WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab - Frequently Asked Questions (FAQ)

Answers to common questions can be found here. If you still have questions please submit them using the email address prequalbiosimilar@who.int

SUBMITTING THE EOI

Q1: How do we submit an EOI?

A1: The submission should be in electronic format (two sets of CD or DVD) in Microsoft Word (required for templates/summaries e.g. QOS-BTP, QIS-BTP-SRA) or text-selectable PDF format (other documentation) which should be sent by registered mail or using a reputable courier and addressed to:

Prequalification Unit (PQT) – Medicines Assessment Team (PQT/MED)
WHO Pilot Prequalification of BTPs and their Corresponding SBPs
Regulation and Prequalification (RPQ)
Access to Medicines and Health Products (MHP)
World Health Organization
20 Avenue Appia
1211, Geneva 27, Switzerland

Please note that the Procedure is described at the following link:
https://extranet.who.int/pqweb/medicines/pilot-prequalification-biotherapeutic-products

For each product sought to be prequalified under this pilot procedure, the applicant should send to the WHO focal point a product dossier (PD) in the Common technical document (CTD) format, together with the other data required, as per the relevant guidelines."

"In submitting an EOI for assessment of a product under this pilot procedure, the applicant must 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 WHO guidelines on submission of documentation for the pilot procedure, including documents comprising relevant product data and information, including those called for in the WHO technical guidelines;
- 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 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."

Q2: Where do we ship the samples of the product?

A2: Samples of the product should be sent to

WHO Prequalification Unit: Medicines
MHP/RPQ/PQT Room M626
World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland
to the attention of Dr Matthias Stahl, Team Lead Medicines Assessment

Q3: Should the samples of the product be sent to WHO in refrigerated condition according to the manufacturer indication?

A3: No. The sample(s) should be obtained from the market (i.e. in market packaging(s)) and should be sent with the respective certificate of analysis. Storage conditions are irrelevant for the purpose of our use of the samples.

Q4: Is a model EOI available?

A4: There is no model EOI for this pilot and no formal "EOI" document is required. The information listed above suffices.

Q5: If the "MAH" for a product is not the manufacturer, can the MAH still submit the EOI?

A5: As stated in the Pilot procedure, there is no restriction on the manufacturing site as long as the requested product is marketed in the country of registration and the required documents are submitted.

In the case where the applicant for prequalification is not the same as the marketing authorization holder, supporting documentation defining the responsibilities of the PQ applicant and the MAH should be submitted.

Choosing the RBP (full assessment pathway)

Q6: Can any RBP be 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 (full assessment pathway)?

A6: No. The RBP must be obtained and purchased from the market of an SRA, in which it has been licensed and approved on the basis of a full dossier with comprehensive data on non-clinical and clinical studies.

Q7: What countries are considered to be SRAs for the purpose of obtaining an RBP?

A7: For the purpose of obtaining an RBP, a Stringent Regulatory Authority (SRA) is a regulatory authority that is:

a) a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission, and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or

b) an ICH observer prior to 23 October 2015, namely: Health Canada and the European Free Trade Association, as represented by Swissmedic; or

c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.

Q8: Can the batches of the RBP, 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, have been purchased from any market (provided that the RBP is approved by a SRA)?

A8: No. The batches of the RBP 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 must be obtained and purchased from an SRA market. Information on the market where the RBP was purchased and evidence of that purchase should be included in the documentation submitted for PQ.

Q9: What information should be submitted for the RBP that 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?

A9: The information for the RBP that has been 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 should include:

- the demonstration that the RBP has been approved by an SRA (web-link to SRA page mentioning RBP approval)
- the demonstration that the RBP batches used have been obtained and purchased from the SRA market
- documentation regarding the shipping and storage of the RBP used in the comparability and similarity exercise (quality, non clinical and clinical) from the time of purchase of the product through to the completion of the comparability and similarity exercises
- evidence that the selected RBP has been licensed and approved by an SRA based on a full product dossier containing data on non-clinical and clinical studies and full quality, safety and efficacy data.

Q10: The RBP that has been used as the comparator for head-to-head comparability studies with our SBP in order to demonstrate analytical similarity has been obtained and purchased from an SRA market. As part of the demonstration of analytical similarity, a non-SRA approved RBP has also been compared using state-of-the-art, sensitive, and orthogonal methods. The data demonstrates high similarity of the SBP, the SRA-approved RBP, and the non-SRA approved RBP. Therefore, the non-clinical and clinical studies to demonstrate similarity between the SBP and the RBP in terms of safety and efficacy have been conducted using the non-SRA approved RBP. Is this acceptable for the purpose of the prequalification?

A10: No. The batches of the RBP 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 must be obtained and purchased from the SRA market. The data generated using a non-SRA approved RBP to show similarity in terms of quality, safety and efficacy will be considered only as supportive data.

Q11: We have used two different SRA-approved RBP as the comparator for head-to-head comparability studies with the SBP in order to show similarity in terms of quality, safety and efficacy. Is this acceptable for the purpose of prequalification?

A11: No. One SRA-approved RBP should be used as comparator across all head-to-head comparability studies with the SBP in order to show similarity in terms of quality, safety and efficacy.

Others:

Q12: What is the deadline for submission of EOI?

A12: No deadline has been set for submitting applications under this pilot.

Q13: For proposing a teleconference or a face to face meeting with WHO Pilot on prequalification of Biotherapeutic Products, is there a procedure that needs to be followed? Is advance notification required?

A13: The existing general procedure may be used to request a meeting. A link to the meeting request form is available at https://extranet.who.int/pqweb/medicines/pre-submission-meetings.

Q14: Regarding trastuzumab, we have 150mg and 440mg strengths available, but not the 60mg strength. Can we submit dossiers for 150mg and 440mg strengths?

A14: 60 mg; 150 mg; 440 mg are invited; you may apply for any or all of the invited strengths.

Q15: Regarding rituximab, our drug is approved for certain indications. Can we apply for prequalification for our drug rituximab, SBP?

A15: The product applied for should have the same indications as approved by the SRA. The product will be prequalified for the invited indications only (indications present on the published EOI).

Q16: Our product is approved by an SRA, but it is not on the market at the present time. Can we apply for the pilot project (abridged assessment pathway)?

A16: No. As stated in the published guidelines on submission of documentation for abridged assessment your product must currently be on the market of the reference SRA's country or region at the time of application.

For BTPs/SBPs that are planned to be marketed within 3 years however the prequalification procedure can start provided a target date for the product entry into market can be identified by the Applicant.

Q17: Based on the defined Prequalification procedures, what are the timelines for the process steps?

A17: No precise duration for each step has been set at the moment for this pilot. Key Performance indicators for the Prequalification Team will be applicable to the pilot (https://extranet.who.int/pqweb/medicines/key-performance-indicators-who-prequalification). Since late 2017, strict response timelines for manufacturers were also introduced – 30, 60 or 90 days depending on the deficiencies.

Q18: Please provide guidance on where to find the reference number of SBP required in QIS section A1-1.

A18: Product reference number (WHO number) is assigned by WHO at the time the product is accepted for assessment after screening. This number is then used throughout the life cycle of the product within the PQ programme.

Q19: Which data should be submitted to provide the evidences that the principles outlined in the most recent version of the WHO guidelines on the international packaging and shipping of vaccines are followed to demonstrate suitability of the packaging/shipping to regions outside of climatic zone II.

A19: Stability studies should address the boundaries applied during the shipping validation study so that defined temperature and environmental conditions (e.g. light, humidity) are set to ensure product quality to the end user (according to ICHQ1R2).

The product should be maintained at required temperature while shipped from the manufacturing site to any market worldwide. For this purpose, an Operational Qualification (OQ) study should be conducted providing evidence, according to WHO guideline, that the shipment containers are able to maintain the required temperature while exposed to a continuous external temperature of 43°C for 48 hours.

Furthermore, a Performance Qualification (PQ) study should be conducted to provide evidence that the shipment set up (qualified carriers, qualified transport containers, continuous temperature monitoring with calibrated temperature probes, evaluation of temperature data etc.) can be successfully performed for all shipments and will meet the required criteria (supported by stability data). Since a PQ study cannot be performed for every single country where the product is going to be shipped, the PQ study should be based on a criticality assessment for shipment lanes. It is likely that an active container and/or temperature controlled vehicle would need to be used in order to comply with these requirements.

Finally, storage conditions (as in Product Information) and any special precautions for storage (including storage conditions after reconstitution/first opening, where applicable) should be described.

Short term storage excursions outside the label storage condition that may occur during shipping should be detailed and supported by appropriate data.

Differences from the approach above should be justified, and the equivalence of the approach should be discussed and supported by data, including a summary of the packaging procedures for international shipments (including box sizes and types, packing volumes, etc.), the validation protocols and reports of the shipping boxes used for supply of the product based on its prequalification status.