

Annex 15

Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format

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1. Introduction

1.1 Background

In its forty-fifth report, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations published the *Procedure for prequalification of pharmaceutical products (1)* which outlines the procedure and considerations for the process undertaken by WHO in providing United Nations agencies with advice on the acceptability in principle of pharmaceutical products for procurement by such agencies. The above-mentioned report states:

“This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended norms and standards of acceptable quality”.

As mentioned in this report, when submitting an Expression of Interest (EOI) for product evaluation, the applicant should send to the WHO focal point (together with the other data requirements) a *product dossier (PD)*, in the format specified in the WHO guidance documents on submitting product data and information.

Through the International Conference on Harmonisation (ICH) process, considerable harmonization has been achieved in the organization of the registration documents with the issuance of the common technical document (CTD) guideline (2-5). This recommended format in the CTD guideline for registration applications has become widely accepted by regulatory authorities both within and beyond the ICH Regions.

This document provides recommendations on the format and presentation for these types of PDs.

1.2 Objectives

These guidelines are intended to:

- assist applicants in the preparation of PDs for multisource products by providing clear general guidance on the format of these dossiers;
- fully adopt the modular format of the CTD as developed by ICH; and
- provide guidance on the location of regional information (Module 1) and other general data requirements.

These measures are intended to promote effective and efficient processes for the development of these PDs and the subsequent assessment procedures.

1.3 Scope

These guidelines apply to PDs for multisource pharmaceutical products containing existing active pharmaceutical ingredients (APIs) of synthetic

or semi-synthetic origin and their corresponding finished pharmaceutical products (FPPs). For the purposes of these guidelines, an existing API is one that has been previously authorized through a finished product by a stringent regulatory authority (SRA).¹ APIs from fermentation, biological, biotechnological or herbal origin are covered by other guidelines.

These guidelines primarily addresses the organization of the information to be presented in PDs for multisource products. They are not intended to indicate what studies are required. They merely indicate an appropriate format for the data that have been acquired. Applicants should not modify the overall organization of the CTD as outlined in the guidelines.

1.4 General principles

These guidelines present the agreed-upon common format for the preparation of a well-structured CTD for PDs that will be submitted to WHO. A common format for the technical documentation will significantly reduce the time and resources needed to compile PDs for the prequalification of multisource pharmaceutical products and will ease the preparation of electronic submissions. Assessments and communication with the applicant will be facilitated by a standard document containing common elements. In addition, exchange of regulatory information between national medicine regulatory authorities (NMRAs) and with WHO will be simplified.

Ultimately, this is intended to support the objectives of the WHO-managed Prequalification of Medicines Programme in listing pharmaceutical products of acceptable safety, efficacy and quality in the interest of public health.

These *general filing guidelines* should be read in conjunction with other applicable WHO and ICH reference documents and guidelines that provide further guidance and recommendations on the topic-specific content requirements for multisource products, notably:

- *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (6)*;
- *Bioequivalence trial information form (BTIF) (7)*;
- *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part (8)*;
- *Quality overall summary — product dossier (QOS-PD) (9)*.

¹ Stringent regulatory authority (SRA): a regulatory authority which is:
— a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or
— an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic, Health Canada and World Health Organization (WHO), and may be updated from time to time); or
— a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (may be updated from time to time).

Together, these guidelines, templates and reference documents mentioned within them are intended to assist applicants and WHO by harmonizing with international approaches and facilitating the preparation and subsequent assessment procedures for PDs through the integration of the internationally accepted CTD format and, where possible, terminology.

Once implemented these guidelines will supersede the following guidelines and template which were in use previously:

- *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*;
 - Supplement 1 — Dissolution testing;
 - Supplement 2 — Extension of the WHO List of Stable (not easily degradable ARV) APIs;
- *Pharmaceutical Quality Information Form (PQIF)*.

2. Glossary

active pharmaceutical ingredient (API)

Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings (1).

applicant

The person or entity who, by the deadline mentioned in the invitation, submits an expression of interest (EOI) to participate in this procedure in respect of the product(s) listed in the invitation, together with the required documentation on such product(s) (1).

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling (1).

manufacturer

A company that produces, packages, repackages, labels and/or relabels pharmaceutical products (1).

multisource (generic) pharmaceutical products

Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable (6).

3. **Organization of a product dossier for a multisource product in common technical document format**

The CTD is organized into five *modules*. Module 1 is region-specific. Modules 2, 3, 4 and 5 are intended to be common for all regions. Conformance with these guidelines should ensure that Modules 2, 3, 4 and 5 are provided in a format acceptable to WHO and to regulatory authorities.

This section provides an overview of module contents for a multisource product in greater detail.

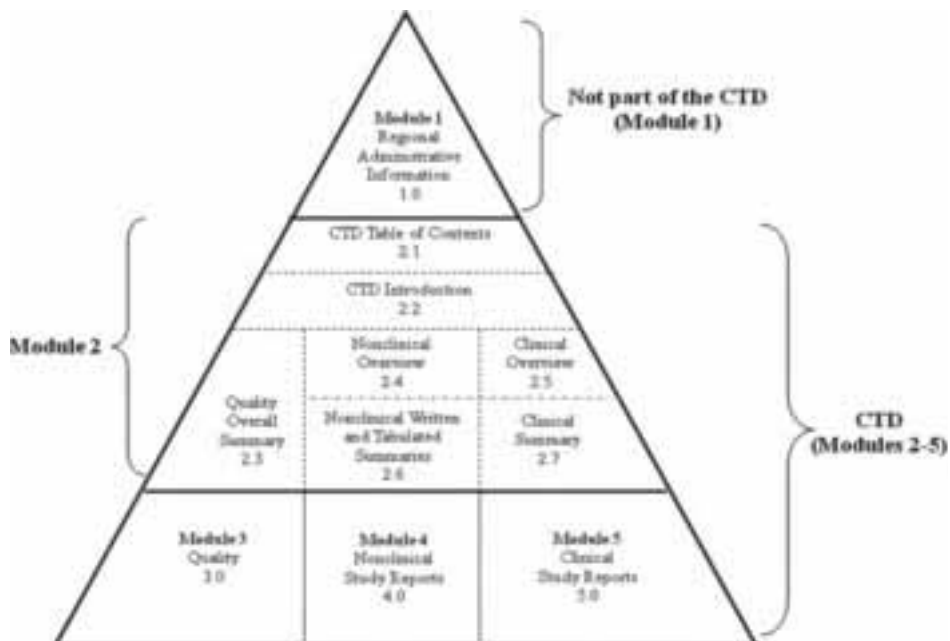
- **Module 1: Administrative information and prescribing information**
 - This module should contain documents specific to WHO and each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by WHO and the relevant regulatory authorities.
 - A summary of the bioequivalence/bioavailability information should be provided according to WHO's *Bioequivalence Trial Information Form (BTIF)* (7).
 - Quality information summary (QIS): see WHO's *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part for instructions* (8).
- **Module 2: CTD summaries**
 - This Module should begin with a general introduction to the pharmaceutical, including its pharmacological class, mode of action and proposed clinical use. In general, the Introduction should not exceed one page.
 - A summary of the quality information should be provided according to WHO's *Quality overall summary — product dossier (QOS-PD)* template (9).
 - The organization of these summaries is described in Guidelines for ICH M4, M4Q and M4S (3-5).
- **Module 3: Quality**
 - Information on quality should be presented in the structured format described in ICH M4Q and WHO's *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part* (8).
- **Module 4: Nonclinical study reports**
 - Generally not applicable for multisource products (some exceptions may apply).
- **Module 5: Clinical study reports**
 - The human study reports and related information should be presented in the order described in ICH M4E (3) and WHO's *Multisource (generic)*

pharmaceutical products: guidelines on registration requirements to establish interchangeability (6).

The overall organization of the CTD is presented in Figure 1.

Figure 1

Organization of the CTD



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In preparing PDs for multisource products, it is acknowledged that certain modules or sections of the CTD would generally *not be applicable* (e.g. Module 4 — nonclinical study reports, although some exceptions may apply) and should be marked as such.

4. Modules (including Module 1) of a product dossier for a multisource pharmaceutical product

This section outlines filing considerations for PDs in the CTD format. Table 1 provides an overview of the presentation of the PD, including modular structure and main headings.

Table 1

Modular format of PDs for multisource products in CTD format

Module 1 — Administrative information and prescribing information
1.0 Cover letter
1.1 Table of contents of the application including Module 1 (Modules 1–5)
1.2 Application information:
1.2.1 Copy of the expression of interest (EOI)
1.2.2 Manufacturing and marketing authorization(s)/international registration status and/or the WHO certificate of pharmaceutical product (CPP)
1.2.3 Copy of certificate(s) of suitability of the <i>European Pharmacopoeia</i> (CEP) (including any annexes)
1.2.4 Letters of access for active pharmaceutical ingredient master files (APIMFs)
1.2.5 Good manufacturing practices (GMP) information
1.2.6 Biowaiver requests in relation to conducting a comparative bioavailability study
1.3 Product information:
1.3.1 Summary of product characteristics (SmPC)
1.3.2 Labelling (outer and inner labels)
1.3.3 Package leaflet (also known as patient information leaflet or PIL)
1.4 Regional summaries:
1.4.1 Bioequivalence trial information form (BTIF)
1.4.2 Quality information summary (QIS)
1.5 Electronic review documents (e.g. product information, BTIF, QIS, QOS–PD)
1.6 Samples (e.g. FPP, device(s), certificates of analysis)
Module 2 — Common technical document (CTD) summaries
2.1 CTD Table of contents (Modules 2–5)
2.2 CTD Introduction
2.3 Quality overall summary — product dossier (QOS–PD)
2.4 Nonclinical overview — generally not applicable for multisource products (some exceptions may apply)
2.5 Clinical overview
2.6 Nonclinical written and tabulated summaries — generally not applicable for multisource products (some exceptions may apply)
2.7 Clinical summary
Module 3 — Quality
3.1 Table of contents of Module 3
3.2 Body of data
3.3 Literature references

Module 4 — Nonclinical study reports — generally not applicable for multisource products (some exceptions may apply)
4.1 Table of contents of Module 4
4.2 Study reports
4.3 Literature references
Module 5 — Clinical study reports
5.1 Table of contents of Module 5
5.2 Tabular listing of all clinical studies
5.3 Clinical study reports
5.3.1 Reports of biopharmaceutical studies
5.3.7 Case-report forms and individual patient listings
5.4 Literature references

Additional guidance for some of the sections to be included in Module 1 is provided below:

1.0 Cover letter

The cover letter submitted with the PD should include a clear statement by the responsible person submitting the PD, indicating that the information submitted is true and correct.

1.2.2 Manufacturing and marketing authorization(s)/international registration status

List the countries in which:

- the FPP (or set of FPPs) has been granted a marketing authorization;
- the FPP (or one or more of the set of FPPs) has been withdrawn from the market; and
- an application for the marketing of the FPP (or one or more of the set of FPPs) has been rejected, deferred or withdrawn.

For further guidance see section 3.2.P.3.1 of the *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part (8)*.

1.4 Regional summaries

The regional summaries should be prepared in accordance with the available WHO templates, which are available on the WHO Prequalification web site.

1.5 Electronic review documents

Electronic submission of documentation (CD or DVD) should be submitted in Microsoft Word (required for templates/summaries, e.g. QOS–PD, QIS, BTIF) or text-selectable PDF format (other documentation).

1.6 Samples (e.g. FPP, device(s))

A sample and certificate of analysis of the FPP(s) and device(s) should be provided to enable visual inspection of the pharmaceutical product, the packaging materials and the label as well as comparison of the data with those in the SmPC, labelling and the package leaflet.

Draft labelling may be submitted at the time of dossier submission when labelling for marketing has not been finalized. For guidance regarding labelling, refer to the information on WHO public assessment reports (WHOPARs) available on the Prequalification web site under Information for Applicants (Prequalification Guidelines).

5. Module 3 — quality

For Module 3.2.S Drug substance (or active pharmaceutical ingredient (API)), there are three options to satisfy the information requirements for APIs within the Prequalification Programme. In brief these are:

- Option 1: certificate of suitability of the *European Pharmacopoeia* (CEP) procedure;
- Option 2: active pharmaceutical ingredient master file (APIMF) procedure; or
- Option 3: full details in the PD.

All options require the submission of information in CTD format (3.2.S), although the content may differ in places. The *Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part (8)* provides detailed guidance on this issue and on the preparation of the FPP information by the applicant.

6. Module 5 of a product dossier for a multisource pharmaceutical product

The majority of PDs for multisource products are supported by one or more pivotal comparative bioavailability studies. When filing a PD in the CTD format, it is anticipated that only the following relevant sections of Module 5 will normally be required.

Module 5: Clinical study reports

- 5.1 Table of contents for Module 5
- 5.2 Tabular listing of all clinical studies
- 5.3 Clinical study reports
 - 5.3.1 Reports of biopharmaceutical studies
 - 5.3.1.2 Comparative bioavailability and bioequivalence study reports

- 5.3.1.3 In vitro–in vivo correlation study reports if available
- 5.3.1.4 Reports of bioanalytical and analytical method for human studies²
 - 5.3.7 Case-report forms (CRFs) and individual patient listings: only CRFs for subjects who experienced serious adverse events should be included. All CRFs should be available upon request.
- 5.4 Literature references

For guidance regarding biowaivers, refer to the biowaiver implementation documents available on the Prequalification web site. For guidance regarding comparator products, refer to the information available under Guidance on bioequivalence studies on the Prequalification web site.

7. Guidance on format and presentation of a product dossier in common technical document format

7.1 Guidance on format

Throughout the CTD, the information should be displayed in an unambiguous and transparent manner. Text and tables should be prepared using margins that allow the document to be printed on both A4-sized paper (European Union and Japan) and 8.5 × 11-inch paper (US). The left-hand margin should be sufficiently large that information is not obscured whatever the method of binding. Fonts for text and tables should be of a style and size large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text.

Acronyms and abbreviations should be defined the first time they are used in each module.

References should be cited in accordance with the current edition of the *Uniform requirements for manuscripts submitted to biomedical journals*, International Committee of Medical Journal Editors (ICMJE).³ Copies of relevant pages of references should be provided, with a copy of the full article in the case of a publication. English translations should be provided as necessary.

7.2 Guidance on presentation

The paper copies of the application should be bound for easy access to information.

² Bioanalytical or analytical methods for BA/BE or in vitro dissolution studies should ordinarily be provided in the individual clinical study reports. However, where a method is used in multiple studies, the method and its validation should only be included once in section 5.3.1.4 and referenced in the appropriate individual clinical study reports.

³ The first edition of the *Uniform requirements for manuscripts submitted to biomedical journals* was conceived by the Vancouver Group and was published in 1979.

Each binder should be labelled with the proprietary name (if applicable) and the non-proprietary name of the FPP (e.g. “Name ABC” Abacavir (as sulfate) 300 mg tablets) and the company name of the applicant. For ease of reference, the following information could also be included on the label of each binder (space permitting): the volume number for that binder (out of the total number of volumes *for that module*), the section(s) contained within each volume and the date of the application (month and year), e.g.:

FPP “Name ABC”
Nonproprietary name
Applicant “XYZ”
Module 3 — Quality
Volume 1 of 3
Module 3.1 — 3.2.S.3
Month/year

8. Variations

All variation applications should be submitted using the CTD format, regardless of the original PD format.

In the case of the filing of a variation, applicants would normally provide only the relevant modules or sections affected by the change. For example, if the variation was for a change in the shelf-life of the FPP, only those sections affected by the change would need to be submitted (10).

An updated and annotated QIS should be provided with each variation application.

References

1. Procedure for prequalification of pharmaceutical products. Revision. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 10.
2. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy (ICH M4E) together with the complementary ICH Questions and Answers documents for the above mentioned guidelines.
3. Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (ICH M4) (2003): Efficacy.
4. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality (ICH M4Q) (2003): Quality.
5. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety (ICH M4S) (2003): Safety.
6. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability In: *WHO Expert Committee on*

Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 7.

7. Bioequivalence trial information form (BTIF) on: <http://apps.who.int/prequal/>.
8. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part: on: <http://apps.who.int/prequal/>.
9. Quality overall summary - product dossier (QOS-PD): on: <http://apps.who.int/prequal/>.
10. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report.* Geneva, World Health Organization, 2009 (WHO Technical Report Series, No. 953), Annex 2.