

APPENDIX 6 : GUIDELINE ON REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs) (Version 2.3)

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1. INTRODUCTION

- 1.1. A significant part of the quality of a finished 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 standardized quality assessment and inspection procedures.
- 1.2. The National Pharmaceutical Regulatory Division (NPDRA) under the purview of the Ministry of Health Malaysia has introduced mandatory control of APIs as part of the requirements in the product registration application.
- 1.3. The implementation began with voluntary submission for New Drug Products in April 2011 and followed by;

- **Phase 1** - New Drug Products (January 2012)
- **Phase 2** - Scheduled Poison
 - a) New Application (Generic Product):-
 - i. Parenteral Dosage Form : 1 July 2014
 - ii. Oral Dosage Form : 1 July 2016
 - iii. Others : 1 July 2018

- b) Registered Product (Pharmaceutical products containing Scheduled Poison):-
All Dosage Form : Expire on 1 January 2020 onwards

* API Information must be submitted at least **one year before the expiry date**.

Reference:

- i) [Bil \(12\) dlm BPFK/PPP/01/03 Jld1 17 March 2011](#)
- ii) [BPFK/PPP/07/25 \(7\) 16 January 2014](#)
- iii) [Bil \(11\) dlm BPFK/PPP/01/03 Jld3 27 June 2014](#)

- **Phase 3** - Generic Product NOT containing Scheduled Poison (to be determined)

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

- A general understanding of the production and quality control activities of the manufacturer;
- Assessment of APIs data and information, including changes and variations, submitted by the product registration holder (PRH)/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 (Part II-S).

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 ([WHO Technical Report Series No.970,2012](#)).

2.2 CLASSIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENT (API)

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 final APIs of new products for registration and current/exist in registered products. 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. Please refer to relevant guidelines available for Biologics.
- 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. Premixing of API is part of the product manufacturing process; therefore information on premixed API should be submitted under Part II-P. Submission for Part II-S solely includes information on API only.
- 3.5. Separate registration of the API is not requirement for the purpose of product registration. However, the required technical documentation pertaining to each API should be submitted with the new product registration application.
- 3.6. Assessment of an API will be performed once submission of a new product registration application has been done.
- 3.7. Assessment of an API will also be performed for a registered product prior to a product renewal application (as stated in item 1.3).

4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION

4.1 HOW TO SUBMIT

The API(s) information can be submitted to NPRA through one of the following three options:

- Option 1: Drug Master File (DMF) procedure; or
- Option 2: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 3: Full details of “Part II-S ACTD” in the Product Dossier

Note:

- The PRH should attach:
 - i) a cover letter (clearly indicating the product name, API name, option for API submission) and
 - ii) API submission checklist
<http://npra.moh.gov.my/index.php/guidelines-central>
- The PRH shall submit Part II-S ACTD as part of product application. In cases where required information as per ACTD is not available, the DMF is accepted.
- The DMF must be submitted via electronic copy (CD) directly to the NPRA to maintain confidentiality of the contents.
- The NPRA 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 for each option of API Information submission are summarized as in table 1:

Table 1:
Summary of documents required for API Information Submission:

Option	Documents required
Option 1 (DMF)	<ul style="list-style-type: none"> Part II-S ACTD via the online system (Open Part only) DMF (See Section 5 for details) Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).
Option 2 (CEP)	<ul style="list-style-type: none"> Part II-S ACTD via the online system (as deemed appropriate) CEP (See Section 6 for details); and, Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).
Option 3 (Full ACTD)	<ul style="list-style-type: none"> Full details of Part II-S ACTD via the online system.(See Section 7 for details) Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and, Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).

*GMP certificates for **ALL** manufacturers involved in manufacturing process of API.

4.2.1 Separate API information must be provided for each API for:

- i. Finished product contains more than one API
- ii. API from different manufacturing site
- iii. API from different synthesis route

- 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 The NPRA reserves the right to request for **any** additional information about the API when deemed appropriate.

4.3 OTHER CONSIDERATIONS

In the spirit of harmonisation of regulatory activities and optimisation of efficient assessment, The NPRA may 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 and World Health Organization (WHO).

4.4 PROCESSING FEE

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

5. OPTION 1 :DRUG MASTER FILE (DMF)

- 5.1. The Drug Master File (DMF) is a document that may 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 NPRA should contain the information as required under sections listed in Part II-S ACTD.
- 5.3. DMF is generally created to allow an authorized party other than the holder of the DMF to refer the DMF without disclosing the contents of the file to any other party.
- 5.4. The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR) / ACTD provide details on the information to be included in the API sections of an application dossier.
- 5.5. Where the API and the finished product are manufactured by the same manufacturer, information on the production, quality control and stability of the API may be submitted as part of the dossier for the finished product (ACTD) rather than in a separate DMF. However, the company is not precluded from submitting a DMF for the API.
- 5.6. The DMF is divided into two parts, namely the Open (or PRH's) part and the Closed (or restricted) part.
- 5.7 The documents required for an application making a reference to a DMF are as follows:
 - **From the PRH:**
 - Open part of the DMF, as part of the submitted product dossier (the open part contains most of the information in Part II-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
 - **ALL** manufacturers involved in manufacturing process of API.
 - S3 Characterisation
 - 3.1 Elucidation of Structure and other Characteristics
 - 3.2 Impurities
 - S4 Control of API/Drug Substance
 - From API manufacturer:
 - 4.1 Specification of API
 - 4.2 Analytical Procedures
 - 4.3 Validation of Analytical Procedures
 - 4.4 Batch Analysis-minimum three batches
 - Certificate of Analysis (COA)-minimum two batches.
 - 4.5 Justification of Specification

 - From Finished product manufacturer:
 - 4.1 Specification of API
 - Certificate of Analysis (COA)-minimum two batches.
 - S5 Reference Standards or Materials
 - (from API manufacturer AND finished product manufacturer).
 - S6 Container Closure System
 - S7 Stability
- **From the API Manufacturer:**
 - The Complete DMF (open part AND closed part); S1-S7.
The closed part contains the confidential information in section Part II-S ACTD - i.e. section S2);
 - 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.
The Letter of Access from API Manufacturer/ holder of the DMF authorizes the NPRA to refer to the DMF, in support of the application for a finished product. Thus, the Letter of Access must state the following:
 - The name of the finished product (product name, dosage form and product strength) to be registered;
 - The PRH responsible for finished product registration; and,
 - A declaration that both the PRH and the NPRA 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.

The PRH is responsible to ensure that the complete DMF (i.e. both the *Open part* and the *closed part*) submitted to NPRA directly by the API Manufacturer.

- 5.8. The API Manufacturer may submit the DMF via electronic copy (CD) directly to the NPRA to maintain confidentiality of the contents. The information contained in the closed 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.
- 5.9. Separate DMF must be provided for each API for:
 - i. Finished product contains more than one API
 - ii. API from different manufacturing site
 - iii. API from different synthesis route
- 5.10. Upon receipt of the DMF, a BPFK/NPRA DMF number will be assigned to the application for product registration. For future correspondences, the PRH and the API Manufacturer should make a reference to the BPFK/NPRA DMF number. The NPRA will directly contact API Manufacturer for any correspondence pertaining to API information in closed part. The PRH is required to include a copy of the API Manufacturer's Letter of Access in the application.
- 5.11. API Manufacturer is responsible to maintain and update the DMF. The PRH should file a variation once they are notified with the changes to the DMF.

5.12. API Manufacturer Obligations:

- Any change or addition, including a change in authorization related to specific PRH, shall be submitted to the NPRA 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 PRH who has referenced the DMF of the pertinent change. Such notice should be provided well before making the change in order to permit the PRH to supplement or amend any affected application(s) as needed.

5.13. The 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 API, evidence needs to be submitted by the PRH that the API is obtained from a reliable source and consistently comply with the applicable pharmacopoeial specifications. Any non-pharmacopoeial specifications need to be assessed by the NPRA to determine their appropriateness and adequacy to ensure the quality of the API.

5.14. 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 pharmacopoeia monograph. Where particular impurities found in the substance are not listed in the monograph, a justification (including toxicological data, if appropriate) should be provided. Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A and Q3C guidelines.

6. OPTION 2 : 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 used to demonstrate the purity of a given API 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 NPRA.
- 6.3. The PRH should submit a copy of the most current CEP including all annexes, 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 PRH and the NPRA shall be notified of any future change in the API specifications or in the manufacturing process that will likely affect the product's quality or safety.

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

- 6.4. Along with the CEP, the PRH should submit the following information in the product dossier.
- **S1 General Information**
 - **S.1.1 Nomenclature**
 - **S.1.2 Structure**
 - **S.1.3 General properties** - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section.

▪ **S2 Manufacture**

2.1 Manufacture(s) / Site of Manufacture

- **ALL** manufacturers involved in manufacturing process of API.

2.5 Process Validation and/or Evaluation

In the case of sterile APIs, data on the sterilization process of the API, including validation data, should be included in the product dossier(S 2.5).

- **S.3.1 Elucidation of structure and other characteristics**- studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.

▪ **S.4.1 Specification**

- i. The specification from the API manufacturer
- ii. The specification of the finished product manufacturer

Note: Specification should include all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that were not controlled in the CEP and Ph.Eur. monograph, such as polymorphs, impurities and/or particle size distribution.

- **S.4.2/ S.4.3 Analytical procedures and validation**– for any methods used by the API manufacturer and in addition to those in the CEP and Ph.Eur. monograph.

▪ **S.4.4 Batch analysis**

- i. Results from minimum three batches of at least pilot scale, demonstrating compliance with Ph. Eur. monograph and including any additional tests/limits listed on the CEP (e.g. residual solvents, additional impurity tests).
- ii. Certificate of Analysis (COA)-minimum two batches each from **both** API manufacturer and finished product manufacturer.

- **S.5 Reference standards or materials** – information on reference standards from **both** API manufacturer and finished product manufacturer.

- **S.6 Container closure system**- specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container closure system and the PRH declares to use the same container closure system.

- **S.7 Stability**

- i. Proposed retest period, or shelf life
- ii. Proposed storage condition (temperature and packaging)
- iii. Stability data

Exception: where the CEP specifies a re-test period that is the same as or of longer duration, and storage conditions which are the same or higher temperature and humidity as proposed by the PRH.

- 6.5 The NPRA reserves the right to request for any additional information about the API when deemed appropriate.
- 6.6 The PRH is responsible to submit the latest CEP updates, with annexes, as soon as it is available from the API Manufacturer.
- 6.7 Separate CEP must be provided for each API for:
- i. Finished product contains more than one API
 - ii. API from different manufacturing site
 - iii. API from different synthesis route

7. OPTION 3 : FULL DETAILS OF “PART II-S : ACTD” IN THE PRODUCT DOSSIER

- 7.1. Information on the API sections (ACTD Part II-S: S1-S7), including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the product dossier.
- 7.2. The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR) / ACTD provide details on the information to be included in the API sections of an application dossier.
- S1 General Information
 - 1.1 Nomenclature
 - 1.2 Structure
 - 1.3 General Properties
 - S2 Manufacture
 - 2.1 Manufacture(s)/ Site of Manufacture
 - **ALL** manufacturers involved in manufacturing process of API.
 - 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
 - S3 Characterisation
 - 3.1 Elucidation of Structure and other Characteristics
 - 3.2 Impurities
 - S4 Control of API/Drug Substance
(submission should include information from API manufacturer AND finished product manufacturer).
 - 4.1 Specification of API
 - 4.2 Analytical Procedures
 - 4.3 Validation of Analytical Procedures
 - 4.4 Batch Analysis-minimum three batches,
Certificate of Analysis (COA)-minimum two batches.
 - 4.5 Justification of Specification

- S5 Reference Standards or Materials
(from API manufacturer AND finished product manufacturer).
- S6 Container Closure System
- S7 Stability

7.3. Separate dossier (Part II-S : ACTD) must be provided for each API for:

- i. Finished product contains more than one API
- ii. API from different manufacturing site
- iii. API from different synthesis route

7.4. Where the API and the finished product are manufactured by the same company, information on the production, quality control and stability of the API may be submitted as part of the dossier for the finished product (ACTD) rather than in a separate DMF. However, the company is not precluded from submitting a DMF for the API.

8. STABILITY DATA OF API

8.1. Current stability test data for an API should be provided, for at least 3 primary batches. These data should include:

- The type of stability study and stability protocol
- API name, API manufacturer, packaging particular
- Batch details (e.g., batch number, date of manufacture, batch size)
- The general test methodology (e.g., duration of study, storage conditions of temperature and humidity, list of relevant testing, testing frequency, etc.);
- Proposed retest period or shelf-life;
- Proposed storage condition;

A storage temperature must be specified, e.g:

- Do not store above 25 °C
- Do not store above 30 °C
- Store in a refrigerator (2 °C to 8 °C)
- Store in freezer

Other special storage condition, e.g:

- Protect from light
- Protect from moisture

- The analytical test methods (e.g., assay method of quantitation, determination of degradation products, moisture etc) with reference;
- Validation of test methods;
- Specification;
- Results of tests; and,
- Conclusions.

8.2. In circumstances where an API retest period has not been established and complete long term stability data is not available at the time of submission, the minimum stability data required are as follows:

- At least 12 months of long term data and 6 months of accelerated data on at least 3 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 long term studies which can be extrapolated not more than 12 months covered by the long term data.*

A letter of commitment (to provide complete long term stability data when study is completed/when requested) should be submitted.

- 8.3. Where the API is sourced from multiple sites or from different route of synthesis, stability data from each source should be provided.
- 8.4. The NPRA may request for additional stability data if deemed necessary for the evaluation of the application.
- 8.5. 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 PRH.

9. MANUFACTURINGSITE INSPECTION

- 9.1. Depending on the outcome of the evaluation of the API dossier, a risk-based approach will be used in the planning of manufacturing site 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 organizations.
- 9.2. The NPRA shall plan and coordinate the performance of inspections at the manufacturing site of the API and that of the key intermediate (if relevant) to assess compliance with the relevant sections of the relevant GMP Guidelines, and to compare the technical information on the manufacturing process given in the API dossier with the manufacturing process actually carried out on the manufacturing site.
- 9.3. All such inspections shall be performed by inspectors deemed to possess sufficient qualifications and experience. In order to perform such inspections, the inspectors have to be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in the area of GMP. Such inspectors shall perform the inspections and report on its findings in accordance with established Standard Operating Procedures (SOPs) so as to ensure a standard harmonized approach.

10. MAINTENANCE OF APPROVAL STATUS

- 10.1. Manufacturer of finished product 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. The PRH is responsible to provide the NPRA 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 safety, purity and quality of the API that has been previously approved. For those APIs approved by the NPRA, an evaluation of such variations shall be performed with accordance to the Malaysian Variation Guidelines (MVG).
- 10.2. Random samples of APIs supplied to manufacturers of finished products may be taken for independent testing if needed. Certificates of Analysis released by the API Manufacturer as well as specifications for test methods shall be provided by the API Manufacturer or the PRH to the NPRA for review upon request. In the event of failure to meet the established criteria for testing, the NPRA shall proceed to investigate and communicate this problem to the manufacturer concerned.
- 10.3. The NPRA may conduct a re-evaluation of the APIs at a 5 years interval. If, as a result of this re-evaluation, 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 PRH and API Manufacturer shall be issued from the NPRA regarding such decision.
- 10.4. 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 API 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 NPRA, changes made in the sourcing of key intermediates, route of synthesis, facility or other production, require that reassessment be made.

REFERENCES AND GUIDELINES

a) Guidelines on the Technical Requirements Related to the Quality of Active Pharmaceutical Ingredients

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 PRH are advised to refer to these guidelines available at the relevant website such as:

- Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part
http://apps.who.int/prequal/info_general/documents/TRS970/TRS_970-Annex4.pdf
- Guideline on Active Pharmaceutical Ingredient Master File (APIMF) Procedure.
(http://apps.who.int/prequal/info_applicants/Guidelines/APIMF_Guide.pdf)
- The ASEAN Common Technical Dossier (ACTD) For The Registration Of Pharmaceuticals For Human Use Organization Of The Dossier
<http://npra.moh.gov.my/index.php/guidelines-central>
- The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: Quality – M4Q(R1)
(http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf)
- Impurities in New Drug Substances
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2_Guideline.pdf
- Impurities: Guideline For Residual Solvents
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Step4/Q3C_R6_Step4.pdf
- Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A
<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>
- Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

- Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.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>
- Certification database for information on Certificates of Suitability (CEPs) granted by the EDQM.
https://extranet.edqm.eu/publications/recherches_CEP.shtml
- WHO List of Prequalified Active Pharmaceutical Ingredients
http://apps.who.int/prequal/info_applicants/API_PQ-List.htm

b) 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**
<http://www.ema.europa.eu/pdfs/vet/qwp/084699en.pdf>
- ASEAN Stability Guideline
<http://npra.moh.gov.my/index.php/guidelines-central>