dossier requirements for Type 1 variation:

1. **Renaming (e.g. street name, postal code) of Manufacturing Site of Drug Substance**
   - **Condition:** The manufacturing site of the drug substance remains at the same physical location.
   - **Supporting Documents:**
     i. Updated information of the manufacturer of the drug substance
     ii. A declaration from the applicant that manufacturing site remains the same and that the remaining does not involve changes of the manufacturing process and/or quality of the product.

2. **Withdrawal/Deletion of Manufacturer (Drug Substance, Drug Product, Packager or Batch Releaser)**
   - **Supporting Documents:**
     i. Reason for withdrawal/deletion

3. **Minor Change of Manufacturing Process of Drug Substance**
   - **Conditions:**
     - The synthetic route remains the same;
     - Specification of the drug substance remains the same;
     - No change in the physical properties;
     - No new impurities or change in level of impurities which would require further qualifications in safety studies.
   - **Supporting Documents:**
     i. Relevant CTD section S;
     ii. Tabulation of the current and proposed process with changes highlighted;
     iii. Batch analysis data (in a comparative table) of at least two batches (pilot scale or production scale) manufactured according to the currently approved and proposed process;
     iv. A declaration from the applicant that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the level of impurities, which require further safety studies;
     v. A declaration from the applicant that the specification of the drug substance has not changed or if there is any change to the specification (i.e. tightening), the texts of the current and proposed specifications should be provided (in a comparative table where possible).
vi. A declaration from the applicant that the relevant stability studies of the drug substance in accordance with the relevant guidelines have been started and that the relevant stability studies will be finalized; data should be provided only if outside specification (with proposed action).

4. **Change of batch size of drug substance**
   - **Condition:**
     - The change does not affect the reproducibility of the process.
   - **Supporting documents:**
     i. Amended relevant CTD Section S;
     ii. Batch analysis data (in a comparative table) on a minimum of one production batch manufactured to both the currently approved and the proposed batch sizes. Batch data on the next 2 full production batches should be available on request or reported if outside specification (with proposed action);
     iii. Specification of the drug substance.

5. **Change to comply with accepted pharmacopoeia(s) for drug substance**
   Pharmacopoeia accepted by NPCB are EP, USP, BP and JP.
   - **Conditions:**
     - Change is made exclusively to comply with an update of relevant monograph of the pharmacopoeia;
     - Exclude change from one accepted pharmacopoeia to another.
   - **Supporting documents:**
     i. Tabulation of the current and revised specifications with changes highlighted;
     ii. Revised specification of the drug substance;
     iii. Batch analysis of the drug substance for all tests in the new specification

6. **Change of test procedure of drug substance**
   - **Condition**
     - Results of method validation show new test procedure to be at least equivalent to the former procedure.
   - **Supporting documents**
     i. Description of the analytical methodology, a summary of validation data, and comparative analytical result between the current test and the propose one, if appropriate;
     ii. Specification of the drug substance;
     iii. A declaration from the applicant that the specification of the drug substance has not changed.

7. **Tightening of specification or addition of new test parameter(s) and limit(s) of drug substance**
- **Condition**
  - New test method does not concern a novel non-standard technique or a standard technique used in a novel way

- **Supporting documents**
  1. Tabulating of the current and revised specification of drug substance with changes highlighted;
  2. Revised specification of drug substance;
  3. Batch analysis of the drug substance for all tests in the new specification
  4. Description of any new analytical method and summary of the validation data, if applicable.

8. **Extension of shelf life or retest period of drug substance**
   - **Condition**
     - The studies must show compliance with specification

   - **Supporting documents**
     1. Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested shelf life or retest period;

9. **Change of imprints, bossing or other markings on tablet or printing on capsules, including addition or change of inks used for product marking**
   - **Conditions**
     - New markings do not cause confusion with other tablets or capsules;
     - The inks have not been rejected for pharmaceutical use;
     - Release and shelf life specifications of the drug product have not changed (except for appearance).

   - **Supporting documents**
     1. Details of the proposed new inks (where applicable);
     2. Detailed drawing or written description of the current and proposed imprint/ bossing/ marking/ ink;
     3. Official letter of commitment to inform users of the relevant changes, and that the current products stocks will be exhausted before the product labeled with the new name is marketed;
     4. A declaration from the applicant that the release and shelf life specifications of the product have not changed (except for appearance).
**Type II**: Major variation is considered a major change and approval is required prior to implementation. The applicant is responsible for ensuring that all the necessary validation has been conducted to demonstrate that the change does not reduce the quality, safety or efficacy of the product.

Dossier requirements for Type 2 variation:

1. **Change or inclusion of Manufacturing site(s) of drug substance**
   Supporting documents:
   i. CTD section S, CEP for the drug substance or both the open and closed portions of the DMF;
   ii. Tabulation of the differences compared with the registered manufacture information (if applicable);
   iii. Batch analysis data (in a comparative tabular format) for at least 2 batches (minimum pilot scale) of the drug substance from the current and proposed manufacturers/sites;
   iv. A letter of commitment to conduct the appropriate stability study for the drug product manufactured with the drug substance from the proposed manufacturer.

2. **Major change of manufacturing process of drug substance**
   Supporting documents:
   i. Relevant CTD section S;
   ii. Tabulation of the current and proposed process with changes highlighted;
   iii. Batch analysis data (in a comparative tabular format) for at least 2 batches (minimum pilot scale) manufactured according to the currently approved and proposed process;
   iv. A declaration from the applicant that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the level of impurities, which require further safety studies;
   v. If any potential new impurities are detectable at an acceptable limit of detection, appropriate evidence must be provide;
   vi. A declaration from the applicant that the specification of the drug substance has not changed or if there is any change to the specification (i.e. tightening), the texts of the current and proposed specifications should be provided (in a comparative tabulation form where possible);
   vii. Relevant stability studies of the drug substance in accordance with the relevant guidelines should be provided;
   viii. A letter of commitment to conduct the appropriate stability study for the drug product manufactured with the drug substance from the new manufacturing process, and report if any results fall outside shelf life specification (with proposed action).

3. **Change of specification of drug substance**
   Supporting documents
   i. Scientific and/or historical data used to support the change;
ii. Currently registered version of the release and/or shelf life specifications with the proposed change(s) clearly highlighted, underscored, or otherwise indicated (in a comparative tabulation form).