# Prequalification of biotherapeutic and biosimilar products

## Joint UNICEF, UNFPA and WHO meeting

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Global Health Supplies:
Paradigm Shifts in Market Authorization, Procurement and Supply Chains Approaches
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# Prequalification of biotherapeutics (BTPs) and similar biotherapeutic products (SBP)

- Development of the prequalification of rituximab and trastuzumab project
- Results and future of the prequalification of rituximab and trastuzumab project
- Prequalification pilot project for human insulin
- APIMF-like pathway for human insulin
- Prequalification of therapeutics against COVID-19
- Expert Review panel for BTPS and SBPs
- Prequalification of biological product for diagnostic use (in-vivo skin tests)
- Conclusions

# The prequalification of rituximab and trastuzumab
## Pilot background

- The quality, safety and efficacy, product handling and post-prequalification requirements differ greatly compared to small molecules

- Trastuzumab and rituximab were selected for the pilot based on disease prevalence, evidence of efficacy and safety, and comparative cost-effectiveness, and the availability of WHO technical guidance on evaluation of BTPs

- In concert with prequalification of small molecules, the pilot project for BTPs/SBPs offers two distinct pathways to prequalification:
  - Full assessment pathway of SBPs for rituximab or trastuzumab that have been registered by a non-stringent regulatory authority (SRA) based on a reference biotherapeutic product (RBP) approved by an SRA.
  - Abridged assessment pathway of rituximab or trastuzumab BTPs, or their corresponding SBPs, approved by an SRA and marketed in the country of registration.

- The procedure is divided into 4 different phases:
  - Pre-submission meeting with the applicant (mainly in case of full assessment pathway)
  - Dossier submission, followed by screening phase;
  - Assessment of the dossier
  - Inspections of manufacturing sites and/or clinical sites as applicable (only in case of full assessment pathway)

# The prequalification of rituximab and trastuzumab
# Development of procedures I

- The abridged assessment pathway of rituximab or trastuzumab BTPs, or their corresponding SBPs, approved by an SRA and marketed in the country of registration:
  - WHO will rely on assessment and inspections of manufacturing/clinical sites conducted by the SRAs
  - Verification that the product proposed for prequalification is identical to the SRA-approved product
  - The SRA approved dossier will not be assessed again and is not required
  - Data that are not assessed and approved by the SRA will be required and assessed by PQ:
    - ✓ arrangements for product handling in LMIC,
    - ✓ product packaging and shipping
    - ✓ handling of product complaints and recalls
    - ✓ pharmacovigilance system with consideration of potential differences in infrastructures and routine clinical practices

- The full assessment pathway of rituximab or trastuzumab SBPs that have been registered by a non-stringent regulatory authority (SRA) based on a reference biotherapeutic product (RBP) approved by an SRA:
  - the RBP must be approved by an SRA, obtained and purchased from the SRA market
  - understanding of production and quality control;
  - assessment of the product dossier: product data and information on safety, efficacy and quality
  - inspections of DP and DS manufacturing site (GMP), clinical testing units or CROs (GCP/GLP)
  - random sampling and testing of DS and DP supplied by the applicant (if required)

# The prequalification of rituximab and trastuzumab
## Development of procedures II


- WHO Pilot Procedure for Prequalification of BTPs: rituximab and trastuzumab
- WHO Guidelines on submission of documentation for full assessment
- WHO Guidelines on submission of documentation for abridged assessment
- WHO template for Module 2.3 quality overall summary: product dossier (QOS-BTP)
- WHO template for the Quality Information Summary (QIS) of the Biotherapeutic Product Approved by Stringent Regulatory Authority (SRA) (QIS-BTP-SRA)
- WHO template for the screening checklist for Biotherapeutic Products and their corresponding SBPs – full and abridged assessment pathways, respectively
- WHO assessment template for Biotherapeutic Products and their corresponding SBPs – full and abridged assessment pathways, respectively
- WHO assessment template - additional data
- WHO letter templates (screening, acceptance for assessment, request for additional data)
- Template for dossiers tracker tools

- WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab - Frequently Asked Questions (FAQ)
- WHO PQ-specific addendum to the RMP (elaborated in further detail below)
- Definition of applicant commitment for an SRA approved product with the inclusion of pharmacovigilance summary reports (also amended to the WHO PQ-specific addendum to the RMP)
- Letter of Prequalification for the applicant
- Design of a public list of prequalified biotherapeutic products/similar biotherapeutic products
- General minimum requirements for international BTPs packaging and shipping (elaborated in further detail below)
- Template of the WHO Public Assessment Report (WHOPAR) for the prequalified product
- Definition of the WHOPAR content for a product approved/not approved by SRA

# Full assessment pathway - most common dossier deficiencies

- The applicant's approach to the biosimilar comparability exercise (quality) was poorly performed and applicable guidelines had not been followed.

- The origin of the Reference Biotherapeutic Product (RBP) was not acceptable: the pilot specifies that the reference product must be obtained/purchased from an SRA market and not from a non-SRA/local market.

- Clinical pivotal PK/PD studies were not performed, and pivotal safety/efficacy studies were not appropriately designed and/or sufficiently powered and/or were performed with locally procured RBP.

- Product characterization (for both the biosimilar product and the RBP) was not sufficient according to applicable guidelines.

# Abridged assessment pathway - most common dossier deficiencies

- Absence, or insufficient evidence of adherence to WHO guidelines on international packaging and shipping (i.e. shipping validation data not in line with applicable WHO guidelines).

- Handling complaints and product recalls not adapted to LMICs

- Risk minimization plan not appropriately adapted to LMICs due to differences in routine clinical practices and infrastructures compared to LMICs

- Absence of other documentation as required by guidelines (e.g. certificate of pharmaceutical product (CPP), product quality review (PQR)).

# The prequalification of rituximab and trastuzumab completion of the pilot

As further experience gained through advisory meeting, PSM and product assessment rounds, guidelines were revised.

- Revision of the WHO Pilot Procedure for Prequalification of BTPs: rituximab and trastuzumab
- Revision of the WHO Guidelines on submission of documentation for full assessment
- Revision of the WHO Guidelines on submission of documentation for abridged assessment
- Revision of the Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Team - Biotherapeutic Products (BTPs)
- Revision of WHO template for the Quality Information Summary of the Biotherapeutic Product Approved by Stringent Regulatory Authority (SRA) (QIS-BTP-SRA)
- Revision of WHO assessment template for Biotherapeutic Products and their corresponding SBPs – full and abridged assessment pathways
- Revision of WHO Pilot Procedure for Prequalification of Biotherapeutic Products: rituximab and trastuzumab - Frequently Asked Questions (FAQ)

An improvement in the quality of submitted dossiers and a tendency towards a decrease in time to prequalification was observed.

# Pilot project results
# A platform for prequalification of BTPs/SBPs

The procedures, guidelines and templates drafted during the review of 27 dossiers and the prequalification of 16 products provided a valuable basis for the prequalification of different biotherapeutics with other therapeutic indications.

Although requirements may need to be adapted to molecule-specific characteristics, such adjustments are expected to be minor.

The following EOIs for different therapeutic indications build on this platform:

- 2nd Invitation to Manufacturers of human insulin and insulin analogues

- 8th Invitation to Manufacturers of therapeutics against COVID-19
  - IL-6 inhibitors (tocilizumab and sarilumab)
  - Neutralizing antibodies (casirivimab and imdevimab, sotrovimab)

- 1st Invitation to Manufacturers of therapeutics against Ebola Virus Disease
  - A combination of atoltivimab, maftivimab and odesivimab
  - Ansuvimab-zykl

# A pilot project spin-off
# The Expert Review Panel for BTPs/SBPs

ERP is an independent advisory body of technical experts that assesses the quality risks of BTPs/SBPs that do not meet all stringent requirements and provides advice for the purpose of aiding procurement decisions regarding time-limited procurement.

The experience gained from the pilot was key to develop an ERP procedure for BTPs to define quality and clinical criteria for product allocation into risk categories

The ERP will provide procurement agencies with advice to aid procurement decisions. Furthermore, ERP will assist procurers and other stakeholders in identifying quality deficiencies in dossiers and areas where improvement is needed for urgently needed products.

# The Prequalification project for human insulin

# Pilot Procedure for Prequalification of Human Insulin

The 1st Invitation for Manufacturers **– published on 13 Nov 2019 -** of human insulin injection and human intermediate-acting insulin in vial **(recently includes also long-acting insulin analogues).**

Inclusion of wide range of products:

- Human insulin BTPs that have been approved by SRA
- Human insulin BTPs, that have not been registered by SRAs (or by any other NRAs)
- Human insulin «stand-alone» product
- Human insulin SBPs

Limited data are required because of the nature and history of the molecule:

- For product claimed to be SBP: demonstration of similar pharmacokinetic (PK) and pharmacodynamic (PD) profiles is considered the mainstay of proof of similar efficacy
- For product not claimed to be SBP: comparative PK and PD profiles of the product to be prequalified and the comparator human insulin + comparative safety data usually of 6-month duration

# First human insulins prequalified

**NEWS 27 September 2022**

The first human insulins have been prequalified by WHO: fast-acting human insulin 100 IU/ml and intermediate-acting human insulin 100 IU/ml from Novo Nordisk A/S. The manufacturer of these newly prequalified products has recently addressed the thermostability of the products and updated the storage conditions to provide the option to store the products at temperatures up to 30˚C for four weeks before opening. These updated storage conditions for the prequalified products will greatly facilitate the use of these essential medicines under challenging temperature conditions where there is limited access to refrigeration in relevant low- and middle-income countries.

- **BT-DM001** - Insulin human - solution for injection, 100 IU/ml (vial) - Novo Nordisk A/S
- **BT-DM002** - Insulin human - solution for injection, 100 IU/ml (cartridge) - Novo Nordisk A/S
- **BT-DM003** - Intermediate-acting, insulin human - suspension for injection, 100 IU/ml (vial) - Novo Nordisk A/S
- **BT-DM004** - Intermediate-acting, insulin human - suspension for injection, 100 IU/ml (cartridge) - Novo Nordisk A/S

| WHO Reference Number | International nonproprietary name (INN) | Therapeutic area | Applicant | Dosage Form and Strength | Date of prequalification |
|---|---|---|---|---|---|
| BT-DM001 (a) | Insulin Human | Biotherapeutics - Diabetes | Novo Nordisk AS, Novo Allé 1, Bagsværd, 2880, Denmark | Solution for injection 100 IU/mL | 27 Sep 2022 |
| BT-DM002 (a) | Insulin Human | Biotherapeutics - Diabetes | Novo Nordisk AS, Novo Allé 1, Bagsværd, 2880, Denmark | Solution for injection 100 IU/mL | 27 Sep 2022 |
| BT-DM003 (a) | Insulin Human | Biotherapeutics - Diabetes | Novo Nordisk AS, Novo Allé 1, Bagsværd, 2880, Denmark | Suspension for injection 100 IU/mL | 27 Sep 2022 |
| BT-DM004 (a) | Insulin Human | Biotherapeutics - Diabetes | Novo Nordisk AS, Novo Allé 1, Bagsværd, 2880, Denmark | Suspension for injection 100 IU/mL | 27 Sep 2022 |

# Work in progress: APIMF-like pathway for human Insulin

- Despite a broad rage of h-insulin (and analogues) invited products, and limited clinical data required by PQT/MED and initiatives such as WHO Global diabetes compact, insulin applications remains scarce

- The APIMF-like pathway for h-insulin would protect proprietary information and “know-how” of the DS manufacturer.

- The DS can be provided to several DP manufacturers

- APIMF-like pathway could increase DP manufacturers to take full responsibility of h-insulin to be prequalified.

- APIMF is currently not applicable in any SRA framework to biologics because of the complex nature of the biological molecules however, h-insulin is:

  - Relatively simple and well-characterized.
  - Degradation pathways are well-studied and understood and controls can be in place

- It needs to be ensured that the DP manufacturers will be in the condition to take the full responsibility of the prequalified finish products

# Work in progress: APIMF-like pathway for human Insulin

DS manufacturer

Applicant part

DP manufacturer

Applicant part

DP manufacturer

Applicant part

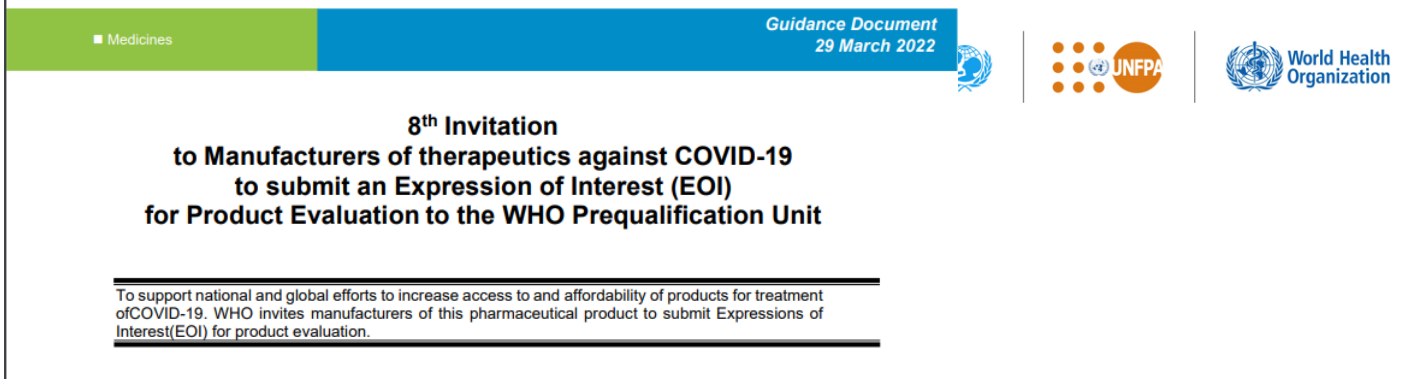
DP manufacturer

WHO PQT/MED

Applicant part

Restricted part

# The Prequalification of therapeutics against COVID-19




- IL-6 inhibitors:
  - Tocilizumab IV 20 mg/mL for further dilution prior to intravenous infusion.
  - Sarilumab 200 mg/1.14 mL and 150 mg/1.14 mL for further dilution prior to intravenous infusion.

- Neutralizing antibodies:
  - Casirivimab + imdevimab (IV or subcutaneous):
    - Co-packaged 6 mL single-use vials: Casirivimab 6 mL vial containing 300 mg of casirivimab per 2.5 mL (120mg/mL). Imdevimab 6 mL vial containing 300 mg imdevimab per 2.5 mL (120 mg/mL).
    - Co-packaged 20 mL multi-dose vials: Casirivimab 20 mL multi-dose vial containing 1,332 mg of casirivimab per 11.1 mL (120 mg/mL). Imdevimab 20 mL multi-dose vial containing 1,332 mg imdevimab per 11.1 mL (120 mg/mL).
  - Sotrovimab solution for infusion, 500 mg/8 mL (62.5 mg/mL) single use vial

# Prequalification of COVID-19 BTPs results (May 2022)

A total of 3 tocilizumab dossier received and prequalified

| WHO Reference Number | International nonproprietary name (INN) | Therapeutic Area | Applicant | Dosage form & strength | Date of prequalification |
|---|---|---|---|---|---|
| BT-CV001 (a) | Tocilizumab | COVID-19 | Roche Registration GmbH, Emil-Barell-Strasse, Grenzach-Wyhlen, 79639, Germany | Concentrate for solution for infusion 20 mg/mL (Each vial contains 80 mg of tocilizumab in 4 mL) | 10 Feb 2022 |
| BT-CV002 (a) | Tocilizumab | COVID-19 | Roche Registration GmbH, Emil-Barell-Strasse, Grenzach-Wyhlen, 79639, Germany | Concentrate for solution for infusion 20 mg/mL (Each vial contains 200 mg of tocilizumab in 10 mL) | 10 Feb 2022 |
| BT-CV003 (a) | Tocilizumab | COVID-19 | Roche Registration GmbH, Emil-Barell-Strasse, Grenzach-Wyhlen, 79639, Germany | Concentrate for solution for infusion 20mg/ml (Each vial contains 400 mg of tocilizumab in 20 mL) | 10 Feb 2022 |

# Work in-progress: prequalification of biological product for diagnostic use (in-vivo skin tests)

**Plan to initiate a pilot WHO prequalification process for in-vivo skin test, using TB-skin test as the test case.**

- The most commonly used tests for diagnosis of Mtb infection are tuberculin skin tests (TSTs) and interferongamma release assays (IGRAs)
  - TST has a rather high sensitivity, its specificity is low, especially for BCG vaccinated subjects and for subjects infected with atypical mycobacteria. Further global shortage of TST
  - IGRAs have a higher specificity and similar sensitivity compared to TSTs. However, IGRAs are costly and require additional laboratory facilities for testing
- Newer in-vivo tests contain recombinant Mtb specific antigens and should combine high sensitivity and specificity with ease-of-use.
  - considered as medicinal products used for diagnosis or monitoring of a disease
  - governed by the same regulatory rules and principles as for other medicinal products

The drafting of the procedures and guidelines is based on the experience gained for other BTPs/SBPs. Additional expert assessors will be required.

# Outcomes

- The pilot project platform (guidances, procedures) for anti-cancer molecules well adapted to the prequalification of h-insulin, COVID-19 and Ebola virus disease BTPs/SBPs and can also be useful for the assessment of such products within the framework of PQTm's Expert Review Panel or Emergency Use Listing.
- Addressing recurrent dossier-related deficiencies by fine-tuning PQ guidelines led to an increase of the submitted dossiers' quality and resulted in the tendency towards a decrease in time to prequalification
- Guidance documents applicable across BTP/SBPs (i.e. PQ-specific addendum to the RMP, frequently asked questions) are available on PQTm website (https://extranet.who.int/pqweb/medicines/pilot-prequalification-biotherapeutic-products) and are frequently updated.
- The WHO PQ-specific addendum to the RMP is an important, innovative control mechanism taking the level of LMIC healthcare systems into consideration and is applicable not only to BTP/SBPs but also to small molecule medicines if the toxicity profile is significant
- APIMF-like pathway for human Insulin may represent a game changer for h-insulin prequalification
- Prequalification of biological product for diagnostic use (in-vivo skin tests) will be based on the experience gained for other BTPs/SBPs is taking shape

**https://extranet.who.int/pqweb/medicines/pilot-prequalification-biotherapeutic-products**

*Osani Circle Game - taken by Jean-Pierre Hallet*

‘UBUNTU, how can one of us be happy if all the other ones are sad?’

(‘UBUNTU’ in the Xhosa culture means: **I am because we are**)

# Thanks for your attention!!