Biotherapeutics for cancer: ensuring quality, safety and efficacy

Joint UNICEF, UNFPA and WHO meeting with manufacturers and suppliers
2–5 December 2019, UN City, Copenhagen, Denmark

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World Health Assembly Resolution: WHA 67.21

Access to biotherapeutic products (BTPs) including SBPs and ensuring their quality, safety, and efficacy (2014)

Resolution requests the WHO Director General to:

- Support Member States in developing and strengthening regulatory frameworks that promote access to quality, safe, efficacious and affordable biotherapeutic products (BTPs), including similar biotherapeutic products (SBPs)

- Encourage and promote cooperation and exchange of information, as appropriate, among Member states in relation to BTPs, including SBPs

- Updating the 2009 WHO guidelines on evaluation of SBPs
  - considering the technological advances for the characterization of BTPs
  - considering national regulatory needs and capacities

Essential medicines and health products goals

Safeguard public health ensuring that medicines are of the required quality, safety and efficacy, appropriately manufactured, stored, distributed, dispensed, accessible and affordable.
Products manufactured in 194 WHO member states: different quality standards

- Different Competent Authorities
- Different procedural, and administrative guidelines
- Different quality, safety, efficacy and PV guidelines
- Different legal framework
- Different authorizations

Products of different quality standards

UN-Agencies

UN-Member states

Intergovernmental organizations
Example from SRAs

Centralised Procedure (via EMA)
- Single authorization (27 MS)
- Shared and harmonized procedural, and administrative guidelines
- Shared and harmonized quality safety and efficacy and PV guidelines
- Shared and harmonized legal framework
- Rigorous system

Drug Registration – IND process (via FDA)
- Single authorization (50 States)
- Shared and harmonized procedural, and administrative guidelines
- Shared and harmonized quality safety and efficacy and PV guidelines
- Shared and harmonized legal framework
- Rigorous system

Mutual Recognition Agreement

1 stringent quality standard

Copenhagen, Denmark  2 – 5 December 2018
WHO answer: Prequalification of Medicines program

- **Prequalification** of medicine is a very well established program started in 2001 for medicines, starting in HIV/AIDS, then expanding to malaria and tuberculosis. **Currently 8 therapeutic areas.**

- **Prequalification (PQ) is a service** provided by WHO to provide UN agencies and WHO Member States with guidance on the acceptability of health products (medicines, vaccines, in vitro diagnostics, medical devices and vector control products) for procurement by such agencies and Member States.

- **Products meeting WHO technical guidance on quality, safety and efficacy** operational packaging and presentation specifications and compliant with WHO recommended GxPs.

- Pilot for PQ of rituximab & trastuzumab and corresponding SBPs: EOI published on 5 July 2018 (first dossier received on 24 Oct 2018)

- Drafting of **Pilot-specific** PQ of rituximab and Trastuzumab procedural, and administrative guidelines started in 2017.
Prequalification tools

Administrative tools

Decl. of Helsinki
GxPs
ICH topics
SRA decisions
Ph. Monographs

WHO Technical Report Series

Prequalification procedure
Voluntary base

- Assessment harmonisation
- Transparency of decision
- Avoid duplication of work by NMRA
- Faster national registration (CRP)
- Provide guidance
- Capacity building
- Ensuring normative and technical excellence at country level
1. WHO Pilot Procedure for Prequalification of BTPs: rituximab and trastuzumab

2. 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

3. WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities.
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://www.who.int/biologicals/biotherapeutics/TRS_987_Annex4.pdf?ua=1

http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf
   http://www.who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf?ua=1


8. 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

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

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

1. Full assessment pathway of SBPs for rituximab or trastuzumab that have been registered by non-SRAs (based on a Reference biotherapeutic product (RBP) approved by a SRA) and marketed in the country of registration.

2. Abridged assessment pathway of rituximab or trastuzumab BTPs, or their corresponding SBPs as applicable, that have been approved by stringent regulatory authorities (SRAs) and marketed in the country of registration.
Full assessment pathway - STEPS

1. **Publication** of the invitation for EOI by WHO

   **EOI** by applicant to participate in WHO PQ Programme

   - **Cover letter-QOS-BTP**
     - Dossier (?)
     - SMF – Manufacturer (?)
     - CRO-MF (?)

2. **Pre-submission meeting**
   Discussing QOS-BTP observations, deficiencies and critical issues for submitting a viable dossier

3. **Receipt and processing of EOIs** and screening
   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 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

   - 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

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Deficiencies: 

**SAME STANDARDS as for SRA**

WHO stringent Quality standard
Abridged assessment pathway - STEPS

1. Publication of the invitation for EOI by WHO
   - Cover letter
   - SRA-related approvals
   - QIS_BTP_SRA

2. EOI by applicant to participate in WHO PQ Programme

3. Receipt and processing of EOI and screening for completeness of documentation
   - Documentation completeness

3A. Screening of appropriateness of dossier / SRA approval reliance by WHO
   Assessment: aspects non approved by SRA (PQ-specific)
   Communication with the applicant

3B. SRA inspection reliance
   Communication with the applicant, manufacturer and CRO

4. Final decision on prequalification
   Relying on the scientific assessment and inspections conducted by the SRA concerned – Evaluation of PQ-specific aspects
   - Publication of WHOPAR
   - Publication of WHOPIR
   - Negative evaluation outcomes according to WHO SOP

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

6. Maintenance of list of prequalified products
   SRA-based approval (WHO notification)
Conclusions
manufacturers from 194 MS: 1 quality standard

WHO procedural, and administrative guidelines
WHO quality, safety, efficacy and PV guidelines
WHO trained assessors/Inspectors
WHO list of prequalified products
WHO transparency of process and informations

Prequalification of medicines programme

- Assure safety, quality, efficacy & appropriateness of medical products used in LMICs: medicines and biotech/biosimilars
- Increase competition to shape the market

WHO stringent quality standard

List of prequalified medicines

UN-Agencies
UN-Member states
Intergovernmental organizations

• Avoid duplication of work by NMRA
• Faster national registration (CRP)
• Provide guidance
• Capacity building
• Ensuring normative and technical excellence at country level
Inequality is the cause of all local movements. There is no rest without equality

Leonardo da Vinci - From Codex Atlanticus, folio 288 (1508-1510)

Thanks for your attention!!