



WHO standards for biotherapeutics: Tools for regulatory convergence

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“Together for a healthier world”

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Key Themes of WHO's 13th General Programme of Work 2019-2023

Mission

Promote Health - Keep the World Safe - Serve the Vulnerable

Strategic Priorities

Health Coverage: 1 billion more people with health coverage
Health Emergencies: 1 billion more people made safer
Health Priorities: 1 billion lives improved

NEW Cluster

Access to Medicines, Vaccines and Pharmaceuticals (MVP)
Dr. Mariângela SIMÃO, Assistant Director General

at EB 2019

Roadmap on **access** to medicines and vaccines

http://www.who.int/medicines/access_use/road-map-medicines-vaccines/en/

World Health Organization (WHO)



WHO is a specialised agency of the UN serving as the directing and coordinating authority for international health matters and public health on behalf of its 194 Member States.

WHO is operating at 3 levels, HQ in Geneva, 6 regional offices and 150 country offices

Principle objective - *the attainment by all people of the highest possible level of health.*

WHO is responsible for providing leadership on global health matters, shaping the health research agenda, **setting norms and standards**, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

Setting norms and standards and promoting their implementation is affirmed as **a core function** of WHO for the period 2014-2020.

WHO Activities to assist Regulators: Focus on Access and

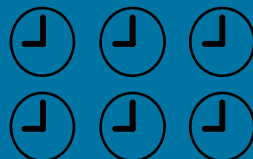
Outcomes: Ensuring normative and technical excellence drives impact at country level



Technologies, Standards and Norms	Regulatory Systems Strengthening	Prequalification Programme	Safety & Vigilance
<ul style="list-style-type: none">• Set global norms and standards (written & physical) and nomenclatures• Increase common understanding on regulatory requirements by authority and manufacturer• Standardize approach used by quality control labs	<ul style="list-style-type: none">• Set effective and efficient regulatory systems in LMICs through collaborative & harmonized approaches with reliance principles• Increase confidence in medical products produced in LMICs	<ul style="list-style-type: none">• Assure safety, quality, efficacy & appropriateness of medical products used in LMICs: vaccines, medical devices, cold chain equipment, vector control products & in vitro diagnostics• Increase competition to shape the market	<ul style="list-style-type: none">• Increase knowledge of real life adverse events and coordinate actions taken against adverse events• Mitigate risks and protect against substandard / falsified products• Contain antimicrobial resistance



Decreased regulatory burden



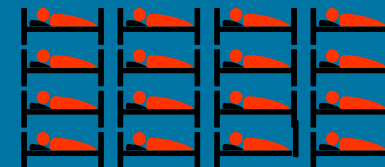
Reduced time for regulation



Increased regulatory capacity in LMIC



Decreased cost of regulation



Reduced mortality and morbidity

WHO norms and standards for biologicals

69th meeting of the ECBS (29 Oct-2 Nov 2018) -Executive Summary:

http://www.who.int/biologicals/WHO_ECBS/en/

Global written standards

Total 97 docs (Recommendations/ Guidelines)

General docs that apply to vaccines & BTP: 10

General documents that apply to all vaccines: 12

Vaccine specific: 66

BTP specific: 9

Global measurement standards

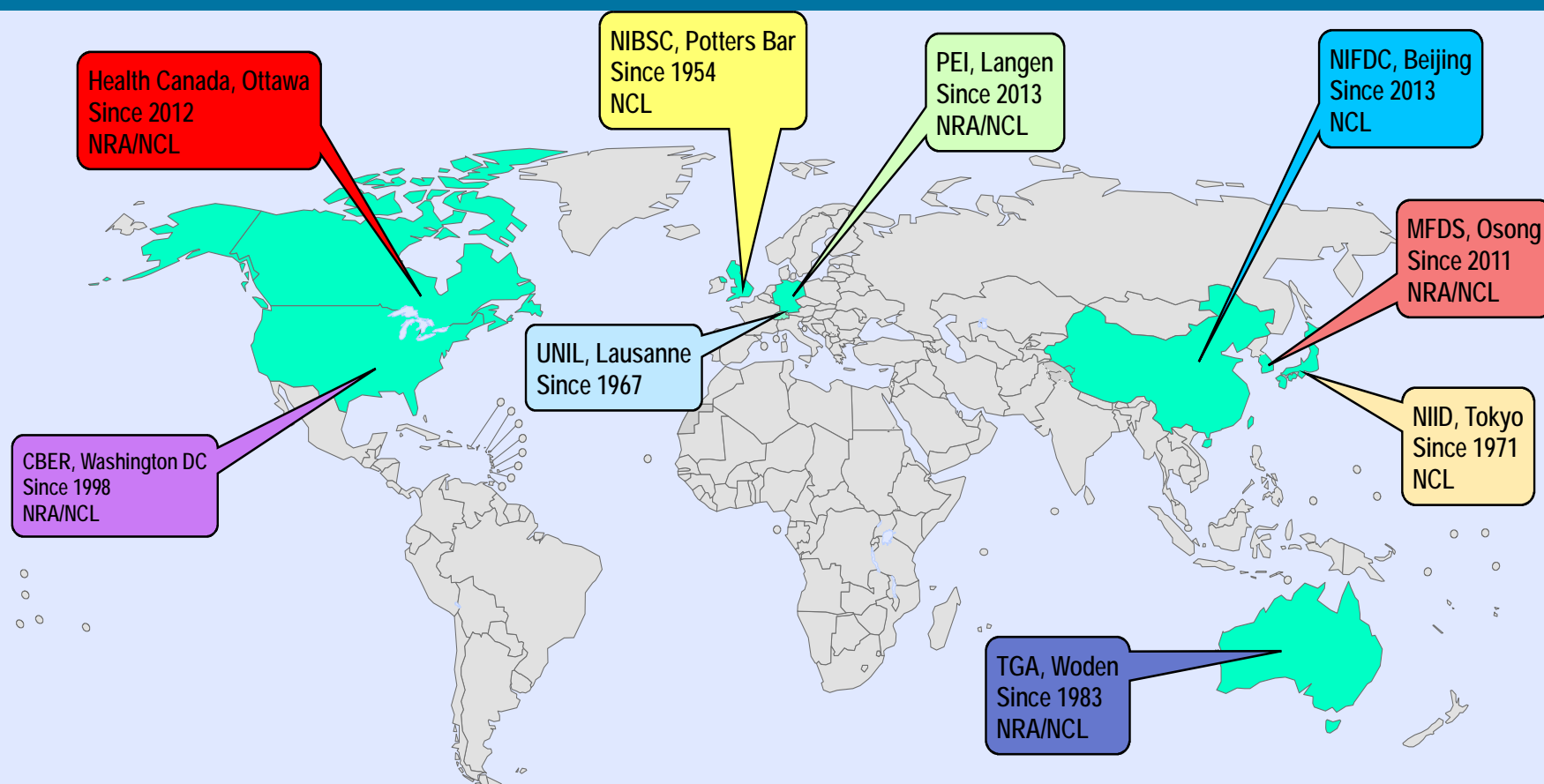


Scientific evidence

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

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

WHO COLLABORATING CENTERS IN THE AREA OF VACCINE RESEARCH AND STANDARDIZATION



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First-ever WHA Resolution on biotherapeutics: Urges

- WHA 67.21, 2014: "Access to BTPs including similar biotherapeutic products and ensuring their quality, safety, and efficacy"

Member States	WHO
To develop the necessary scientific expertise to facilitate development of solid, scientifically-based regulatory frameworks	To support MS in strengthening their capacity in the area of the health regulation of BTPs, including SBPs
To develop or strengthen, national regulatory assessment and authorization frameworks	To support the development of national regulatory frameworks that promote access to quality, safe, efficacious and affordable BTPs, including SBPs
To work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to BTPs/SBPs	To encourage and promote cooperation and exchange of information among MS in relation to BTPs/SBPs
	To convene the WHO ECBS to update the SBP GLs adopted in 2009 <ul style="list-style-type: none">• taking into account the technological advances for the characterization of BTPs; and• considering national regulatory needs and capacities

18th International Conference of Drug Regulatory Authorities (ICDRA)



To provide drug regulatory authorities of WHO MS with a forum to meet and discuss ways to strengthen collaboration.

Held every two years, well established forum for NRAs, WHO and interested stakeholders to determine priorities for regulation of medicines.

- 18th ICDRA, Dublin, Ireland, 5-7 September 2018
 - Government officials and regulators from more than 100 WHO MS
 - Main theme: **"SMART SAFETY SURVEILLANCE: A LIFE-CYCLE APPROACH TO PROMOTING SAFETY OF MEDICAL PRODUCTS"**
 - General issues: Benchmarking, Reliance, Collaboration
 - Specific themes: Public Health Emergencies, Biosimilars, Advanced therapies etc
 - ICDRA recommendations:
https://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/en/

WHO Guidelines for BTP including SBP

information available at <http://www.who.int/biologicals/biotherapeutics/en/>



- **For approval**

Originator Biotherapeutic (BTP)	Similar Biotherapeutic Product (SBP)
WHO <i>Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology</i> , adopted by WHO ECBS 2013 (requested by ICDRA 2010)	<ul style="list-style-type: none">• WHO <i>Guidelines on evaluation of similar biotherapeutic products</i>, adopted by WHO ECBS 2009 (requested by ICDRA 2006)• WHO <i>Guidelines on evaluation of monoclonal antibodies as SBPs</i>, adopted by the WHO ECBS 2016 (requested by ICDRA 2014)• Draft WHO Q&A: <i>Similar biotherapeutic products</i>, adopted by the WHO ECBS 2018 (requested by ICDRA 2014)

- **For post-approval management**

BTP licensed as generics	Post approval changes (variations) for BTP & SBP
<i>Regulatory assessment of approved BTPs</i> , adopted by WHO ECBS 2015 (requested by ICDRA 2010)	WHO <i>Guidance on procedures and data requirements for changes to approved BTPs</i> , adopted by WHO ECBS 2017 (requested by ICDRA 2014)

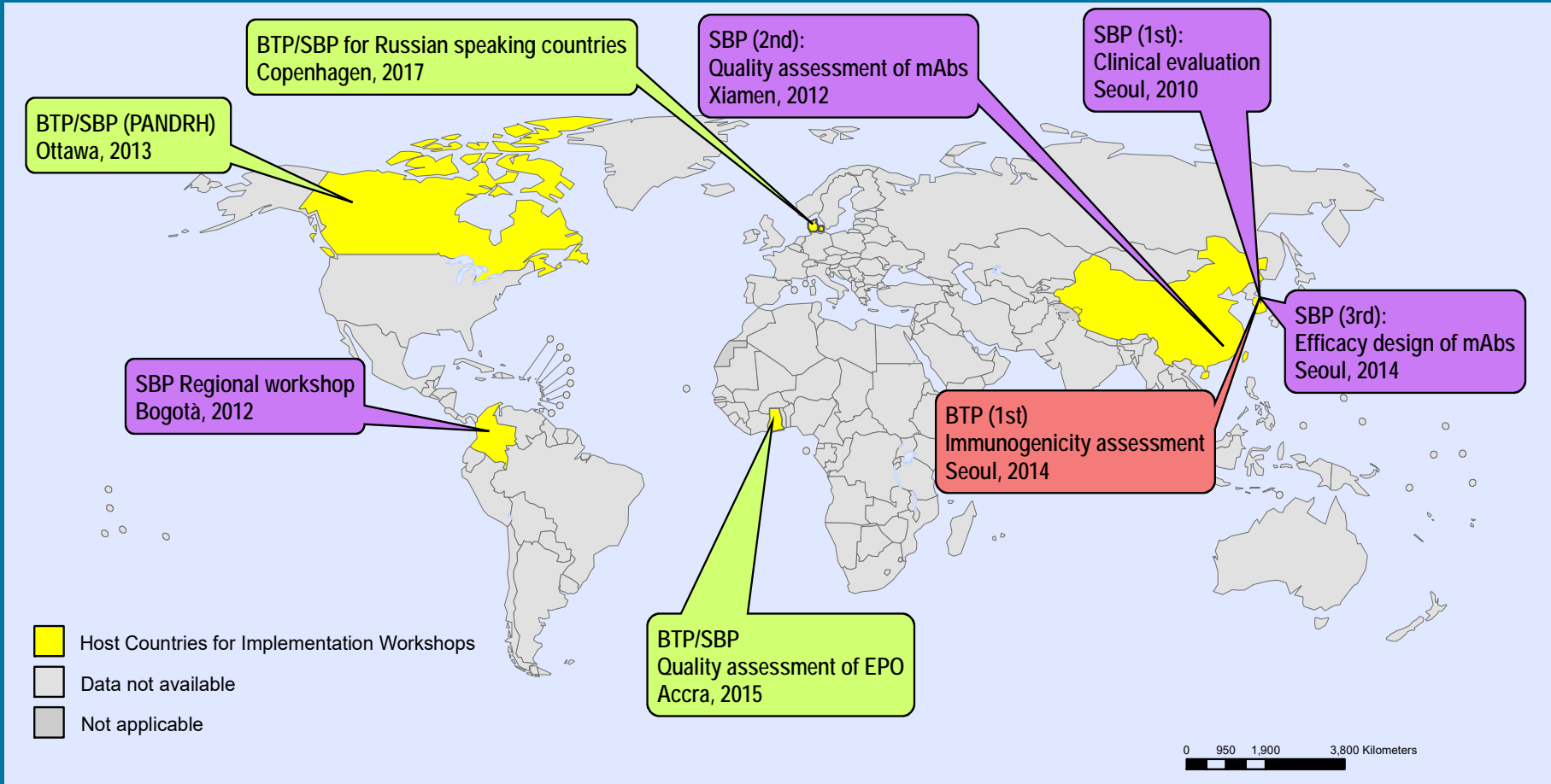
Implementation of standards:

(requested by ICDRA 2010, 2014, 2016)



- **Implementation workshops** on the guidelines has become an increasingly important tool in achieving regulatory convergence.
 - WHO HQ & RO to Organize
 - Supported by Collaborating Centers, national regulatory authorities and WHO RO/CO
 - Share experience among countries
 - Obtain information from countries
 - Their use and their capacity to follow the guiding principles in WHO documents
 - Their interpretation
 - Practice some of evaluation principles through case studies
- **Publications:** e.g. meeting reports, case studies, lectures, Q&A.
- **Collaborative activities** with other initiatives

Implementation Workshop on BTP including SBP (2010-2017)



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Implementation workshops for BTP/ SBP Guidelines



- Adopted: SBP by ECBS 2009; BTP by ECBS 2013

	Global level				Regional level		
Imp. workshop	1 st SBP	2 nd SBP	3 rd SBP	1 st BTP	SBP & BTP in AFR, Eng spk countries	SBP in EUR, Russian spk countries	SBP & BTP in EMR
When	Aug 2010	May 2012	May 2014		Sept 2015	July 2017	July 2018
(Co-) Host Where	MFDS Korea	NIFDC China	MFDS Korea		Ghana FDA Ghana	WHO EURO Denmark	WHO EMRO Oman
Participants	11 NRAs	16 NRAs	23 NRAs		16 NRAs	10 NRAs	19 NRAs
Main topic	Clinical study design: Eq vs NI	Quality assessment of mAbs	Efficacy study design on mAbs	Immuno-genicity assess of mAbs	Quality assessment of EPO		Strengthen regulation: Pre- & Post-licensure

Publications: Outcomes of implementation workshops



When	Type & Topic	Publication
1 st WS for SBP 2010	Meeting report	<i>Biologicals</i> 39 (5), 2011
	Special lecture: Statistical considerations for confirmatory clinical trials for SBPs	
	Case study: Comparing equivalence and non-inferiority approaches	
2 nd WS for SBP 2012	Case study: The role of the quality assessment (of mAbs) in the determination of overall biosimilarity	<i>Biologicals</i> 42 (2), 2014
3 rd WS for SBP 2014	Case study: Efficacy study design and extrapolation: Infliximab & Rituximab	<i>Biologicals</i> 43 (1), 2015
1 st WS for BTP 2014	Special lecture: Immunogenicity assessment of BTPs: An overview of assays and their utility	<i>Biologicals</i> 43 (5), 2015
	Case study: Assessment of unwanted immunogenicity of mAbs: TNF antagonist & CD20 mAbs	
WS in AFR & EUR 2015, 2017	AFR Meeting report	WHO web, 2016
	Case study: The role and influence of the quality assessment of EPO	In preparation

ICDRA recommendations to WHO and collaboration with IPRP BWG



Activities/ Deliverables with IPRP	ICDRA recommendations
Template for Public Assessment Summary Information for biosimilars to assure consistency and transparency of the review process, 2016	2010: Develop a template for Member States to share information on the scientific basis for licensing SBPs
Reflection paper on extrapolation of indications in authorization of biosimilar products, 2017	2014: Amend GLs on evaluation of SBP by providing additional information , e.g. extrapolation of indication, evaluation of mAbs, acceptance of RBP, comparability exercise
Manual for regulatory reviewers: The basics of analytical comparability for biosimilar monoclonal antibodies, 2017 (English, Russian, Spanish versions)	2014: <ul style="list-style-type: none"> Update norms, standards, and tools to facilitate further development of expertise for regulatory evaluation of biologicals. Facilitate implementation of existing GLs
Establishment of IPRP BWG Regulatory Information Sharing Platform by 2018	2014 & 2016: <ul style="list-style-type: none"> Continually update information regarding WHO standards for biologicals through regional and/or inter-regional networks and initiatives. Provide a forum for information-sharing on collaborative efforts that leads to better access

Regulatory convergence: opportunities and challenges



1. Science based WHO standards for science based regulation - common tools

2. WHO roles in regulatory convergence:

- Set of definitions as a tool for common understanding in all member states
- Provision of international standards for regulatory evaluation of biologicals
- Educational and training tools for improving the expertise at NRAs - implementation workshops with lectures and case studies.

3. Many international and regional initiatives - an opportunity for update on WHO standards through regulatory, industry and Ph networks but also challenge:

- DCVRN, PANDRH, AVAREF, ASEAN, APEC Harm. Center, IPRF, CoRE
- IFPMA, IGBA, Medicines for Europe, DCVMN, BIO, DIA, CASSS
- Pharmacopoeias, FIP

4. Successful collaboration with IABS: NGS, HCT, cell therapies

5. Opportunities for collaboration in the area of trainings: IPRP Biosimilars Working group and APEC CoE and RHSC - biotherapeutics including biosimilars

Many thanks to...



World Health
Organization

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