Joint UNICEF, UNFPA and WHO meeting with manufacturers and suppliers, 5 Dec 2024

Norms and Standards for Biological Products: An update

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On behalf of: WHO/MHP/HPS/TSS/NSB

World Health Organization

Outline of the presentation

- Concept of WHO written and measurement standards
- Update on WHO standards for Vaccines, BTP and CGTP
  - written standards
  - measurement standards
- Forthcoming consultations and workshops
- Useful/relevant web resources

WHO and standards-setting

A core function of WHO, set out in its Constitution (1946, Article 2)- is ***"to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products"*, as well as *"to standardize diagnostic procedures as necessary"*.**

Norms & Standards for Biologicals

- WHO has played a key role for over 70 years in establishing the WHO **Biological Reference Materials** necessary to standardize biological products as well as developing WHO **Guidelines and Recommendations** for the production, control and licensing of biological products and technologies.

- This work is **accomplished through** WHO biological programme, WHO Collaborating Centers, and WHO Expert Committee on Biological Standardization (**ECBS**); involves close collaboration with international scientific and professional communities, regional and national regulatory authorities, manufacturers and expert laboratories worldwide.

- Outcomes are published in WHO **Technical Report Series** (TRS): *https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/trs-publications-listing*

WHO written standards
- Guidelines, Recommendations, etc.

- Developed based on scientific evidence and international consensus
- Technical specifications that help define safe and efficacious vaccines, provide guidance for NRAs and manufacturers on international regulatory expectations for the production and quality control, non-clinical and clinical evaluation of vaccines
- **Intended to be scientific and advisory in nature**
  - serve as a basis for setting national requirements and WHO prequalification
  - leave space for NRAs to formulate additional/ more specific requirements
- Taking into consideration guidance issued by other bodies – intention to complement them, not to create a conflict
- Living documents - will be updated in light of future advances in scientific knowledge and experience in the field

WHO measurement standards
- International Reference Preparations

WHO's role- "To define an internationally agreed unit to allow comparison of biological measurements worldwide".

- Established through **scientific studies** involving participation of a large number of laboratories worldwide.

- Serve as reference sources of defined biological activity expressed in an **internationally agreed unit**.

- Basis of a **uniform reporting system**, helping physicians and scientists involved in patient care, regulatory authorities and manufacturing settings to communicate in a **common language** for designating the activity or potency of biological preparations used in prophylaxis or therapy, and ensuring the reliability of *in vitro* biological diagnostic procedures used for diagnosis of diseases and treatment monitoring.

WHO International Standards

- Established by the Expert Committee on Biological Standardization (ECBS) with an assigned International Unit of biological activity.
- Standards of highest order that serve as the primary standards for **characterization/calibration** of the activity of secondary standards (regional, national, in-house working standards); calibration/validation of assays.
- Tool for **monitoring** production consistency and product quality, enable **comparison** of results across laboratories/assays globally.
- Support **regulatory convergence** in the evaluation of biological products at the global level.
- Facilitate **development** of vaccines, diagnostics and therapeutics.
- Recognized by **other international standards-setting bodies** (e.g., World Trade Organization, International Standards Organization)

WHO written standards for regulatory evaluation of vaccines (1)

Source: *https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards/vaccine-standardization*

General topics and regulatory guidance

- ✓ **Nonclinical evaluation** of vaccines (TRS 927, ECBS 2003)
- ✓ **Nonclinical evaluation** of vaccine adjuvants and adjuvanted vaccines (TRS 987, 2013)
- ✓ **Clinical evaluation** of vaccines (TRS 1004, ECBS 2016)
- ✓ Guidelines for assuring the quality, safety and efficacy of **plasmid DNA** vaccines (TRS 1028, ECBS 2020)
- ✓ Evaluation of the quality, safety and efficacy of **messenger RNA vaccines** for the prevention of infectious diseases: regulatory considerations (TRS 1039, ECBS 2021)
- ✓ Guidelines on **regulatory preparedness** for the oversight of **pandemic** or other emergency use vaccines in importing countries (TRS 1054, ECBS 2023)
- ✓ **Guidelines on:** Cell substrates for vaccine production; Stability evaluation of vaccines; Vaccine lot release; GMP for biological products; Extended Controlled Temperature Conditions (ECTC); Post-approval changes (subject to revision); etc.

WHO written standards for regulatory evaluation of vaccines (2)

Guidelines/ Recommendations for specific types of vaccines: polio, rabies, influenza, pneumococcal, DTP and combined vaccines, rotavirus, malaria, typhoid, HPV, RSV, etc. Details are available here.

Vaccine-specific standardization

BCG (Tuberculosis)	Human Papillomavirus (HPV)	Respiratory Syncytial Virus (RSV) vaccines
Cholera	Influenza	Rift Valley Fever
Combined DT-Based Vaccines	Japanese encephalitis (JE)	Rotavirus
Covid-19	Malaria	Rubella
Dengue	Measles	Smallpox
Diphtheria	Meningococcal meningitis	Synthetic peptide vaccines
DNA vaccines	Messenger RNA vaccines	Tetanus
Ebola	Mumps	Tick-borne encephalitis
Enterovirus 71	Pertussis	Typhoid fever
Haemorrhagic fever with renal syndrome	Plant-derived vaccines	Viral vector vaccines
Haemophilus influenzae (Hib)	Pneumococcus	Varicella
Hepatitis A	Poliomyelitis	Yellow Fever
Hepatitis B	Rabies	
Hepatitis E		

Highlights in 2023

- **ECBS meetings in March and October 2023**
  - Established:
    - **3 written standards** (Guidelines for nonclinical and clinical evaluation of Mabs, Considerations for regulatory framework for CGTP in March 2023 and Guidelines for pandemic vaccines in Oct 2023)
    - **22 measurement standards** (new and replacement) for vaccines, biotherapeutics, blood products, IVD, standards for use in PHE and high throughput sequencing technologies
  - Endorsed: **19 proposals** for developing new/replacement standards
  - ❑ Published in **TRS 1048**, and **TRS 1054**

- **Workshops to facilitate implementation of WHO standards into practice**

  1) International standards for quality control of polio vaccines including OPV and IPV, 31 Oct – 2 Nov 2023, Indonesia

  2) Manual for the preparation of reference materials for use as secondary standards in antibody testing, 14-16 Nov 2023, Indonesia

  - ❑ Meeting reports published on WHO website

- **Biosimilars access toolkit – in collaboration with other teams in MHP**

- **Scientific leadership – publications in the scientific journals and on WHO web site**

Highlights in 2024

- **ECBS meetings in March and October 2024**
  - Established:
    - **4 written standards** (COVID-19 mAb, RSV mAb, rotavirus vaccines, blood establishments)
    - **13 measurement standards** (new and replacement) for vaccines, biotherapeutics, blood products, IVD, CGTP products, PHE and high throughput sequencing technologies
  - Endorsed: **14 proposals** for new/replacement standards
  - ❑ Published in **TRS 1059**; TRS XXXX for Oct ECBS is in preparation.

- **Workshops to facilitate implementation of WHO standards into practice**

  1) WHO Considerations in Developing a Regulatory Framework for Human Cells and Tissues and for Advanced Therapy Medicinal Products. 14 – 16 May 2024, held in Muscat, Oman

  ❑ Meeting report published on WHO website

  2) WHO Workshop on Implementation of Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines in importing countries. 7 – 9 Aug 2024, Istanbul, Türkiye

- **Contributed to ICDRA Oct 2024**
  1) workshop on Regulation of Advanced Therapy Medicinal Products
  2) workshop on medical standards together in collaboration with NSP

80th ECBS meeting held on 7-11 Oct 2024

1. **Executive Summary** published on WHO web site on 18 October 2024: https://www.who.int/publications/m/item/78th-ecbs-meeting-october-2023

Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 7 to 11 October 2024

18 October 2024 | Publication

Download (90.8 kB)

Overview

The 80th meeting of the WHO Expert Committee on Biological Standardization (ECBS) was held from 7 to 11 October 2024 as a hybrid meeting, with ECBS members meeting in person in Geneva and other participants attending virtually.

2. TRS (full report) is under preparation and will be published in 2025 on WHO website

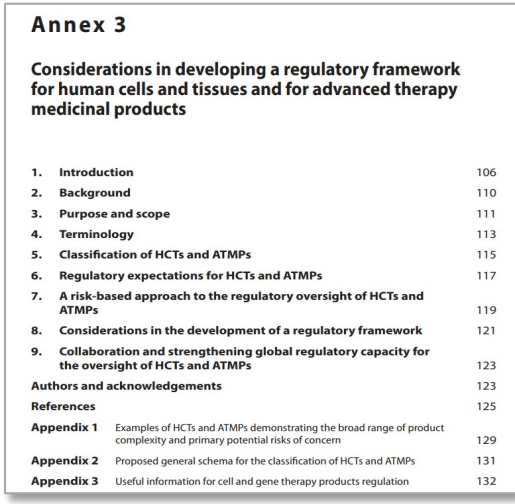
- **3 written standards were adopted by the ECBS**
  - ✓ Nonclinical and clinical evaluation of RSV monoclonal antibodies and related products intended for the prevention of respiratory syncytial virus disease
  - ✓ Recommendations to assure the quality, safety and efficacy of rotavirus vaccines (Revision of TRS 941, annex 3)
  - ✓ Good practices for blood establishments

World Health Organization

Cell and Gene Therapy Products

WHO initiative:

- WHA resolution
- Several teams are engaged in the area of cell and gene therapy products
- **“Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products” – written standard established by the ECBS in March 2023**
- First implementation workshop in Oman – Executive Summary



Annex 3

Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products

Review of the situation with regulatory frameworks in selected countries

- To understand the current global regulatory landscape on cell and gene therapy products regulation
- To define the needs and explore options for meeting these needs

Collaboration with the networks of experts – IABS, EDQM, IPRP

- Workshops, webinars, surveys and
- other activities of common interest in improving current situation - publications (i.e, meeting reports, case studies)

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Biosimilars

Completed:

1. Revision of WHO guidelines, April 2022 (TRS No. 1043)

Annex 3

Guidelines on evaluation of biosimilars

Replacement of Annex 2 of WHO Technical Report Series, No. 977

2. Two articles published in 2023 and 2024

DOI: 10.1111/nyas.14965

ORIGINAL ARTICLE

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

WHO guidelines on biosimilars: Toward improved access to safe and effective products

Hye-Na Kang[1] | Meenu Wadhwa[2] | Ivana Knezevic[1] | Clive Ondari[1] | Mariangela Simao[1]

DOI: 10.1111/nyas.15217

ORIGINAL ARTICLE

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

The importance of World Health Organization international reference standards in the product life cycle of biosimilars

Hye-Na Kang[1,#] | Meenu Wadhwa[2,#] | Ivana Knezevic[1] | Chris Burns[2] | Elwyn Griffiths[3]

Ongoing & Planning: Implementation of GLs

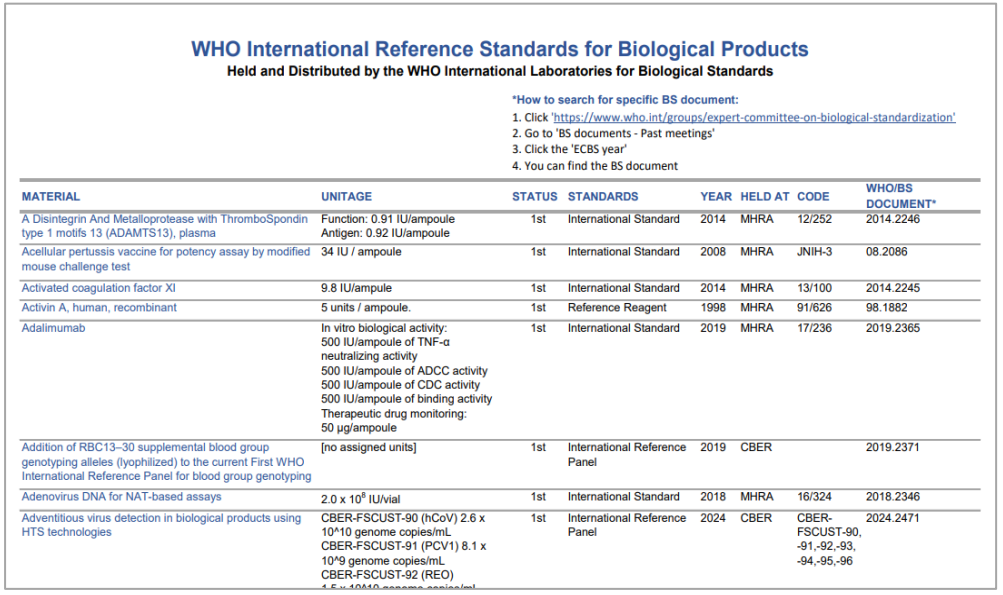
- **2 topics identified and case studies prepared**
  - Small molecules (Insulins)
    - CMC and non-clinical aspects (also cover device issue)
    - Clamp trial – the pivotal clinical trial (also cover immunogenicity issue)
  - Large molecules (mAbs)
    - Streamlined evaluation
- **Implementation workshop (2025)**
  - In EM including some countries from AF region
  - Review country situation
  - Hands-on training for regulators by using the developed case studies

World Health Organization

Catalogue of WHO international reference standards for biological products

- Has been **updated** to include WHO measurement standards adopted by March 2024
- Will be updated more promptly following ECBS meetings
- Continuous improvements are underway to enhance its informativeness

<Catalogue of the WHO International Reference Standards for Biological Products>



WHO International Reference Standards for Biological Products

Held and Distributed by the WHO International Laboratories for Biological Standards

*How to search for specific BS document:
1. Click 'https://www.who.int/groups/expert-committee-on-biological-standardization'
2. Go to 'BS documents - Past meetings'
3. Click the 'ECBS year'
4. You can find the BS document

MATERIAL	UNITAGE	STATUS	STANDARDS	YEAR	HELD AT	CODE	WHO/BS DOCUMENT*
A Disintegrin And Metalloprotease with ThromboSpondin type 1 motifs 13 (ADAMTS13), plasma	Function: 0.91 IU/ampoule Antigen: 0.92 IU/ampoule	1st	International Standard	2014	MHRA	12/252	2014.2246
Acellular pertussis vaccine for potency assay by modified mouse challenge test	34 IU / ampoule	1st	International Standard	2008	MHRA	JNIH-3	08.2086
Activated coagulation factor XI	9.8 IU/ampule	1st	International Standard	2014	MHRA	13/100	2014.2245
Activin A, human, recombinant	5 units / ampoule.	1st	Reference Reagent	1998	MHRA	91/626	98.1882
Adalimumab	In vitro biological activity: 500 IU/ampoule of TNF-α neutralizing activity 500 IU/ampoule of ADCC activity 500 IU/ampoule of CDC activity 500 IU/ampoule of binding activity Therapeutic drug monitoring: 50 µg/ampoule	1st	International Standard	2019	MHRA	17/236	2019.2365
Addition of RBC13–30 supplemental blood group genotyping alleles (lyophilized) to the current First WHO International Reference Panel for blood group genotyping	[no assigned units]	1st	International Reference Panel	2019	CBER		2019.2371
Adenovirus DNA for NAT-based assays	2.0 x 10^8 IU/vial	1st	International Standard	2018	MHRA	16/324	2018.2346
Adventitious virus detection in biological products using HTS technologies	CBER-FSCUST-90 (hCoV) 2.6 x 10^10 genome copies/mL CBER-FSCUST-91 (PCV1) 8.1 x 10^9 genome copies/mL CBER-FSCUST-92 (REO)	1st	International Reference Panel	2024	CBER	CBER-FSCUST-90, -91,-92,-93, -94,-95,-96	2024.2471

World Health Organization

WHO written standards for biologicals: recently established by the ECBS

- ✓ Guidelines for assuring the quality, safety and efficacy of plasmid DNA vaccines (TRS 1028, ECBS 2020)
- ✓ Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations (TRS 1039, ECBS 2021)

- ✓ Guidelines for the production and QC of mAbs for use in humans – *(replacement of Annex 3 of TRS 822)* (TRS 1043, ECBS 2022)
- ✓ Guideline for the preclinical and clinical evaluation of mAbs and related products for the prevention and treatment of infectious diseases (TRS 1048, ECBS 2023).
  - Disease specific supplements for mAbs for COVID-19 (TRS 1059, ECBS 2024), RSV (ECBS Oct 2024*), rabies, malaria, HIV to be developed in coming years*

- ✓ WHO manual for the preparation of reference materials for use as secondary standards in antibody testing (TRS 1043, ECBS 2022)

- ✓ Guidelines on regulatory preparedness for the oversight of pandemic or other emergency use vaccines importing countries- *(replacement of TRS 1004, Annex 7)* – expanded scope and guidance for vaccines for pandemic and emergency use (TRS 1054, ECBS 2023)

WHO written standards: revision/new/ from 2024 onwards

- ✓ Recommendations to assure the quality, safety and efficacy of rotavirus vaccines - *(replacement of TRS 941, annex 3)*- (ECBS Oct 2024)

- ✓ Good practices for blood establishments – replacement of the 2011 WHO Guidelines on GMP for blood establishments. (ECBS Oct 2024)

- **NEW- Guidelines on the phasing out of animal tests for the quality control of biological products**– **Public consultation by 10 January 2025** (ECBS, Oct 2025)

- Recommendations for the preparation, characterization and establishment of international and other biological reference standards **(revision of TRS 932, annex 2**) – Consultations in 2025 (ECBS, 2026)

- Guidelines for PAC for vaccines and biotherapeutic products (**revision of TRS 993, Annex 4**) to review reporting categorization of PACs and to include risk-based approach and reinforce reliance mechanism (ECBS, 2026)

Planned meetings in 2025

- WHO Drafting Group meeting to discuss revision of Recommendations for the preparation, characterization, and establishment of international and other biological reference standards (revision of TRS 932, Annex 2), 24-26 February 2025, WHO, Geneva, Switzerland
- Informal consultation on WHO Guidelines on the phasing out of animal tests for the quality control of biological products, 27-28 February 2025, WHO, Geneva, Switzerland
- Implementation workshop on CGTP – April 2025
- Implementation workshop on the evaluation of biosimilars – June 2025
- Informal consultation (virtual) on revision of TRS 932, Annex 2 (see above), June/July 2025
- WHO drafting group meeting on revision of guidelines on PAC (vaccines & BTPs)- June/July 2025
- 81st meeting of the Expert Committee on Biological Standardization (ECBS): 13-17 October 2025
- WHO Working Group Meeting on Cell and Gene Therapy Products, November 2025

Useful/relevant resources

- **Health products policy and standards**
  - https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications
- **Expert Committee on Biological Standardization (ECBS)**
  - https://www.who.int/groups/expert-committee-on-biological-standardization
- **Standardization of vaccines**
  - https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards/vaccine-standardization
- **Standardizing biotherapeutic products**
  - https://www.who.int/activities/standardizing-biotherapeutic-products
- **Cell, Tissue and Gene Therapy Products**
  - https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards/cell--tissue-and-gene-therapy-products
- **International biological reference preparations**
  - https://www.who.int/activities/providing-international-biological-reference-preparations

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- stakeholders including manufacturers, regulators
- WHO colleagues
- funding agencies
- and more…

Contact for further information

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World Health Organization