Version 1

APPENDIX 14:

REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS

TABLE OF CONTENTS

1. INTRODUCTION:

1.1. A significant part of the quality of a finished pharmaceutical product is dependent on the quality of the Active Pharmaceutical ingredients (APIs) used for its formulation. Thus, a proper system of qualification of suppliers is necessary to ensure a constant sourcing of APIs of appropriate quality and to safeguard the public health interests. This will be done through standardised quality assessment and inspection procedures.

1.2. The National Pharmaceutical Control Bureau (NPCB) under the purview of the Ministry of Health Malaysia will introduce mandatory control of APIs as part of the requirements in the product registration application. This will be implemented prospectively according to a phased timeline established by the NPCB.

1.3. The implementation will begin with voluntary submission for New Chemical Entities in April 2011 and followed by;

- Phase 1- New Chemical Entity (mandatory in Jan 2012)
- Phase 2- Scheduled Poison, (to be determined)
- Phase 3- Non-scheduled Poison (to be determined)

1.4. The procedure for control of APIs established by the NPCB is based on the following principles:

- A general understanding of the production and quality control activities of the manufacturer;
- Assessment of API data and information, including changes and variations, submitted by the MAH/API manufacturer. These data should include the manufacturing process, material specifications and test data and results;
- Assessment of the manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key raw materials and APIs during and after purification through compliance with Good Manufacturing Practice (GMP);
- Random sampling and testing of APIs (post marketing surveillance);
- Handling of complaints and recalls; and
- Monitoring of complaints from other agencies and countries.

1.5. This guideline is intended to provide guidance regarding the requirements to be included for APIs in the quality part of the product dossier.

2. DEFINITION

2.1. Definition of Active Pharmaceutical Ingredient (API)

- Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active

ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body *(World Health Organisation (WHO))*.

2.2. Classification of Active Pharmaceutical Ingredient (API)

2.2.1 API classification can be divided into:

- Inorganic substances;
- Organic substances (isolated from materials of animal or human origin); and
- Organic substances (synthetic or semi-synthetic or isolated from herbal sources or micro-organisms).

3. SCOPE

3.1. This Guideline encompasses the APIs of new products for registration. This is applicable to all pharmaceutical products (excluding traditional products, veterinary products, and health supplement products) both locally manufactured and imported.

3.2. Biological active substances and immunological active substances are excluded from the scope of this Guideline.

3.3. APIs used in products for export only (FEO) are exempted from the requirement for submission of the Drug Master File (DMF) and Certification of Suitability (CEP) in the product application.

3.4. The DMF and CEP are only applicable for final APIs and not API intermediates.

3.5. Separate registration of the APIs is not a requirement for the purpose of product registration. However, the required technical documentation pertaining to each API should be submitted with the new online product registration application.

3.6. Assessment of an API will be performed once submission of an application for registration of a product using the said API is made by a Marketing Authorization Holder (MAH).

4. PROCEDURE FOR SUBMISSION

4.1. How to submit

4.1.1 The MAH of the product registration shall submit Part 2.S ACTD as part of online product application. Where any information required as per ACTD is not available the DMF will be required.

4.1.2 The DMF may be submitted via an electronic copy (CD) or a hardcopy (optional) directly to the NPCB to maintain confidentiality of the contents.

4.1.3 The NPCB may accept a CEP issued by European Directorate for the Quality of Medicine (EDQM) in lieu of the DMF of an API.

4.2. **Required Information**

4.2.1 Documents required:

- Part 2.S ACTD via the online system.
- DMF or CEP (*See Section 5 and 6 for details*).
- Current GMP certificate or any other evidence of GMP compliance from a regulatory authority(as deemed appropriate); and,
- Certificates of Analysis (2 batches).

4.2.2 In order to gain approval for an API;

- The data should be sufficient to justify the specifications and testing of the API (including validated analytical methods).
- The information should confirm the identity and stability of the API by providing appropriate structure elucidation and stability studies; and,
- The control of the API manufacturing process as well as the ability to produce an API with reproducible physical properties and impurity profiles should be demonstrated.

4.2.3 Any additional information regarding the API shall be requested by the NPCB, as deemed necessary.

4.3 Other considerations

4.3.1 In the spirit of harmonisation of regulatory activities and optimisation of efficient assessment, The NPCB will take into consideration the evaluation of relevant APIs by the regulatory authorities of the reference countries (Australia, Japan, France, Switzerland, United Kingdom, Canada, Sweden, and the United State of America) and other PIC/S countries.

4.4 Processing Fee

4.4.1 Not required as the API application is already incorporated in the application for product registration.

5. DRUG MASTER FILE (DMF)

5.1. The Drug Master File (DMF) is a document 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.

5.2. The DMF submitted to the NPCB should contain the information as required under sections listed in Part 2.S ACTD.

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

5.4. DMF's are generally created to allow an authorized party other than the holder of the DMF to refer the DMF without disclosing to that party the contents of the file.

5.5. The ASEAN Common Technical Requirements (ACTR) provides details on the information to be included in the API sections of an application dossier.

5.6. If drug product contains more than one API, the information within part 2.S (ACTD) must be provided for each API.

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

5.8. The DMF is divided into two parts, namely the Open (or MAH's) part and the Closed (or confidential) part.

5.9 In situations where the MAH is not the API manufacturer or does not have access to detailed confidential documentation, the MAH is allowed to submit the the Open part through the product registration application and the Closed (or confidential) part is submitted by the API manufacturer directly to NPCB.

5.10 The documents required for an application making a reference to a DMF are as follows:

- **From the MAH:**
  - Open part of the DMF *from the MAH*, as part of the submitted product dossier (the open part contains most of the information in Part 2.S (ACTD) - i.e. sections S1, S2.1 and S3 to S7);
    - S1 General Information
      - 1.1 Nomenclature
      - 1.2 Structure
      - 1.3 General Properties
    - S2 Manufacture
      - 2.1 Manufacture(s)/Site of Manufacture

- S3 Characterisation
  - 3.1 Elucidation of Structure and other Characteristics
  - 3.2 Impurities
- S4 Control of API/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 the API Manufacturer:**
  - The complete (open part and closed part) DMF from the API manufacturer. The closed part contains the confidential information in section Part 2.S.2. ACTD- i.e. section 2);
    - S2 Manufacture
      - 2.1 Manufacture(s)/Site of Manufacture
      - 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
  - An original Letter of Access (see below).
    The Letter of Access authorises the NPCB to refer to the DMF, in support of the application for a drug product. Thus, the Letter of Access must state the following:

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

5.11. The API Manufacturer may submit the DMF via electronic copy (CD) or hardcopy (optional) directly to the 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 Access. The confidential information will not be disclosed to any third party without a written authorization from the API Manufacturer.

5.12. Upon receipt of the DMF or CEP, a reference number will be assigned to the application for product registration. For future correspondences, the MAH and the API Manufacture should make a reference to this assigned reference number.

Should there be deficiencies within the restricted part of the DMF; The NPCB will raise queries directly with the API Manufacturer. The MAH referencing a DMF is required to include a copy of the API Manufacturer's Letter of Access in the application.

5.13. API Manufacturer is responsible to maintain and update the DMF. The MAH should file a variation once they are notified with the changes to the DMF.

5.14. API Manufacturer Obligations:

- Any change or addition, including a change in authorisation related to specific MAH, shall be submitted to the NPCB 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.
- Should any change to a DMF is necessary, the API Manufacturer shall notify each affected MAH who has referenced the DMF of the pertinent change. Such notice should be provided well before making the change in order to permit the MAH to supplement or amend any affected application(s) as needed.

5.15. A DMF is not required for common inorganic salts (for example, sodium chloride, and other common electrolytes) used and regarded as API 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 MAH 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.

5.16. Where a DMF is submitted for an API controlled according to a pharmacopoeia 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, a justification (including toxicological data, if appropriate) should be provided.

6. CERTIFICATES OF SUITABILITY (CEP)

6.1. CEP stands for certification of suitability of European Pharmacopoeia monographs/Certificate of Pharmacopoeia.

6.2. The CEP is a document that is used 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 grant a CEP for

given API, the suppliers of the API can prove such suitability to their pharmaceutical industry clients and the NPCB.

6.3. The MAH should include a copy of the most current CEP in the dossier, together with the following:

- A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision and
- A declaration from the API manufacturer that the local MAH and the NPCB shall be notified should there be any future change in the API specifications in the manufacturing process that is likely to affect the product's quality or safety.

Note: All such written statements must state the name of the drug product (product name, dosage form and product strength) to be registered and the local MAH responsible for finished product registration.

6.4. Further technical information as required by the NPCB (e.g. regarding functionality tests or stability data when a retest period is not stated on the CEP) shall be submitted as part of the application for product registration.

6.5. If reference is made to a CEP, the Marketing Authorization Holder (MAH) should submit a copy of the ***valid*** CEP, including all annexes, in lieu of a DMF. However, the following documents must accompany the CEP.

- 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 (e.g residual solvents, additional impurity tests); and,

- In case of sterile API, full description of the sterilization process as specified on the CEP as well as results of any tests (particularly the tests in the monograph) and validation data should be provided.

- 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.

***** *In cases where the drug product manufacturer tests the CEP certified API according to specification other than Ph.Eur (i.e. USP, JP, In-House etc) data covering S 4.1 to S4.5 should be submitted by the MAH.*

6.6 The NPCB reserves the right to request for any additional information about the API when deemed appropriate.

6.7. The MAH's responsibility to submit the latest CEP updates, with annexes, as soon as it is available from the API manufacturer.

7. STABILITY DATA OF API.

7.1 Stability test data for an API should be provided, for at least 3 primary batches. These data should include:

- Batch details (e.g., batch number, date of manufacture);
- The general test methodology (e.g., duration of study, storage conditions of temperature and humidity, time points when samples were removed for analysis etc.);
- The analytical test methods (e.g., assay method of quantitation, determination of degradation products, moisture etc);
- Validation of test methods;
- Results of tests; and,
- Conclusions.

7.2 In circumstances where an API retest period has not been established and 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 re-test date 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.*

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

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

7.5 Stability data is not required where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant

8. SITE INSPECTION

8.1 Depending on the outcome of the evaluation of the API dossier, a risk-based approach will be used in the planning of inspections,the approach will take into account the type

of APIs as well as the outcome, results and reports of inspections conducted by other regulatory authorities or competent organisations.

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

8.3. All such inspections shall be performed by auditors deemed to possess sufficient qualifications and experience in order to perform such inspections, to be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in the area of GMP. Such auditors shall perform the inspections and report on its findings in accordance with established Standard Operating Procedures (SOPs) so as to ensure a standard harmonised approach.

9. MAINTENANCE OF APPROVAL STATUS

9.1. Manufacturers of finished products should establish a mechanism by which manufacturers/suppliers of an API shall provide information on any changes (i.e., variations) in manufacture and control that may have impact on the safety, purity and quality of the API. It is the MAH's responsibility to provide the NPCB with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not havean impact on the safety, purity and quality of the API that has been previously approved. For those APIs approved by the NPCB, an evaluation of such variations shall be performed with accordance to the ASEAN Variation Guidelines.

9.2 . 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 API manufacturer as well as specifications for test methods shall be provided by the API manufacturer or the MAH to the NPCB for review upon request. In the event of failure to meet the established criteria for testing, the NPCB shall proceed to investigate and communicate this problem to the manufacturer concerned.

9.3. The 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 an API and/or specified manufacturing site(s) no longer complies with the recommended standards, such APIs and manufacturing sites will be removed from the approved list. . Prior notice to the MAH and API manufacturer shall be issued from the NPCB regarding such decision.

9.4. Re-evaluation may also be done in any situation deemed necessary, including the following:

- If any omissions by the manufacturer in the initial assessment procedure or during the follow-up activities is evident in relation to the requirements. This includes compliance with GMP.

- If any batch(s) of supplied APIs is considered not to be in compliance with the agreed specification of the API;

- If the CEP, or an API for which a CEP dossier was submitted, is cancelled or refused based on the assessment of the dossier for any other reason;and,

- If, in the opinion of the NPCB, changes made in the sourcing of key intermediates, route of synthesis, facility or other production, require that reassessment be made.

10. ABBREVIATIONS

ACTD	ASEAN Common Technical Dossier
API	Active Pharmaceutical Ingredient (Interchangeable with drug substance or active substance). The term API Manufacturer is interchangeable with DMF Holder.
DMF	Drug Master File (interchangeable with Active Substance Master File)
CEP	Certificate of Suitability of European Pharmacopoeia monographs issued by the EDQM
GMP	Good Manufacturing Practice
EDQM	European Directorate for the Quality of Medicine and Healthcare
MAH	Marketing Authorisation Holder
NPCB	National Pharmaceutical Control Bureau, Ministry of Health
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
WHO	World Health Organisation

11. REFERENCES AND GUIDELINES

11.1. Guidelines on the content of Drug Master File

The technical requirements related to the quality of active pharmaceutical ingredients have already been addressed elsewhere, (such as in the ASEAN, WHO, ICH, EDQM and EMA guidelines), and applicants are advised to refer to these guidelines available at the relevant website such as:

- The Asean Common Technical Dossier (ACTD) For The Registration Of Pharmaceuticals For Human Use Organization Of The Dossier (http://portal.bpfk.gov.my/index.cfm?menuid=46&parentid=15)

- The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: Quality – M4Q(R1) (http://www.ich.org/LOB/media/MEDIA556.pdf)

- Procedure For Assessing The Acceptability,In Principle, Of Active Pharmaceutical Ingredientsfor Use In Pharmaceutical Product Http://Apps.Who.Int/Prequal/Info_General/Documents/TRS953/TRS_953-Annex4.Pdf

- Guideline On Submission Of Documentation For A Multisource (Generic) Finished Pharmaceutical Product (FPP): Preparation Of Product Dossiers (PDS) In Common Technical Document (CTD) Format Http://Apps.Who.Int/Prequal/Info_General/Documents/Generic_Guide/Genericguideline_PDS_CTD-Format.Pdf

- Guideline on Active Pharmaceutical Ingredient Master File (APIMF) Procedure. (http://apps.who.int/prequal/info_applicants/Guidelines/APIMF_Guide.pdf)

- Guideline on Summary Of Requirements For Active Substances. In The Quality Part of the Dossier. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002813.pdf)

- Content of the Dossier for Chemical Purity and Microbiological Quality (PA/PH/CEP 04 1 4R) http://www.edqm.eu/medias/fichiers/Content_of_the_Dossier_for_Chemical_Purity_Microbiological_Quality.pdf

- Content of the Dossier for a Substance for TSE Risk Assessment (PA/PH/CEP (06) 2) http://www.edqm.eu/medias/fichiers/Content_of_the_Dossier_for_a_Substance_for_TSE_Risk_Assessment.pdf

- Certificates of Suitability for Sterile Active Substances (PA/PH/Exp. CEP/T (06) 13, 1R)
  http://www.edqm.eu/en/New-Applications-29.html

11.2. **Guidelines on Stability Testing**

The following Guidelines may be consulted in the context of stability testing:

- WHO Technical Report Series, No. 953, 2009 Annex 2: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (http://www.who.int/medicines/publications/pharmprep/PDF_TRS953_WEB.pdf)

- International Conference on Harmonisation. *ICH Q1A* (*R2*)*: Stability testing of new drug substances and products*
  (http://www.ich.org/LOB/media/MEDIA419.pdf)

- International Conference on Harmonisation. *ICH Q1B: Photostability testing of new drug substances and products*
  (http://www.ich.org/LOB/media/MEDIA412.pdf)

- International Conference on Harmonisation*. ICH Q1C: Stability testing of new dosage forms*
  (http://www.ich.org/LOB/media/MEDIA413.pdf).

- International Conference on Harmonisation*. ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products*
  (http://www.ich.org/LOB/media/MEDIA414.pdf).

- International Conference on Harmonisation. *ICH Q1E: Evaluation for stability data*
  (http://www.ich.org/LOB/media/MEDIA415.pdf).

- Note For Guidance On Stability Testing: Stability Testing Of New Drug Substances And Products (CPMP/ICH/2736/99)
  (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002651.pdf)

- Note For Guidance On. Stability Testing Of Existing Active Substances And Related Finished Products
  (www.ema.europa.eu/pdfs/vet/qwp/084699en.pdf)

- ASEAN Stability Guideline
  (http://portal.bpfk.gov.my/index.cfm?menuid=46&parentid=15)