WHO Guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products.

Preparation of product dossiers in common technical document format

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1. Introduction

The World Health Organization (WHO) provides United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products for procurement by such agencies. This activity of WHO aims to facilitate access to priority essential medicines that meet WHO-recommended on technical guidelines and reference standards. This service is called prequalification. The purpose of the United Nations prequalification assessment is to provide assurance that candidate products: (a) meet WHO recommendations on quality, safety and efficacy, including compliance with WHO's recommended standards for good manufacturing practices (GMP) and good clinical practice (GCP); and (b) meet the operational packaging and presentation specifications of the relevant United Nations agency. The aim is to ensure that the products provided through the United Nations for use in different countries are safe, effective and suitable for the target populations.

In the recent years, a great number of biotherapeutic products has demonstrated success in treating many life-threatening chronic diseases. However, innovative biotherapeutic products are expensive and their use has been limited. The expiration of the patents on key biotherapeutic products is opening the door for quality assured similar biotherapeutics which are expected to contribute to a substantial increase in their availability at affordable prices.

As some biotherapeutic products have already been listed in the WHO Model List of Essential Medicines, the WHO Department of Essential Medicines and Health Products is requested to explore options to facilitate access to quality assured biotherapeutics and similar biotherapeutics at affordable prices.

The World Health Organization (WHO) recognizes the global use of Common Technical Document (CTD) guideline (1-4) and its format developed by the International Council for Harmonisation (ICH) and many manufacturers have a prepared dossier in CTD format that they have used to register the product in one or more countries. Furthermore many countries that import prequalified medicinal products require submission of a CTD format dossier for registration of the products.

These guidelines are intended to:

- assist applicants in the preparation of a product dossier (PD) for similar biotherapeutic product (SBP) 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.

2. Scope

This guideline applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines, plasma derived products, and their recombinant analogues are excluded from the scope of this document.

These guidelines primarily addresses the organization of the information to be presented in PDs for SBPs. 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.

3. General procedure and data requirements

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 SBPs 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 regulatory authorities (NRAs) and with WHO will be simplified.

Ultimately, this is intended to support the objectives of the WHO-managed Prequalification Programme in listing medicinal 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 SBPs, notably:

- Guidelines on evaluation of similar biotherapeutic products (SBPs) (5);
- Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) (6);

Together, the sections of these applicable parts the 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.

4. Glossary

The definitions given below apply to the terms used in this procedure and should be read in conjunction with the draft "WHO Guideline on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products approved by stringent regulatory authorities" and the draft "WHO pilot procedure for prequalification of similar biotherapeutic products" published on the WHO web site. Terminologies may be used differently in other context.

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).

Contract research organization (CRO)

An organization (commercial, academic or other) to which an applicant may have transferred some of its tasks and obligations in relation to the conduct of clinical studies with the product submitted to WHO for assessment under the current procedure.

Drug product

A pharmaceutical product type that contains a drug substance, generally in association with excipients.

Drug substance

The active pharmaceutical ingredient and associated molecules that may be subsequently formulated, with excipients, to produce the drug product. It may be composed of the desired

product, product-related substances, and product- and process-related impurities. It may also contain other components such as buffers.

Head-to-head comparison

Direct comparison of the properties of the SBP with the RBP in the same study.

Immunogenicity

The ability of a substance to trigger an immune response or reaction (e.g. development of specific antibodies, T cell response, allergic or anaphylactic reaction).

Impurity

Any component of the new drug product that is not the drug substance or an excipient in the drug product.

Invitation for expressions of interest (EOIs) or invitation

Invitation calling upon interested parties (e.g. manufacturers or other applicants) to submit an expression of interest (EOI) to WHO by a specified deadline for the purpose of participating in the WHO prequalification procedure in respect of the product(s) listed in the invitation. Such an EOI should be accompanied by the required documentation on the product(s) in question.

Manufacturer

Any person or legal entity engaged in the manufacture of a product subject to marketing authorization or licensure. In other documents, "manufacturer" may also refer to any person or legal entity that is an applicant or holder of a marketing authorization or product licence where the applicant assumes responsible for compliance with the applicable product and establishments standards.

Originator product

A biotherapeutic product which has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.

Prequalification

WHO prequalification was established to ensure that selected health products, including diagnostics, medicines, vaccines, immunization-related equipment and devices and vector control products for high burden diseases meet global standards of quality, safety and efficacy, in order to optimize use of health resources. The programme is based on a transparent and scientifically sound assessment process and evaluates the acceptability, in principle, of pharmaceutical products for purchase by United Nations (UN) and other procurement agencies.

Agencies using information resulting from the prequalification procedure should perform additional steps of qualification prior to purchasing, such as ensuring financial stability and standing of the supplier, ability to supply the required quantities, security of the supply chain, preshipment quality control and other related aspects.

Reference biotherapeutic product (RBP)

A reference biotherapeutic product is used as the comparator for head-to-head comparability studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP. It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

Similarity

Absence of a relevant difference in the parameter of interest.

Similar biotherapeutic product (SBP)

A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

Stringent regulatory authority (SRA)

For this pilot procedure, stringent regulatory authority ("SRA") uses the definition described in the *TRS 1003, the report of the 51st WHO Expert Committee on Specifications for Pharmaceutical Preparations meeting*. The categories of SRA are extracted below.

a. a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or

b. an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or

c. a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).

5. Organization of a product dossier for a SBP in CTD 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 SBP 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 biosimilarity information should be provided according to the applicable guidelines on SBP (5-6).
- Risk management plan and methods used to report adverse events should also be provided.

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 applicable guidelines (5-6).
- The organization of these summaries is described in Guidelines for ICH M4, M4Q and M4S (1-4).

Module 3: Quality

- Information on manufacturing and quality should be presented in the structured format

described in ICH M4Q.

Module 4: Nonclinical study reports

- Information on nonclinical study reports should be presented in the structured format described in ICH M4S.

Module 5: Clinical study reports

- The human study reports and related information should be presented in the order described in ICH M4E (3).

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

Only if the Module 3 data demonstrate sufficient comparability of the candidate SBP to the RBP, the reduced Module 4 and 5 data packages could be submitted.

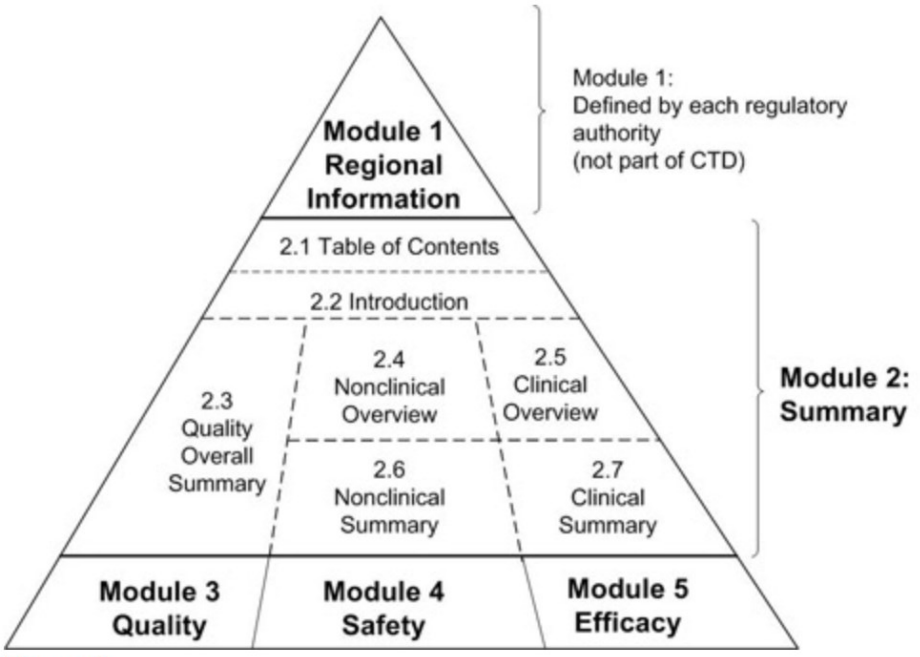

Figure 1

This figure is reproduced with the kind permission of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

6. Modules (including Module 1) of a product dossier for a SBP

The SBP data for a similar biotherapeutic product should follow the structure of the CTD format for the applicable sections. However specific requirements that such applications should fulfil are detailed in ICH M4 guideline.

Module 1:

Additional guidance for some of the applicable 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 DP has been granted a marketing authorization;
- the DP has been withdrawn from the market; and
- an application for the marketing of the DP has been rejected, deferred or withdrawn.

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 or text-selectable PDF format (other documentation).

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

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).

Module 3 — quality

The applicable guidelines (5,6) provides detailed guidance on the preparation of the SBP information by the applicant.

Module 4 Non-clinical study reports

The non-clinical part of the guideline addresses the pharmaco-toxicological assessment of the SBP. The establishment of safety and efficacy of a SBP usually requires the generation of some non-clinical data with the SBP.

The demonstration of a high degree of molecular similarity between the SBP and RBP should significantly reduce the need for nonclinical studies since the RBP will already have a significant clinical history. Nonclinical studies should be conducted with the final formulation of the SBP intended for clinical use.

The applicable guidelines (5,6) provides detailed guidance on this issue and on the preparation of the SBP information by the applicant.

Module 5 of a product dossier for a SBP

Clinical studies should be designed to demonstrate comparable safety and efficacy of the SBP to the RBP and therefore need to employ testing strategies that are sensitive enough to detect relevant differences between the products, if present The guidelines on evaluation of similar biotherapeutic products (SBPs) (5,6) provides detailed guidance on this issue and on the preparation of the SBP information by the applicant.

7. Guidance on format and presentation of a product dossier in CTD

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). 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.

Each binder should be labelled with the proprietary name (if applicable) and the non-proprietary name of the DP 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.:

DP “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. 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 DP only those sections affected by the change would need to be submitted.

References

1. 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.
2. Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (ICH M4) (2003): Efficacy.
3. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality (ICH M4Q) (2003): Quality.
4. Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety (ICH M4S) (2003): Safety.
5. WHO Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977, 2009
6. WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 1004, 2016