INTRODUCTION TO PILOT PROJECT FOR WHO PREQUALIFICATION (PQ) OF BIOSIMILARLS FOR CANCER TREATMENT
The Proposal

To initiate a pilot WHO prequalification process for similar biotherapeutic products, proposing to use **rituximab and trastuzumab** as the test cases:

- Innovative biotherapeutics are expensive: use limitation
- rituximab and trastuzumab one of the first monoclonal antibody therapies included in WHO Model List of Essential Medicines
- regulatory assessment of monoclonal antibodies are less complex compared to other biotherapeutic products
- established WHO technical guidance for evaluation of monoclonal antibodies and SBP* exist
- some SRAs now have extensive experience in evaluating innovator biotherapeutic products as well as corresponding SBPs

* SBP: Similar Biotherapeutic Product; SRA: Stringent Regulatory Authority
The pilot WHO prequalification will assess

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

*RBP: Reference Biotherapeutic Product*
**Timelines**

- **Concept note:** 4 May 2017
- **Public consultation on procedure and GLs:** 21 July 2017
  - WHO *pilot procedure* for prequalification of SBP
  - WHO guidelines on submission of documentation for **SBP approved by SRA**
  - WHO guidelines on submission of documentation in CTD* format
- **End of public consultation:** 16 Aug 2017
- **Review and finalization** of procedure and guidelines according to comment received: **ongoing** (October 2017)
- **Publication of invitation for EOI***: (October 2017)

* CTD: Common Technical Document; Expression of Interest
Procedure and guidelines public consultation

Comments from: BIO, IAPO, IFPMA, IGBA, Mexico (COFEPRIS), Korea (MFDS)....

Main comment: to better distinguish two assessment pathways, for applicants with products approved by a stringent regulatory authority and for applications with products that were approved by other NRAs.
Published document considered:


WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products for rituximab and trastuzumab”

PQ purpose

candidate products provided through the United Nations for use in different countries:

(a) meet WHO technical guidance on quality, safety and efficacy or performance, including compliance with GxPs*

(b) meet relevant operational packaging and presentation specifications.

Applicable for

prequalification of rituximab and trastuzumab or SBPs for rituximab or trastuzumab.

* GxPs: Good Clinical Practice, Good Distribution Practice, Good Laboratory Practice, Good Manufacturing Practice,
WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products for rituximab and trastuzumab”

Two pathways

1) **abridged assessment** on SBPs for rituximab and trastuzumab that are approved by SRA

2) **full assessment** on SBP that have already been registered by non-SRAs, using SRA-approved RBP as comparator and marketed (in the authorized country).
WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products for rituximab and trastuzumab”

Principles I:

• a general understanding of the production and quality control;
• reliance on information supplied by or originated from stringent national regulatory authorities, which may lead to waivers for the requirements;
• an assessment of required product dossier (product data and information on safety, efficacy and quality (requirements as laid down in the WHO guidelines for the evaluation of SBPs and monoclonal antibodies as SBPs should be met)
• inspection of DP and DS manufacturing site, clinical testing units or CROs
• random sampling and testing of DS and DP supplied by the applicant (if required)
WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products for rituximab and trastuzumab”

Principles II:

• handling of complaints and recalls reported to WHO
• Risk Management Plan
• monitoring of complaints from agencies and countries;
• a rationale for the choice of the RBP takes into among others of the suitable marketing duration, marketed use and market experience;
• the demonstration that the RBP has been licensed based on product dossier containing full quality, safety and efficacy data;
• a similarity 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 of the SBP;
• evidence of the similarity of the SBP to a suitable RBP based on evaluation of the whole data package for each of the quality, non-clinical, and clinical parameters
WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products for rituximab and trastuzumab”

STEPS (NORMALLY):

• a screening procedure to ensure that the submitted dossier is complete
• assessment of product dossiers, which must include product data and information
• inspection of manufacturing sites of Drug Substances and Drug Products, to assess compliance with cGMP;
• inspection of clinical sites (if applicable), to assess compliance with cGCP and cGLP as appropriate.
WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products for rituximab and trastuzumab”

STEPS (SRA-approved SBPs)

Provided that the SRA or the applicant shares product information on the product, WHO will consider such products for inclusion in the list of WHO-prequalified products on the basis of the scientific assessment and inspections conducted by the stringent regulatory authority concerned, and the exchange of relevant information.
### WHO Guidelines on submission of documentation for the pilot procedure for PQ of SBPs approved by SRA

#### For both the RBP and the SBP
- A covering letter
- A copy of the marketing authorization, or the equivalent thereof, issued by the licensing SRA

#### For the RBP
- copy of the marketing authorization in SRA and SmPC* and patient information
- A public assessment report, such as the Scientific Discussion of the European Public Assessment Report (EPAR), issued by the reference SRA

#### For the SBP
- a statement confirming that the DP will, at the time of submission and after prequalification, in all respects be the same as the product registered with the reference SRA.
- a statement indicating that the product is actually on the market of the reference SRA’s
- Identity of the SRA-approved RBP with consideration on RBP quality, efficacy and safety in a given population, the duration and marketed use and market experience
- copy of the marketing authorization in SRA and SmPC and patient information
- List of DS/DP approved manufacturer
- A tabular listing of the SBP batches manufactured for the market of the reference SRA’s region or country since approval or during the past five years
- The quality information summary for the SBP (QIS-SBP*).

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* SmPC: Summary of Product Characteristics; QIS: Quality Information Summary
WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products for rituximab and trastuzumab”

When planning inspections the following points will be considered:

- whether the manufacturing site has been inspected by either WHO or a 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 cGxP;
- 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.
WHO Pilot Procedure for Prequalification of Similar Biotherapeutic Products for rituximab and trastuzumab”

An inspection of manufacturing site(s) or CRO may not be required if:

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

EOI by applicant to participate in WHO PQ Programme

3. Receipt and processing of EOIs and screening\(^1\) for completeness of documentation

3A. Assessment of dossiers by WHO in two parallel tracks:
- quality part
- clinical part

Communication with the applicant

3B. Inspection in three parallel tracks:
- manufacturing site of DS, DP
- clinical research sites

Communication with the applicant, manufacturer and CRO

4. Final decision on prequalification
In the case that the product dossier and inspected manufacturing and clinical sites are found to be acceptable

4. Final decision on prequalification

5. Listing of prequalified product and manufacturing site(s) on the WHO web site

5. Listing of prequalified product

6. Maintenance of list of prequalified products
Sampling and testing, handling of variations and complaints, re-inspection, requalification, etc. WHO may suspend or remove products from the list.

EOI by applicant to participate in WHO PQ Programme

- Cover letter
- Dossier
- SMF - Manufacturer
- CRO-MF

- Documentation completeness
- Comparability data

- Finding of dossier assessment
- GxP inspection reports

- Publication of WHOPAR
- Publication of WHOPIR
- Negative evaluation outcomes according to WHO SOP

any changes in manufacture and control that may have an impact on the safety, efficacy and quality of the product
1. **Publication** of the invitation for EOI by WHO

**EOI by applicant to participate in WHO PQ Programme**
- Cover letter
- Dossier
- SMF - Manufacturer
- CRO-MF

3. **Receipt and processing of EOIs and screening**¹ for completeness of documentation

- Documentation completeness
- Data provided by SRA

3A. **Assessment of dossiers/SRA reports** by WHO in two parallel tracks:
- quality part
- clinical part

**Communication with the applicant**

3B. **Potential inspection in three parallel tracks**:
- manufacturing site of DS, DP
- clinical research sites

**Communication with the applicant, manufacturer and CRO**

4. **Final decision on prequalification**
on the basis of the scientific assessment and inspections conducted by the SRA concerned, and the exchange of relevant information between the SRA/WHO

- Finding of dossier assessment
- GxP inspection reports

5. **Listing of prequalified product** and manufacturing site(s) on the WHO web site

- Publication of WHOPAR
- Publication of WHOPIR
- Negative evaluation outcomes according to WHO SOP

6. **Maintenance of list of prequalified products**
Sampling and testing, handling of variations and complaints, re-inspection, requalification, etc. WHO may suspend or remove products from the list.

any changes in manufacture and control that may have an impact on the safety, efficacy and quality of the product
Concept of reliance: Collaborative registration procedure

• Any products that are prequalified by WHO must still be approved for use by NRAs (WHO-PQ does not substitute for an NRA’s evaluation and market approval)

• NRAs should be willing participate in the procedure and be listed in the Participating Countries table in WHO site* (if not listed NRAs may be invited to participate by WHO if applicants express interest)

• Applicants submit the same dossier as the one approved by WHO (only minor administrative differences are permitted)

• WHO shares information with via a secure internet-based platform, subject to confidentiality undertakings and agreed restrictions on use.

• The NRA can, of course, decline to apply the collaborative procedure. If so, it will be requested to indicate to WHO its reasons for not doing so

* https://extranet.who.int/prequal/content/collaborative-registration-faster-registration.
Thanks for your attention!!