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

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1. Introduction

The World Health Organization (WHO) recognizes the scientific evaluation of similar Biotherapeutic product (SBP) by Stringent Regulatory Authorities (SRA), which apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO. Where an applicant shares with WHO information on an SBP that has been approved by a stringent SRA (hereinafter called the reference SRA) and that is invited for prequalification, WHO will consider such SBPs for inclusion in the list of WHO-prequalified products, as and when information about such a product becomes available to WHO and when the applicant in question expresses interest in the product being prequalified by WHO.

2. Scope

These guidelines intend to assist applicants with the submission of documentation for prequalification of similar biotherapeutic products that are approved by stringent regulatory authorities.

3. Glossary

The definitions given below apply to the terms used in this procedure and should be read in conjunction with the draft “WHO pilot procedure for prequalification of similar biotherapeutic products" and the draft “WHO Guideline on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products. Preparation of product dossiers in common technical document format” 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).

4. Guidelines on submission of documentation

Submission of an expression of interest for evaluation of an SBP that has already received the approval of a SRA involves preparation and submission of a number of documents, in electronic format (i.e. on CDs or DVDs) as detailed in the applicable guidelines (3).

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:

1) A covering letter, which should include:
   - a statement indicating that the information submitted is true and correct;
   - 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;
   - a statement indicating that the product is actually on the market of the reference SRA's country or region.
   - a rationale for the choice of the RBP by the manufacturer of the SBP that takes in consideration a proven RBP efficacy and safety in a given population, the duration and marketed use and market experience.
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 requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.
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, preferably on the website of the SRA itself, if available.
4) As it concerns the RBP the applicant should provide 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

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

6) A public assessment report, such as the Scientific Discussion of the European Public Assessment Report (EPAR), issued by the reference SRA for both the RBP and the SBP. Assessment report(s) issued by the reference SRA that are not publicly available may be requested for the SBP.

7) 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 (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.

8) A copy of the currently approved DS and DP specifications for the RBP (if available) and SBP (release and shelf-life), dated and signed or certified by authorized personnel, with the description of the analytical test procedures.

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, relevant for use of the product within the scope of the Prequalification Programme, will be included in the WHO public assessment report (WHOPAR) as a separate piece of information. Such information could be communicated to the reference SRA where appropriate. The SRA-approved product information will not be changed. WHO would normally not inspect the manufacturing site(s) of an SRA-approved product; however, there may be circumstances necessitating an inspection to be conducted in collaboration with the reference SRA, upon application or after prequalification of the SBP.

Variations to and renewal of the marketing authorization of an SBP that has been prequalified by WHO based on the approval by an SRA, remain the responsibility of 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 SBP, 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 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. Products that received United States Food and Drug Administration (US-FDA) tentative approval or positive

opinions under Article 58 of European Union Regulation (EC) No. 726/2004 or the Canada S.C. 2004, c. 23 (Bill C-9) procedure, are not within the scope of these guidelines. Such products can be co-listed on the WHO list of prequalified products in accordance with mutual agreements between WHO and these regulatory authorities.

References

1. WHO Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977, 2009
2. WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 1004, 2016
3. 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