Prequalification of biotherapeutic and biosimilar products

Joint UNICEF, UNFPA and WHO meeting

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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)
- Outcomes

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:
    - ✓ 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)

Full assessment pathway - most common deficiencies

- **RBP origin** – WHO pilot procedure for prequalification specifies innovator product to be obtained / purchased from SRA market.
- The **approach to the biosimilar comparability exercise** was not properly understood (3 batches compared batch to batch)
- **The similarity range/acceptance criteria** not based on limits derived from analysis of a number of batches of RBP
- **Characterization and biosimilarity** are different.
- **Product characterization** (for both the biosimilar product and the RBP) not sufficient according to applicable guidelines
- **Biological potency assays** should be explained clearly
- **Process development** section insufficient. **Process changes** not performed according to ICHQ5E
- **Clinical pivotal PK/PD studies not performed and pivotal safety efficacy studies not appropriately designed and/or sufficiently powered and/or performed with locally procured RBP**
- **PV plan** should be as per WHO guideline including risk minimization plan, special populations, and traceability of PV events.

Abridged assessment pathway - most common deficiencies

- **Absence of / 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 LMIC**

- **Pharmacovigilance system and risk minimization plan** not appropriately adapted to LMIC due to differences in routine clinical practices and infrastructures in SRA-countries compared to LMIC

- **Absence of some further documentation as required by guidelines** (eg CPP; certificate of pharmaceutical product, PQR; product quality review).

The prequalification of rituximab and trastuzumab
Development of procedures

- 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

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 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 2nd Invitation for Manufacturers **– published on 17 May 2022-** of human insulin injection and human intermediate-acting insulin in vial **(including also long-acting insulin analogues).** Few dossier submitted despite:

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
- Inclusion of long-acting insulin analogues

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

The guidelines on active pharmaceutical ingredient master file for h-insulin procedure: an innovative procedure for BTPs

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

- First 4 h-insulin products prequalified the 27 Sep 2022 - Novo Nordisk A/S; first 2 insulin analogue (Insulin glargine) products prequalified 5 May 2023 (Sanofi-Aventis Deutschland GmbH)

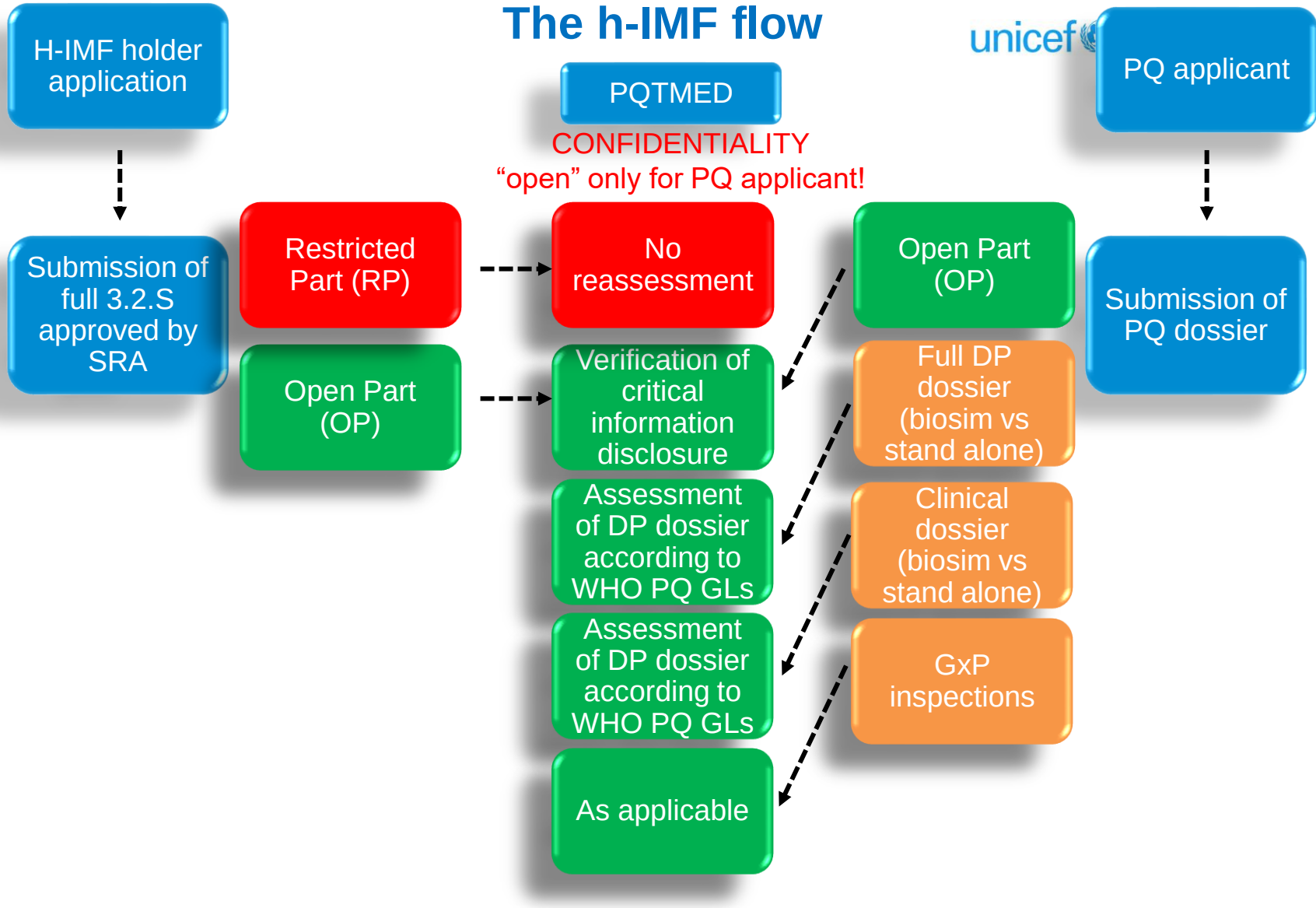
- The APIMF-like pathway (human insulin Master File – h-IMF) is an innovative pathway published the 28 Aug 2023. H-IMF is expected to facilitate access to human insulin: the DS/API can be provided by one manufacturer to several finished product manufacturers

- H-IMF is a possibility offered to API manufacturers and PQ applicants to protect proprietary information and “know-how” of the DS manufacturer while at the same time ensuring the PQ applicant can take full responsibility for the quality of finished Drug Product.

The guidelines on active pharmaceutical ingredient master file for h-insulin procedure: key concept

- Objective: to increase the number of h-insulin manufacturers and prequalified h-insulin products
- The procedure has been designed taking into account the API master file (APIMF) procedure, a well-established procedure used to preserve the confidentiality of some API information when the API is procured by several finished product manufacturers
- Not currently applied to BTPs however, h-insulin is a relatively simple molecule, well understood in terms of molecular characteristics and clinical effects
- Measures to reduce risks of nondisclosure of confidential information from the DS to the DP manufacturer.
- Procedure applies only to DS (CTD module 3.2.S) that is already approved by a stringent regulatory authority (SRA) within the context of a marketing authorization of a DP.
- Therefore, no reassessment of CTD module 3.2.S but a verification that critical information is shared with DP manufacturer.

The h-IMF flow



PREQUALIFICATION

The h-IMF requirements

H-IMF holder

- OP and RP
- Declaration that h-IMF is the same as approved by SRA
- MA and CPP (if available)
- Complete CTD 3.2.S
- Letter of access
- Assessment report form the SRA (or authorisation to access to them)

PQ applciant

- Ensure access to all relevant information of DS manufacturing
- OP with version number
- DP dossier (Q and clinical)

Key content of the open part

- Description of the manufacturing process and controls:
  - Manufacturing process and controls that are key to control the quality of the DP
- Detailed description of the control of material derived from human, animal and recombinant origin
- A summary of the analytical procedure should be part of the OP
- Detailed information on the current Internal Reference Standard (IRS) used for analytical method development/calibration, in-process testing, release and stability testing should be part of the OP and/or of the technical agreement.

Finished product assessment approaches

The module 3.2.S is not reassessed since part of an SRA approval in the context of an authorized product.

WHO will assess the FP dossier according to the principles laid down in “WHO Pilot Procedure for Prequalification of Biotherapeutic Products: human insulin”.

- If the product is claimed to be biosimilar: The full 3.2.P dossier is expected (in addition to the h-IMF required documentation). In case the biosimilarity claim is robust enough, demonstration of similar pharmacokinetic (PK) and pharmacodynamic (PD) profiles is considered the mainstay of proof of similar efficacy of the biosimilar and the reference insulin
- If the product is not claimed to be a biosimilar: The full 3.2.P dossier is expected (in addition to the h-IMF required documentation). Comparative PK and PD profiles of the product to be prequalified and the comparator human insulin should be demonstrated
- If the product is claimed to be a technology transfer version of the SRA approved product containing the same active ingredient, a complete ICHQ5E comparability exercise (process, product and analytical methods) and tech transfer report should be submitted. Different level of clinical data may be required on a case by case basis.

Questions and dossier gaps – finished product manufacturer

- Process Validation study batches for the purpose of local registration. Do we need to reperform dedicated PV study batches for WHO PQ purpose?
  No, if the validation refers to the process that will be used to manufacture the product to be prequalified and the PV exercise is sufficiently recent

- Do we have to perform another Analytical Method Transfer (AMT) activity if we have different presentations (e.g. cartridge and vials)
  No, if the analytical methods are the same.

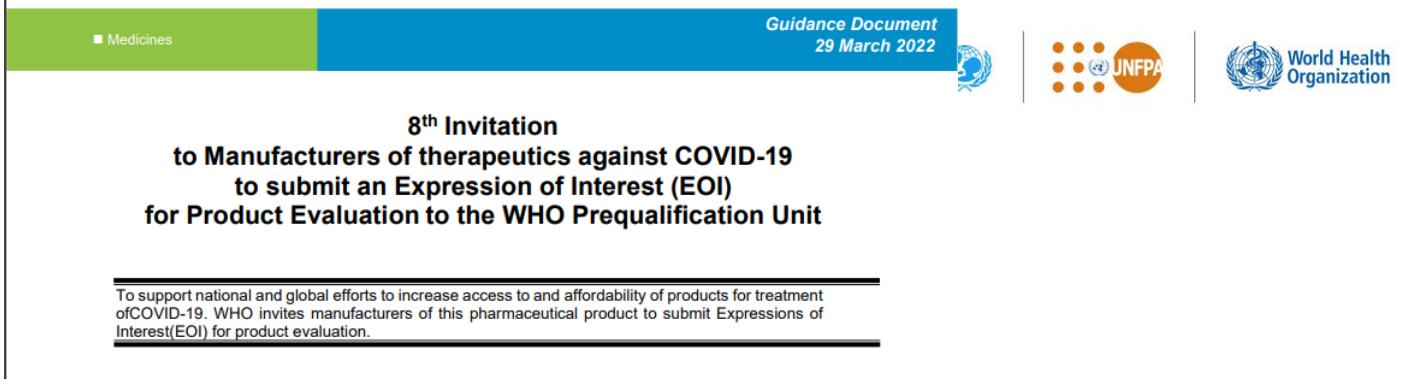
- Can we submit our dossier depending on the API analysis done by the h-IMF manufacturer associated with our assessment of certificate of analysis?
  Specifications used to control the quality of the received DS should be unambiguously detailed by the Manufacturer. See also cGMP requirements (e.g. requirements for incoming material and in particular active substances)

- Can we rely on the DS manufacturer clinical dossier?
  On a case by case basis considering availability of a full documented tech transfer and a full ICHQ5E comparability exercise (process, product and analytical method)
  For product claimed to be SBPs or stand-alone insulin PQ procedure and requirements applies.

The h-IMF requirements – deficiencies so far

- **H-IMF submitted as «stand-alone» dossier:** the h-IMF is only reviewed in connection with a specific product dossier. An h-IMF is never approved *per se.* The quality of the DS and its suitability for use in the DP needs to be justified in the relevant product dossier
- The **complete DS data on quality** (CTD - Module 3) should be submitted
- **CoA of the MCB, WCB** should be attached to the OP.
- **DS impurities description in the OP** is too general: Process-related impurities should be described. Product-related impurities should be completed (HMW missing, control measures not summarized) Impurity removal discussion should be summarized, elemental impurities and risk assessment should be mentioned.
- **Analytical procedures:** analytical methods developed in-house should be described as much as possible.
- **Reference standards or materials:** Detailed information (with the inclusion of the CoA) on the current Internal Reference Standard (IRS) used for analytical method development/calibration, in-process testing, release and stability testing should be part of the OP

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

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

Prequalification of biological product for diagnostic use (in-vivo skin tests)

Initiating 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 interferon-γ 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 (not published yet since no SRA-approved product and consequently no product would be eligible) is based on the experience gained for other BTPs/SBPs

ERP of SIILTIBCY a novel diagnostic tool for detecting Mycobacterium Tuberculosis (Mtb) Infection using Mtb-specific antigens

Stop TB Partnership
Leave no one behind
END TB
A partnership hosted by UNOPS

NEWS ALERT - 10 October 2024 I Geneva

BREAKING NEWS: Only $1.50 to Detect TB Infection With the Next-Generation SIILTIBCY Test

Available now in Stop TB GDF Catalog

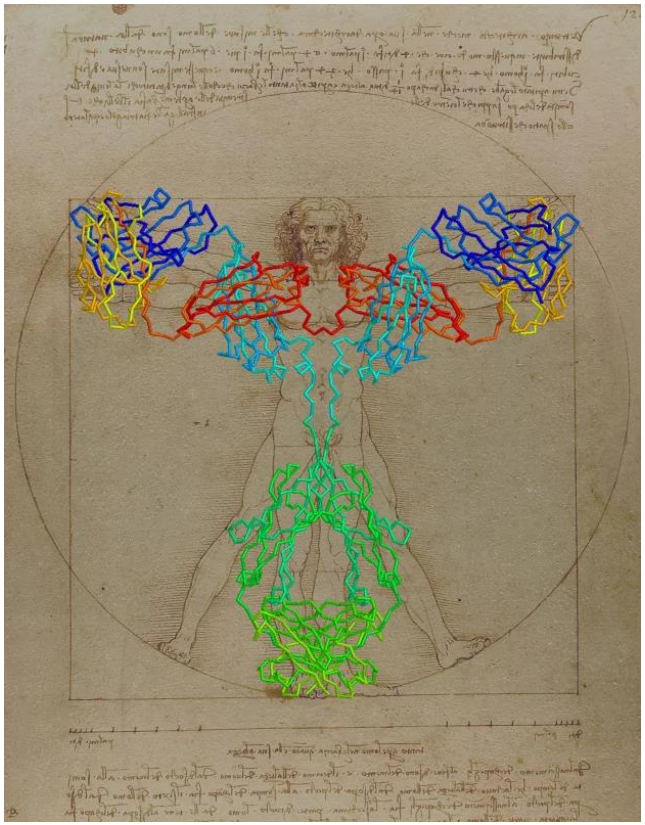
"The prompt GF ERP review and approval following the August 2024 European Medicines Agency acceptance of key product data will expedite availability to countries who need this test and **highlights the importance of advanced planning and collaboration across many partners, including the WHO Prequalification Programme, the Global Fund, Stop TB's GDF, USAID, National TB Programmes, implementers, and civil society organizations"** said Brenda Waning, Chief of Stop TB's Global Drug Facility.

Outcomes

- The anti-cancer pilot project has provided a platform (guidances, procedures) for the prequalification of h-insulin, COVID-19 and Ebola virus disease BTPs/SBPs as well as for an Expert Review Panel mechanism or Emergency Use Listing, as needed.
- Addressing dossier-related deficiencies by fine-tuning PQ guidelines led to an increased quality of the submitted dossiers and 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 also applicable to small molecule medicines if the toxicity profile is significant
- An APIMF-like pathway for human Insulin may represent a game changer for h-insulin prequalification
- Prequalification of biological products for diagnostic use (in-vivo skin tests) is based on the experience gained from other BTPs/SBPs

Inequality is the cause of all local movements. There is no rest without equality

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



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