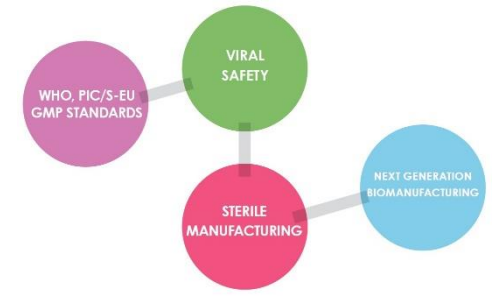




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Newly revised WHO GMP for biological products

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18 December 2019

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GaBI Workshop on GMP for Biologicals/Biosimilars



**World Health
Organization**

Background

- WHO GMP for biological products (TRS 822), 1992
- As the **annex** to WHO GMP for pharmaceutical products: main principles
- Widely **used** or adopted by regulators and stakeholders
- **Mandatory** guidelines for medicine and vaccine prequalification programmes
- Strong **request** for revision and update of GMP for biologicals

Revision Process

- First attempted revision started in 2007
 - Working group meeting in 2007 and preliminary draft in 2008
- This revision:
 - Drafting group meeting in Oct 2013
 - Consultation in July 2014
 - Progress report to ECBS and ECSPP 2014
 - First round public consultation on WHO website Feb 2015
 - Drafting group meeting April 2015
 - Submission to ECBS as BS 2015 2253
 - Public consultation on WHO website July-September 2015
 - Comments on BS document
 - ECBS reviewed and adopted (TRS 999 annex 2)
 - ECSPP adopted based on the outcome of ECBS (TRS 996 annex 3)

Challenges to the drafting group

- Definition of Biologicals
- Supplementary Document (Fill-in the Gaps to existing document: 961,986 etc.)
- To give **ORIENTATION** on Strategy and Focus of requirements for Biologicals without detail “how-to-do”
- To consider vaccines and other biologicals equally

Revision principles

- Annex to the GMP for pharmaceutical products: main principles
- Principles in GMP for Sterile pharmaceuticals as applicable
- Focus on special considerations to biologicals
 - e.g. QC, Biosafety/biocontainment, Environment monitoring, Production and campaign production, Use of animal, Starting materials(Seed lot/Cell bank), Quality Risk Assessment, QMS, etc.
- Other related publications to be referenced
 - Process validation for vaccines.
 - Environmental monitoring for vaccines
 - Risk assessment in TRS 981 Annex 1 and ICH Q9, Q10.

Outline of the revised GMP

- Introduction
- Scope
- Terminology
- Principles and general considerations
- Pharmaceutical quality system and quality risk management
- Personnel
- Starting materials
- Seed lot and cell bank
- Premises and equipment
- Containment
- Clean rooms
- Production
- Campaign production
- Labelling
- Validation
- Quality control
- Documentation
- Use of Animals

Key changes/updates: Scope

- Apply to manufacture and testing of biologicals for human use
- Apply to manufacturing procedures (table illustration)
- allergens, antigens, vaccines, certain hormones, cytokines, monoclonal antibodies (mAbs), enzymes, animal immune sera, products of fermentation (including products derived from rDNA), biological IVDs and ATMPs
- For human whole **blood**, blood components and plasma-derived products for therapeutic use follow the *separate* WHO guidance
- The preparation of **investigational** medicinal products for use in clinical trials should follow the *basic principles of GMP* set out in these and other WHO GMP guidelines
- Collection of plant, organ, tissue or fluid of animals and Collection, cutting, mixing, and/or initial processing (animal source)

Table 1

Scope of the current document (illustrative)

| Type and source of material | Example products | Application of this document to steps in manufacture | | | |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------|-------------------------|
| 1. Animal or plant sources: non-transgenic | Heparins, insulin, enzymes, proteins, allergen extract, ATMPs, animal immune sera | Collection of plant, organ, tissue or fluid | Cutting, mixing and/or initial processing | Isolation and purification | Formulation and filling |
| 2. Virus or bacteria/fermentation/cell culture | Viral or bacterial vaccines, enzymes, proteins | Establishment and maintenance of MCB, WCB, MSL/ MVS, WSL/WVS | Cell culture and/or fermentation | Inactivation when applicable, isolation and purification | Formulation and filling |
| 3. Biotechnology fermentation/cell culture | Recombinant products, mAbs, allergens, vaccines, gene therapy (viral and non-viral vectors, plasmids) | Establishment and maintenance of MCB, WCB, MSL, WSL | Cell culture and/or fermentation | Isolation, purification and modification | Formulation and filling |
| 4. Animal sources: transgenic | Recombinant proteins, ATMPs | Master and working transgenic bank | Collection, cutting, mixing and/or initial processing | Isolation, purification and modification | Formulation and filling |
| 5. Plant sources: transgenic | Recombinant proteins, vaccines, allergens | Master and working transgenic bank | Growing and/or harvesting | Initial extraction, isolation, purification and | Formulation and filling |

Key changes/updates: General considerations

- General considerations:
 - Annex to GMP for pharmaceuticals: main principles
 - Biological nature: variability, sensitive, contamination
 - Protection of personnel: pathogenicity of microbials
 - Protection of environment
 - Emphasize in-process control
 - Consistency
 - Importance of QRM

Key changes/updates: Personnel

- There are 6 articles (6.1-6.7)
 - Personnel scientific background relevant to their duties
 - Health status: vaccination and regular health check
 - Special trainings: cleaning, disinfection, hygiene, microbiology
 - Restriction of movement: not pass area of live microbial, animal tissue, toxin, venom or from animal area to product area or different organisms. If unavoidable, follow the contamination measures.
 - Personnel in animal facility be restricted from entering production
 - Staff assigned to BCG not work with other infectious agent and health check
 - Reassignment of staff in BCG and animal quarter not allowed until pass health check.

Key changes/updates: starting materials

- Retain info describing the source and quality of the biological materials used for at least 1 year after the expiry date of the finished products and according to local regulations. Longer is better for AEFI investigation.
- Identity test for each lot. Materials for formulation to be tested on each container.
- For sterile material to reduce the risk of contamination sample taken at the time of use.
- The transport of critical materials, reference materials, active substances, human tissues and cells to the manufacturing site should be controlled

Key changes/updates: cell bank and seed lot

- WHO GMP for APIs section 18 on cell culture and fermentation
- Control of Feeder cell in place
- Cell bank and seed lot system to avoid genetic drift
 - Maximum passages between seed lot to final product
- During establishing seed lot and cell bank, no other live or infectious material be handle simultaneously
- Storage at an appropriate condition
 - A stock inventory should be kept
 - Minimize contamination
 - In two or more separate sites
 - Control and restrict access

Key changes/updates: Premises/Production-1

- **QRM** is the basis for design, production, control strategy etc.
- **Live and spore-forming** organisms are prevented from entering non-related areas or equipment
 - With validate effective containment and decontamination of the live microorganisms, multi-product facilities may be justifiable
- Killed vaccines, including those made by rDNA techniques, toxoids and bacterial extracts may after inactivation be dispensed into containers on the same premises as other sterile products
- Cleaning and sanitation: handling growth media
 - Environmental and personnel safety precautions should be taken during the cleaning and sanitization processes
- Use closed system where practicable

Key changes/updates: Premises/Production-2

- In manufacturing facilities, the mix-up of entry and exit of personnel should be avoided through the use of **separate changing rooms** or through **procedural controls** for BRG 3-4
- The QRM process should be the basis for implementing the technical and organizational measures required **to control the risks of contamination and cross-contamination**
- In cases where a viral inactivation or removal process is performed, measures should be taken (for example, in relation to facility layout, unidirectional flow and equipment) to avoid the risk of recontamination of treated products by non-treated product

Key changes/updates: Premises/Production-3

- A procedure should be in place to address equipment and/or accessories **failure** (such as air vent filter failure) which should include a product impact review.
- Where **adverse donor** (human or animal) health information becomes available after procurement and/or processing, and this information relates to product quality, then appropriate measures should be taken – including product recall, if applicable

Key changes/updates: Campaign production

- The decision to use a facility or filling line for campaign manufacture should be justified
- Campaign-based manufacturing **facility layout** and design of the premises and equipment shall permit effective decontamination
- **Killed vaccines**, including those made by rDNA techniques, toxoids and bacterial extracts may after inactivation be dispensed into containers on the same premises as other sterile products
- **Validation** of campaign change procedures and proper acceptance criteria for residues based on toxicity data on untoward mix-up or cross contamination
- Use of additional analytical technique with **higher sensitivity** for checking residues for campaign production as compared to normal production

Key changes/updates: Containment

- Avoid airborne dissemination of live organisms
 - **Drainage** system to minimize cross-contamination
 - **BRG 3 or 4 and spore-forming** organisms dedicated live area
 - Use of pathogen above BRG 3 be permitted by NRA
 - **BCG** production dedicated equipment and utilities
 - **GAP III** for polio production
 - Air handling system, Exhaust air filtration, design to minimize cross contamination
 - BRG 3 no air recirculation
 - A dedicated non-recirculating ventilation system and HEPA-filtering of exhaust air for BRG 4 organisms
 - Handling accident

Key changes/updates: Quality control

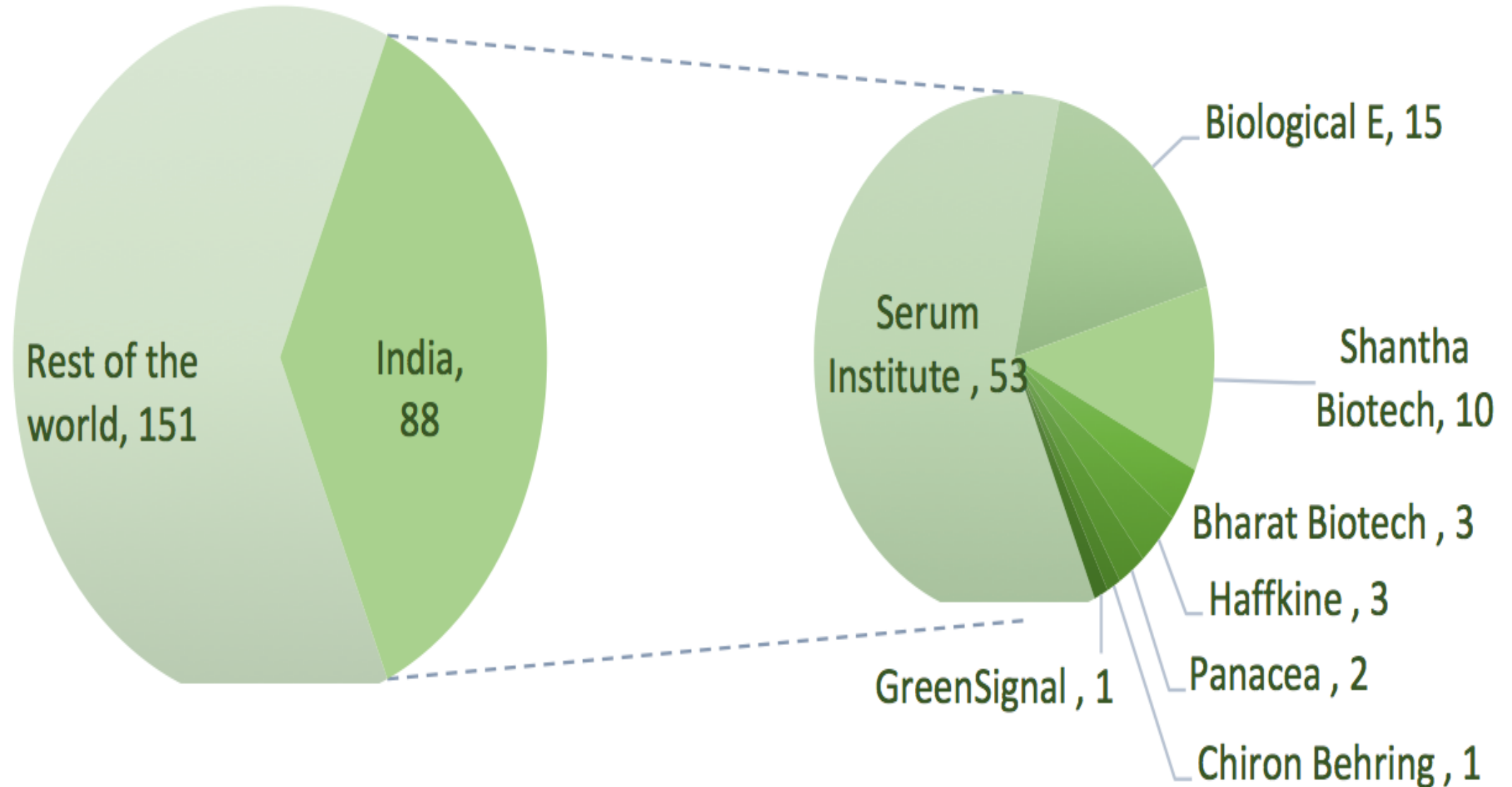
- **Reference sample:** A sample of a batch of starting material, packaging material, intermediate or finished product which is stored for the purpose of being analysed should the need arise during the shelf-life of the batch concerned. 1 year beyond the expiry date
- **Retention sample:** A sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes

Summary

- The balance of **quality is priceless** versus **quality has a price must be in favour of the patients and recipients.**
- GMP compliance is not a one-off exercise, **Sustainable over life cycle of the product**
- Manufacturer **knowledge management** is critical
- WHO TRS should help clarify expectations and drive consistency between industry and regulators through the globe.

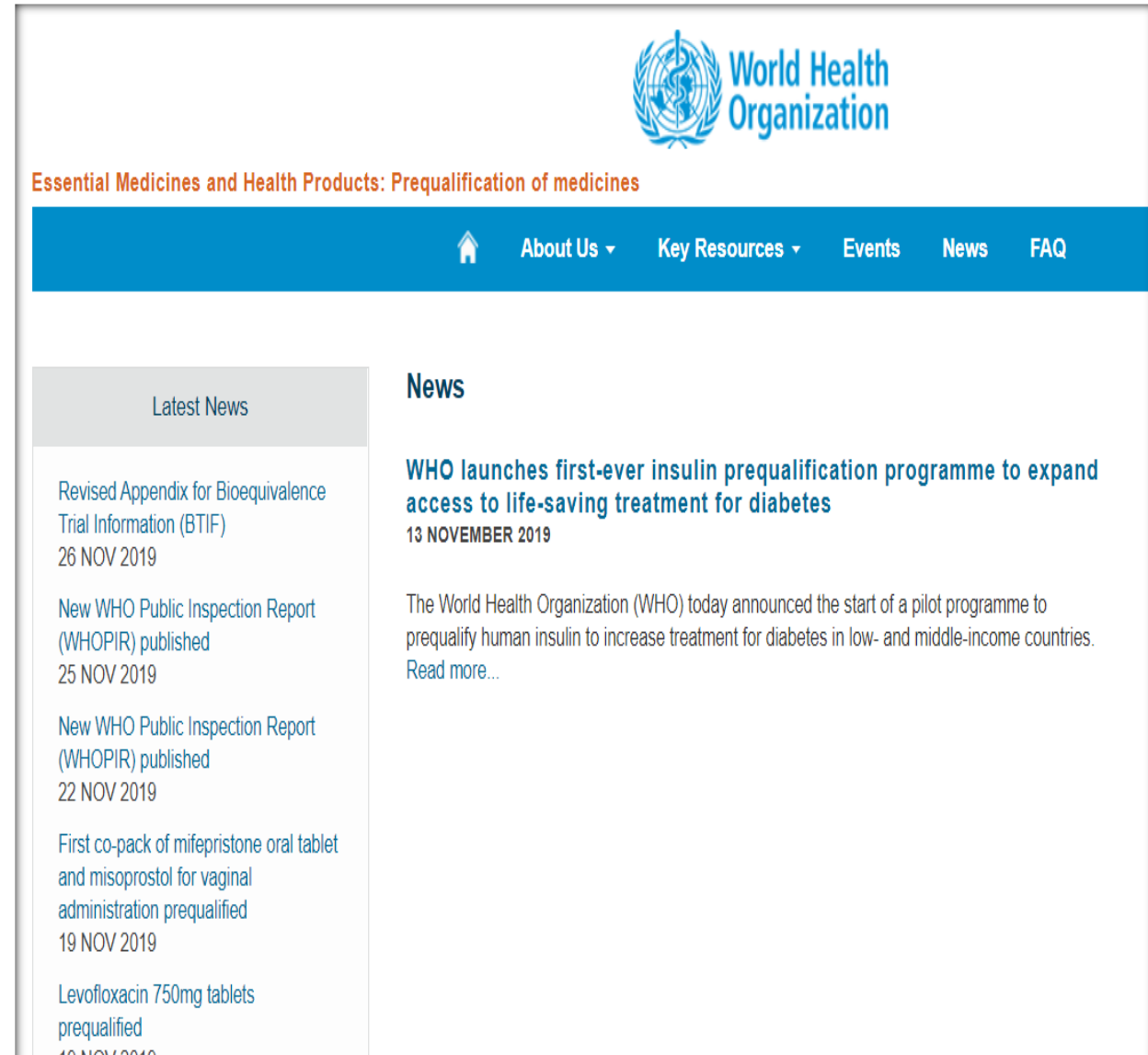
Back-up slides

Number of WHO PQed Products , Global/India



WHO Pilot Prequalification for: Rituximab & Trastuzumab and Human Insulin

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



The screenshot shows the WHO website's 'Essential Medicines and Health Products: Prequalification of medicines' section. The page features the WHO logo and a navigation menu with links for 'About Us', 'Key Resources', 'Events', 'News', and 'FAQ'. A 'Latest News' sidebar lists several recent updates, including a revised appendix for bioequivalence trial information (BTIF) on 26 Nov 2019, two new WHO Public Inspection Reports (WHOPIR) on 25 Nov 2019 and 22 Nov 2019, and the prequalification of a first co-pack of mifepristone oral tablet and misoprostol for vaginal administration on 19 Nov 2019. The main content area highlights a news item titled 'WHO launches first-ever insulin prequalification programme to expand access to life-saving treatment for diabetes', dated 13 November 2019. The text of this news item states: 'The World Health Organization (WHO) today announced the start of a pilot programme to prequalify human insulin to increase treatment for diabetes in low- and middle-income countries. Read more...'

WHO Technical Report Series: GMP related

GMP Main Principles: TRS 986 annex 2 (2014)

Biological products: TRS 999 annex 2 (2016)

Sterile products: TRS 986 annex 6 under review

Quality Risk Management: TRS 981 annex 2

Guidelines on validation: TRS 981 annex 2 WHO (2019)

Guidance on good data and record management
practices: WHO TRS No. 996 (2016)

WHO Technical Report Series: Product Specific (production and QC)

Poliomyelitis vaccines: TRS 1016 annex 4 (2019)

Recombinant Hepatitis E vaccines: WHO TRS 1016
annex 2 (2019)

Ebola vaccines: WHO TRS 1011 annex 2 (2018)

Recombinant human papillomavirus virus-like particle vaccines:
WHO TRS 999 annex 4 (2016)

Antivenom: WHO TRS 1004 annex 5 (2017)