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GaBI Educational Workshops

First MENA Educational Workshop on
SIMILAR BIOTHERAPEUTIC PRODUCTS/BIOSIMILARS

1 September 2015, Le Meridien Dubai, United Arab Emirates

WHO standards for evaluation of biotherapeutics including biosimilars

Ivana Knezevic, MD, PhD

1 September 2015

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International

First MENA Educational Workshop on Biosimilars

WHO standards for evaluation of biotherapeutics including biosimilars

Dubai, 1st September 2015

Dr Ivana Knezevic, WHO/HIS/EMP

World Health Organization

Outline

- World Health Organization – mission and governance
- WHO International Standards
  - written (eg, Guidelines, Recommendations)
  - measurement (Int. Standards and Reference Preparations)
- Resolution on BTP and SBP: WHA 67.21
- 16th International Conference of Drug Regulatory Authorities (ICDRA) recommendations
- ***Regulatory Assessment of approved BTPs – new document***
- Key events in 2015

World Health Organization

- WHO is the directing and coordinating authority for health within the United Nations system on behalf of its 194 Member States (MS).
- WHO has now more than 7000 people working in 150 country offices, in 6 regional offices and at the HQ in Geneva.
- WHO fulfils its objectives through its 6 core functions:
  - 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 & standards and promoting & monitoring their implementation are affirmed as **WHO core function** for the period 2014 - 2019.
- WHO is not a regulatory authority but **mandated to assist** national regulatory authorities.

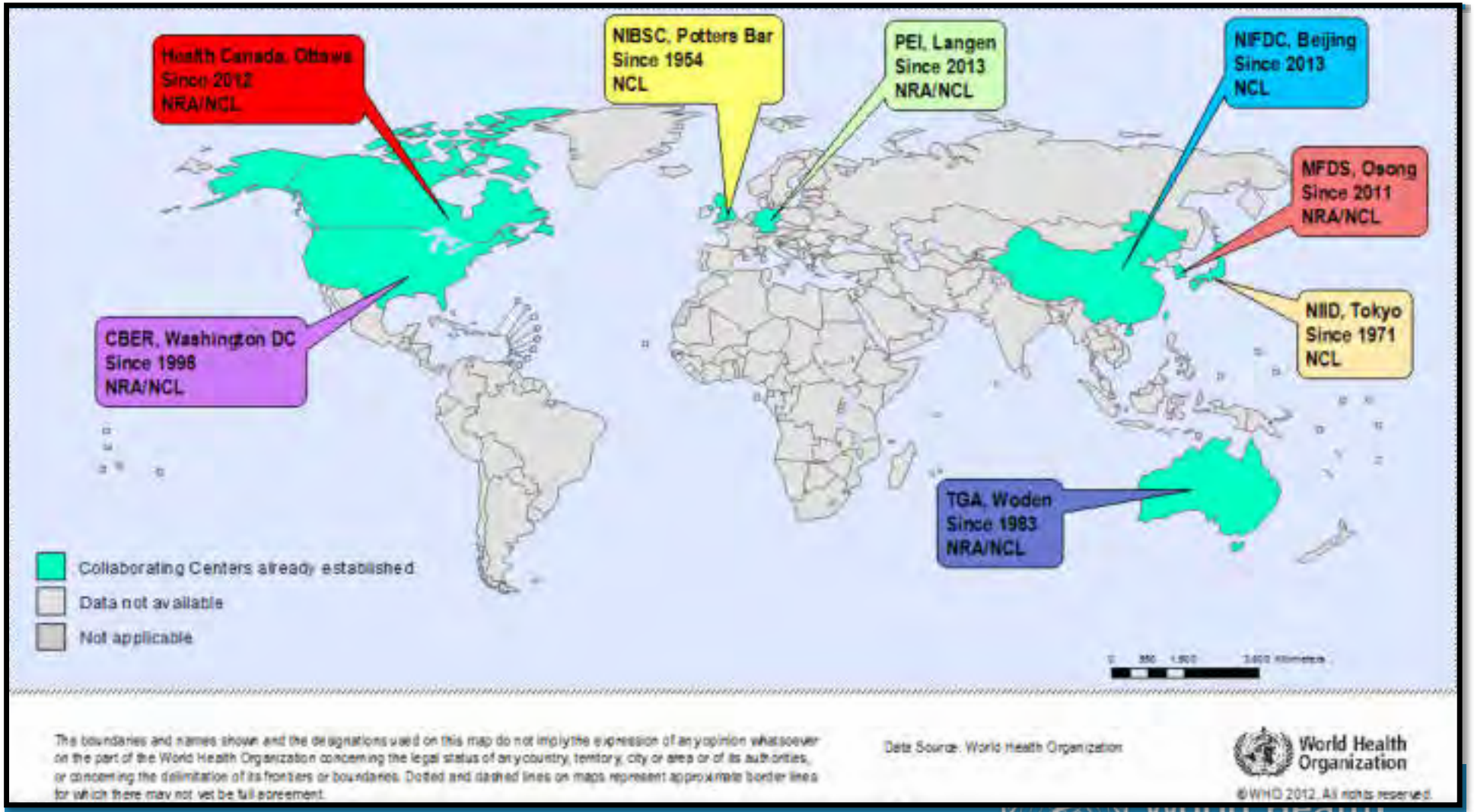
Governance of WHO

- The **World Health Assembly** (WHA)
  - Supreme decision-making body for WHO
  - Attended by delegations from all WHO MS
  - Focuses on a specific health agenda prepared by the Executive Board
  - Main functions: to determine the policies of the Organization
  - Annual meeting in May every year
- The Executive Board (EB)
  - Composed of 34 technically qualified members elected for three-year terms.
  - Main functions: to implement the decisions and policies of the WHA, and advise and generally to facilitate its work.
  - Annual Board meeting in January when the members agree upon the agenda for the WHA and the resolutions to be considered by the WHA.
- Director-General: Head of WHO, nominated by EB and appointed by WHA
- WHO secretariat

WHO Biological Standardization

- WHO has played a key role for over 60 years in establishing the **WHO Biological Reference Materials** necessary to standardize biological materials as well as developing **WHO guidelines and recommendations** to assure the quality, safety, and efficacy of biological products.
- These norms and standards, based on scientific consensus achieved through international consultations, **assist WHO Member States** in ensuring the quality and safety of biological medicines and related in vitro biological diagnostic tests worldwide.
- The Organization accomplishes this biological standardization work through
  - its biological programme coordinated by a Secretariat at WHO HQ;
  - the WHO **Expert Committee on Biological Standardization** (ECBS) selected from an Expert Advisory Panel on Biological Standardization; and
  - WHO **Collaborating Centres** for Biological Standardization.

WHO Collaborating Centres for Biological Standards



World Health Organization

WHO norms and standards for biologicals

www.who.int/biologicals

Global measurement standards

Scientific evidence

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

Reference preparations for vaccines and biotherapeutics

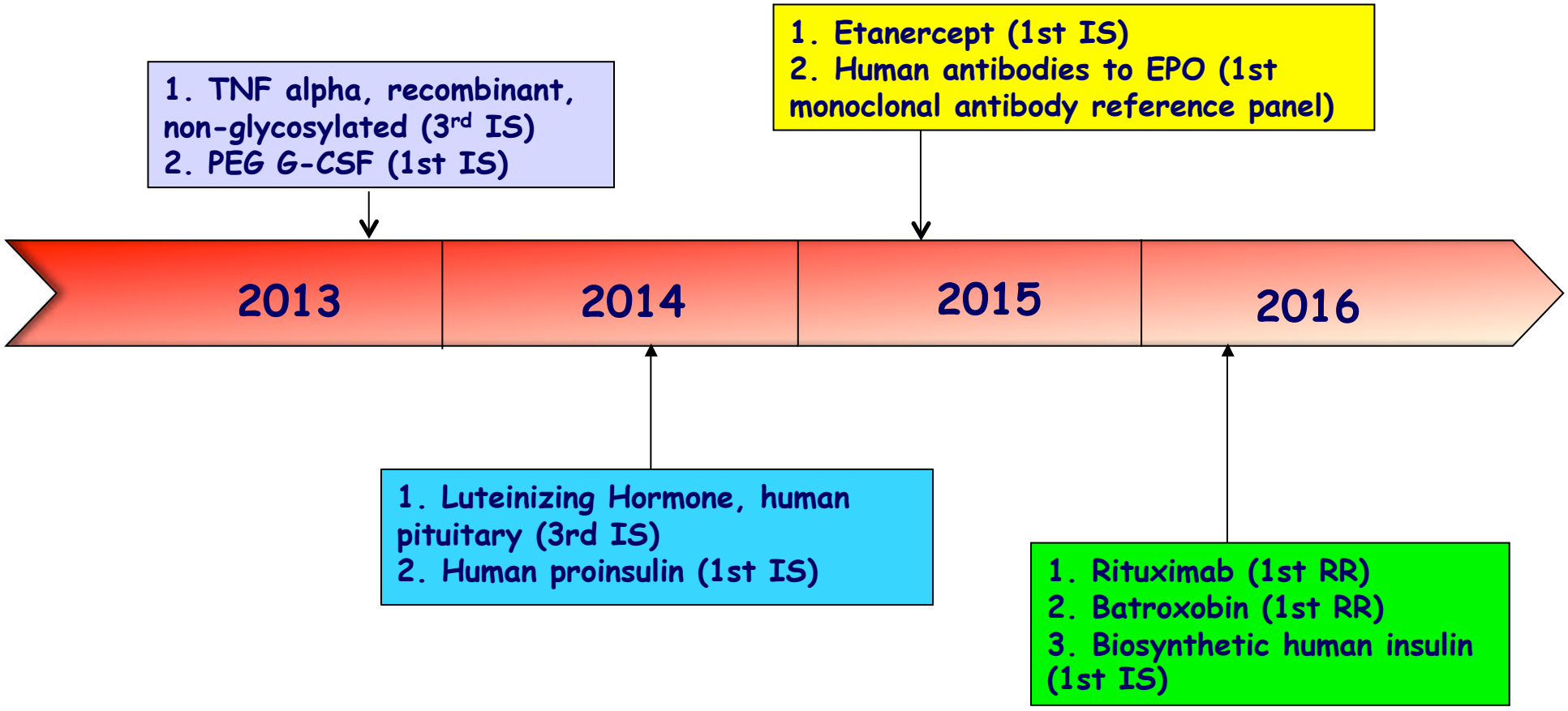
Measurement standards:
essential elements for development, licensing and lot release

World Health Organization

Measurement Standards for BTPs

- Information available on the following links:
  - WHO web (http://www.who.int/bloodproducts/catalogue/Cyto2015.pdf?ua=1)
  - NIBSC web (http://www.nibsc.org/products/biological_reference_materials/product_catalogue.aspx)
  - Intended use of measurement standards in the development of SBP: Review article by Thorpe R, Wadhwa M, *Biologicals* 39, 2011 (requested by ICDRA 2010)
- Relevant document
  - Recommendations for the preparation, characterization and establishment of international and other biological reference standards, Annex 2, WHO TRS No. 932, ECBS 2004
  - WHO manual for the establishment of national and other secondary standards for vaccines, WHO/IVB/11.03, 2011

Development of measurement standards for biotherapeutics, 2013 - 2016



World Health Organization

Written Standards for Evaluating BTPs

Information available at http://www.who.int/biologicals/biotherapeutics/en/

- WHO Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, WHO Technical Report Series (TRS) No. 977, ECBS 2009 (requested by ICDRA 2006)
- Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, Annex 4, WHO TRS 987 – ECBS 2013 (requested by ICDRA 2010)
  - ***NEW:*** **Addendum**: DRAFT_Regulatory assessment of approved BTPs, to be submitted to the ECBS 2015 (requested by ICDRA 2010)
- Recommendations for the Evaluation of Animal Cell Cultures as Substrates for the manufacture of biological medicinal products and for the characterization of cell banks, Annex 3, WHO TRS No. 978, ECBS 2010.

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.

Key principles for the licensing of SBPs

- **SBPs are not generic medicines** and many characteristics associated with the authorization process and marketed use of generic medicines generally do not apply.
- **Effective regulatory oversight: critical for assuring Q, S, E of SBPs**
- **Stepwise approach**

- Demonstration of similarity of SBP to RBP in terms of quality is a prerequisite for the reduction of the non-clinical and clinical data set required for licensure.
- If major differences are found in the quality, non-clinical and clinical studies, the product should not be considered as "similar" and, therefore, other options for its further development should be considered (eg, stand alone).

Important to note that biotherapeutics which are not shown to be similar to a RBP should not be described as "similar", nor called a "SBP".

Quality

- Development of an SBP
  - Thorough characterization of a number of representative lots of the RBP
  - Engineering a manufacturing process that will reproduce a product that is highly similar to the RBP in all critical product quality attributes
- The quality comparison showing molecular similarity between the SBP and the RBP provides the underlying rationale for predicting that the clinical safety and efficacy profile of the RBP should also apply to the SBP
  - So that the extent of the non-clinical and clinical data required with the SBP can be reduced
- To evaluate comparability
  - The manufacturer should carry out a comprehensive physicochemical and biological characterization of the SBP in **head-to-head comparison** with the RBP

Reference Biotherapeuctic Product (RBP)

- RBPs should have been marketed for a suitable duration and have a volume of marketed use
- RBPs should be licensed based on a full Q, S and E data set
- The same RBP used throughout the development of the SBP
- An SBP should not be considered as a choice for RBP
- The active substance of the RBP and the SBP must be shown to be similar
- The dosage form and route of administration of the SBP should be the same as that of the RBP
- NRAs may need to consider establishing additional criteria to guide the acceptability of using a RBP licensed or resourced in other countries

WHA 67.21: Urges Member States

- to develop or strengthen, as appropriate, national regulatory assessment and authorization frameworks, with a view to meeting the public health needs for BTPs, including SBPs;
- to develop the necessary scientific expertise to facilitate development of solid, scientifically-based regulatory frameworks that promote access to products that are affordable, safe, efficacious and of quality, taking note of the relevant WHO guidelines that may be adapted to the national context and capacity;
- to work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to quality, safe, efficacious and affordable BTPs, including SBPs;

WHA 67.21: Requests WHO

- to support Member States in strengthening their capacity in the area of the health regulation of BTPs, including SBPs;
- to support, as appropriate, the development of national regulatory frameworks that promote access to quality, safe, efficacious and affordable BTPs, including SBPs;
- to encourage and promote cooperation and exchange of information, as appropriate, among Member States in relation to BTPs, including SBPs;
- to convene the WHO Expert Committee on Biological Standardization to update the 2009 guidelines, taking into account the technological advances for the characterization of BTPs and considering national regulatory needs and capacities and to report on the update to the Executive Board;
- to report to the Sixty-ninth World Health Assembly on progress in the implementation of this resolution.

16th ICDRA recommendations – Biosimilars (Workshop H) – part 3

- **3. WHO guidelines on biotherapeutic products and on SBP**

3.1. Member States

- Implement existing WHO guidelines and subsequent updates in full, and monitor levels of implementation over time.
- If national standards differ from WHO standards, inform WHO of the rationale for this situation.

3.2. WHO

- Amend Guidelines on evaluation of SBP by providing additional information on:

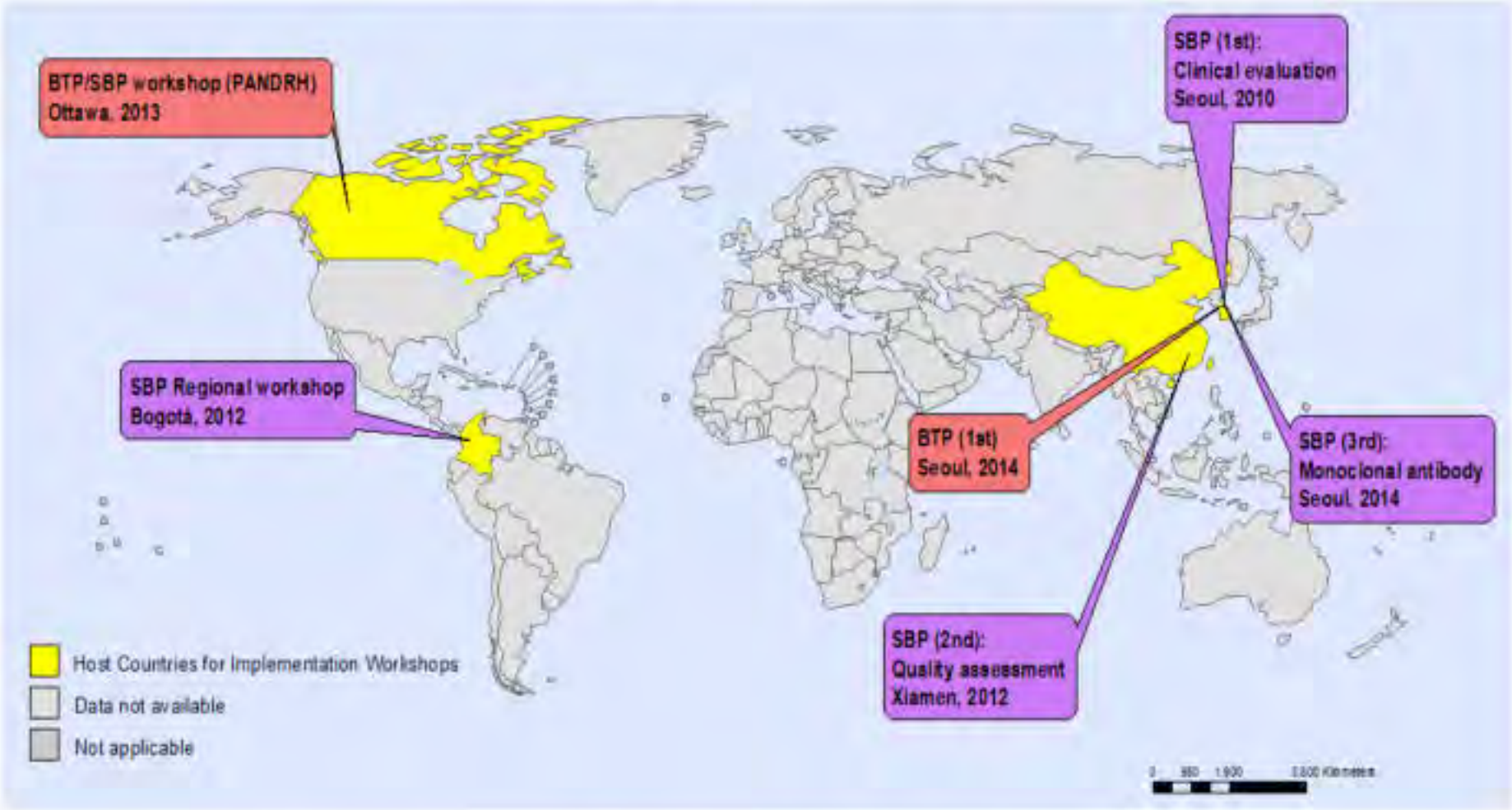
- extrapolation of indication;

- special considerations for evaluation of monoclonal antibodies;

- acceptance criteria and evaluation of reference biotherapeutic products (RBP) including the reliance on reference agencies;

- the design, conduct and interpretation of data for comparability exercise.

Implementation Workshop on BTP including SBP (2010-2014)



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization

World Health Organization

World Health Organization

Implementation workshops for BTP/ SBP Guidelines

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

Imp. workshop	1st SBP	2nd SBP	3rd SBP	1st BTP
When	Aug 2010	May 2012	May 2014	
Host Where	MFDS Korea	NIFDC China	MFDS Korea	
Participants	NRAs from 11 countries + Industry	NRAs from 16 countries + Industry	NRAs from 23 countries + Industry	
Main topic for case study practice	Clinical study design: Eq vs NI	Quality assessment	Efficacy study design on mAbs	Immunogenicity assessment of mAbs

- Announcement: 1) at WHO web; and 2) database for all training activities, http://www.who.int/medicines/training/emp_training_activities/en/

Outcomes of various consultations and implementation workshops

- **Agreed** Biosimilars **should not** be regulated under generic (chemical) drugs regulations – additional considerations essential
- **Agreed** Head to head comparability exercise of quality, safety and efficacy is essential for a product to be considered to be a biosimilar (SBP). However, once licensed, a biosimilar has its own life cycle.
- **If major differences found** in quality, nonclinical or clinical studies, a product should **not be** considered to be a Biosimilar. Other options for its further development and licensing need to be considered (eg a stand alone pathway)
- **Such products should not be called "similar"**

Outcomes of more recent implementation workshops

- Increasing alignment between jurisdictions: noted importance of WHO in furthering standardized global approach, a convergence, but many challenges
- Most biotherapeutics in developing countries licensed by a stand alone approach with reduced data package rather than strict comparability exercise
- Some countries have regulatory pathway for "non-innovative biotherapeutic products" but requirements generally unclear
- Comparability studies with RBP: concept not well understood and used
- Lack of expertise and capacity for evaluation of biotherapeutics at NRA

An important outcome of all implementation workshops

- Identification of some "copy" products licensed with insufficient or inappropriate data
- Some "copy" products already licensed as "biogenerics", a term which should not be used since it suggests a generic pathway
- Lack of harmonization of regulatory oversight of biotechnology products in general (not just biosimilars)
- Sometimes a range of different products on the market in one jurisdiction

Implementation workshops for BTP/SBP GLs: Case studies & Publications

When	Topic of simulated case study	Publication
1st WS for SBP 2010	Special lecture: **Statistical considerations** for confirmatory clinical trials for SBPs	*Biologicals* 39, 2011
	Comparing equivalence and non-inferiority approaches	
2nd WS for SBP 2012	The role of the **quality assessment** in the determination of overall biosimilarity	*Biologicals* 42, 2014
3rd WS for SBP 2014	**Efficacy study design and extrapolation**: Infliximab & Rituximab	*Biologicals* 43, 2015
1st WS for BTP 2014	Special lecture: **Immunogenicity assessment** of biotherapeutic products: An overview of assays and their utility	submitted to *Biologicals,* April 2015
	Assessment of unwanted immunogenicity of mAbs: TNF antagonist & CD20 mAbs	

Informal consultations on: 1) SBP; and 2) regulatory assessment 27-30 April 2015, Geneva, Switzerland

- **Participants: 57 from 26 countries**
  - Regulators: 29 from 19 countries representing 6 WHO regions
  - EMA representative
  - WHO consultants
  - Representatives of manufacturers' associations: IFPMA, IGPA, EGA, ALIFAR, DCVMN (China, Indonesia)
  - Individual manufacturers: Korea, Russia
  - WHO RO: EURO, PAHO
  - WHO HQ

Informal consultation on SBP, 27-28 April 2015 Summary & Outcomes (1)

1. **Current WHO SBPs guidelines**
   - No need to revise document
   - Review of WHO GL and GLs issued by EMA, Health Canada, US FDA etc showed that
     - Biosimilarity concept is clear
     - All guiding principles are still relevant and up to date

2. **Guidelines for SBPs mAbs**
   - No separate document BUT **addendum** to SBP GL
   - Comparability exercise should be explained through the examples that illustrate application of guiding principles. In particular:
     - analytical data interpretation,
     - clinical trial design and extrapolation of indications,
     - Criteria for selection of RBP
   - Some details to be developed as case studies for implementation workshops.

Informal consultation on SBP, 27-28 April 2015 Summary & Outcomes (2)

3. **Other issues to be addressed**
   - To (re) emphasize/ provide more details on:
     - Aim of biosimilarity exercise
     - Stepwise approach
     - RBP: understanding of selection and its impact
   - Product specific guidance: addendum on mAbs but maybe also on Insulin, G-CSF, EPOs etc
   - Post-approval changes
   - Evaluation of biosimilarity in terms of comparability study design
     - Quality
       - Analytical methodologies for evaluation of quality
       - Focus on Assessment and Interpretation of data
     - Nonclinical: Role of in vivo animal testing

Informal consultation on SBP, 27-28 April 2015 Summary & Outcomes (3)

- Clinical evaluation
  - Selection of sensitive population, endpoints
  - Design of clinical trials, statistical considerations, and interpretation
  - Extrapolation of indications

4. Q & A for BTPs including SBPs

- Points to be addressed with explanatory notes.
- Some specific examples including mAbs focussed on SBP development to help with understanding of principles, data interpretation, acceptance criteria etc

5. Best Practice

- Transparency in decision-making: availability of assessment reports
- Consider review process issues e.g. possibility to review additional data for same application
- Information sharing among NRAs, meetings, publications etc

Informal consultation on RA, 29-30 April 2015 Summary & Outcomes

- Value of document: Useful for
  - raising awareness of a need to complete data for some already approved products
  - Updating national requirements and guidance
  - Screening check-list for dialogue between regulator and manufacturer
  - Improving practices for evaluation of Q,S and E of biologicals throughout the product life-cycle in the interest of making efficacious and safe products available to patients.
- No separate document BUT **addendum** to BTP GL
- Title: changed: Regulatory ~~Risk~~ Assessment
- Scope: Clear objectives
  - To cover products not complying with current international standards and do not adhere with up-to-date standards
  - Primarily intended for rDNA derived BTPs but aspects are also relevant for other biologicals.

Regulatory assessment of approved BTPs: Development & key events in 2014 - 2015

- 1st round of public consultation, 11 Feb – 12 March 2014
- Discussion in 1st Implementation workshop for BTPs, May 2014
- Prepare 3rd draft, Q3 2014
- 2nd round of public consultation, 16 Dec 2014 – 30 Jan 2015
- An informal consultation, 29-30 April 2015
- Prepare 4th draft & editorial review, June 2015
- Submit to ECBS 2015, July 2015
- ***3rd round of public consultation, July – Sept 2015***
- ECBS review for adoption, 13 Oct 2015
- Implementation workshops planned from 2016

Development of training material(s) in collaboration with ICH International Pharmaceutical Regulators Forum – WG on Biosimilars

- Background: WHO has taken a part of IPRF Biosimilar working group to discuss and harmonize the issues and challenges in terms of regulation of biosimilars among IPRF member countries.

- Agreed collaboration: Develop training material(s)
  - Subject: Analytical comparability for biosimilar monoclonal antibodies (also requested by ICDRA 2014)
  - Drafting group: IPRF experts + WHO experts
  - Timeline
    - F2F meeting, 3 July 2015
    - 1st draft, by Oct 2015
    - Joint seminar WHO & IPRF, Nov 2015
    - Consultations, Q4 2015 – Q1 2016
    - Publish the material at IPRF & WHO web, 2Q 2016
    - Develop the material into e-learning tool, 4Q 2016

Key events in 2015

- WHO consultations in April 2015, in Geneva:
  - Review of SBP guidelines: to identify issues to be amended/ updated: 27-28 April
  - Regulatory Risk Assessment of BTP: 29-30 April
- Development of new and replacement of existing reference preparations (measurement standards)
- New concept of IS and reference preparations for BTP:
  - Survey: July 2015
  - Consultation: 21-22 September 2015, WHO, Geneva
- Regional workshops and support to several networks of regulators and manufacturers – from April to Dec 2015
  - Workshop in African region – 8-10 September 2015, Ghana
- Training materials, case studies, Q&A
- Other activities in response to the requests from WHO member states (pre-ICDRA and ICDRA) as stated in ICDRA recommendations

Thank you

Further information and contact

Biological standardization website: www.who.int/biologicals

Biotherapeutic Products

http://who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en/

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World Health Organization