

WHO Pilot Procedure for Prequalification of Biotherapeutic Products: human insulin

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1. Introduction

The World Health Organization (WHO) Prequalification Unit (PQT) 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 will undertake a pilot procedure for prequalification of biotherapeutic products containing the active ingredient human insulin, to evaluate whether candidate products: (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) 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 may 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".

Human insulin was discovered as a treatment for diabetes approximately 100 years ago and has been on WHO's Essential Medicines List since the first list was published in 1977. In spite of this, current insulin prices and availability pose a barrier to treatment in most low- and middle-income countries. In higher income countries, there are several sub-populations that cannot reliably access this life-saving medication because it is unavailable, unaffordable or both (3).

As stated in the WHO Model List of Essential Medicines (6), insulin is used principally to treat diabetes. Insulin BTPs, and the corresponding SBPs, have been selected for this WHO pilot procedure because: (i) insulin is a life-saving medication; (ii) current insulin prices pose a barrier to treatment in most low- and middle-income countries; (iii) there is established WHO technical guidance for evaluation of biotherapeutic protein products prepared by recombinant DNA technology (7) and on evaluation of similar biotherapeutic products (SBPs) (8, 9).

Given that BTPs, including their corresponding SBPs, are 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 human insulin, following either one of two pathways:

- 1) full assessment of human insulin BTPs, or the corresponding SBPs, that have not been registered by SRAs (hereinafter referred to as "Full Assessment") (4); and
- 2) abridged assessment of human insulin BTPs, or the corresponding SBPs, that have been approved by a stringent regulatory authority (SRA) and marketed in the country of registration (hereinafter referred to as "Abridged Assessment") (5).

Therefore, WHO's RPQ¹ is exploring options to facilitate access to human insulin, including corresponding insulin similar biotherapeutic products (SBPs), at affordable prices.

3. Scope

This WHO pilot procedure for prequalification of BTPs or their corresponding SBPs is specifically focused on human insulin and will be carried out using either Full Assessment or Abridged Assessment pathways, as further described below (4, 5). The Full Assessment will include, among other requirements WHO's inspection of the relevant manufacturing facilities and clinical research sites, based on information submitted by the manufacturer of such products. Evaluation and inspection is based on WHO-recommended technical standards and guidance including those mentioned above.

This document addresses technical, communication, policy and other aspects of the WHO pilot procedure for the prequalification of human insulin BTPs and corresponding SBPs. Based on the experience gained during the pilot process, WHO reserves the right to revise the prequalification procedure accordingly.

4. Glossary

The definitions given below apply to the terms used in this pilot procedure and should be read in conjunction with the "*WHO Guidelines on submission of documentation for the pilot procedure for prequalification of biotherapeutic products for human insulin – full assessment pathway. Preparation of product dossiers in common technical document format*" (4) and the "*WHO Guidelines on submission of documentation for the pilot procedure for prequalification of human insulin approved by stringent regulatory authorities – abridged assessment pathway*" (5) 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, 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: (i) human insulin BTPs, or corresponding SBPs, that have been approved by SRAs and marketed in the country of registration, or (ii) human insulin BTPs, or corresponding SBPs, that have not been registered by SRAs (in case the product is claimed to be a human insulin SBP the approval should have been based on a 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.

Comparator for clinical studies

A comparator for clinical studies for BTPs is an established human insulin product approved by an SRA with a pharmacological profile similar to that of the product to be prequalified.

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. This refers to a 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 products: (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; 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. Principles

This WHO pilot procedure is based on the following principles and conditions:

GENERAL

- the invitations for EOI for prequalification of human insulin BTPs or corresponding SBPs is published on the WHO website;
- It is the applicant's responsibility to monitor and investigate product complaints and promptly report these to WHO, as necessary or required;
- It is the applicant's responsibility to promptly communicate to WHO any safety concerns arising from its product;
- WHO monitors complaints and safety concerns from United Nations agencies and WHO Member States;
- WHO has a general understanding of the applicant's production and quality control activities;
- It is the applicant's responsibility to provide a WHO prequalification-specific addendum to the risk management plan (RMP) and to undertake pharmacovigilance and related activities according to the agreed RMP
- It is the applicant's responsibility to submit, following each marketing authorization, a summary on how the applicant has addressed, after product prequalification, any potential differences in healthcare settings, compared to SRAs (if applicable), that have required a revision of the adequacy of the safety concerns, pharmacovigilance activities, risk minimisation measures and/or traceability of the product.
- WHO's inspection of finished Drug Product (DP) and Drug Substance (DS) manufacturing site(s) for compliance with current good manufacturing practices (cGMPs) and current good distribution practices (cGDPs);
- WHO's inspection of clinical testing units or contract research organizations (CROs) performing clinical trials for compliance with current good clinical practice (cGCP), current good laboratory practices (cGLPs);

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.

- It is the applicant's responsibility to provide random sampling and testing of DS and DP if requested by WHO;

Human insulin SBPs – Abridged and/or full assessment pathway

- It is the applicant's responsibility to source and purchase the RBP, used to conduct the similarity exercise (quality characteristics, non-clinical and clinical data set), from an SRA market
- It is the applicant's responsibility to promptly communicate to WHO any safety concerns arising from the RBP on which its prequalification application is based, in the case of SBPs;
- WHO relies on information supplied by or originated from SRAs, which may result in WHO determining (in its sole discretion) to waive one or more of the requirements listed below;
- It is the applicant's responsibility to demonstrate that the selected RBP has been licensed and approved by an SRA based on a product dossier containing comprehensive data on non-clinical and clinical studies / full quality, safety and efficacy data;
- It is the applicant's responsibility to conduct a similarity exercise(s), starting with comparison of quality characteristics, of the SBP and RBP that represents the prerequisite for the reduction of the non-clinical and clinical data set required for licensure of the SBP and prequalification;
- It is the applicant's responsibility to provide evidence of the similarity of the SBP with a suitable RBP based on evaluation of the whole data package for each of the quality, non-clinical, and clinical parameters, i.e., the totality of evidence.

Human insulin BTP and/or SBP - full assessment pathway

- WHO's assessment of the required product dossier submitted by the applicant, which must include product data and information on quality, non-clinical and clinical aspects, including product formulation, manufacture and test data and results. Product data and information should meet the requirements described in the WHO guidelines on the evaluation of BTPs (7) or of SBPs (8, 9);
- It is the applicant responsibility to source and purchase the comparator used for clinical studies from an SRA market.
- It is the applicant's responsibility to provide WHO with all results of pharmaceutical (physico-chemical, biological and microbiological) tests, pre-clinical (toxicological and pharmacological) tests and clinical trials related to the product to be prequalified.
- It is the applicant's responsibility to document that the manufacturer is authorized in their country to produce medicinal products for human use.
- It is the applicant's responsibility to provide WHO with the details of any decision to refuse authorization in any country and the reasons for such a decision.
- It is the applicant's responsibility that after the product is listed in the prequalification list, with respect to the methods of manufacture and control provided in the prequalified dossier, to take into account technical progress and introduce any changes that may be required to enable the prequalified product to be manufactured and checked by means of generally accepted scientific methods. Those changes shall be subject to WHO evaluation (refer to paragraph 15)
- It is the applicant's responsibility to ensure that the product information is kept up to date with the current scientific knowledge. The proposed changes shall be subject to WHO evaluation

- the applicant is encouraged, once a product is prequalified by WHO via the full assessment route, to apply for the collaborative procedure³ which facilitates the assessment and accelerated national registration of a WHO-prequalified product.

Furthermore, WHO may collaborate with national regulatory authorities (NRAs) regarding the product dossier assessments and site inspections. Subject to the terms of section 6 below, WHO's prequalification of human insulin BTPs, or corresponding SBPs as applicable, may also be based on approval of such products by SRAs.

WHO recommends that applicants expressing interest in participating in the prequalification procedure: (i) inform the NRAs in the country of manufacture and/or the country where an application for registration has been submitted of their intention to do so, and (ii) request such NRAs to collaborate with WHO in the prequalification process including, in particular, the quality assessment process. Applicants should provide the NRAs with the necessary authorization to discuss the relevant product files with WHO representatives during the product dossier assessment and site inspections (subject to appropriate confidentiality provisions, if necessary).

6. Steps of the pilot procedure

WHO will undertake a Full Assessment of the quality, non-clinical and clinical aspects of the candidate human insulin BTPs or corresponding SBPs (based on a Reference biotherapeutic product (RBP) approved by an SRA), that have not been registered by SRAs (4). In case the product is claimed to be a BTP, the full assessment will include an evaluation of the complete set of information on quality, non-clinical and clinical aspects. In case the product is claimed to be an SBP, the Full Assessment will include an evaluation of data, to be submitted by the applicant, demonstrating similarity of the SBP to a suitable RBP in terms of quality characteristics, biological activity, and clinical aspects.

Alternatively, WHO will undertake an Abridged Assessment of human insulin BTPs, or corresponding SBPs, as applicable, if the products have been approved by stringent regulatory authorities (SRAs) (5) and marketed in the country of registration.

Any products, whether BTPs or SBPs, that are prequalified by WHO under this pilot procedure must still be approved for use by the NRAs of the countries for which market entry is sought.

The prequalification of a product pursuant to this pilot procedure is not a substitute for any NRA's evaluation and market approval according to applicable local regulatory and other requirements. NRAs, using reliance and collaborative principles, may leverage prequalification reports to facilitate their evaluation and approval.

The flowcharts appearing under Appendixes 1 and 2 describe the steps under the Full Assessment and Abridged Assessment, respectively.

The steps of the Full Assessment pathway (Appendix 1) under this pilot procedure include, but are not limited to:

- the publication of an invitation for expression of interest (EOI) by WHO;
- A presubmission meeting with the PQTm before the submission by the applicant of the EOI.

³ *Collaborative Procedure between the World Health Organization Prequalification of Medicines Programme and National Medicines Regulatory Authorities in the Assessment and Accelerated National Registration of WHO-Prequalified Pharmaceutical Products* (hereinafter, the "collaborative procedure")
<https://extranet.who.int/prequal/content/collaborative-registration-faster-registration>

- submission by the applicant to WHO of an EOI to participate in this pilot procedure;
- a screening procedure to ensure that the dossier(s) submitted by the applicant as part of its EOI is complete;
- assessment of product dossier, which must include product data and information as specified in the applicable guidelines for submission (4), available on the WHO website;
- inspection of manufacturing sites of Drug Substances and Drug Products, if applicable, to assess compliance with cGMPs and cGDPs; and
- inspection of clinical sites (if applicable) to assess compliance with cGCP and cGLPs, as appropriate.

The steps of the Abridged Assessment pathway (Appendix 2) under this pilot procedure include, but are not limited to:

- The publication of an invitation for expression of interest (EOI) by WHO;
- submission by the applicant to WHO of an EOI to participate in this pilot procedure;
- a screening procedure to ensure that the dossier(s) submitted by the applicant as part of its EOI is complete;
- assessment of prequalification-specific data and information as specified in the applicable guidelines for submission (5), available on the WHO website;
- reliance on the assessment of the product dossier, inspections of manufacturing sites and/or clinical sites conducted by the SRAs. However, WHO reserves the right to conduct inspections of manufacturing sites and/or clinical sites in connection with an Abridged Assessment if, in WHO's discretion, such inspections are necessary or required.

To note: By submitting an EOI, the applicant undertakes to share information with WHO on all relevant aspects of manufacture and control of the specified products along with changes made and/or planned. Applicants must provide the necessary information to WHO by submitting a product dossier, in the prescribed format, and other information as requested by WHO.

WHO reserves the right to terminate the prequalification assessment of a specific product if the applicant is not able or not willing to provide the required information or to implement corrective actions which WHO may require within a specified time period, or if the information supplied is inadequate to conduct this procedure.

7. Invitation for expressions of interest

The products that will be listed in the invitation for EOIs are considered by WHO to be vital for the effective diagnostic, treatment or prevention of specified diseases. The invitation will be open and transparent, inviting all relevant parties to submit an EOI for the products listed.

Such an invitation will be published on the WHO website and possibly also through other media, such as the international press. For each product sought to be prequalified under this pilot procedure, the applicant should send to the WHO Group Leader Medicine Assessment a product dossier (PD) in the Common technical document (CTD) format, together with the other data required, as per the relevant guidelines (4, 5).

8. Presubmission meeting with PQT

Before the submission of the complete dossier according to the applicable full assessment pathway WHO guidelines, a pre-submission meeting (PSM) is required. A PSM may also be suitable in some cases for the abridged pathway. The purpose of the WHO PSM is in part to discuss how the applicant will address the requirements of the applicable WHO guidelines.

The applicant should fill out an application for a PSM using the online form, and the requirement for and suitability of a PSM for the intended product will be assessed.

In order to plan for the PSM, the applicant should fill out the QOS-BTP and submit it to the Group Leader Medicine Assessment, together with the non-clinical and clinical overall summaries, before the planned pre-submission meeting. The QOS-BTP template is available on the PQT web page together with other relevant information.

It is noted that a PSM should be scheduled only when the dossier is close to be complete and ready to be submitted to the WHO.

During the PSM the applicant should provide brief information on the sites involved in the product manufacturing control and development, including clinical sites/CROs, as well as production experience and robustness, complaints and recalls. The applicant should discuss the most important product's quality characteristics, biological activity, non-clinical and clinical aspects with the inclusion of all clinical trials performed. Furthermore, the applicant should discuss compliance with WHO standards on GMP, GCP, GLP and GDP and compliance with guidelines on the international packaging and shipping of vaccines, with the inclusion of distribution set-up. Finally, the applicant should discuss adherence of the pharmacovigilance plan, risk management plan and post-marketing safety reports to WHO guidelines.

9. Data and information to be submitted

In submitting an EOI for assessment of a product under this pilot procedure, the applicant must send the following to the WHO Group Leader Medicine Assessment:

- a covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct;
- a product dossier, in the format specified in the WHO guidelines on submission of documentation for the pilot procedure (4, 5), including documents comprising relevant product data and information, including those called for in the WHO technical guidelines (7, 8, 9);
- if applicable, a site master file (SMF) for each manufacturing site listed in the product dossier, in the format specified in the WHO guidance documents for submitting an SMF; and
- if applicable, a contract research organization master file (CROMF) for each clinical site listed in the product dossier, in the format specified in the WHO guidance documents for submitting a CROMF (9).

All documentation must be submitted 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.

For the purposes of this pilot procedure, the documentation required to be submitted by the applicant to WHO will differ depending on whether the product is being assessed under:

- Full Assessment pathway of human insulin BTPs or corresponding SBPs (based on a

Reference biotherapeutic product (RBP) approved by an SRA), that have not been registered by SRAs (i.e., BTPs/SBPs for human insulin not registered by SRAs); or

- Abridged Assessment pathway (i.e., BTPs/SBPs for human insulin approved by SRAs).

Applicants submitting data under the Full Assessment pathway should note that the similarity exercise for an SBP versus a relevant RBP is an important requirement of a quality dossier. Such exercise should be discussed separately in section 3.2.R when presenting the data in CTD - module 3.

Guidance and instructions for the submission of the product dossiers for the Full Assessment pathway (4) or for the Abridged Assessment pathway (5) are available on the WHO website.

Normally an applicant is also the manufacturer of the Drug Product. In case an applicant is not the manufacturer of the Drug Product, then the applicant must submit to WHO all relevant documentation (including, but not limited to, contract manufacturing documentation) demonstrating that the applicant is in full control of the manufacturing process for, and quality assurance of, the candidate products submitted for prequalification by WHO.

- Full assessment of human insulin BTPs not registered by SRAs

The full assessment of human insulin BTPs will include an evaluation of the data, to be submitted by the applicant, on the quality, non-clinical and clinical aspects of the proposed BTP.

The WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (7) was adopted by the Expert Committee on Biological Standardization (ECBS) in 2014. This document provides the scientific principles which should be applied for the demonstration of a positive benefit/risk profile of the product sought to be prequalified under this pilot procedure.

Detailed Pharmaceutical (physico-chemical, biological or microbiological) tests, non-clinical (toxicological and pharmacological) tests and results of appropriate clinical trials according to applicable guidelines (4,7) for the demonstration of a positive benefit/risk profile should be submitted. In assembling the dossier for the present pilot procedure, applicants shall also take into account the scientific guidelines relating to the quality, non-clinical and clinical aspects of medicinal products as adopted by WHO and other applicable regulatory guidelines (and in particular ICH, EMA, US-FDA, PMDA).

With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of applicable Pharmacopoeia (e.g. International, European and USP).

All information which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.

- Full assessment of human insulin SBPs (based on a Reference biotherapeutic product (RBP) approved by a SRA) not registered by SRAs

The Full Assessment of human insulin SBPs will include an evaluation of data, to be submitted by the applicant, demonstrating similarity of the SBP to a suitable RBP in terms of quality characteristics, biological activity, non-clinical and clinical aspects. Demonstration of similarity between an SBP and RBP should be based on scientific evidence and a comprehensive similarity

exercise. The applicant must provide WHO with the necessary evidence to support all aspects for a successful SBP qualification. WHO provides guidance on the evidence needed for a product to be considered as an SBP (8, 9).

WHO *Guidelines on evaluation of similar biotherapeutic products (SBPs)* (8) was adopted by the Expert Committee on Biological Standardization (ECBS) in 2009 and the complementary question and answer document to the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs) (9) was adopted in 2018. These documents provide the scientific principles, including the stepwise approach, which should be applied for demonstration of similarity between the SBP and the RBP. High similarity at the quality level is regarded as a prerequisite for moving forward into comparative nonclinical and clinical studies and for potential inclusion of a product in the WHO list of prequalified products. The assessment of the product dossier will include evaluation of the totality of evidence from quality, nonclinical and clinical parameters. It should be noted that clinical studies cannot be used to resolve substantial differences or lack of evidence in physicochemical characteristics and biological activity between the RBP and the SBP.

- *Abridged Assessment of human insulin BTPs, or their corresponding SBPs, that have been approved by SRAs*

The Abridged Assessment will include a verification of the data, to be provided by the applicant, demonstrating that the product submitted for WHO prequalification is the same as that approved by an SRA in all respects (5).

- *Irrespective of the assessment pathway*

The applicant should submit evidence that the product sought to be prequalified under this pilot procedure: (a) meets WHO's 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) adheres to the principles laid out in the WHO guidelines on the international packaging and shipping of vaccines (1); and (c) meets relevant operational packaging and presentation specifications.

The applicant should provide WHO with a risk management plan in line with an SRA-adopted format and post-marketing safety reports applicable to international markets, including LMICs at the time of submission of the prequalification application according to the relevant WHO Guidelines (i.e., WHO *guidelines on evaluation of similar biotherapeutic products* (8), WHO *Guidelines on the quality safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* (7). A WHO prequalification-specific addendum to the RMP as detailed on the PQT web page is also required.

10. Screening of dossiers submitted

Each product dossier submitted by an applicant will be screened for completeness before being assessed. Dossiers submitted for products which are not listed in an invitation for EOIs or have not otherwise been invited by WHO will not be accepted for assessment.

Similarly, WHO will not consider product dossiers that are incomplete. In this context, comparability data are an essential component of complete product dossiers of human insulin claimed to be SBPs, including those not approved by SRAs.

Absence of a comprehensive comparability section will be grounds for not accepting a product dossier

for assessment, as assessment under this pilot procedure cannot proceed without these comparability data. The applicant will be informed if an incomplete dossier has been received and will be requested to complete the product dossier within a specified time period. In the event of non-compliance with such request, the product dossier may be rejected on grounds of incompleteness and returned to the applicant. Only product dossiers that are considered complete as the result of the screening will be retained by WHO for assessment.

After screening, if the product dossier is accepted for assessment, the applicant will be informed of this and of the product dossier reference number, by letter of agreement issued by WHO (hereinafter the “Letter of Agreement”). The Letter of Agreement will serve as an agreement between WHO and the applicant for the participation in prequalification and a commitment to comply with the provisions of the prequalification procedure.

11. Dossier assessment

The product information submitted in the product dossier will be assessed by teams of experts (assessors) appointed by WHO. The assessors involved in the product dossier assessment must have the relevant qualifications and experience in all aspects of assessment of biotechnological pharmaceutical products in general, and in the assessment of SBPs in particular. The assessors will be appointed in accordance with a standard operating procedure (SOP) established by WHO. The assessors will act as temporary advisers to WHO. The assessors must comply with the confidentiality and conflict of interest rules of WHO, as described in the relevant sections of this procedure.

The assessment of a product dossier will be done in accordance with SOPs established by WHO for that purpose so as to ensure uniformity in evaluation and timeliness of assessment activities.

Following the assessment of each part of the product dossier, the outcome of the review will be communicated to the applicant. Applicants are expected to submit responses to comments and any additional information that may be requested by WHO, within the deadline stipulated by WHO. The applicant may apply to WHO for extension of such a deadline, and present proper written justification. If all responses and additional information requested are not received by WHO within the stipulated deadline (including any extensions thereof, if applicable), the applications and prequalification assessment of the relevant product(s) may be suspended by WHO.

An applicant may request a meeting with the WHO experts to clarify issues identified by WHO with respect to the applicant’s product dossier. WHO may provide scientific advice to applicants regarding the product dossier as well as production and control requirements.

12. Site inspections

WHO will plan and coordinate, in accordance with SOPs established by WHO and based on quality risk management (QRM) principles, the performance of inspections of the site(s) of manufacture of the Drug Substances and the Drug Products, and of the clinical testing sites or CROs.

The following factors will be taken into account when planning inspections:

- whether the site(s) has been inspected by either WHO or an SRA, and the results of that inspection;
- the results of previous inspection(s) by WHO or an SRA or a regulatory authority that is a member of PIC/s;
- history of compliance of the company or facility with cGMPs, cGCP and cGLPs, as appropriate;
- the outcome of the assessment of data submitted to WHO;

- complexity of the site, processes and product;
- number and significance of known quality defects (e.g. complaints, recalls);
- major changes to, e.g. buildings, equipment, processes, key personnel;
- site experience with manufacturing and testing of a product; and
- test results of official control laboratories.

The inspections of the manufacturing site(s) are conducted to assess compliance with cGMPs, as recommended by WHO, and include data verification. SMFs submitted by the applicant will be reviewed before an inspection is performed.

The inspections of clinical testing sites or CROs are carried out to assess compliance with cGCP and cGLPs, and to perform data verification. The WHO norms and standards applicable to inspections of Drug Substances and Drug Products, and of clinical testing units or CROs, will follow the principles of inspections that are described in the WHO website at

<https://extranet.who.int/prequal/content/inspections-0>.

The requirements found in the website above may be revised by WHO from time to time.

The inspections of manufacturing sites and clinical sites will be performed by a team of inspectors usually including experts appointed by WHO, preferably from NRA inspectorates, who will act as temporary advisers to WHO. The inspectors must have the relevant qualifications and experience to perform such inspections, be competent in areas such as production and quality control of biotherapeutics, and have appropriate experience in cGMPs and cGCP or cGLPs. The inspectors must comply with the confidentiality and conflict of interest rules of WHO, as described in the relevant sections of this procedure.

A WHO staff member will coordinate the team and will normally lead the inspection team. Each team will perform the inspections and report its findings to WHO in accordance with SOPs established by WHO for that purpose so as to ensure a standard harmonized approach. A representative of the NRA of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facilities to assess the compliance with cGMPs and cGCP or cGLPs.

In accordance with SOPs established by WHO and based on QRM principles, an on-site inspection by a WHO inspection team may be waived provided that the site in question is found by WHO to meet the applicable WHO recommended standards following a desk review of requested inspection reports, the applicant's response(s) to the relevant inspectorate describing corrective actions to any deficiencies identified in the inspection reports and an acceptable product quality review report for the identified product(s).

For Abridged Assessments, WHO will normally rely on inspections of manufacturing sites and/or clinical sites conducted by SRAs (5). However, WHO reserves the right to conduct inspections of manufacturing sites and/or clinical sites in connection with an Abridged Assessment if, in WHO's discretion, such inspections are necessary or required.

13. Reporting and communication of the results of the assessment

As part of the prequalification process, WHO may share the applicant's EOI, application, product dossiers and related information with interested NRAs, subject to WHO entering into an appropriate confidentiality undertaking with such NRAs. Furthermore, the outcome of any joint review of information by WHO and NRAs may be used by WHO, at its discretion, as part of the prequalification assessment process.

Each assessment and inspection team will finalize its reports according to the established WHO SOP and format, describing the findings and including recommendations to the applicant, manufacturer(s)

and/or CROs where relevant.

The findings from the product dossier assessment including, but not limited to, deficiencies of the documentation and data submitted, shall be communicated in writing to the applicant requesting submission of the missing data and information, as appropriate.

The inspection report will be communicated to the manufacturer or CRO as applicable. With the written agreement of the manufacturer or CRO, a copy of the inspection report may also be provided to the applicant (if other than the manufacturer or CRO). If any additional information is required, or corrective action has to be taken by the manufacturer or CRO, WHO will postpone its decision on the acceptability of the site(s) concerned until such information has been evaluated or the corrective action has been taken and found satisfactory in light of the specified standards.

WHO reserves the right to terminate the prequalification procedure for a specific product if the applicant is not able or not willing to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete this procedure.

In the event of any disagreement between an applicant and WHO, an SOP established by WHO for the handling of such disagreements will be followed to discuss and resolve the issue.

As WHO is responsible for the prequalification procedure, the ownership of the reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports subject always, however, to the protection of any commercially sensitive confidential information of the applicant, manufacturer(s) and/or testing organization(s).

“Confidential information” in this context means:

- confidential intellectual property, know-how and trade secrets (including, e.g. formulas, processes or information contained or embodied in a product, unpublished aspects of trade marks, patents, etc.); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the Letter of Agreement between WHO and each applicant, manufacturer or CRO before the assessment of the product dossier or inspection of the manufacturing and clinical testing sites may commence.

The cancellation or withdrawal, at any time and for any reason, of an application for prequalification assessment of a specific product will not prejudice or otherwise affect WHO’s aforementioned rights. Similarly, if the prequalification assessment and/or a prequalified product is suspended or delisted, at any time and for any reason, such suspension or delisting will not prejudice or otherwise affect WHO’s aforementioned rights.

14. Outcome of the prequalification procedure

Once WHO is satisfied that the prequalification procedure is complete for the relevant candidate product, and that the product as well as its manufacturing sites and clinical testing sites meet all WHO-recommended guidelines and standards, then the product (as manufactured at the specified manufacturing site(s)) will be included in the WHO list of prequalified products. The WHO list of prequalified products will be compiled in accordance with an SOP established by WHO for final decision-making on inclusion in the list. The list will be published on the WHO website and will specify the characteristics of the prequalified products, as described in Appendix 3 to this procedure.

An applicant will receive a letter from WHO concerning the outcome of the prequalification assessment process in regard of the candidate product. Once the product is included in the WHO list of prequalified products, the applicant will be responsible for keeping WHO continuously updated on all relevant aspects of the manufacture and control of such product(s) and to meet any

requirements, as agreed with WHO.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, and subject to the protection of any commercially sensitive confidential information, WHO will publish on the WHO website and make publicly available the following information:

- WHO Public Assessment Reports (WHOPAR(s)) on the product dossier assessments;
- WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers and CROs, that were found to be in compliance with WHO-recommended guidelines and standards;
- Negative evaluation outcomes in accordance with SOPs established by WHO, including field safety notices, notices of concern as well as notices of suspension as applicable.

In addition to the foregoing, WHO reserves the right to use, publish, issue, share with NRAs and other relevant authorities of WHO Member States as well as with United Nations agencies and other relevant intergovernmental organizations, and/or make publicly available (in each case, in accordance with the provisions of this document, including provisions regarding the protection of any commercially sensitive information of the manufacturer) any outcomes, reports, notices and/or results — whether in draft or final form, and whether positive or negative — arising from or relating to the prequalification assessment process and/or any prequalified product including, without limitation, any WHO Notices of Concern, WHO Notices of Suspension, WHO information notices to end-users, manufacturer-issued field safety notices, and/or any confidential information to which WHO may gain access in the course of the prequalification process.

The decision to include a product in the WHO list of prequalified products is made by WHO, based upon information available to it at that time, i.e., information in the submitted product dossier and on the status of cGMPs, cGLPs and cGCP at the facilities used in the manufacture and testing of the product at the time of the site inspection(s) conducted by WHO or at the time of the site inspection(s) conducted by an SRA, the outcome of which has been determined by WHO to meet the applicable WHO-recommended standards, in accordance with the terms of this procedure. This decision is subject to change on the basis of new information that may become available to WHO. If serious safety and/or quality concerns arise in relation to a prequalified product, WHO may delist the product after evaluation of the new evidence and a risk–benefit assessment, or may suspend the product until results of further investigations become available and are evaluated by WHO.

Applicants and manufacturers must understand that WHO does not issue any approvals, certificates or licenses of prequalified products; this responsibility lies with the NRA of each country. Furthermore, WHO does not, as a matter of policy, endorse any specific commercial product over another. 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 from 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 list of WHO prequalified products.

15. Maintenance of prequalification status

Applicants are required to communicate details to WHO of any changes or amendments (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the product.

The “Guidelines on procedures and data requirements for changes to approved biotherapeutic products” (10) plus the general principles outlined in the existing WHO Guidance on variations for pharmaceuticals (11) and vaccines (12) will be applicable to WHO-prequalified BTPs, including SBPs, during this pilot. Variations to and renewal of the marketing authorization of a BTP or an SBP that has been prequalified by WHO under the Abridged Assessment pathway (i.e., based on the approval by an SRA) will remain the responsibility of the reference SRA.

It is the applicant's responsibility to provide WHO with the appropriate documentation (referring to relevant parts of the product dossier) to prove that any intended or implemented variation will not have a negative impact on the quality of the product that has been prequalified. WHO will undertake an evaluation of variations according to the established WHO guidelines and SOPs, and will communicate the outcome thereof to the applicant. Adherence to the reporting requirements specified in the respective WHO Guidance on variations will be verified during the routine surveillance inspections carried out by WHO.

Certificates of analysis of final products released by the manufacturer and specifications and test methods should be provided, upon request, by the manufacturer or applicant to WHO for review. In the event of failure to meet the established criteria for testing, WHO will investigate the problem and communicate the outcome of this investigation to the manufacturer and applicant, if other than the manufacturer.

Complaints concerning prequalified products communicated to WHO will be investigated in accordance with an SOP established by WHO for that purpose. After investigation, WHO will provide a written report of the problem and include recommendations for action where relevant. WHO will make the report available to the applicant/manufacturer, and to the NRA of the country where the manufacturing site is located and any other relevant NRA(s). Subject to the protection of commercially sensitive confidential information as referred to above, WHO shall be entitled to make such reports public. In addition, WHO reserves the right to share the full report with the relevant authorities of interested United Nations agencies, international procurement agencies or WHO Member States who rely on WHO PQ for their procurement decisions.

Manufacturers of prequalified products and associated DS manufacturers will be re-inspected at regular intervals as determined by WHO, normally once every three years from the date of prequalification, unless inspections of the aforementioned manufacturers by an SRA have occurred within such three-year timeframe. In the event of the latter, manufacturers of prequalified products and associated DS manufacturer(s) must provide WHO with such SRA inspection reports, promptly at the request of WHO. Re-inspections are conducted to verify compliance with cGMPs, as recommended by WHO, and include data verification.

Furthermore, in order to maintain their prequalification status, WHO may arrange for prequalified BTPs or SBPs, as applicable, to be requalified at regular intervals.

Every five years from the date of prequalification, or when requested to do so by the WHO Prequalification Programme, the holder of a prequalified product may be required to submit data and information in relation to the product to WHO for assessment. The purpose of this assessment is to verify that the product conforms to current norms and standards, and to verify the consistency of the quality of the product and its manufacturing process(es) over the identified period.

General principles outlined in the existing WHO procedure and guidelines on the requalification for pharmaceuticals and vaccines will be applicable to requalification of prequalified BTPs or SBPs.

Re-inspection and/or requalification may also be performed:

- if any fraud or omissions by the applicant, manufacturer(s) of a Drug Product or Drug Substance, or CROs in the initial assessment procedure or during the follow-up activities, become evident; and
- if WHO, United Nations agencies or WHO Member States consider that a batch or batches of supplied WHO-prequalified product are not in compliance with the specifications which were found to be applicable upon prequalification.

If, as a result of re-inspection or requalification, it is found that a product and/or specified manufacturing site no longer complies with the WHO recommended standards, such products and manufacturing sites may be suspended or removed from the WHO list of prequalified products.

Failure of a manufacturer or applicant to participate in re-inspection or requalification (as applicable) may also lead to suspension or removal from this list.

16. Cost recovery

WHO reserves the right to charge for prequalification activities.

17. Confidentiality undertaking

The assessors and inspectors will treat all information to which they will gain access during the assessments and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the prequalification procedure, as confidential and proprietary to WHO or parties collaborating with WHO in accordance with the terms set forth below.

Assessors and inspectors will take all reasonable measures to ensure that confidential information:

- is not used for any purpose other than the assessment/inspection activities described in this document; and
- is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they are clearly able to demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of WHO (including by the applicants or manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by the applicants or manufacturers); or
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

18. Conflict of interest

Before undertaking the work, each assessor and inspector will be required to sign a declaration of interest, in addition to the abovementioned confidentiality undertaking. If, based on this declaration of interest, WHO considers that there is no risk of a real or perceived conflict of interest (or that there is only an insignificant and/or irrelevant conflict of interest), and WHO thus considers it appropriate for the assessor or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO. In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All inspectors furthermore agree that, at the applicant's or CRO's request, WHO will advise the applicant or CRO, in advance, of the identity of each inspector and the composition of the team performing the site inspection, and provide curricula vitae of the inspectors.

The applicant or CRO will then have the opportunity to express possible concerns regarding any of the inspectors to WHO before the visit. If such concerns cannot be resolved in consultation with WHO, the applicant or CRO may object to a team member's participation in the site visit. Such an objection must be made known to WHO by the applicant or CRO within 10 days of receipt of the proposed team composition. In the event of such an objection, WHO reserves the right to cancel all

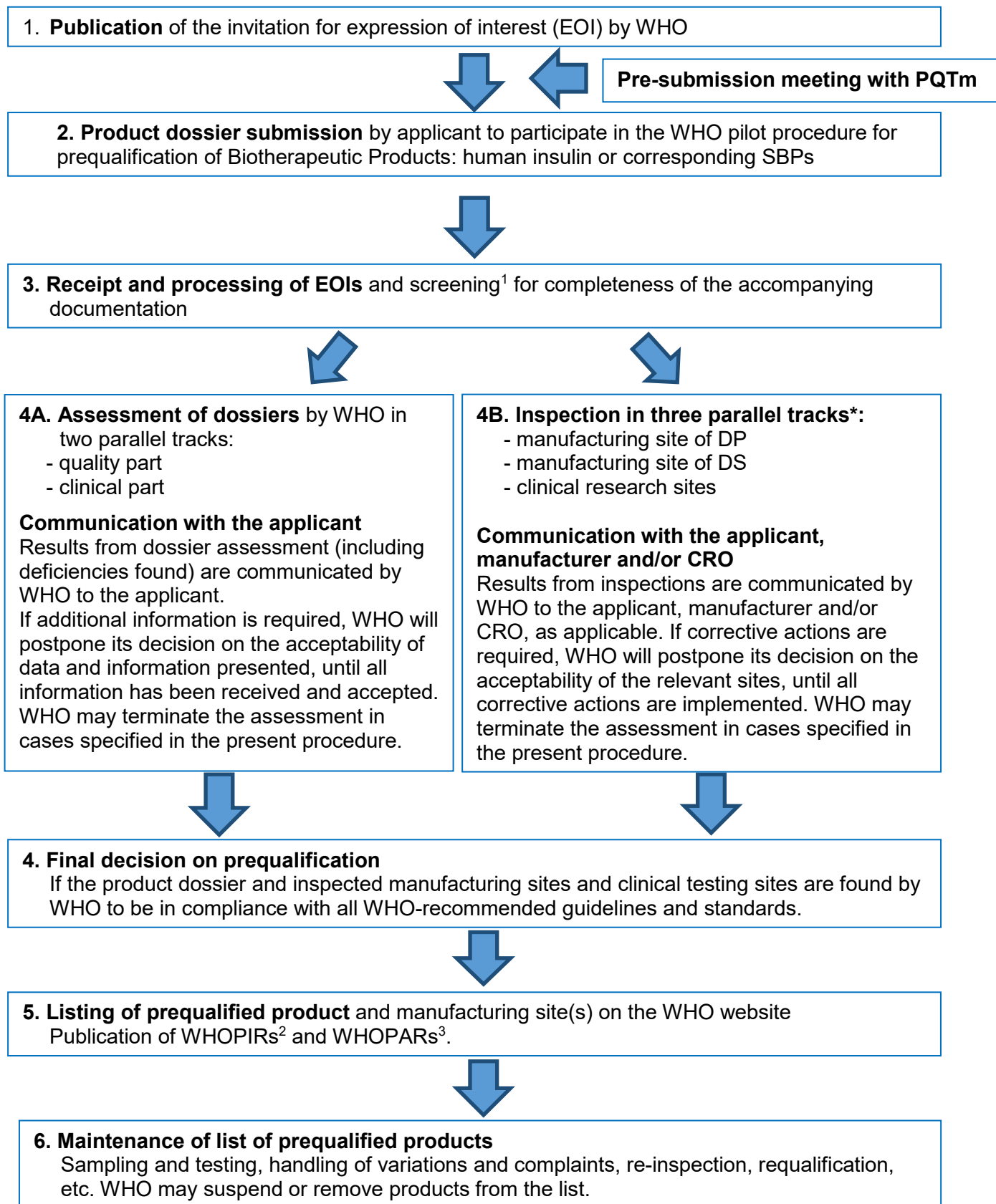
or part of its agreement with, and the activities to be undertaken by, that inspector.

19. Disputes; Privileges and immunities of WHO

In the event of any dispute or disagreement between the applicant, manufacturer and/or CRO, on the one hand, and WHO, on the other hand, arising from or relating to the prequalification assessment process, an SOP established by WHO for the handling of such disputes and disagreements will be followed to discuss and resolve the issue.

By virtue of WHO's status as a specialized agency of the UN, WHO, its officials and experts performing missions for WHO (including, e.g. the prequalification assessors and inspectors) enjoy privileges and immunities under national and international laws and conventions, including the Convention on the Privileges and Immunities of the Specialized Agencies, adopted by the General Assembly of the United Nations on 21 November 1947 (the 1947 Convention). Nothing contained in or relating to this document or the prequalification assessment will constitute or be deemed as a waiver of any of the privileges or immunities which WHO, its officials and/or experts performing missions for WHO enjoy pursuant to the 1947 Convention or otherwise under any national or international law, convention or agreement, and/or as submitting WHO, its officials and/or experts aforesaid to any national court jurisdiction.

Appendix 1. Flowchart of Full Assessment under this WHO pilot procedure

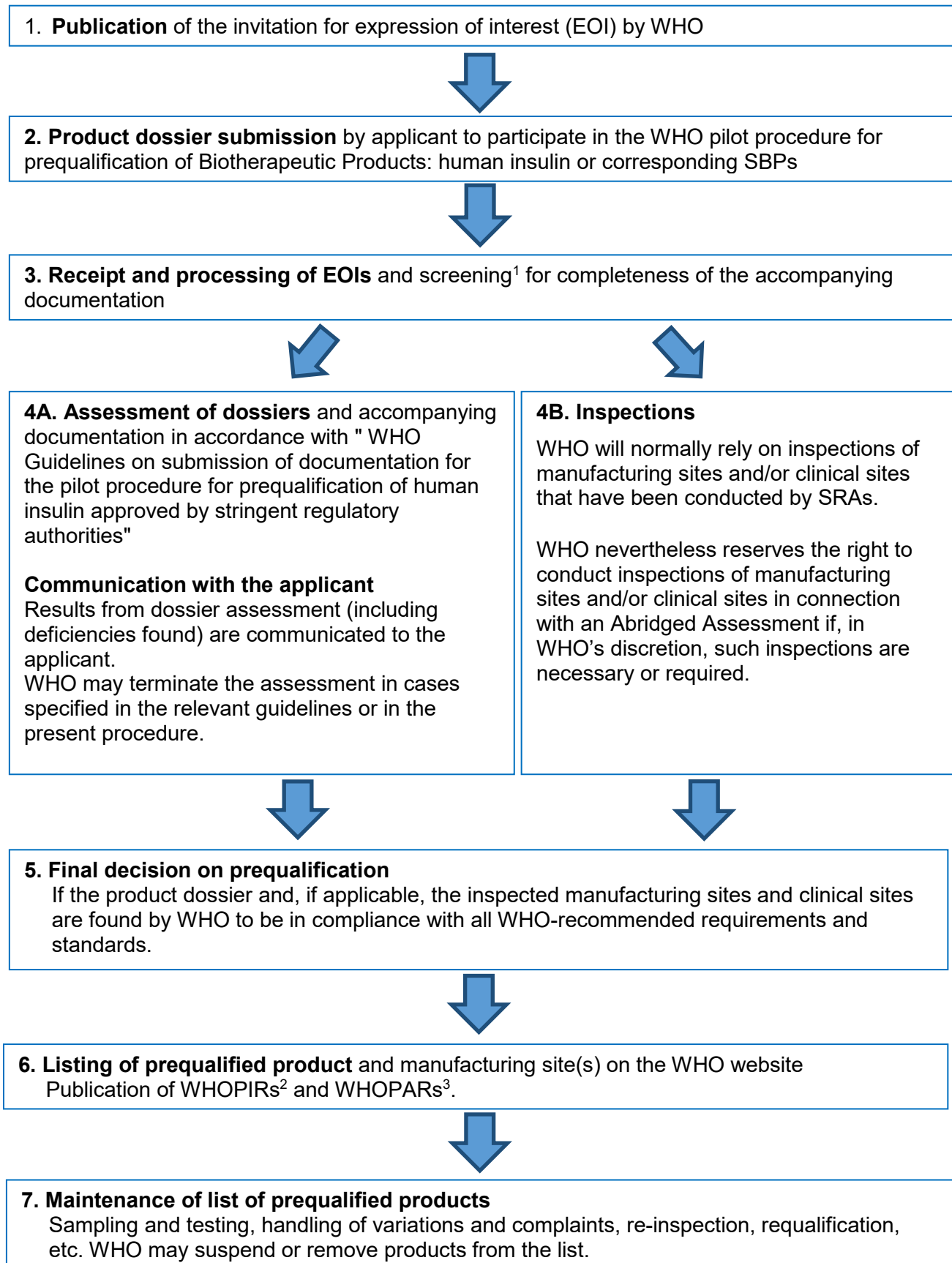


¹ Screening of dossiers will be conducted. Incomplete dossiers will not enter assessment unless necessary complete information has been provided

² WHOPIRs: WHO Public Inspection Reports

³ WHOPARs: WHO Public Assessment Reports

Appendix 2. Flowchart of Abridged Assessment under this WHO pilot procedure



¹ Screening of dossiers will be conducted. Incomplete dossiers will not enter assessment unless necessary complete information has been provided

² WHOPIRs: WHO Public Inspection Reports

³ WHOPARs: WHO Public Assessment Reports

Appendix 3. Characteristics of the prequalified biotherapeutic product including corresponding SBP to be made available for public access on the WHO website

- WHO product reference number
- International Nonproprietary Name (INN) of Drug Substance(s) (DS)
- Dosage form and strength
- Proprietary (or Trade) name of the drug product (DP) in the SRA country/region (if applicable)
- Name of applicant and official address
- Name of manufacturer of Drug Product (DP)
- Physical address of manufacturing site(s) (and unit, if applicable)
- Name of Drug Substance manufacturer, physical address of manufacturing site(s) (and unit, if applicable)
- Description of the Drug Product (DP) (as in Product Information, e.g. powder for concentrate for solution for infusion; concentrate for solution for infusion, white powder, clear, colourless liquid, excipients)
- Pack size(s), primary and secondary packaging material(s)
- Storage conditions (as in Product Information) and any special precautions for storage (including storage conditions after reconstitution/first opening, where applicable) shelf-life of the DP (including in-use period and conditions, where applicable)
- summary of product characteristics
- package leaflet
- labelling
- The shipment and transportation conditions in line with the principles laid out in the WHO guideline for international packaging and shipping of vaccines
- PQ-specific addendum to the RMP

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. Basu, Yudkin J, Kehlenbrink S, Davies JI, Wild SH, Lipska KJ, Sussman JB, Beran D. Lancet Diabetes Endocrinol. 2019 Jan;7(1):25-33
4. WHO Guidelines on submission of documentation for the pilot procedure for prequalification of biotherapeutic products for human insulin – full assessment pathway - Preparation of product dossiers in common technical document format
5. WHO Guidelines on submission of documentation for the pilot procedure for prequalification of human insulin approved by stringent regulatory authorities – abridged assessment pathway
6. WHO Model List of Essential Medicines, 21th List 2019
7. 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
8. WHO Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 977, 2009
9. WHO Questions and Answers: similar biotherapeutic products
10. Guidelines for the preparation of a contract research organization master file, Annex 7, Technical Report Series No. 957, 2010
11. Guidelines on procedures and data requirements for changes to approved biotherapeutic products
12. WHO guidelines on variations to a prequalified product
13. Guidance on reporting variations to a prequalified vaccine