WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products

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1. Introduction

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

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

Considering the values that biotherapeutic products can provide and the fact that some biotherapeutic products have already been listed in the WHO Model List of Essential Medicines, WHO Department of Essential Medicines and Health Products was requested to explore options to facilitate access to quality-assured biotherapeutics and similar biotherapeutics at affordable prices.

All biotherapeutic products, including similar biotherapeutic products, are highly complex and regulatory assessment of those products can be challenging in some countries. For these reasons, the Regulation of Medicines and other Health Technologies unit has initiated a pilot procedure for prequalification of similar biotherapeutic products.

This document addresses technical, communication and policy aspects of the pilot procedure. Based on the experience gained during the pilot process, procedures will be revised accordingly.

2. Glossary

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

3. Purpose and principles

The purpose of this WHO procedure is to evaluate whether similar biotherapeutic products meet WHO standards [1,2] and are manufactured in compliance with current good manufacturing practices (hereinafter referred to as cGMP).

This procedure established by WHO is based on the following principles:

- the SBPs eligible for prequalification listed in invitations for EOI[1];
- assessment of product dossier is based on product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- inspection of finished Drug Product and Drug Substance manufacturing site(s) for compliance with cGMP;
- inspection of clinical testing units or contract research organizations (CROs) performing clinical trials for compliance with current good clinical practices (hereinafter referred to as cGCP) and current good laboratory practices (hereinafter referred to as GLP);
- reliance on the information supplied by stringent national regulatory authorities;
- random sampling and testing of DS and DP supplied by the applicant;

[1] EOI for the pilot procedure for prequalification of SBPs will be published in September 2017

- handling of complaints and recalls reported to WHO;
- monitoring of complaints from agencies and countries;
- a rationale for the choice of the RBP by the manufacturer of the SBP that takes into consideration a proven RBP efficacy and safety in a given population, the duration and marketed use and market experience;
- the demonstration that the RBP has been licensed based on a full quality, safety, and efficacy data;
- a comparability exercise(s) starting with comparison of the 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;
- the demonstration of SBP similarity to a suitable RBP based on evaluation of the whole data package for each of the quality, non-clinical, and clinical parameters.

Concept of reliance: Collaborative registration procedure

Any products, including SBPs that are prequalified must still be approved for use by the national regulatory authorities (NRAs) of the countries for which market entry is sought. Repeated assessment and inspection of the already-prequalified products not only consume scarce regulatory resources but also extend the time needed to make them available to patients. WHO has therefore designed a collaborative procedure that enables NRAs to make use of work already carried out by WHO, strengthen their own regulatory oversight processes, and ensure that much-needed products reach patients more quickly.

As described in the introduction, one of the reasons behind in initiating the pilot procedure for prequalification of SBP is to ensure access to quality-assured products. In this context, once a product is prequalified, the applicant is strongly encouraged to submit prequalified SBP for accelerated registration by using the collaborative procedure which facilitates the assessment and accelerates national registration of a prequalified product. More details on the collaborative registration procedure are available at https://extranet.who.int/prequal/content/collaborative-registration-faster-registration.

Furthermore, WHO may collaborate with national regulatory authorities (NRAs) regarding dossier assessments and inspections. Subject to the terms of section 4 below, the prequalification of a product may also be based on approval by a stringent regulatory authority (SRA).

WHO recommends that applicants expressing interest in participation in the prequalification procedure inform the NRAs in the country of manufacture of their intention and request them to collaborate with WHO in the quality assessment process. It is recommended that applicants provide the NRAs with the necessary authorization to discuss the relevant product files with WHO representatives during dossier assessment and site inspections (subject to appropriate confidentiality provisions, if necessary).

4. Steps of the procedure

WHO undertakes a comprehensive evaluation of the quality, safety and efficacy of similar biotherapeutic products, based on information submitted by the applicants, and inspection of the relevant manufacturing and clinical sites. (A flowchart showing the prequalification process is provided in Appendix 1).

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. Interested applicants provide the necessary information to WHO by submitting a product

dossier in the prescribed format, and other information as requested.

The procedure will normally include:

- assessment of product dossiers, which must include product data and information as specified in the applicable guidelines[1,2], available on the WHO web site (http://www.who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en/);
- inspection of manufacturing sites of DS and DP, to assess compliance with GMP;
- inspection of clinical sites (if applicable), to assess compliance with GCP and GLP as appropriate.

If the evaluation above demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO-recommended standards, the product will be included in the list of pharmaceutical products that are considered to be acceptable.

WHO reserves the right to terminate the evaluation of a specific product if the applicant is not able to provide the required information, and/or is unable to implement any corrective actions which WHO may require within a specified time period, or when the information supplied is inadequate to complete this procedure.

WHO recognizes the evaluation of relevant products by SRAs which apply standards for quality equivalent to those recommended by WHO. Provided that the SRA is willing to share certain information with WHO on the products in question, WHO will consider such products for inclusion in the list of WHO-prequalified products. It will do so as and when information about such products becomes available to WHO and when the holders of the regulatory approval of such products express their interest in having these products prequalified by WHO[3]. These products will be added to the list of products prequalified by WHO, on the basis of the scientific assessment and inspections conducted by the regulatory authority concerned, and the exchange of relevant information between the regulatory authority and WHO.

An inspection of a manufacturer or CRO may not be required if:

1. There has been an inspection by an SRA; and
2. The inspection was conducted within the last three years; and
3. Information on the inspection (including inspection report and responses to any deficiencies) is available for review by WHO; and
4. Based on this and other available information, it is determined[1] that the site(s) in question meet(s) the applicable WHO-recommended standards.

With a view to coordinating inspection activities, avoiding duplication and promoting information sharing without prejudice to the protection of any confidential and or proprietary information of the applicants and manufacturers in accordance with the terms of this procedure, WHO may disclose inspection related information to regulatory authorities of WHO Member States as well as to regulatory authorities that are members of the PIC/S.

5. Invitation for expressions of interest

The pharmaceutical products listed in an invitation for EOIs are considered by WHO to be vital for the effective treatment and prevention of the specified diseases (including HIV/AIDS, malaria and tuberculosis) or for reproductive health. These products are normally included in either the WHO Model List of Essential Medicines or the relevant WHO treatment guidelines and recommendations (or both).

The products included in the WHO Model List of Essential Medicines are those that satisfy the

priority health-care needs of a population. They are selected, among other criteria, on the basis of disease prevalence, evidence on efficacy and safety, and analysis of comparative cost-effectiveness. Products included in WHO treatment guidelines are selected on the basis of an assessment of the evidence for benefits, risks, costs and appropriateness for use in a variety of situations, taking into account the needs of special populations and the values and preferences of the groups (professional and patient) using them.

Each invitation will be open and transparent, inviting all relevant parties to submit an EOI for the pharmaceutical products listed. Such an invitation will be published on the WHO web site and possibly also through other media, such as the international press.

In situations of high public health concern as determined by WHO, the Organization may also directly invite relevant parties to submit specified product dossiers for evaluation by WHO under this procedure without publication of an invitation for EOI.

As described in the draft Guidelines on submission of documentation for the WHO pilot prequalification of SBP, the applicant should send a product dossier (PD) to the WHO focal point (together with the other data required), in the format specified accordingly.

Through the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process, considerable harmonization has been achieved on the organization for the Quality module of the registration documents with the issuance of the Common technical document (CTD) –ICH M4 guideline. This format, recommended by ICH guideline has become widely accepted by regulatory authorities both within and beyond the ICH regions.

The product data for a SBP should follow the structure of the CTD format for the applicable sections, however specific requirements that such applications should fulfil are detailed in ICH M4 guideline. Guidance and instructions developed for the submission of the dossiers for SBPs are made available on the WHO web site.

6. Scientific rationale, data and information to be submitted

Interested parties are expected to submit documentation on the pharmaceutical products as called for in the invitation for EOIs. Applicants should submit their product dossiers with the required information to the WHO focal point. Guidance and instructions developed for the submission of the dossiers are made available on the WHO web site.

Normally the applicants who participate in the WHO prequalification scheme for pharmaceutical products are the manufacturers of the DP. In the case that an applicant is not the manufacturer of the DP, all relevant documentation, including (but not limited to) contract manufacturing documentation, should be submitted, demonstrating that the applicant is in full control of the manufacturing process for, and quality assurance of, the products submitted for prequalification.

If considered necessary or desirable by either party, and before the actual evaluation process starts, a discussion may be held between the manufacturer and WHO. This meeting should be scheduled as early as possible with a predefined agenda to address questions sent in advance to WHO by the manufacturer.

In submitting an EOI for product evaluation, the applicant should send the following to the WHO focal point:

- 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 draft WHO guidelines on submission of

documentation for the WHO pilot procedure for prequalification of similar biotherapeutic products, documents on submitting product data and information, including those requested in the WHO technical guidelines[1,2] ;

- 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
- a contract research organization master file (CROMF) for each clinical site listed in the dossier, in the format specified in the WHO guidance documents for submitting a CROMF.

All documentation should be submitted in English.

For the purposes of this procedure, different requirements for documentation to be submitted apply to the following categories of products:

- Similar biotherapeutic product – DPs to be assessed by WHO;
- Similar biotherapeutic product – DPs approved by SRAs.

The documentation requirements for each of the above categories can be found on the WHO web site at: http://www.who.int/medicines/regulation/global_consultation_prequal_similar_biotherapeutic/en/

These requirements are subject to revision in the future.

A SBP will be added to the list of products prequalified by WHO on the basis of data to be submitted demonstrating similarity to the RBP in terms of quality characteristics, biological activity, safety and efficacy. The similarity should be based on a comprehensive comparability exercise. Decision making regarding the demonstration of SBPs similarity to RBP should be based on scientific evidence. The onus is on the applicant to provide the necessary evidence to support all aspects for a successful SBP qualification. The WHO web site provides guidance on the evidence needed for a product to be considered as a SBP[1,2].

WHO Guidelines[1] on evaluation of similar biotherapeutic products (SBPs) were adopted by the Expert Committee on Biological Standardization (ECBS) in 2009. This document provided the scientific principles, including the stepwise approach, which should be applied for demonstration of similarity between the SBP and the reference biotherapeutic product (RBP). High similarity at the quality level is regarded as a prerequisite for enabling the use of a tailored nonclinical and clinical program for the inclusion in the list of products prequalified by WHO. The decision on the inclusion of the SBP in the list of products prequalified by WHO should be based on 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 in physicochemical characteristics and biological activity between the RBP and the SBP.

From a regulatory perspective, mAb assessment is based on the same principles as those used for the evaluation of other rDNA-derived biotherapeutic proteins. On the other hand, biosimilar mAbs should also comply with the criteria established for demonstration of similarity. Therefore, guidelines on evaluation of monoclonal antibodies as SBP[2] should be read in conjunction with both the WHO Guidelines on evaluation of similar biotherapeutic products[1] and the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology.

Additionally, guidance on various aspects of rDNA-derived medicines, SBPs and mAbs are also available from several other bodies.

7. Screening of dossiers submitted

Each product dossier submitted by an applicant will be screened for completeness before being evaluated. 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 dossiers that are incomplete. The applicant will be informed that an incomplete dossier has been received and will be requested to complete the dossier within a specified time period. In the event of non-compliance, the dossier may be rejected on grounds of incompleteness and returned to the applicant. Dossiers that are considered complete as the result of the screening will be retained by WHO for assessment. After screening, if the dossier is accepted for assessment the applicant will be informed of this, including the dossier reference number, by letter. This letter 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.

8. Dossier assessment

The product information submitted in the dossiers will be assessed by teams of experts (assessors) appointed by WHO. The assessors involved in dossier assessment must have the relevant qualifications and experience in the fields of pharmaceutical development, quality assessment of biotechnological pharmaceutical products, quality assurance, biopharmaceutics and other relevant fields. The assessors will be appointed in accordance with a standard operating procedure (SOP) established by WHO. The assessors should preferably be from NRAs and they will act as temporary advisers to WHO. The assessors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure.

The assessment of product dossiers 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. If needed, WHO may provide training to these experts. Following the assessment of each part of the dossier, 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 as soon as possible. Within one month, the applicant should inform WHO of the estimated time frame required to address and respond to all queries. The procedure is usually suspended (i.e. WHO will not undertake any further action) until all required responses and any additional information is received by WHO. Each applicant may request a hearing or meeting with the WHO experts involved in the assessment of this applicant's dossier to clarify issues identified by the WHO experts. WHO may provide technical assistance to applicants regarding appropriate product dossier to be submitted as well as production and control requirements.

9. Site inspection

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 DS and the DP, and of the clinical testing units or CROs.

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

- the results of previous inspection(s) by WHO or an SRA, and history of compliance of the company or facility with GMP, GCP and or GLP 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 GMP 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 units or CROs are carried out to assess compliance with GCP and GLP, and to perform data verification. The WHO norms and standards applicable to inspections of DS and DP, and of clinical testing units or CROs, can be found on the WHO web site at https://extranet.who.int/prequal/content/inspections-0.

These requirements may be revised from time to time.

The inspections 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 GMP and GCP or GLP. The inspectors must comply with the confidentiality and conflict of interest rules of WHO, as laid down in the relevant sections of this procedure. If needed, WHO may provide training to these experts.

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 GMP and GCP or GLP.

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 to meet the applicable WHO recommended standards following a desk review of requested inspection reports, the manufacturers 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).

10. Reporting and communication of the results of the evaluation

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 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 this procedure for a specific product if the applicant is not able 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 exchange of letters, to be concluded before the assessment of the product dossier or inspection of the manufacturing and clinical sites, between WHO and each applicant, manufacturer or CRO. Notwithstanding the foregoing, WHO reserves the right to share the full assessment and inspection reports with the relevant authorities of any interested Member State of the Organization and interested United Nations agencies.

11. Outcome of the prequalification procedure

Once WHO is satisfied that this procedure is complete for the relevant product, and that the WHO-recommended standards are met, the product, as manufactured at the specified manufacturing site(s), will be included in the list of prequalified biotherapeutic products. The list of prequalified biotherapeutic 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 web site and will specify the characteristics of the prequalified biotherapeutic products, as described in Appendix 2 to this procedure.

Each applicant will receive a letter of prequalification from WHO informing it of the outcome of the quality assessment process in regard of the submitted product(s). Once the product(s) are included in the list of prequalified biotherapeutic products, the applicant shall 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, WHO will — subject to the protection of any commercially sensitive confidential information — publish WHO Public Assessment Reports (WHOPAR(s)) on the product dossier assessments and WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers and CROs, that were found to be in compliance with WHO-recommended guidelines and standards. These reports will be published on the WHO web site. Subject always to the protection of commercially sensitive confidential information, WHO shall also be entitled to publish negative evaluation outcomes in accordance with SOPs established by WHO. These include notices of concern as well as notices of suspension.

The decision to list a pharmaceutical product is made based upon information available to WHO at that time, i.e. information in the submitted dossier and on the status of GMP, GLP and GCP 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.

12. Maintenance of prequalification status

Applicants are required to communicate details to WHO of any changes (variations) in manufacture and control that may have an impact on the safety, efficacy and quality of the product. Guidance on variations to prequalified SBP will be developed for public comments. Further changes may be considered once the "Guidelines on procedures and data requirements for changes to approved biotherapeutic products" are finalized and approved by the Expert Committee on Biological Standardization.

It is the applicant's responsibility to provide WHO with a safety specification and pharmacovigilance plan at the time of submission of the prequalification application as described in the WHO Guidelines on evaluation of similar biotherapeutic products.

It is the applicant's responsibility to provide WHO with the appropriate documentation (referring to relevant parts of the 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 communicate the outcome to the applicant within the prescribed time lines. Adherence to the reporting requirements will be verified during the inspections carried out by WHO. Certificates of analysis of final products released by the manufacturer and specifications for test methods should be provided by the manufacturer or applicant to WHO for review upon request. 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. Subject always to the protection of commercially sensitive 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 Member States of the Organization and interested United Nations agencies.

Manufacturers of prequalified products and associated DS manufacturers will be re-inspected at regular intervals as determined by WHO, but normally at least once every three years. Re-inspections are conducted to verify compliance with GMP as recommended by WHO and include data verification.

Furthermore, in order to maintain their prequalification status, WHO will arrange for prequalified products 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 is 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 information and data submitted in relation to prequalification, 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.

The procedure and guidelines on the requalification of prequalified SBPs will be developed in the future.

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

- if any fraud or omissions by the applicant, manufacturer(s) of an DP or DS, or CROs in the initial assessment procedure or during the follow-up activities, become evident; and
- if WHO or any United Nations agency considers that a batch or batches of supplied

prequalified biotherapeutic products 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 list of prequalified biotherapeutic 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.

13. Cost recovery

For the WHO pilot procedure, fees associated with prequalification will be waved.

14. 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 above-mentioned project, 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 manufacturers); or
- was in the public domain at the time of disclosure by or on behalf of WHO (including by 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.

15. Conflict of interest

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest. If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the assessor or inspector in question to undertake this work, he/she will discharge his/her functions exclusively as adviser to WHO.

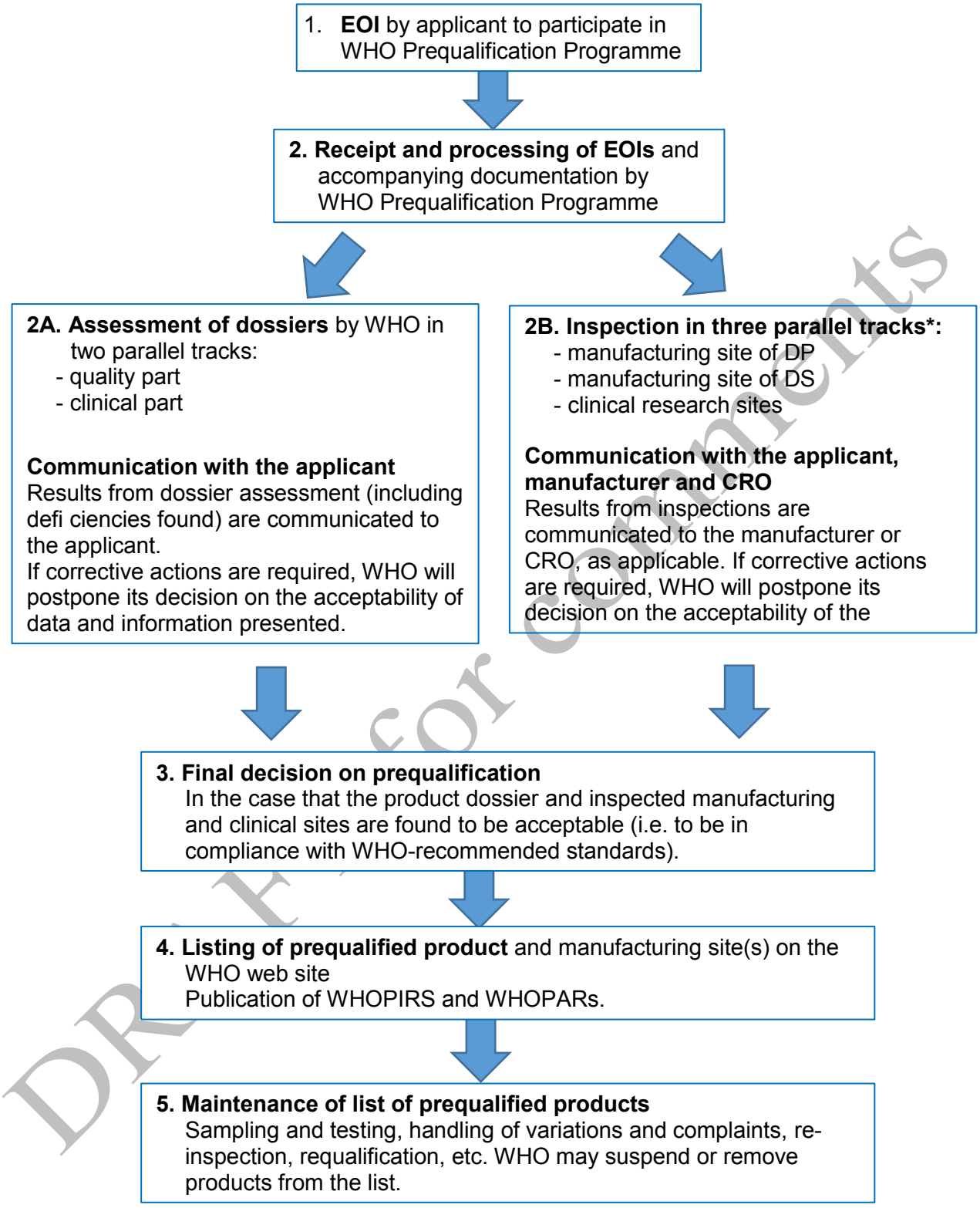
In this connection, each assessor and inspector is required to confirm that the information disclosed by him/her in the declaration of interest is correct and complete, and that he/she will immediately notify WHO of any change in this information.

All inspectors furthermore agree that, at the manufacturer's or CRO's request, WHO will advise the manufacturer 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 manufacturer or CRO then has 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 manufacturer 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 manufacturer 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.

Appendix 1. Flowchart of WHO prequalification of biotherapeutic products



EOI, expression of interest;
DP, drug product;
DS, Drug Substance;
CRO, contract research organization;
WHOPIR, public inspection report;
WHOPAR, public assessment report.

*Taking into account any known specific risk(s) associated with the product(s), the results of previous inspections conducted by WHO or an SRA, any complaints (if known), the scope and detail of the inspection report, the number and type of any GMP deficiencies reported, the comprehensiveness of the manufacturer›s response and the timelines for implementation of corrective action(s).

Appendix 2. Characteristics of the prequalified pharmaceutical product to be made available for public access on the WHO web site

- WHO product reference number
- International Nonproprietary Name (INN) of active pharmaceutical ingredient(s) (DS)
- dosage form and strength
- trade name(s) of the product (if applicable)
- name of applicant and official address
- name of manufacturer of DP
- physical address of manufacturing site(s) (and unit, if applicable)
- name of DS manufacturer, physical address of manufacturing site(s) (and unit, if applicable)
- product description
- pack size(s), primary and secondary packaging material(s)
- storage conditions
- shelf-life (provisional, if applicable)
- summary of product characteristics
- package leaflet
- labelling

Appendix 3. 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. Guidelines on submission of documentation for the WHO pilot procedure for prequalification of similar biotherapeutic products approved by stringent regulatory authorities