WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities

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1. Introduction

The World Health Organization (WHO) Prequalification programme is managed by the WHO Regulation of Medicines and other Health Technologies (RHT) 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 will undertake a pilot procedure for prequalification of biotherapeutic products for rituximab and trastuzumab, 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 RHT\(^1\) 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 a WHO pilot procedure for prequalification of two biotherapeutic products: rituximab or trastuzumab, following either one of two pathways:

1) full assessment of SBPs for rituximab or trastuzumab that have been registered by non-SRAs (based on a Reference biotherapeutic product (RBP) approved by a SRA) and marketed in the country of registration (hereinafter referred to as “Full Assessment”) (3); and

2) abridged assessment of rituximab or trastuzumab 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”).

As stated in the WHO Model List of Essential Medicines (4), rituximab is used principally to treat (a) diffuse large B-cell lymphoma, (b) chronic lymphocytic leukaemia or (c) follicular lymphoma, whereas trastuzumab is used to treat (y) early stage HER2\(^2\) positive breast cancer or (z) metastatic HER2 positive breast cancer. These two BTPs, and their corresponding SBPs, have been selected for this WHO pilot procedure because: (i) they are some of the first monoclonal antibody therapies listed in the WHO Model List of Essential Medicines; (ii) there is established WHO technical guidance for evaluation of biotherapeutic protein products prepared by recombinant DNA technology (5), of SBPs (6) and of monoclonal antibodies as SBPs (7); and (iii) some SRAs now have extensive experience in evaluating these BTPs and their corresponding SBPs.

3. Scope

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

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 Biotherapeutic Products: rituximab and trastuzumab” (8) and “WHO Guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products for rituximab and trastuzumab. Preparation of product dossiers in common technical document format” (3) published on the WHO website. Terms may have different meanings in other contexts.

** Applicant**

The person or entity who, by the deadline mentioned in an invitation for expressions of interest (EOI), submits an EOI to participate in the WHO pilot procedure for prequalification of:

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\(^1\) RHT operates in the Cluster of Access to Medicines, Vaccines and Pharmaceuticals [MVP].

\(^2\) human epidermal growth factor receptor 2
(i) rituximab and trastuzumab BTPs, or their corresponding SBPs, that have been approved by SRAs, or (ii) SBPs for rituximab and trastuzumab that have been approved by non-SRAs (based on a RBP approved by a SRA) and marketed in the country of registration), 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 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. 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 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 expected to induce a difference in clinical effect, such as better impurity profile, could be accepted. No differences exist that 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.
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version June 2018

Stringent regulatory authority\(^3\) (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; 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 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) 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 both the BTP and the SBP:

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 actually on the market of the reference SRA’s country or region; and

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.

The following should also be submitted for the SBP:

1. A rationale for the choice of the SRA-licensed RBP by the manufacturer of the SBP that takes in consideration the RBP’s quality, efficacy and safety in a given population, the suitable marketing duration, the marketed use and market experience.

2. The latest SRA-approved product information (summary of product characteristics (SmPC), or

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\(^3\) 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.
an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling). Provide a web link to the SRA-approved product information, preferably on the website of the SRA itself, if available.

3. 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). Provide a web link to the SRA-approved product information of the RBP, preferably on the website of the SRA itself, if available.

4. A list of the SBP’s SRA-approved manufacturer(s) of the DP and DS, including manufacturers of intermediates, primary packaging sites and DS and DP release-testing sites for each of the DP and DS, with the physical address of the manufacturing site(s) (and unit if applicable).

5. A tabular listing of the SBP 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.

6. The quality information summary for the SBP. The QIS-SRA template, available at http://www.who.int/medicines/regulation/prequalification/QIS-BTP-SRA_June2018.docx, should be fully completed and submitted with the application. The QIS-SRA provides a condensed summary of key information on the SBP as approved by the reference SRA at the time of application for prequalification of the SBP.

7. 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 for the SBP. 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 Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab.

8. Safety specification, pharmacovigilance plan, risk management plan and post-marketing safety reports, according to the WHO Guidelines on evaluation of SBPs (6, 7).

9. The evidence that the RBP has been 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. Please note that only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP.

The following should also be submitted for the BTP:

1. Safety specification, pharmacovigilance plan, risk management plan and post-marketing safety reports, according to the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (5).

2. 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). Provide a web link to the SRA-approved product information, preferably on the website of the SRA itself, if available.

3. A list of the SRA-approved manufacturer(s) of the drug product (DP), including manufacturers...
of intermediates, primary packaging sites and release-testing sites, with the physical address of the manufacturing site(s) (and unit if applicable).

4. A list of the SRA-approved manufacturer(s) of the Drug substance (DS) used in the manufacture of the DP, with the physical address of the manufacturing site(s) (and unit if applicable).

5. A tabular listing of the 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 batch number, batch size (number of units), date of manufacture and pack type/size. Also provide a copy of the most recent product quality review, prepared according to the requirements of the reference SRA.

6. A sample(s) of the product in market packaging(s). This should be provided with the submission to enable visual inspection thereof. Attach the respective certificate of analysis.

7. 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.

8. The quality information summary for the BTP. The QIS-SRA template, available at http://www.who.int/medicines/regulation/prequalification/QIS-BTP-SRA_June2018.docx, should be fully completed and submitted with the application. The QIS-SRA provides a condensed summary of key information on the DP as approved by the reference SRA at the time of application for prequalification of the DP.

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 a 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 and then submit it to PQ with evidence of approval by the reference SRA.

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 BTP or SBP as captured in the Quality Information Summary approved by the reference SRA (QIS-SRA), the product information, the SBP specification and test procedures, where appropriate, immediately after the variation has been approved by the reference SRA.

Changes to the product information, the QIS-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
   http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.23_eng.pdf?ua=1

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 pilot procedure for prequalification of
   similar biotherapeutic products for rituximab and trastuzumab. Preparation of product dossiers
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   http://www.who.int/medicines/regulation/prequalification/02_GLs_Submission_Pilot_FullPath
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5. WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared
   http://www.who.int/biologicals/biotherapeutics/TRS_987_Annex4.pdf?ua=1

6. WHO Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical
   Report Series No. 977, 2009
   http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex
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7. WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products
   http://www.who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf?ua=1

8. WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and
   trastuzumab
   http://www.who.int/medicines/regulation/prequalification/01_Pilot_Prequalification_BTPs_June20
   18.pdf

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.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex5.pdf?ua=
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