

WHO Guidelines on submission of documentation for the procedure for prequalification of biotherapeutic products or their corresponding similar biotherapeutic products approved by stringent regulatory authorities

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1. Introduction

The World Health Organization (WHO) Prequalification programme is managed by the WHO department of Regulation and Prequalification (RPQ) to provide United Nations agencies and WHO Member States with guidance on the acceptability, in principle, of medicines, vaccines, in vitro diagnostics, immunization and other medical devices, and vector control products for procurement by such agencies and Member States.

Accordingly, for the purpose of providing guidance to interested United Nations agencies and WHO Member States in their procurement decisions, WHO undertakes a procedure for prequalification of eligible biotherapeutic products (i.e. listed in invitations for EOI published on the WHO web site), to evaluate whether candidate products: (a) meet WHO technical guidance on quality, safety and efficacy or performance, including compliance with WHO's recommended standards for good clinical practice (GCP), good manufacturing practices (GMP), good laboratory practices (GLP) and good distribution practices (GDP); (b) meet relevant operational packaging and presentation specifications; and (c) adhere to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines (1).

Candidate medicines, vaccines, in vitro diagnostics, immunization and other medical devices and vector control products which are found by WHO to meet its recommended standards of quality, safety and efficacy will be included in the WHO list of prequalified products (as manufactured at the specified manufacturing sites) which are considered to be acceptable, in principle, for procurement by United Nations agencies and WHO Member States. However, any United Nations agencies and/or WHO Member States using information from the WHO list of prequalified products should nevertheless perform additional steps of qualification prior to procuring any products included in such list. Such steps include, but are not limited to, ensuring the supplier's financial stability and standing, as well as its ability to supply the required quantities of the product, the security of the supply chain, pre-shipment quality control and other relevant aspects.

Inclusion in WHO's list of prequalified products does not imply: (a) any approval by WHO of the product and/or manufacturing sites in question (which is the sole prerogative of national authorities), or (b) any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety and/or efficacy in the treatment of any specific diseases, or (c) any warrant that the products have obtained regulatory approval for their specified use or any other use in any country of the world, or that their use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws.

Applicants, manufacturers and/or any other party may not use, for any commercial or promotional purposes: (i) the results of the prequalification assessment; (ii) the participation in the WHO prequalification assessment process; (iii) the inclusion of any product in the WHO list of prequalified products; and/or (iv) the WHO's name, acronym or emblem. Additionally, WHO will not accept any liability or responsibility whatsoever for any injury, death, loss, damage or other prejudice of any kind that may arise as a result of or in connection with the procurement, distribution and/or use of any product as to which WHO has published the prequalification assessment results and/or which is or has been included in the WHO list of prequalified products.

2. Objective

In recent years, a great number of biotherapeutic products (BTPs) have demonstrated success in treating many life-threatening chronic diseases. In May 2014, the World Health Assembly (WHA) adopted Resolution WHA67.21 (2) on “Access to biotherapeutic products, including similar biotherapeutic products, and ensuring their quality, safety and efficacy”.

Considering the value that BTPs can provide and the fact that some BTPs have already been listed in the WHO Model List of Essential Medicines, WHO’s RPQ¹ is exploring options to facilitate access to BTPs, including similar biotherapeutic products (SBPs), at affordable prices.

Given that BTPs, including corresponding SBPs, are highly complex and that the regulatory assessment of those products according to internationally acceptable guidelines and standards can be challenging in some countries, WHO’s Prequalification Programme has developed the present WHO procedure for prequalification of BTPs following either one of two pathways:

1) full assessment of SBPs that have been registered by non-SRAs (based on a Reference biotherapeutic product (RBP) approved by an SRA) (hereinafter referred to as “Full Assessment”) (3); and

2) abridged assessment of BTPs, or their corresponding SBPs as applicable, that have been approved by stringent regulatory authorities (SRAs) and marketed in the country of registration (hereinafter referred to as “Abridged Assessment”).

3. Scope

These guidelines are intended to assist applicants with the submission of documentation for prequalification of originator BTPs and their corresponding SBPs that are approved by stringent regulatory authorities.

The abridged process mainly relies on information supplied by or originated from SRAs however, aspects related to supply to low- and middle-income countries and/or regions outside climatic zone II require associated supporting data.

This document addresses the organization of the information to be presented in product dossiers (PDs) for above-mentioned products. They are not intended to indicate what studies are required, but merely indicate an appropriate format for the data that have been acquired.

4. Glossary

The definitions given below apply to the terms used in this pilot procedure and should be read in conjunction with the “*WHO Pilot Procedure for Prequalification of BTPs or their corresponding SBPs*” (8) and “*WHO Guidelines on submission of documentation for the procedure for prequalification of similar biotherapeutic products. Preparation of product dossiers in common technical document format*” (3) published on the WHO website. Terms may have different meanings in other contexts.

¹ RPQ operates in the Division of Access to Medicines and Health Products [MHP].

Applicant

The person or entity who submits an EOI to participate in the WHO pilot procedure for prequalification of: (i) originator BTPs, or their corresponding SBPs, that have been approved by SRAs, or (ii) SBPs that have been approved by non-SRAs (based on an RBP approved by an SRA), together with the required documentation on such product(s).

Comparability exercise or Similarity exercise

Head-to-head comparison of a biotherapeutic product with a licensed reference biotherapeutic product (RBP) with the goal of establishing similarity in quality, safety and efficacy. Products should be compared in the same study using the same procedures.

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 above-mentioned procedure.

Drug product (DP)

A pharmaceutical product type that contains a drug substance, generally in association with excipients. The dosage form in the final immediate packaging intended for marketing.

Drug substance (DS)

The active pharmaceutical ingredient and associated molecules that may be subsequently formulated, with excipients, to produce the drug product. Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

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 present in the drug substance or drug product that is not the desired product, a product-related substance, or excipient including buffer components. It may be either process- or product-related.

Invitation for expressions of interest (EOIs)

Invitation calling upon interested parties (e.g. manufacturers or other applicants) to submit an expression of interest (EOI) to WHO 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. The term “manufacturer” also includes any person or legal entity that is an applicant or holder of a marketing authorization or product licence where the applicant assumes responsibility for compliance with the applicable product and other established standards.

Originator Product

BTP licensed and approved by an SRA on the basis of a full dossier with comprehensive data on non-clinical and clinical studies.

Prequalification

Standardized prequalification procedure of WHO to assess, in principle, whether candidate originator BTP or SBP products, as applicable: (a) meet WHO technical guidance on quality, safety and efficacy, including compliance with WHO’s recommended standards for good clinical practice (GCP), good manufacturing practices (GMP), good laboratory practices (GLP) and good distribution practices (GDP); (b) adhere to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines (1); and (c) meet relevant operational packaging and presentation specifications, for the purpose of providing guidance to interested United Nations agencies and WHO Member States in their procurement decisions. United Nations agencies and WHO Member States using information resulting from the WHO prequalification should perform additional steps of qualification prior to purchasing such products, including ensuring financial stability and standing of the supplier, ability to supply the required quantities, security of the supply chain, pre-shipment quality control and other related aspects, including the registration status of the products to be procured.

Reference biotherapeutic product (RBP)

A reference biotherapeutic product that: (a) has been licensed and approved by an SRA on the basis of a full dossier with comprehensive data on non-clinical and clinical studies; and (b) is used as the comparator for head-to-head comparability studies with the SBP in order to show similarity in terms of quality, safety and efficacy. This definition does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

Risk management plan

A detailed description of the activities that continuously ensure patients’ safety and their benefit from a medicinal ingredient. A risk management plan includes:

- safety specifications, which summarize the known and potential safety issues and missing information about the rDNA-derived biotherapeutic;
- a pharmacovigilance plan to further evaluate important known or potential safety concerns and to provide post-marketing data where relevant information is missing;
- a risk minimization plan, which provides proposals on how to minimize any identified or potential safety risk.

Similarity

Absence of a relevant difference in the parameter of interest. A difference that is expected to induce a difference in clinical effect, such as better impurity profile, could be accepted. No differences exist that are expected to induce impact on clinical activities based on a comparability or similarity exercise.

Similar biotherapeutic product (SBP)

A biotherapeutic product that is similar in terms of quality, safety and efficacy to a reference biotherapeutic product.

Stringent regulatory authority² (SRA)

A regulatory authority which is:

- 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. Guidelines on submission of documentation

Submission of an expression of interest for evaluation of an originator BTP and/or its corresponding SBP that has already received the approval of an SRA involves the preparation and submission of a number of documents, in electronic format (i.e. on CDs or DVDs or via a secure link to an online document repository; the link should be sent to prequalbiosimilar@who.int) as detailed in the applicable guidelines (8).

The submission must be in English and must include officially certified English translations of product information and other documents, if applicable. The English language version of the product information, in the case of English translations, should also be submitted as Word files.

The following should be submitted for the originator BTP or the SBP submitted for prequalification:

1. A covering letter, expressing interest in participating in the WHO pilot prequalification procedure, confirming that the information submitted in the product dossier is complete and correct, and including the following statements:
 - a statement confirming that for WHO prequalification, the Drug Product, including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information, will, at the time of submission and after prequalification, in all respects be the same as the product registered with the reference SRA; and
 - a statement indicating that the product is currently on the market of the reference SRA's country or region.
2. A copy of the marketing authorization, or the equivalent thereof, issued by the reference SRA to demonstrate that the product is registered or licensed in accordance with the reference SRA's requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.

² For the purpose of WHO pilot procedure, this interim definition taken from the "[WHO Technical Report Series TRS 1003, Fifty-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations](#)" is used. Note: This interim definition is currently being revised.

3. A copy of the current WHO-type certificate of a pharmaceutical product issued and fully completed, including answers to each question, by the reference SRA.
4. The latest SRA-approved product information (summary of product characteristics (SmPC), or an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling) of the product. Provide a web link to the SRA-approved product information, preferably on the website of the SRA itself, if available.
5. A list of the SRA-approved manufacturer(s) of the DS and DP, including manufacturers of intermediates, primary packaging sites and DS and DP release-testing sites for each of the DS and DP, with the physical address of the manufacturing site(s) (and unit if applicable).
6. A tabular listing of the product batches manufactured for the market of the reference SRA's region or country since approval or during the past five years, whichever is shorter. The table should include at least the following information: the batch number (of both the DS and DP), batch size (number of units), date of manufacture, manufacturing site (of both the DS and DP), expiry date and pack type/size. Also provide a copy of the most recent product quality review, prepared according to the requirements of the reference SRA.
7. The quality information summary for the product. The QIS-BTP-SRA template, available at PQ-BTP web page, should be fully completed and submitted with the application. The QIS-BTP-SRA provides a condensed summary of key information on the BTP as approved by the reference SRA at the time of application for prequalification. The template should be completed (references to data are not accepted) with no sections deleted or altered beyond expansion of tables, etc. "N/A" may be indicated where a section does not apply.
8. A public assessment report, such as the Scientific Discussion of the European Public Assessment Report (EPAR), issued by the reference SRA. Assessment report(s) issued by the reference SRA that are not publicly available may be requested. WHO may use the information contained in these non-public assessment reports for WHO public assessment report purposes in accordance with the provisions of the WHO Procedure for Prequalification of BTPs or their corresponding SBPs.
9. Safety specification, pharmacovigilance plan, risk management plan (RMP) and post-marketing safety reports, according to the WHO Guidelines on evaluation of SBPs (6, 7, 10) or the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (5). The following should be included:

The WHO prequalification-specific addendum to the RMP as detailed in PQ-BTP web page.
10. The arrangements for handling complaints and product recalls used for supply of the product

based on its prequalification status, including provisions for informing WHO and the procurement agencies.

11. A description of the procedure for handling product quality complaints and product recalls with the inclusion of restrictions on distribution or recalls. The procedures should include also details on the root cause investigation process, established timeframe for the completion of the investigation process, definition of serious quality issues, established timelines for recall notification to National Medicine Regulatory Authorities and WHO, description of the recall arrangements and actions to put in place at the distribution level description of the periodical mock-recall for a product distributed in Low-Middle-Income-Countries
12. A sample(s) of the product in market packaging(s) with the respective certificate of analysis. This should be provided with the submission to enable visual inspection thereof. No special transportation is required for the samples for the purpose of this requirement.
13. A copy of the currently approved DP specifications (release and shelf-life), dated and signed or certified by authorized personnel, with the analytical test procedures.
14. Evidence that the principles outlined in the most recent version of the WHO guidelines on the international packaging and shipping of vaccines are followed to demonstrate suitability of the packaging to regions outside of climatic zone II. Differences should be justified, and the equivalence of the approach should be discussed and supported by data, including a summary of the packaging procedures for international shipments (including box sizes and types, packing volumes, etc.), the validation protocols and reports of the shipping boxes used for supply of the product based on its prequalification status.

The following should also be submitted for the SBP:

1. The latest SRA-approved product information (summary of product characteristics (SmPC), or an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling) of the RBP. Provide a web link to the SRA-approved product information of the RBP, preferably on the website of the SRA itself, if available.

Furthermore, WHO may request additional data, when considered necessary, for the use of the product in populations, settings or regions relevant for prequalified products. If necessary, this additional information will be included in the WHO public assessment report (WHOPAR). Such information may be communicated to the reference SRA by WHO. The SRA-approved product information will not be changed by the applicant. WHO would not normally inspect the manufacturing site(s) or clinical testing site(s) of an SRA-approved product; however, there may be

circumstances under which WHO will conduct an inspection in collaboration with the reference SRA (9). Such inspections may occur as part of the prequalification application/assessment process or after prequalification of the product.

Variations to and renewal of the marketing authorization of an originator BTP or SBP that has been prequalified based on the approval by an SRA, remain the responsibility of the reference SRA. The variation will have to be submitted to the reference SRA for approval.

Variations that impact uniquely the prequalified product (e.g. PQ-specific addendum to the RMP, international shipment conditions of the prequalified product etc.) will have to be submitted to WHO for approval.

Once the product has been prequalified, WHO should be provided with a copy of the regulatory approval letter of any changes to the key information on the originator BTP or SBP as captured in the Quality Information Summary (QIS-BTP-SRA), the product information, the product specification and test procedures, where appropriate, immediately after the variation has been approved by the reference SRA.

Changes to the product information, the QIS-BTP-SRA, and the specification and test procedures should be shown in track-change mode in Word files. The clean version (in English language) of the updated product information should also be submitted. Other supporting information may be requested once the variation notification has been submitted.

WHO should be informed immediately in case of discontinuation of the product with the relevant SRA and of any critical safety or quality-related issues reported for batches on the market.

References

1. WHO guidelines on the international packaging and shipping of vaccines, WHO/IVB/05.23
2. WHA 67.21 Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy, 2014
3. WHO Guidelines on submission of documentation for the procedure for prequalification of similar biotherapeutic products. Preparation of product dossiers in common technical document format.
4. WHO Model List of Essential Medicines, 20th List March 2017, Amended August 2017
5. WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, Annex 4, Technical Report Series No. 987, 2014
6. WHO Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977, 2009
7. WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 1004, 2016
8. WHO Procedure for Prequalification of Biotherapeutic Products or their corresponding Similar Biotherapeutic Products.
9. WHO Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities Annex 5, Technical Report Series No. 986, 2014.
10. WHO Questions and Answers: similar biotherapeutic products