WHO biological standardization:

An update

Dr Ivana Knezevic, WHO/MHP/HPS/TSS/NSB

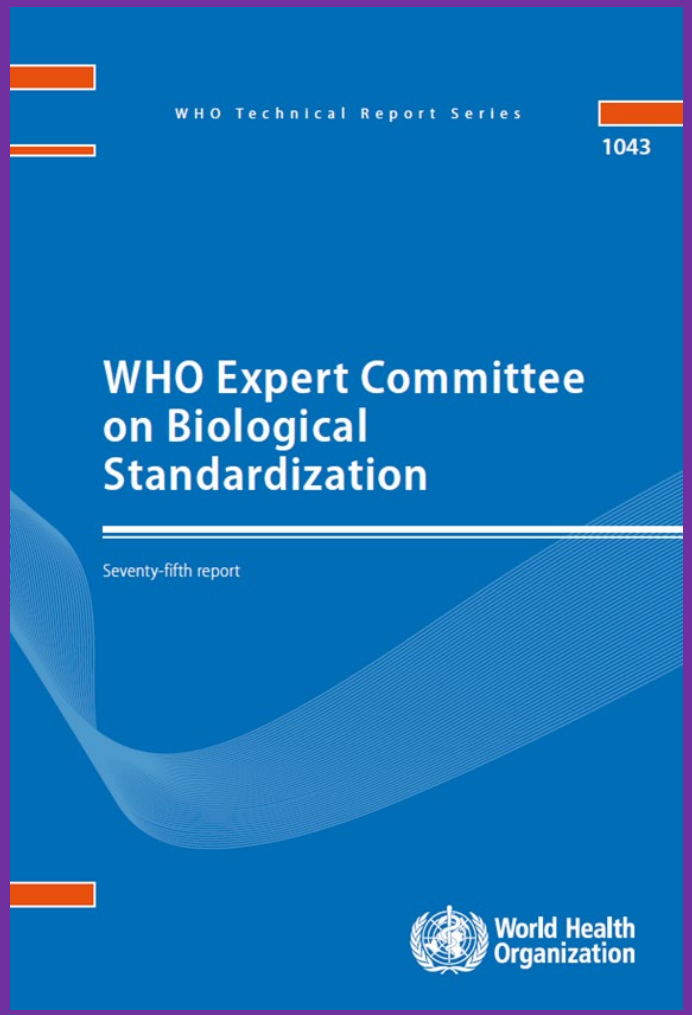
30th November 2023

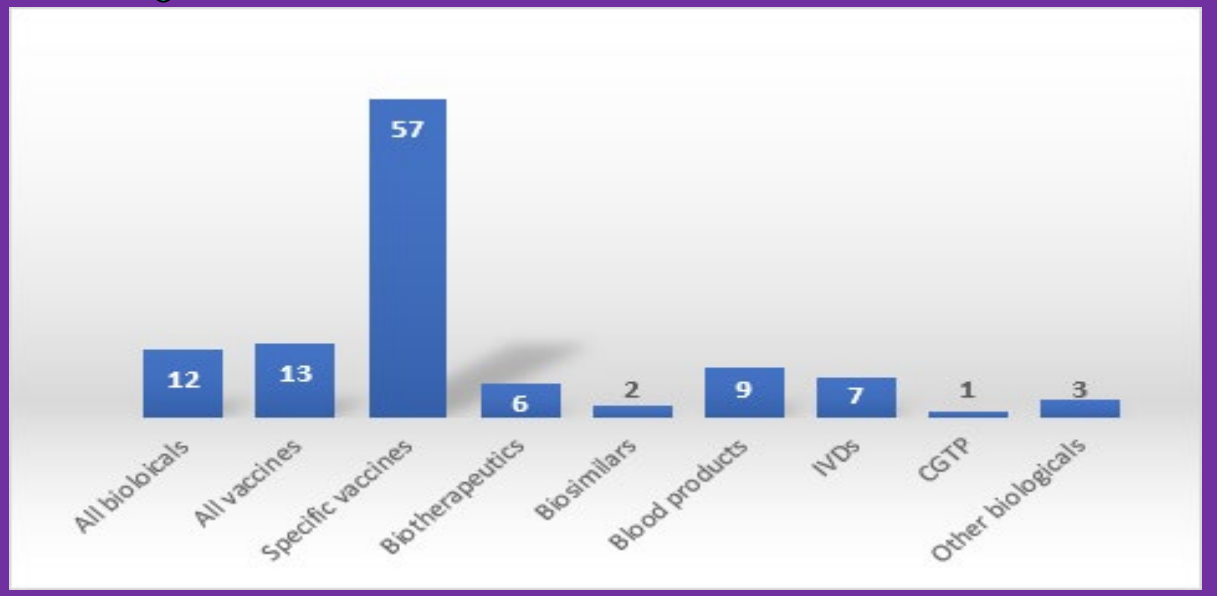
Copenhagen, Danmark

WHO norms and standards for biologicals

Global written standards (111)

https://www.who.int/groups/expert-committee-on-biological-standardization





Global measurement standards (more than 400)

Measurement standards: essential elements for development, licensing and lot release

Scientific evidence

1) Standardization of assays
2) Further development and refinement of QC tests
3) Scientific basis for setting specifications

Concept of WHO Guidelines

1) Provide key principles for evaluation of biologicals as a basis for setting national requirements;

2) Leave space to NRAs to formulate additional/ more specific requirements;

3) Living document that will be developed further in line with the progress in scientific knowledge and experience

4) Assist with the implementation of the guidelines into regulatory and manufacturers practice through:

- Global, regional and national workshops involving regulators, manufacturers and other relevant experts
- Trainings, advisory groups

5) Consider guidance issued by other bodies – intention to complement them, not to create a conflict.

Science based regulation

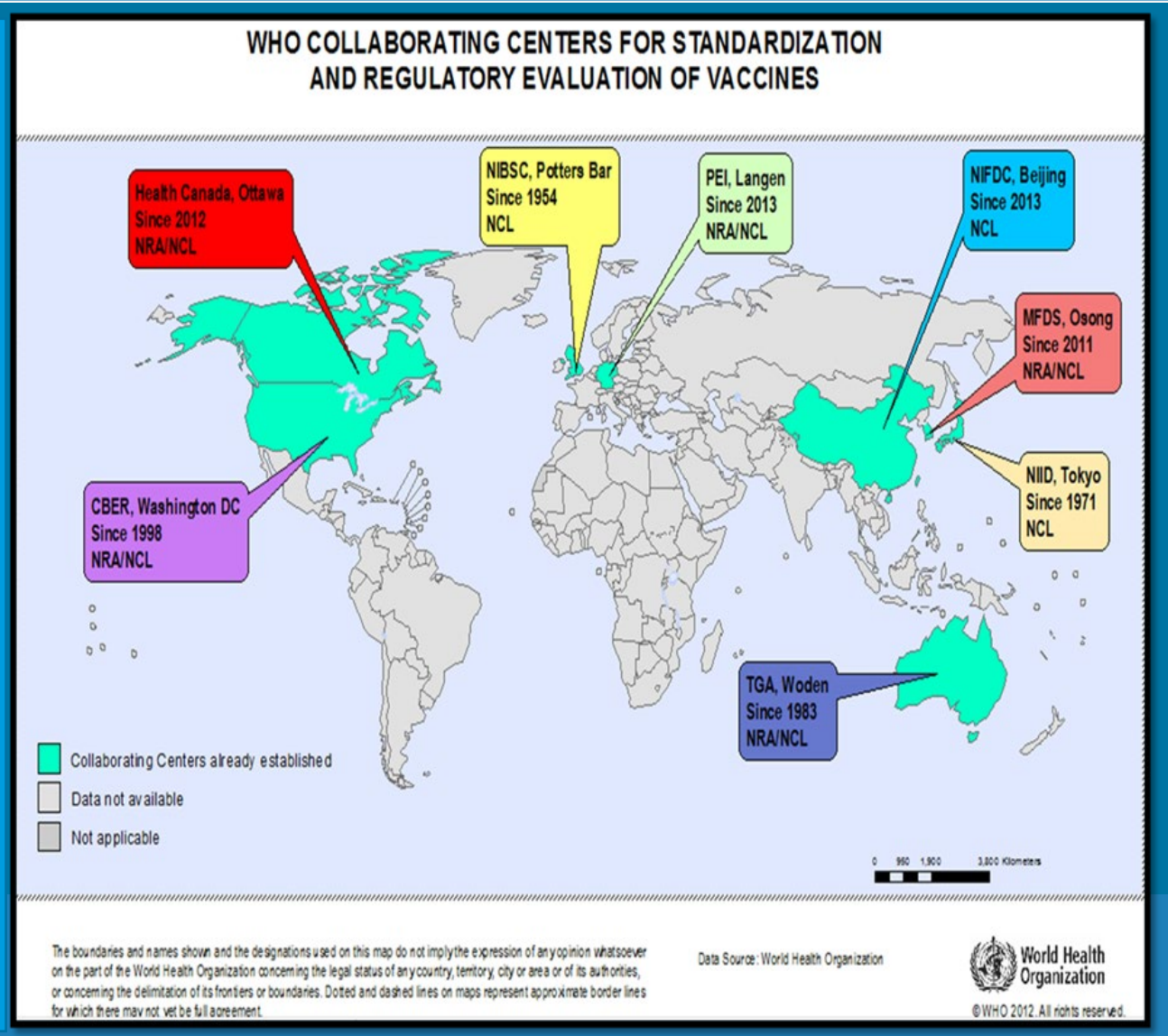
WHO CCs and Custodian Laboratories for Biological Standardization

- **Input provided to the following:**
  - Measurement standards: MHRA (NIBSC) with the input from CCs and other laboratories
    - Vaccines and related substances
    - Biotherapeutics
    - Blood products and related substances
    - In vitro diagnostics
    - Cell and gene therapies
    - PHE (eg, SARS-CoV-2)
    - high-throughput sequencing standards
  - Written standards
  - Implementation workshops

- **CBER re-designation by February 2024**

- WHO CC network for standardization of vaccines – meeting postponed to 2024

- **WHO custodian laboratories for measurement standards: 1) MHRA (NIBSC), 2) PEI, 3) CBER/US FDA and 4) EDQM (antibiotics)**

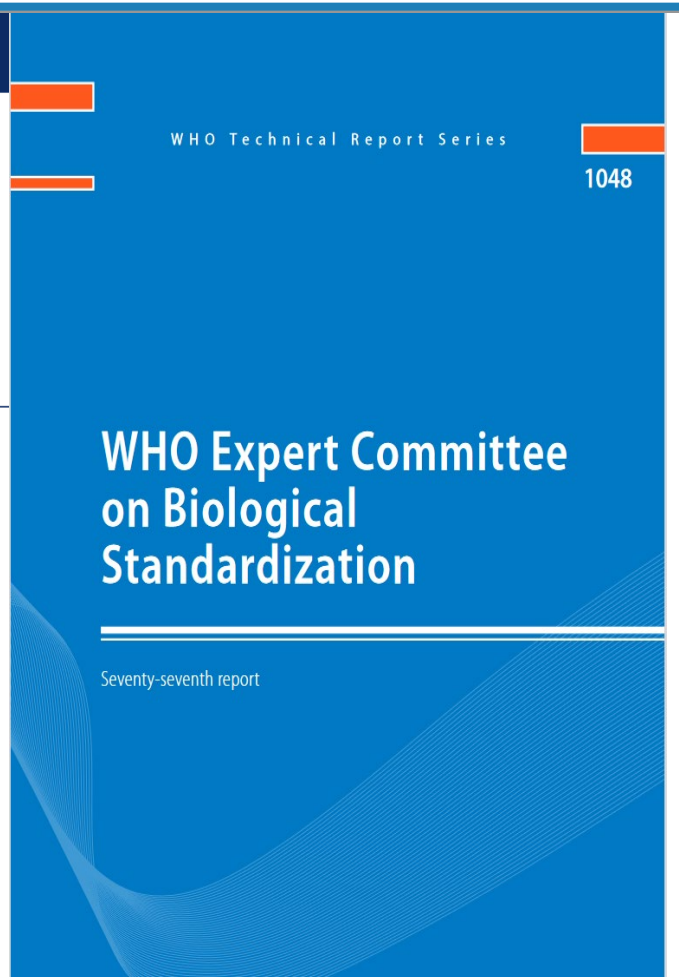


Report of 77th ECBS meeting held on 20-24 March 2023

WHO Technical Report Series 1048

1. Executive Summary published on WHO web site on 6 April 2023: https://www.who.int/publications/m/item/main-outcomes-of-the-meeting-of-ecbs-20-to-24-mar-2023

2. ECBS report (TRS 1048) published on 4 Oct 2023



78th ECBS meeting held on 16 - 19 Oct 2023

1. Executive Summary published on WHO web site on 26 October 2023: https://www.who.int/publications/m/item/78th-ecbs-meeting-october-2023

2. ECBS report (TRS) will be published in 2024

Main outcomes of 78th ECBS meeting (16-19 Oct 2023) - 1

World Health Organization

- **1 written standard for vaccines adopted:**
- Guidelines on preparedness for regulatory oversight of vaccines used in pandemics in importing countries
- **6 new and 5 replacement WHO International reference preparations established**
- **7 proposals for new standards endorsed**

- **Additional topics discussed:**
  - Issues arising from the ongoing COVID-19 pandemic:
    - 1) Mab for COVID-19 and 2) convalescent plasma
  - Animal testing in WHO documents
  - A need for discontinuation of written and measurement standards in the near future

Main outcomes of 78th ECBS meeting (16-19 Oct 2023) - 2

World Health Organization

Table 1
WHO international reference materials established by the ECBS in October 2023

Material	Unitage	Status
Biotherapeutics other than blood products		
Alpha-fetoprotein (human)	7800 IU/ampoule	Second WHO International Standard
Follicle-stimulating hormone and luteinizing hormone for bioassay (human, urinary)	177 IU/ampoule FSH 170 IU/ampoule LH	Sixth WHO International Standard
Thyroid-stimulating hormone (human, pituitary)	11.7 mIU/ampoule	Fourth WHO International Standard
Blood products and related substances		
Thrombin activatable fibrinolysis inhibitor (plasma)	Activity: 0.87 IU/ampoule Antigen: 0.92 IU/ampoule Antigen: 7.43 µg/ampoule (expanded uncertainty limits = 7.05–7.82 with k=2 taken to correspond to a 95% level of confidence)	First WHO International Standard
In vitro diagnostics		
Protein S (plasma)	0.71 IU/ampoule activity 0.83 IU/ampoule free antigen 0.88 IU/ampoule total antigen	Third WHO International Standard
Q fever (*Coxiella burnetii*) antibodies (human plasma)	100 U/ampoule for Phase I antigens 16 U/ampoule for Phase II antigens	WHO International Reference Reagent
Standards for use in high-throughput sequencing technologies		
Gut microbiome DNA extraction (whole cell)	No unitage assigned	WHO International Reference Reagent
Standards for use in public health emergencies		
SARS-CoV-2 RNA for NAT-based assays	7.50 $\log_{10}$ IU/ampoule	Second WHO International Standard
Vaccines and related substances		
Nipah virus antibodies for use in binding assays (human serum)	250 IU/ampoule anti-glycoprotein IgG	First WHO International Standard
Nipah virus antibodies for use in neutralization assays (human serum)	250 IU/ampoule	First WHO International Standard
Ross River virus antibodies for use in neutralization assays (human plasma)	500 U/vial	WHO International Reference Reagent

WHO written standards for biologicals: recently adopted and new/ revision under consideration

1. COVID-19 related documents (recent and upcoming):

1.1. Guidelines for assuring the quality, safety and efficacy of plasmid DNA vaccines (TRS 1028, ECBS, Aug 2020)

1.2. Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations (ECBS, Oct 2021)

1.3. Guidelines for the production and QC of mAbs for use in humans – replacement of Annex 3 of WHO TRS 822 (TRS 1043, ECBS, Apr 2022)

1.4. Guideline for the preclinical and clinical evaluation of mAbs and related products for the prevention and treatment of infectious diseases (ECBS, Apr 2023). Disease specific supplements for COVID-19, RSV, rabies, malaria, HIV to be developed in 2023-2025

1.5. Manual for the establishment of national and other secondary standards for antibodies against infectious agents focusing on SARS-CoV-2 (ECBS, Apr 2022) and preparation of the case studies for the implementation workshop in 2023

2. Revision of PIP guidelines (TRS 1004, Annex 7) to expand the scope and to provide guidance for vaccines for pandemic and emergency use **(ECBS, Oct 2023)**

3. Revision of Guidelines for rota vaccines (TRS 941, annex 3) – revision due to the experience gained since 2006, new generation rotavirus vaccines **(ECBS, Oct 2024)**

4. Revision of Guidelines for PAC for vaccines (TRS 993, Annex 4) to review reporting categorization of some PACs and to include risk-based approach and reinforce reliance mechanism **(ECBS, Oct 2025)**

5. Animal use in testing vaccines and biotherapeutic products – Review of the Report on 3Rs in WHO guidelines presented to the ECBS in October 2023 and follow up actions

WHO written standards: revision/new/ implementation under consideration from 2023/ 2024 onwards

I Revision of the following:

1.1. Recommendations for YFV vaccines (TRS 978, annex 5)
1.2. Guidelines for dengue vaccines (TRS 979, annex 2)
1.3. Recommendations for MMR vaccines (TRS 840, annex 3)
1.4. Guidelines for Vaccine Lot Release (TRS 978, annex 2)
1.5. Recommendations for the preparation, characterization and establishment of international and other biological reference standards (TRS 932, annex 2)
1.6. Recommendations for BCG vaccines (TRS 771, annex 12)
1.7. Guidelines for malaria vaccines (TRS 980, annex 3)

II Standardization of enteric vaccines – new documents in coming years

III Implementation workshops:

3.1. Polio vaccines: 31 October – 2 Nov 2023
3.2. Manual for secondary standards: 14 – 16 November 2023
3.3. Cell and gene therapy products: May 2024
3.4. Biosimilars: July 2024

Many thanks to:

World Health Organization

…team (NSB/TSS/HPS/MHP/WHO)

…colleagues in BTT/TSS/HPS/MHP/WHO and RSS/PQT/MHP/WHO

…members of WHO drafting and Working Groups

…colleagues from Collaborating Centers and Custodian Laboratories

…many individual experts

…stakeholders

Further information and contact

Dr Ivana Knezevic (email: knezevici@who.int) on behalf of NSB/TSS team

Biological standardization website:

Expert Committee on Biological Standardization (who.int)