



Guideline on Submission of Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis

This guideline is based on the World Health Organization (WHO) document WHO/DMP/RGS/98.5 "Marketing Authorization of Pharmaceutical Products with special Reference to Multisource (Generic) Products: a Manual for a Drug Regulatory Authority (DRA)¹" and on the International Conference on Harmonization (ICH) guideline "The Common Technical Document for the Registration of Pharmaceuticals for Human Use: M4Q: Quality; Module 2: Quality Overall Summary (QOS); Module 3: Quality²"

***Note:** Manufacturers interested in having their FPPs evaluated for acceptability in principle for procurement by UN agencies and the Global Drug Facility should submit a product dossier reflecting the data and information requested below. This guideline is a summary of the requirements specified in the WHO and the ICH documents referred to above. Manufacturers / suppliers are reminded to consult the full documents and cited guides when compiling the dossier.*

Suppliers/Manufacturers of Finished Pharmaceutical Products used in the treatment of HIV/AIDS, Malaria and Tuberculosis should submit the following documentation:

A: Covering letter:

The covering letter submitted with the product dossier should contain a clear statement by the responsible person submitting the product dossier, indicating that the information submitted is true and correct.

B. Application for Prequalification of FPPs (Product dossier/file)

The sections should be clearly marked in the table of contents and in the product file (Sections 1 to 4.2). All pages should be numbered.

Applicants should not modify the overall organization of the product dossier as outlined in this guideline.

Table of contents

List the sections, sub-sections and titles as numbered and the relevant page numbers.

¹ http://whqlibdoc.who.int/hq/1998/WHO_DMP_RGS_98.5.pdf

² <http://www.ich.org/cache/compo/276-254-1.html>

INTRODUCTION AND GENERAL INFORMATION

This document is intended to provide guidance on the format of a prequalification application for active pharmaceutical ingredients (APIs) and their corresponding FPPs. Dossiers for prequalification should be presented according to the format of this guide.

The text under the section titles is intended to be explanatory and illustrative only. The content of these sections includes relevant information described in existing guidelines of the World Health Organization³ (WHO) and the International Conference on Harmonization⁴ (ICH). In assembling the product dossier, applicants should also take into account other WHO guidelines relating to the safety, efficacy and quality of FPPs.

Sections 1 to 4 in this guideline merely indicate where the information should be located in the dossier for prequalification of FPPs.

When more than one API is used in a FPP, information should be presented separately as one complete Section 2. ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)] followed by other complete API section(s). Multiple API sections may also be warranted when the same API is made with differences in the route of synthesis and/or purification at two different manufacturing sites.

Different presentations of the FPP (e.g., strengths, container closure types) can be submitted in the same dossier and in one Section 3. FINISHED PHARMACEUTICAL PRODUCT(s) [FPP(s)]. The information that differs between presentations (e.g., compression of tablets of different strengths, container closure system, stability) should be presented separately in the relevant subsections.

When a FPP is supplied with a reconstitution diluent/solvent, separate Section 3. should be presented for the FPP and the reconstitution diluent/solvent.

Safety and efficacy, including bioequivalence part of the dossier should be submitted and the attached template filled in the required information in Part 4.

The applicant only should implement variations to the terms of prequalification of a FPP only after the proposed changes have been evaluated and approved by WHO.

This guideline applies only to APIs manufactured by chemical synthesis or semi-synthetic processes and to FPPs containing such APIs.

Other types of products, such as biologicals, biotechnological and fermentation products, and herbal preparations are evaluated by different guidelines⁵.

³ <http://www.who.int/medicines/>

⁴ <http://www.ich.org/cache/compo/276-254-1.html>

⁵ Compendial APIs manufactured by fermentation and cell culture processes should comply with the general requirements and specific monographs of the European Pharmacopoeia (Ph. Eur.) or the United States Pharmacopoeia (USP). Corresponding FPPs should be assessed by the monographs of the British Pharmacopoeia (BP) or the USP.

For non-compendial APIs manufactured by fermentation and cell culture processes, the ICH-Q6B guide “Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products” should be used.

Section 1. CHARACTERISTICS OF THE FPP

1.1 Details of the product

1.1.1 Name, dosage form and strength of the product

1.1.2 Approved generic name(s) [use International Non-proprietary Name (INN), if any]

1.1.3 Visual description of the FPP

1.1.4 Visual description of the packaging

1.2 Sample

Provide a sample of the FPP(s) to enable visual inspection of the pharmaceutical dosage form, the packaging materials and the label as well as to compare the data with those in the SmPC and the Patient Information Leaflet (PIL).

1.3 Regulatory situation in other countries

List the countries in which

- this product has been granted a marketing authorization
- this product has been withdrawn from the market
- the application for marketing has been rejected, deferred or withdrawn

Section 2. ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)]

The information on the API can be submitted according to the following order of preference:

- As the latest, valid European Certificate of Suitability (CEP) with all appendices. The information, which may not be covered by the CEP, should be provided under points 2.2.2, 2.5.2, 2.6 and 2.7.
- As (a) Drug Master File(s) [DMF(s)] submitted by the API manufacturer, provided that the DMF contains all the information listed under Section 2, or
- By completing Section 2. In this case, the API manufacturer should provide a signed declaration that the synthesis and subsequent purification is conducted in accordance with what is presented in the dossier.

2.1 Nomenclature

2.1.1 International Nonproprietary Name (INN)

2.1.2 Compendial name if relevant

2.1.3 Chemical name(s)

2.1.4 Company or laboratory code, if applicable

2.1.5 Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN)

2.1.6 Chemical Abstracts Service (CAS) registry number

2.2 Properties of API(s)

2.2.1 API not described in BP, PhInt, JP, PhEur, or USP

Provide the following information:

- Chemical structure, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass;
- Isomeric nature including stereochemical configuration;
- Documented evidence of structure and stereochemistry, such as clearly visible, Quality Assurance (QA)-certified copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra, together with professional interpretation of the relevant parts of spectra, X-ray diffractograms, thermograms, and so on;
- Physicochemical and other relevant properties of the API, such as solubility in water, other solvents such as ether, ethanol, acetone, and buffers of different pH; partition coefficient; existence/absence of polymorphs and water/solvent of crystallization; results of hygroscopicity testing; particle size and so on.

2.2.2 API described in BP, PhInt, JP, PhEur, or USP

Identify physicochemical and other properties of the API, which are not included in a pharmacopoeial monograph and are relevant to product safety and efficacy, such as solubility in water, other solvents such as ether, ethanol, acetone, and buffers of different pH; partition coefficient; existence/absence of polymorphs and water/solvent of crystallization; results of hygroscopicity testing; particle size, and so on.

2.2.3 Information from literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

2.3 Site(s) of manufacture

State the name and street address of each facility where manufacture (synthesis, production) occurs. Provide phone number(s); fax number(s) and e-mail addresses. Include any alternative manufacturers.

Provide a valid Manufacturing Authorization for the production of APIs. If available, attach a certificate of GMP compliance.

Reference: WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation⁶ (WHO Technical Report Series, No. 917, 2003)

2.4 Route(s) of synthesis

2.4.1 API not described in BP, PhInt, JP, PhEur, or USP

Provide a flow diagram of the synthetic process(es) that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions, purification steps, catalysts and solvents.

Submit a sequential procedural narrative of the manufacturing process. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time).

When the API is still to be produced in commercial quantities (pilot scale batches), it can be pre-qualified provided scale-up is immediately reported to WHO.

When the submitted route of synthesis consists of a limited number of steps (e.g., one to three), full details of the manufacture of the starting material(s) or key intermediates should be given and/or at least detailed specifications especially regarding the impurity profile including residual solvents and catalysts.

Process validation of critical steps of the synthesis and aseptic processing and sterilization, when applicable, should be included. The scale of manufacture / typical batch size should be stated.

A declaration on the use/non-use of material of animal or human origin should be provided.

Starting materials from vegetable origin should be fully characterized, and a contaminant profile should be established and submitted.

Explain alternate processes and describe with the same level of detail as the primary process. It should be demonstrated that batches obtained by alternate processes have the same impurity profile as the principal process. If the obtained impurity profile is different, it should be demonstrated as to be acceptable according the requirements described further in the text for "impurities".

Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or submitted.

Provide external environmental impact statement (aquatic, atmospheric and terrestrial environment, potential for harm, disposal sites and methods).

2.4.2 Specifications of raw materials and intermediates used in the synthesis

Provide specifications for starting materials, reagents, solvents, catalysts, and intermediates (if isolated during the process) in the synthesis. Provide information demonstrating that materials

⁶ http://whqlibdoc.who.int/trs/WHO_TRS_917_annex3.pdf

meet standards appropriate for their intended use (including the clearance or control of adventitious agents), as appropriate.

2.4.3 API described in BP, PhInt, JP, PhEur, or USP

An outline of the route of synthesis should be provided (a simplified flow chart and a qualitative description of the manufacturing method, including the name of solvents, reagents and catalysts) with special emphasis on the final steps including purification procedures.

2.5 Specifications

2.5.1 API not described in BP, PhInt, JP, PhEur, or USP

Provide justification for the API specification.

Reference: ICH-Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances + Decision trees.

http://www.ich.org/MediaServer.jserv?@_ID=430&@_MODE=GLB

Characterize and analyze synthesis impurities, including residual solvents, which may be present in API. Particular attention should be given to justifying cases where testing for possible impurities are omitted, e.g., due to the fact that the impurity has not been detected in any batches or will not potentially be present due to a particular method of production.

References

Q3A(R) Impurities in New Drug Substances

http://www.ich.org/MediaServer.jserv?@_ID=422&@_MODE=GLB

FDA (CDER) Guidance for Industry – ANDAs: Impurities in Drug Substances (Rev. 1, January 2005). <http://www.fda.gov/cder/guidance/6422dft.htm>

Q3C Impurities: Guideline for Residual Solvents

Q3C (M) Impurities: Residual Solvents (Maintenance) Permissible Daily Exposure (PDE) for Tetrahydrofuran and N. Methylpyrrolidine

http://www.ich.org/MediaServer.jserv?@_ID=423&@_MODE=GLB

Provide analytical validation information, including experimental data for the analytical procedures used for testing the API and impurities. Include test methods in sufficient detail for them to be replicated by another laboratory.

References

WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials⁷.

ICH-Q2A Text on Validation of Analytical Procedures

http://www.ich.org/MediaServer.jserv?@_ID=417&@_MODE=GLB

ICH-Q2B Validation of Analytical Procedures: Methodology

http://www.ich.org/MediaServer.jserv?@_ID=418&@_MODE=GLB

⁷ WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32nd report. Geneva, WHO, 1992 (WHO Technical Report Series, No. 823) in “Quality assurance of pharmaceuticals – A compendium of guidelines and related materials.” Volume 1. WHO, Geneva, pp. 119-124 (1997)

Provide information on the preparation and studies to establish the identity, purity and assay value of in-house primary (absolute) and secondary (working) standards.

Submit Certificate of Analysis (CoA) of in-house primary standards for use in assays, including

- assay by two different validated methods,
- identification and control of impurities,
- storage instructions, and
- duration of use of the standards.

Reference

ICH Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

Provide verified certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

2.5.2 API described in BP, PhInt, JP, PhEur, or USP

Provide a copy of the monograph together with any test methods referenced in the monograph but not appearing in it. Note that the current monograph should always control the quality of the API.

The quality of the API should meet not only the requirements of specific monographs but also those described in the general monographs of a pharmacopoeia on APIs, excipients and other substance for pharmaceutical use.

Tests and limits should, as a minimum, comply with the relevant pharmacopoeial requirements. Whenever, an API has been prepared by a method liable to leave impurities not controlled in the pharmacopoeial monograph, these impurities (based on 3 to 10 batch analysis results), including residual organic solvents, as well as their maximum tolerance limits should be declared and controlled by a suitable test procedure.

Provide details of any specifications for potentially critical quality variables (e.g. polymorphs, particle size, loss on drying, as identified during development chemistry) additional to those in the pharmacopoeia.

Provide verified certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

2.6 Container closure system

Provide a description of the container closure system(s), including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

Provide only a brief description for non-functional secondary packaging components (e.g., those that do not provide additional protection). Provide additional information on functional secondary packaging components.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, if applicable, and/or safety of materials of construction.

2.7 Stability testing

2.7.1 Stress testing (forced degradation)

Publications from peer-reviewed literature could be submitted to support/replace experimental data.

Stress testing of the API can help to identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Degradation paths for pharmaceutical compounds are typically reactions of hydrolysis, oxidation, photolysis, and/or acid-base chemistry. To force these reactions, the API or FPP is placed in solution expediently, for example, under the conditions shown in the following table.

Stress factor	Conditions
Heat	60°C
Humidity	75% RH or greater
Acid	0.1N HCl
Base	0.1N NaOH
Oxidative	3% H ₂ O ₂
Photolytic	Metal halide, Hg Xe lamp, or UV-B/fluorescent
Metal ions (optional)	0.05 M Fe ²⁺ or Cu ²⁺

The objective is not to completely degrade the active compound but to generate degradation to a small extent, typically 10-30% loss of active by assay when compared with non-degraded compound. This target is chosen so that some degradation occurs, but it is not so severe that secondary products are generated. (Secondary degradation products are degradation products of degradation products and in most cases are not observed during stability studies.) In the total absence of degradation products after 10 days, the API is considered stable. If degradation is detectable but its extent is less than 10%, then the stress factors or the stress conditions, or both, should be increased.

Stress testing is to be carried out on a single batch of the API. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

Solid-state degradation can also be considered. For APIs, placing a solid sample at elevated temperatures —e.g., 60-120 °C, or 5-10 °C below the melting point— can generate some degradation compounds. Because of the harsher conditions, these compounds may not be observed under the accelerated stress studies. However, this approach serves to generate degradation products that can be used as a worst case to assess the analytical method performance.

Examining degradation products under stress conditions is also useful in developing and validating suitable analytical procedures. However, it may not be necessary to examine

specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions. Results from these studies form an integral part of the information provided to WHO.

For APIs not described in an official pharmacopoeial monograph, there are two options:

When available, it is acceptable to provide the relevant data published in the “peer review” literature to support the proposed degradation pathways.

When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to regulatory authorities.

Reference

ICH-Q1A (R2) Stability Testing of New Drug Substances and Products

http://www.ich.org/MediaServer.jserv?@_ID=419&@_MODE=GLB

2.7.2 *Regulatory stability testing*

Summarize the stability testing program and report the results of stability testing of not less than three (minimum one production scale and two pilot scale) batches of the API as described in Annex 1. The data for each attribute should be discussed, trends analyzed and a re-test date should be proposed. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the dossier, a cross-reference will suffice. If different methodology was used, provide validation of tests for impurities including degradants and assay and for other tests as necessary.

At the time of submitting the dossier, the general requirements are:

Storage temperature (°C)	Relative humidity (%)	Minimum time covered by data at submission (months)
Accelerated: 40±2	75±5	6
Intermediate: 30±2	65±5	12
Long term: 25±2	60±5	12

Provide the post-approval stability protocol and stability-testing commitment, when applicable.

References

For APIs, follow ICH guidelines:

Q1A (R2) Stability Testing of New Drug Substances and Products

http://www.ich.org/MediaServer.jserv?@_ID=419&@_MODE=GLB

Q1B Stability Testing: Photostability Testing of New Drug Substances and Products

http://www.ich.org/MediaServer.jserv?@_ID=412&@_MODE=GLB

Q1E Evaluation for Stability Data

http://www.ich.org/MediaServer.jserv?@_ID=415&@_MODE=GLB

A storage statement should be proposed for the labelling (if applicable), which should be based on the stability evaluation of the API.

A re-test period should be derived from the stability information, and the approved retest date should be displayed on the container label and CoA.

It is preferred if all pre-qualification applications contain data from complete long-term studies at 30°C ± 2 °C/65 % RH ± 5% RH by July 2006.

Section 3. FINISHED PHARMACEUTICAL PRODUCT(S) [FPP(S)]

3.1 Manufacturing and marketing authorization

Submit a valid Manufacturing Authorization for pharmaceutical production.

Submit a Marketing Authorization to demonstrate that the product is registered or licensed in accordance with national requirements.

3.2 Pharmaceutical development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. The draft ICH guidelines Q8: Pharmaceutical Development http://www.ich.org/MediaServer.jserv?@_ID=1707&@_MODE=GLB and Q9: Quality Risk Management http://www.ich.org/MediaServer.jserv?@_ID=1957&@_MODE=GLB contain useful information on the subject, in particular on the development of high quality manufacturing processes.

3.2.1 Company research and development

This section should identify, describe and document the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality, including stability.

- (a) The compatibility of the API with excipients should be documented. Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed and supported by experimental data.
- (b) The choice of excipients, in particular their functions and concentrations should be documented.
- (c) For fixed-dose combination products, the compatibility of APIs with each other should be studied and the results documented.
- (d) A discriminating dissolution method should be developed for the final composition of the FPP, when applicable. Limits should be set for each API in fixed-dose FPPs. The dissolution method should be incorporated into the stability and quality control programs. Multipoint dissolution profiles of both the test and the reference FPPs should be compared [multipoint: at least five (5)]. Dissolution testing should be incorporated into the stability programmed.

Reference: <http://www.fda.gov/cder/guidance/1713bp1.pdf>

- (e) A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage.
- (f) The selection and optimisation of the manufacturing process, in particular its critical aspects, should be explained and documented. Where relevant, the method of sterilisation should be explained and justified.
- (g) Any overages in the formulation(s) should be warranted.
- (h) Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing

antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Usually, in this phase the microbial challenge test could be performed to establish and justify the amount of the antimicrobial preservatives to be used. For this purpose, the drug product should be formulated with different concentrations of preservatives and a microbial challenge test on each of the formulations will give the answer on the “least necessary” but still effective concentration.

(i) The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g., precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.

(j) A tabulated summary of the compositions of the FPP batches (batch number, batch size, manufacturing date and certificate of analysis at batch release) used in clinical trials and in bioequivalence studies and a presentation of dissolution profiles must be provided. A discussion of the documented information and data should be presented. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

Packaging should be selected to ensure the quality of the FPP throughout its shelf life.

Reference: Validation of manufacturing processes

http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46

Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis of past experience to determine whether they might lead to critical situations. Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory.

3.2.2 *Information from literature*

Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section.

3.3 **Formulation**

Provide the formulation for a typical batch *and* for an administration unit, e.g. one tablet, 5 ml of oral solution, or the contents of an ampoule or bag of large volume parenteral solution.

Include excipients that may be removed during processing, those that may not be added to every batch (e.g. acid and alkali), and the qualitative and quantitative composition of any tablet coating, capsule shell and inked imprint on the dosage form. State and justify any overages. State the function(s) of each excipient (e.g. antioxidant, lubricant, and binder).

Where applicable special technical characteristics of excipients should be indicated, e.g. lyophilized, micronised, solubilized, emulsified. The type of water (e.g. purified, demineralized), where relevant, should be indicated.

Indicate any substances whose content may be varied (e.g. inked imprint, tablet coating). Ranges in the content of excipients need justification and explanation how the content is decided for each batch.

3.4 Sites of manufacture

State the name and street address of each facility where *any aspect of* manufacture occurs, including production, sterilization, packaging and quality control. Indicate the activity performed at each site. Provide phone number(s); fax number(s) and e-mail addresses. Include any alternative manufacturers.

For each site where the major production step(s) is/are carried out, attach a certificate issued by the competent authority in terms of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

Submit a valid GMP Certificate.

3.5 Manufacturing process

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified (e.g., blending parameters, LOD of the compression blend, and in-process as well as final yields). In certain cases, environmental conditions (e.g., experimentally documented temperature and relative humidity for hygroscopic FPPs) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section.

Provide a copy of the master formula and a copy of a manufacturing record for a real batch.

For sterile products, details of sterilization processes and/or aseptic procedures used must be described.

Stages of manufacture, at which sampling is carried out for in-process control tests, should be indicated. The in-process tests should be described in full, though reference to methods in other parts of the dossier or an acknowledged pharmacopoeia will suffice.

Documented evaluation of at least three (3) production scale batches should be submitted to provide assurance that the manufacturing process will reliably meet predetermined specifications.

3.6 Manufacturing Process Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

3.7 Process Validation and Evaluation

3.7.1 New (for the generic manufacturer) FPPs

Data should be submitted in the application for prequalification demonstrating the validity of a given process.

Reference: Validation of manufacturing processes

http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46

Concurrent validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. The first three production-scale batches must be monitored as comprehensively as possible. (This careful monitoring of the first three production batches is sometimes regarded as prospective validation.) The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution, and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, subvisual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

Simulation process trials are used mainly to validate the aseptic filling of parenteral products that cannot be terminally sterilized. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. In the past, a level of contamination of less than 0.3% was considered to be acceptable; however, the current target level should not exceed 0.1%.

Challenge experiments are performed to determine the robustness of the process, i.e. its capacity to operate smoothly when parameters approach acceptable limits. The use of ranges of parameters for the quality of the starting materials in experimental batches may make it possible to estimate the extent to which the process is still capable of producing an end-product that meets the specifications.

The progress from pre-formulation → formulation → pilot manufacture → industrial scale manufacture should be shown in the dossier submitted for prequalification to be logical, reasoned and continuous.

Laboratory scale batches are produced at the research and early development laboratory stage; they may be of very small size (e.g. 100-1000x less than production scale). These batches may find many uses, for example to support formulation and packaging development, clinical and/or pre-clinical studies.

Pilot Batches may be used to support formal stability studies and also to support pre-clinical and clinical evaluation. Pilot batch size should correspond to at least 10% of the production scale batch, i.e. such that the multiplication factor for the scale-up does not exceed 10. For oral solid dosage forms this size should generally be 10% of production scale or 100,000 units whichever is the greater.

Full validation studies should be completed for each FPP at the production scale.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme will need to be re-validated once further scale-up is proposed after pre-qualification.

Where validation data on production scale batches are not provided with the application, the applicant should submit the validation protocol described below. This should outline the formal process validation studies to be conducted on production scale batches [usually not less than three (3) consecutive batches]. The Applicant should submit a written commitment that information from these studies will be available for verification after pre-qualification by the WHO inspection team. The protocol should be in the dossier submitted for prequalification and should include the following information as a minimum:

Short description of the process with a summary of the critical processing steps or critical parameters to be monitored during validation.

- FPP specification (release).
- Details of analytical methods (references to appropriate parts in the dossier). In-process controls proposed with acceptance criteria.
- Additional testing intended to be carried out (e.g. with proposed acceptance criteria and analytical validation as appropriate).
- Sampling plan — where, when and how the samples are taken.
- Drug content uniformity is considered essential for FDC-FPPs and should be addressed in the final process validation.
- Details of methods for recording and evaluation of results.
- Proposed timeframe

Following completion of the programmed, a validation report containing the following information and signed by the appropriate authorized person should be generated for examination by WHO:

- Batch Analytical Data
- Certificates of Analysis
- Batch Production Records
- Report on unusual findings, modifications or changes found necessary with appropriate rationale
- Conclusions

Where the results obtained show significant deviations from those expected, WHO need to be informed immediately. In such cases corrective actions should be proposed and any changes proposed in the manufacturing process should receive prior WHO approval by way of variation.

3.7.2 *Established (for the generic manufacturer) FPPs*

Manufacturing as well as in-process and quality control testing data should be evaluated. A total of 10-25 consecutive batches (or more), manufactured over the period of the last 12 months, should be used when reviewing the results, to provide a statistically significant picture. Trend analysis should be presented.

Rejected batches should not be included in the analysis but must be reported together with the reports of failure investigations.

3.8 Specifications for excipients

Include microbiological limits in the specification for excipients of natural origin. Skip testing is acceptable, if justified.

For excipients of human, animal or microbial origin, provide information regarding adventitious agents (e.g., sources specifications; description of the testing performed; viral safety data).

Provide detailed information on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents (TSE-CEP is preferred), bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

For oils of plant origin (e.g., soy bean oil, peanut oil) demonstrate the absence of aflatoxins or biocides.

Only colours permitted by the EU's "List of permitted food colours"⁸, the FDA's "Inactive ingredient guide"⁹ or "Japanese Pharmaceutical Excipients"¹⁰ may be used.

3.8.1 *Excipients not described in PhInt, JP, BP, PhEur, or USP*

For non-compendial excipients(s) and those used for the first time in a FPP or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the API format.

Certificate of analysis for one batch of each excipient should be provided.

3.8.2 *Excipients described in PhInt, JP, BP, PhEur, or USP*

Provide a copy of the monograph together with any test methods referenced in the monograph but not appearing in it. Note that the current monograph should always control the quality of the excipient. Provide details of any specifications additional to those in the pharmacopoeia.

Certificate of analysis for one batch of each excipient should be provided.

⁸ List of permitted food colours, Official journal of the European Communities, 1994. L237. (European Commission Directive 94/36/EC).

⁹ Inactive ingredient guide. Rockville, MD, United States Food and Drug Administration, Division of Drug Information and Research, 1996.

¹⁰ Japanese pharmaceutical excipients. Tokyo, Pharmaceutical and Cosmetics Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (updated annually or biennially).

3.9 Control of the FPP

3.9.1 Specifications for the finished pharmaceutical product

A list of general characteristics, specific standards, tests and limits for results for the FPP must be provided. Two separate sets of specifications may be set out: at manufacture (at release) and at the end of shelf life. Justification for the proposed specifications should be provided.

The following control methods must be included in the specification:

- general characteristics of the pharmaceutical form (physicochemical properties and appearance)
- identification tests of the API(s);
- quantitative determination of API(s);
- unless there is appropriate justification, the maximum acceptable deviation in the API content of the FPP shall not exceed $\pm 5\%$ of the label claim at the time of manufacture;
- purity tests [degradation products, residual solvents or other product (e.g. incompatibilities of APIs in a fixed-dose-combination (FDC) FPP] or process related impurities, microbial contamination);
- pharmaceutical tests, e.g. dissolution;
- physical tests appropriate to the dosage form, e.g. loss on drying, hardness, friability, particle size and apparent density;
- uniformity of dosage units, where applicable;
- The identification tests for colouring materials used and identification and assay of antioxidants, antimicrobial or chemical preservatives with limits. The preservatives content limits of 90-110% at release are normally acceptable without further justification.
- For FDC-FPPs, analytical methods that can distinguish each API in the presence of the other APIs should be developed and validated.
- Acceptance criteria for degradants in FDC-FPPs should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, then its acceptance limits should be calculated with reference to the worst case (API with the smaller area under the curve). Alternatively, the content of such impurities could be calculated in relation to their reference standards.
- Dissolution testing specifications should include all APIs of the finished dosage form and utilize relevant media.

Information on the reference standards or reference materials used for testing of the FPP should be submitted if not previously provided in API part.

Reference

ICH Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

3.9.2 Analytical procedures

All analytical test procedures, including biological and microbiological methods where relevant, must be described in sufficient detail to enable the procedures to be repeated if necessary.

If the product is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced in the monograph but not

appearing in it. Provide details of any specifications and test methods additional to those in the pharmacopoeia.

3.9.3 *Validation of analytical procedures*

All non-compendial test procedures need to be validated. Results of the validation studies, comments on the choice of routine tests and standards must be provided. For pharmacopoeial methods, provide data to demonstrate that the method is applicable to this formulation.

Reference(s)

WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials¹¹.

ICH-Q2A Text on Validation of Analytical Procedures

http://www.ich.org/MediaServer.jserv?@_ID=417&@_MODE=GLB

ICH-Q2B Validation of Analytical Procedures: Methodology

http://www.ich.org/MediaServer.jserv?@_ID=418&@_MODE=GLB

3.9.4 *Batch analysis*

Results of not less than three (3) batch analyses (including the date of manufacture, place of manufacture, batch size and use of batch tested) must be presented. The batch analysis must include the results obtained for all specifications at release.

3.10 Container/closure system(s) and other packaging

The suitability of the container closure system used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

Give a detailed description of the container/closure system(s), including any liner or wadding, and provide details of the composition of each component. Provide the specifications for any part of the container/closure system(s), which comes into contact with the product or is protective. For parenteral products, components that will at any stage come into contact with any part of the product must comply with requirements specified by the BP, EP, JP or USP.

The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate.

Describe other (e.g. outer) packaging, and state what materials they are made from.

3.11 Stability testing

The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the API and the dosage form.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the data set, a cross-reference will suffice. If different methodology was

¹¹ WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32nd report. Geneva, WHO, 1992 (WHO Technical Report Series, No. 823) in "Quality assurance of pharmaceuticals – A compendium of guidelines and related materials." Volume 1. WHO, Geneva, pp. 119-124 (1997)

used, the test procedures applied to the stability tests on the finished product should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. Characterize the possible degradants identified by stress stability testing (see 2.7.1 Stress testing (forced degradation) for details) during development pharmaceuticals (compatibilities of the APIs with each other and with the excipients as well as the effect of temperature on the rate of degradation reactions). The tests for degradants should be validated to demonstrate that they are specific to the FPP being examined and are of adequate sensitivity.

Stability studies should be performed on each individual strength and container size of the finished product unless bracketing or matrixing is applied.

Other supporting data can be provided.

3.11.1 Stability-indicating quality parameters

Stability studies should include testing of those attributes of the FPP that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Characteristics studied should be those in the finished product specification that are likely to be affected by storage and/or not monitored routinely at the time of manufacture, but which may be indicative of the stability/instability of the particular dosage form. These include:

- Physical characteristics (such as organoleptic properties, physical properties characteristic to the dosage form, important quality parameters, e.g., in vitro dissolution, moisture content and change of polymorphs, if relevant). As regards tablets and capsules packed with semi-permeable blister films, loss or uptake of water must be tested during stability studies.
- Efficacy of additives, such as antimicrobial agents, to determine whether such additives remain effective and within the accepted validated range throughout the projected shelf life.
- Chemical characteristics (assay of the API, content of degradation products, content of other ingredients such as preservatives, antioxidants, as well as enantiomeric purity, if relevant).
- Study of the container and closure interaction with the contents, when applicable.
- Where the product is to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection or a concentrate for oral suspension) “in use” stability data must be submitted to support the recommended in-use storage time and conditions for those storage forms.

It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration intended for marketing. A single primary stability batch of the finished product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

Report and discuss the results of stability testing as described in Annex 2. Organize data for all attributes separately and evaluate each attribute in the report. No statistical analysis is required, if the stability data do not show variability or a trend over the time.

Shelf life acceptance criteria should be derived from consideration of all available stability information. The proposed storage conditions should be achievable in practice in the global distribution network.

The summary should include conclusions with respect to in-use storage conditions and shelf life, when applicable.

Long-term studies should cover the whole shelf life. When available long-term stability data on primary batches do not cover the proposed shelf-life period granted at the time of approval, a commitment should be made in writing to continue the stability studies post approval in order to firmly establish the shelf-life period. The post-approval stability protocol should also be provided and should be the same as that for the primary batches, unless otherwise scientifically justified.

Repackaging of bulk finished product will require stability studies in the bulk container and the final container closure system. Expiration dating is linked to the manufacturing date of the dosage form.

3.11.2 Photostability Testing

Photostability testing should be conducted on at least one primary batch of the FPP, if not included in the stress stability tests

Reference: ICH-Q1B: Photostability Testing of New Active Substances and Medicinal Products.

http://www.ich.org/MediaServer.jserv?@_ID=412&@_MODE=GLB

3.11.3 Selection of Batches

At the time of submission data from stability studies should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

Stability data on three primary batches are to be provided. One of the three batches should be of production scale, the remaining two batches at least pilot scale. The composition, batch size, batch number and manufacturing date of each of the stability batches should be documented and the certificate of analysis at batch release should be attached.

The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Where possible, batches of the finished product should be manufactured by using different batches of the API.

3.11.4 Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

3.11.5 Testing Frequency

At the accelerated storage condition, a minimum of three points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are

likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 3, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

3.11.6 Storage Conditions

In general, a FPP should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the finished product after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at six months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

Note: in-use stability testing should be performed on at least two different batches one of which should be investigated close to the end of shelf life.

The long term testing should cover a minimum of 12 months' duration at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested.

Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long term, accelerated, and, where appropriate, intermediate storage conditions for finished products are detailed in Annex 2. The general case applies if a subsequent section does not specifically cover the finished product. Alternative storage conditions can be used, if justified.

3.11.7 General case

Storage temperature (°C)	Relative humidity (%)	Minimum time period covered by data at submission
Accelerated: 40±2	75±5	6
Intermediate: 30±2	65±5	12
Long term: 25±2	60±5	12

Note. Unless otherwise justified, 30°C ± 2°C/65% RH ± 5% RH is the real-time condition for the prequalification project.

When a “significant change” occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

In general, “significant change” for a finished product is defined as:

- A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures.
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., colour, phase separation, hardness).
- And, as appropriate for the dosage form:
 - o failure to meet the acceptance criterion for pH; or
 - o failure to meet the acceptance criteria for dissolution for 12 dosage units.

3.11.8 Finished products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for finished products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

3.11.9 Finished products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as defined below.

Study	Storage condition	Minimum time period covered by data at submission (months)
Long term	25±2 °C / 40±5 % RH or 30±2 °C / 65±5 % RH	12
Intermediate	30±2 °C / 65±5 % RH	6
Accelerated	40±2 °C / NMT 25±5 % RH	6

Note. Unless otherwise justified, 30 ± 2°C and 65 ± 5% RH is the real-time condition for the prequalification project.

Ultimately, it should be demonstrated that aqueous-based finished products stored in semi-permeable containers could withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

A 5% loss in water from its initial value is considered a significant change for a FPP packaged in a semi-permeable container after three (3) months storage at 40 ± 2°C and NMT 25 ± 5% RH.

3.11.10 Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological

and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms, hardness, LOD, etc.).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the finished product, a shelf life and label storage instructions applicable to all future batches of the finished product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analysing data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Reference: ICH-Q1E Evaluation For Stability Data

http://www.ich.org/MediaServer.jserv?@_ID=415&@_MODE=GLB

3.11.11 Extrapolation of data

An API is considered as stable if it is within the defined/regulatory specifications when stored at $25 \pm 2^\circ\text{C} / 60 \pm 5\% \text{ RH}$ (2 years) and $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{ RH}$ (6 months).

If long term data are supported by results from accelerated studies the re-test period/shelf life may be extended beyond the end of long-term studies. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data.

3.11.12 Core Storage Statements

Testing conditions where stability has been shown	Required labelling statement	Additional labelling statement*, where relevant
30°C/65% RH (long term) 40°C/75% RH (accelerated)	None**	Do not refrigerate or freeze
30°C/65% RH (long term)	Do not store above 30°C, or Store below 30°C	Do not refrigerate or freeze
25°C/60% RH (long term)	Do not store above 25°C, or Store below 25°C	Do not refrigerate or freeze

* Depending on the pharmaceutical form and the properties of the product, there may be a risk of deterioration due to physical changes if subjected to low temperatures. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

** The following SmPC and PIL statements are required: this FPP does not require any special storage conditions.

3.12 Container labelling

3.12.1 Outer packaging or, where there is no outer packaging, on the immediate packaging

Labelling should include at least the following:

- (a) The name of the FPP.
- (b) Method of administration.
- (c) A list of API(s) (using INNs if applicable) showing the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume.
- (a) List of excipients known to be a safety concern for some patients, e.g. lactose, gluten, metabisulphites, parabens, ethanol, or tartrazine.
- (b) Instruction on use.
- (c) The batch number assigned by the manufacturer.
- (d) The expiry date in an uncoded form.
- (e) Storage conditions or handling precautions that may be necessary.
- (f) Directions for use, and any warnings or precautions that may be necessary.
- (g) The name and address of the manufacturer, company or person responsible for placing the product on the market.

The labelled storage conditions should be achievable in practice in the distribution network.

For containers of less than or equal to 10 ml capacity that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container need only contain items (a), (b), (c), (f) and (g) —or a logo that unambiguously identifies the company— and the name of the dosage form or the route of administration

3.12.2 Blisters and strips

Blisters and strips should include, as a minimum, the following information:

- (a) Name, strength and pharmaceutical form of the FPP
- (b) Name of the manufacturer, company or person responsible for placing the product on the market.
- (c) The batch number assigned by the manufacturer.
- (d) The expiry date in an uncoded form.

3.13 Product information for health professionals

Propose a copy of the Summary of Product Characteristics (SmPC — see Annex 5 for structure) aimed at medical practitioners and other health professionals and approved by the competent

authority at the time of licensing. The SmPC is an essential part of prequalification and it can only be changed with the consent of WHO.

Reference

A “Guideline on Summary of Product Characteristics – Notice to applicants”, European Commission, Enterprise Directorate-General, Pharmaceuticals and Cosmetics (December 1999).

<http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm#2c>

3.14 Patient information and package leaflet

Provide copies of all package inserts and any information intended for distribution with the product to the patient. The patient information leaflet (PIL) should be in conformity with the SmPC. It should be written in English, should be legible and comprehensible.

3.15 Justification for any differences to the product in the country or countries issuing the submitted WHO-type certificate(s). (Certificates issued in terms of the WHO Certification Scheme for pharmaceutical products moving in international commerce).

When there are differences between the product for which this application is submitted and that marketed in the country or countries which provided WHO-type certificate(s) (issued in terms of the WHO Certification Scheme for pharmaceutical products moving in international commerce), provide arguments and/or data to support the applicability of the certificates despite the differences. Depending on the case, it may be necessary to provide validation data for differences in site of manufacture, specifications, formulation, etc.

Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.

Section 4. INTERCHANGEABILITY

4.1 Bio-equivalence study report

In the case of multi-source (generic) preparations, bio-equivalence study based on the WHO¹² guidelines is required. Bio-equivalence data is required from all oral preparations except aqueous solutions at the time of administration. Orally or parenterally administered aqueous solutions will be assessed by chemical-pharmaceutical characteristics only. Also, bio-equivalence study is required from preparations indicated for serious conditions requiring assured therapeutic response. All compounds in the present list correspond to this characteristic.

Instead of bio-equivalence trial, comparative clinical trial using clinical or pharmacodynamic endpoints can be presented. These endpoints should be justified and validated for the compound and trial should be designed to show equivalence. Trial showing the absence of significant difference cannot be accepted.

Bio-equivalence study report should contain at least the following items:

- Description of study design. The most appropriate study type is two-period randomized crossover study. If other study types were used (e.g. parallel group design), these should be justified by the applicant. In general, single-dose study with sufficiently long period for blood samples collection is acceptable.
- Information about investigators, study site, study dates.
- Data about preparations used: manufacturer, place of manufacture, batch number. Reference preparation in bio-equivalence study should be well known preparation used in most countries of the world. The best acceptable reference is innovator preparation or product from WHO¹³ list of international comparator products if listed.
- Characterization of study subjects. Bio-equivalence study should be normally performed in healthy volunteers. If patients were used, this should be justified by the applicant. Number of subjects should not be smaller than 12. Study report should contain inclusion and exclusion criteria, listing of demographic data of all subjects.
- Description of study procedures. Administration of test products, meals, times of blood sampling or urine collection periods should be described in the clinical report.
- Description and validation of drug determination methods in investigated material. Analytical method should be validated over the measured drug concentration range. Validation should contain methodology and results of sensitivity, specificity, accuracy, precision and repeatability determination.
- All measured drug concentrations should be presented.
- Calculation methodology of pharmacokinetic parameters. Preferred is non-compartmental analysis. If modelled parameters were used, these models should be validated for the compound. All measured and calculated pharmacokinetic parameters should be presented in the report.
- Description of statistical methodology and results of statistical calculations. Statistical calculations should be based on the equivalence evaluation. The statistical method of choice is the two one-sided test procedure and the calculation of 90% confidence intervals of the test/reference

¹² WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report. Geneva, World Health Organization, 1996:114-154 (WHO Technical Report Series, No.863).

¹³ International comparator products for bio-equivalence testing" WHO Drug Information, Vol. 13, No 3, 1999 pp 158-161.

ratios of pharmacokinetic parameters. The main parameters to assess the bio-equivalence are area under the plasma concentration-time curve (AUC) and maximum concentrations (C_{\max}) ratios.

The 90% confidence interval for the AUC-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened.

The 90% confidence interval for the C_{\max} -ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened. In certain cases for drugs with an inherently high intra-subject variability, a wider acceptance range (e.g., 75-133%) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations.

4.2 Summary of pharmacology, toxicology and efficacy of the product

In case of products containing new active ingredients and new combinations of active ingredients provide full information on safety and efficacy as defined in guidelines by the European Union, the US Food and Drug Administration, or the Japanese Ministry of Health and Welfare.

Annexes

Annex 1: [Model Certificate of a Pharmaceutical Product](#)

Annex 2: [Model Batch Certificate of a Pharmaceutical Product](#)

Annex 3: [Model Stability Report of Active Pharmaceutical Ingredient \(API\)](#)

Annex 4: [Model Stability Report of Capsules/Tablets](#)

Annex 5: [Suggested Structure of the Summary of Product Characteristics \(SmPC\)](#)

Annex 6: [Suggested structure of the Package Information Leaflet \(PIL\)](#)¹⁴

Annex 7: [Presentation of Bioequivalence Trial Information \(BTIF\)](#)

Annex 8: [Presentation of Pharmaceutical Quality Information \(PQIF\)](#)

¹⁴ <http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm#2c>