WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab
Q&A

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The Proposal

The WHO pilot procedure for prequalification of BTPs or their corresponding SBPs is specifically focused on rituximab and trastuzumab, and will be carried out using either Full Assessment or Abridged Assessment pathways

- **full assessment** on SBP that have already been registered by non-SRAs, using SRA-approved RBP as comparator and marketed (in the authorized country).

- **abridged assessment** on innovator products or SBPs for rituximab and trastuzumab that are approved by SRA

The pilot WHO prequalification will assess

- Originator products approved by SRAs
- SBPs approved by SRAs
- SBPs approved by non SRAs using 1 SRA-approved RBP as a comparator

* RBP: Reference Biotherapeutic Product

Procedure and guidelines considered

1.WHO guidelines on the international packaging and shipping of vaccines, WHO/IVB/05.23
http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.23_eng.pdf?ua=1

2. WHA 67.21 Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy, 2014 http://apps.who.int/medicinedocs/documents/s21459en/s21459en.pdf

3. WHO Guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products for rituximab and trastuzumab. Preparation of product dossiers in common technical document format
http://www.who.int/medicines/regulation/prequalification/02_GLs_Submission_Pilot_FullPathway_2018.pdf

4. WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities.
http://www.who.int/medicines/regulation/prequalification/03_GLs_Submission_Pilot_AbridgedPathway2018.pdf

5. WHO Model List of Essential Medicines, 20th List March 2017, Amended August 2017
http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1

6. 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
http://www.who.int/biologicals/biotherapeutics/TRS_987_Annex4.pdf?ua=1

Procedure and guidelines considered II

7. WHO Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 977, 2009
http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf

8. WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 1004, 2016
http://www.who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf?ua=1

9. Guidelines for the preparation of a contract research organization master file, Annex 7, Technical Report Series No. 957, 2010
http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPreparationContractResearchOrgMasterfileTRS957Annex7.pdf

10. Guidelines on procedures and data requirements for changes to approved biotherapeutic products
http://www.who.int/biologicals/areas/biological_therapeutics/Annex_3_WHO_TRS_1011_web-7.pdf?ua=1

11. WHO guidelines on variations to a prequalified product
http://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3TRS-981.pdf?ua=1

12. Guidance on reporting variations to a prequalified vaccine
http://www.who.int/immunization_standards/vaccine_quality/PQ_VXA_Variations_V7.pdf?ua=1

Potential applicants so far

- INDIA: 55%
- CHINA: 11%
- IRAN: 11%
- KOREA: 11%
- AUSTRIA: 11%

Assessors

- UK: 39%
- DENMARK: 15%
- SPAIN: 15%
- KOREA: 15%
- ARGENTINA: 15%

GMP-Inspectors

- ITALY: 33%
- KOREA: 33%
- ARGENTINA: 33%

Most frequent Q&A

Q: What is the deadline for submission of EOI?

A: No deadline has been set for submitting applications to the EOI under this pilot. Since we are committed to review the pilot after one year (July 2019), we shall review the response at the end of 2018 to determine if we have received sufficient number of applications to enable us evaluate the pilot.

Q: For proposing a tconf or a face to face with WHO Pilot on Prequalification of Biotherapeutic Products, is a procedure that needs to be followed? Is an advance notification required?

A: No specific procedure has been set for requesting for meeting with PQT under this pilot. However, the existing general procedure may be used to request for a meeting (https://extranet.who.int/prequal/content/pre-submission-meetings-0).

Most frequent Q&A - II

Q: What is the mode of submission of EOI?

A: Preference is that the submission should be in electronic format (two sets of CD or DVD) in Microsoft Word or text-selectable PDF format (other documentation) which should be sent by registered mail or using a reputable courier and addressed to:

Coordinator, Prequalification Team, Room M628
WHO Pilot Prequalification of BTPs and their Corresponding SBPs
Regulations of Medicines and other Health Technologies
Essential Medicines and Health Products
World Health Organization
20 Avenue Appia

Please refer to the plublished "**WHO Guidelines on submission of documentation for the pilot procedure** for prequalification of similar biotherapeutic products for rituximab and trastuzumab Preparation of product dossiers in common technical document format".

Most frequent Q&A - III

Q: Based on the Prequalification procedures defined, **can we know the duration** required by WHO team for each of the provided procedural steps followed and intimating the manufacturers about the same. Eg: How much time will it take for the experts to evaluate our dossier and notify us? Etc…

A: **No precise duration** for each step has been set at the moment for this pilot. But please refer to Key Performance Indicators for the Prequalification Team that will be applicable to the pilot.

KPI 1	% of products prequalified at or below target WHO PQ time	70% (30% for APIs)	Full assessment: 270 calendar days, 350 calendar days for IVDs prequalified without the alternative laboratory mechanism Abridged assessment: 100 calendar days, 180 calendar days for IVDs prequalified without the alternative laboratory mechanism

From: Prequalification Timeline Key Performance Indicators (KPIs) - http://www.who.int/pq-vector-control/PQ_Timeline_KPIs_PQVC_2017.pdf

and relevant annex: http://www.who.int/immunization_standards/vaccine_quality/Annex-KPIs_PQVx_2017.pdf

Most frequent Q&A - IV

Q: Our product is approved by a SRA, but not yet launched the product in the market. Can we apply for the pilot project?

A: As stated in the published Guidelines on submission of documentation for abridged assessment, your product should be on the market of the reference SRA's country or region at the time of application.

Most frequent Q&A - V

Q: As it is mentioned on the page 16 of " WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab" section "Cost Recovery", we are not sure **whether this procedure is free of charge or not.**

A: as mentioned in the first EOI, http://www.who.int/medicines/regulation/prequalification/04_EOI_PQ_BTPs_June2018.pdf?ua=1 "**No fees are applicable** for this 1st Invitation under the WHO pilot procedure".

Most frequent Q&A - VI

Q: If the “MAH” for a product but it is not the manufacturer, can the MAH still submit the EoI?

A: as stated in the Pilot procedure, there is **no restriction** on manufacturing site as long as requested product is marketed in the country of registration and a product dossier is provided together with a site master file for each manufacturing site and a CRO master file for each clinical site listed in the product dossier**.**

Q: Please provide guidance on **where to find the reference number of SBP** on the WHO website.

A: 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.

Most frequent Q&A - VII

Q: Our product is on the market in EU region. Under an EU-specific regulation, QC releasing test site and QP release site **must be within EU territory** and QP must be an EU resident. However, for non-EU market we would like to use non EU-manufacturer and QC release site. Therefore our **PQ-dossier will contain different manufacturers and QC release test site compared to the one submitted for approval in EU**. Would this be acceptable?

A: In case of the abridged pathway, it should be submitted, for both the BTP and the SBP, a statement confirming that for WHO prequalification, the Drug Product, including but not limited to composition/formulation, strength, **manufacturing and manufacturers**, specifications, packaging, product information, will, **at the time of submission and after prequalification, in all respects be the same as the product registered with the reference SRA.**

Most frequent Q&A - VIII

Q: When informed of an AE (adverse event) case of our products distributed through the WHO prequalification program, is there an **obligation to report to WHO and Health Authority** of the country where the case occurred?

A: **Yes. All serious adverse events** related to a prequalified product **should be reported** to the NRA of the country where in occurred and WHO.

Most frequent Q&A - III

Q: what would the respective ADR/SAE reporting procedures be for a) WHO and b) the country's HA?

A: **Please refer to** the published "WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities", "WHO Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977, 2009" and to "WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 1004, 2016"

Reporting procedures at the country level are described by the respective NRA.

Thanks for your attention!!