WHO standards for regulatory evaluation of vaccines and biotherapeutic products – current status and way forward

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Outline

• World Health Organization
• World Health Assembly Resolution on BTP including SBP
• Standardization and regulatory evaluation of biologicals
• Selected topics: post-approval changes of vaccines and biotherapeutics
• Opportunities for regulatory convergence
• Collaboration with APEC, IPRF
• ICDRA
• Points for discussion
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.

More than 7000 people in 150 country offices, 6 regional offices and HQ

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.
The World Health Assembly (WHA)

- WHA is supreme decision-making body of WHO
- attended by delegations from all WHO Member States
- 2 important resolutions adopted by 67th WHA in May 2014:
  1. WHA67.21 Resolution on access to biotherapeutic products (BTP) including biosimilars (SBP)
  2. WHA67.20 Resolution on Regulatory System Strengthening
Key drivers of WHO policy for biologicals

The WHO biologicals standards portfolio extends to over 90 written standards and 400 reference preparations.

Current global public health priorities

• Responding to public health emergencies of international concern
• Access to biotherapeutic products
• Strengthening regulatory systems
First-ever & New Resolution on biotherapeutics: Urges

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

<table>
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<tr>
<th>Member States</th>
<th>WHO</th>
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<tbody>
<tr>
<td>To develop the necessary <strong>scientific expertise</strong> to facilitate development</td>
<td>To support MS in <strong>strengthening their capacity</strong> in the area of the</td>
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<td>of solid, scientifically-based regulatory frameworks</td>
<td>health regulation of BTPs, including SBPs</td>
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<td>To develop or strengthen, national regulatory assessment and authorization</td>
<td>To support the development of <strong>national regulatory frameworks</strong> that promote access to quality, safe, efficacious and affordable BTPs, including SBPs</td>
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<td>frameworks</td>
<td>To encourage and promote cooperation and exchange of information among MS in relation to BTPs/SBPs</td>
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<td>To work to ensure that the introduction of new national regulations, where</td>
<td>To convene the WHO ECBS to update the SBP GLs adopted in 2009</td>
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<td>appropriate, does not constitute a barrier to access to BTPs/SBPs</td>
<td>• taking into account the <strong>technological advances for the</strong></td>
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<td><strong>characterization of BTPs; and</strong></td>
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<td>• considering <strong>national regulatory needs and capacities</strong></td>
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WHO norms and standards for biologicals

Total 91 docs (Recommendations/ Guidelines)
General docs that apply to both vaccines & BTP: 9
General documents that apply to all vaccines: 12
Vaccine specific: 62
BTP specific: 8

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

www.who.int/biologicals
Concept of WHO Measurement Standards

• To define an internationally agreed unit to allow comparison of biological measurements worldwide.
• Established as primary standards and used to calibrate secondary standards, i.e. regional/national pharmacopoeial, and in-house working standards.
• Using well-characterized preparations as references:
  – fundamental to ensuring the quality of biologicals as well as the consistency of production;
  – essential for the establishment of appropriate clinical dosing.
• Reference materials/preparations required to standardize potency, purity, and identity measurements for complex biological materials.
• Made for use in laboratory assays only and should not be administered to humans.
• Distribution: through one of the WHO Collaborating Centers.
• NOTE: NOT reference product.
Development of measurement standards for biotherapeutics, 2013 - 2016

- **2013**
  1. TNF alpha, recombinant, non-glycosylated (3rd IS)
  2. PEG G-CSF (1st IS)

- **2014**
  1. Luteinizing Hormone, human pituitary (3rd IS)
  2. Human proinsulin (1st IS)

- **2015**
  1. Etanercept (1st IS)
  2. Human antibodies to EPO (1st monoclonal antibody reference panel)

- **2016**
  1. Batroxobin (1st RR)
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.
Written Standards for Evaluating BTPs


- **Addendum**: Regulatory assessment of approved BTPs, adopted by the ECBS 2015 (requested by ICDRA 2010)

- **NEW**: Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), adopted by the ECBS 2016

- 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.
## Implementation workshops for BTP/ SBP Guidelines

<table>
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<tr>
<th>Imp. workshop</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; SBP</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; SBP</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; SBP</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; BTP</th>
<th>SBP &amp; BTP in Africa Region</th>
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<tr>
<td><strong>Host Where</strong></td>
<td>MFDS Korea</td>
<td>NIFDC China</td>
<td>MFDS Korea</td>
<td>Ghana FDA Ghana</td>
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<td><strong>Participants</strong></td>
<td>NRAs from 11 countries + Industry</td>
<td>NRAs from 16 countries + Industry</td>
<td>NRAs from 23 countries + Industry</td>
<td>NRAs from 16 countries + Industry</td>
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<td><strong>Main topic for case study practice</strong></td>
<td>Clinical study design: Eq vs NI</td>
<td>Quality assessment of mAbs</td>
<td>Efficacy study design on mAbs</td>
<td>Immunogenicity assessment of mAbs</td>
<td>Quality assessment of EPO</td>
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## Implementation workshops for BTP/SBP GLs: Case studies & Publications

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<tr>
<th>When</th>
<th>Topic of simulated case study</th>
<th>Publication</th>
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<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; WS for SBP 2010</td>
<td>Special lecture: <strong>Statistical considerations</strong> for confirmatory clinical trials for SBPs Comparing equivalence and non-inferiority approaches</td>
<td><em>Biologicals</em> 39 (5), 2011</td>
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<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; WS for SBP 2012</td>
<td>The role of the <strong>quality assessment (of mAbs)</strong> in the determination of overall biosimilarity</td>
<td><em>Biologicals</em> 42 (2), 2014</td>
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<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; WS for SBP 2014</td>
<td><strong>Efficacy study design and extrapolation:</strong> Infliximab &amp; Rituximab</td>
<td><em>Biologicals</em> 43 (1), 2015</td>
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<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; WS for BTP 2014</td>
<td>Special lecture: <strong>Immunogenicity assessment</strong> of biotherapeutic products: An overview of assays and their utility Assessment of unwanted immunogenicity of mAbs: TNF antagonist &amp; CD20 mAbs</td>
<td><em>Biologicals</em> 43 (5), 2015</td>
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Manufacturing changes

• Changes to the vaccine manufacturing process or product labelling information often need to be implemented after a new vaccine has been approved
  – includes, but is not limited to, the product composition, manufacturing process, quality controls, equipment, facilities or product labelling information made to an approved MA or licence by the MA holder. Also referred to as “variation”

• NRA and MA holders should recognize that:
  – any change to a vaccine may impact upon the quality, safety and efficacy of that vaccine;
  – any change to the information associated with the vaccine (that is, product labelling information) may impact on the safe and effective use of that vaccine
General considerations

- Changes are categorized using **risk-based approach**
  - Approval prior to implementation
  - No approval prior to implementation, retain information for audit
  - Administrative changes
  - New application

- Conform to other applicable laws: GMP, GLP or GCP
- Encourage pre-submission dialogue between MA holder and NRA where needed (e.g. clarification on supporting data)
- For change not included in the Guidelines, the NRA should be consulted for proper classification
Categories of changes - 1

• Quality changes: Based on the potential effect of the quality change on the quality attributes of the vaccine, and the potential impact of this on the safety or efficacy of the vaccine, a change is categorized and identified as
  – A major quality change
  – A moderate quality change
  – A minor quality change
Categories of changes - 2

- Safety, efficacy and product labelling information changes
- After assessing the effect of a change related to clinical use or to product labelling information on the safe and effective use of a vaccine, MA holders should classify this change as belonging to one of the following categories:
  - a safety and efficacy change;
  - a product labelling information change;
  - an urgent product labelling information change; or
  - an administrative product labelling information change (in cases where prior approval before implementation is needed).
Special changes

Certain major changes, such as

- changes in the vaccine antigen composition (e.g., additional types),
- use of new cell substrates (e.g., use of cells unrelated to the established master cell bank (MCB) or pre-MCB material) or
- changes in the composition of vaccine adjuvants

are generally considered to be a new product and as such require the submission of a product licence.

- In some countries a change in the quantity of antigen per dose of vaccine also requires a new product licence application.

- Administrative changes related to acquisitions and mergers, company names or contact information should be submitted directly to the NRA as general correspondence to the MA or product licence.
Different regulatory pathways

- Full review
- Expedited procedures - NRA of procuring countries are encouraged to adopt
  - Recognition of decision of a competent NRA
  - Review decision of NRA of producing country or another competent NRA
  - Partial review and evaluation of supporting data

The responsibility of the final regulatory decision on the approval of the change still lies with the receiving NRA
Post-approval changes for BTP – timeline for development of WHO Guidelines

- Drafting/working group prepared preliminary draft: May 2016
- Circulate to the critical reviewers and relevant experts: by June 2016
- Identify issues to be raised in Aug meeting: by end July 2016
- Drafting/working group meeting: 30-31 Aug 2016, WHO HQ
- Prepare the 1st draft: by Sept 2016
- Post at WHO web (1st round of public consultation): 11 Oct – 16 Dec 2016
  http://www.who.int/biologicals/WHO_PAC_for_BTP_1st_DRAFT_HK_3_Oct_2016.pdf?ua=1
- Analyze comments and identify major issues: by March 2017
- Informal consultation to discuss comments and revise the draft: 27-28 April 2017, Korea
- Prepare the 2nd draft: by mid June 2017
- Submit to the ECBS & Post for the 2nd round of public consultation: July 2017
- ECBS review: Oct 2017
Special considerations for PAC for BTP

• Special considerations
  – Comparability exercise, e.g. need and extent
  – Bridging studies, e.g. manufacturing changes that should require nonclinical and/or clinical bridging studies
  – Similar biotherapeutic products: after approval, a SBP has its own life cycle.

• Reporting categories for quality changes
  – major quality change;
  – moderate quality change;
  – minor quality change; or
  – quality changes with no impact
Opportunities for regulatory convergence

- WHO standards as common tools for regulatory evaluation of biologicals - science based standards for science based regulation
- WHO role in regulatory convergence:
  - Terminology 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 - lectures and case studies, e-learning programmes
- A number of international and regional initiatives - an opportunity for regular update on WHO standards through regulatory, industry and Ph networks:
  - DCVRN, PANDRH, AVAREF, ASEAN, APEC Harm. Center, IPRF, CoRE
  - IFPMA, IGBA, Medicines for Europe, DCVMN, BIO, DIA
  - Pharmacopoeias, FIP
- Important to map out all initiatives and prioritize WHO activities
- Collaboration with Universities in the context of regulatory science
Collaborations with APEC

- **APEC Regulatory Harmonization Steering Committee (RHSC)**
  - Formed in June 2009
  - To serve unique role in promoting regulatory convergence
  - Determined the BTPs for area of focus for the APEC Training Centers of Excellence (CoE) for regulatory science

- Developed guidelines in cooperation with APEC RHSC
  - Title: Good review practices: guidelines for national and regional regulatory authorities
  - First set of guidelines of its kind globally and addresses an important gap identified at the ICDRA 2012
  - Developed through an inter-organizational collaboration.
  - The full text as adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2014.
  - Published: in WHO Drug Information 29 (1), 2015; and WHO TRS No. 992, Annex 9
BTPs CoE Pilot Training

• One of the activities of the APEC RHSC Biotechnological Products Roadmap: To Reach a High Level of Regulatory Convergence by 2020.

• 3 phase curriculum: Developed in collaboration with WHO
  – Phase 1 (on-line): Introduction to Biologics,
  – Phase 2 (on-site): Comparability throughout the life-cycle
  – Phase 3 (on-site): Clinical considerations for the biosimilar assessment

• Pilot trainings
  – 13 - 16 Sept 2016: Northeastern University, United States
  – 8 - 11 Nov 2016: Seoul National University, Republic of Korea

• Trainees
  – Regulators, e.g. from Chile, China, Indonesia, Malaysia, Mexico, Papua New Guinea, Peru, the Philippines, Russia, Thailand, and Viet Nam
Development of material(s) in collaboration with ICH IPRF

- WHO has been involved in the ICH International Pharmaceutical Regulators Forum (IPRF) Biosimilar Working Group with the aim to improve regulatory convergence.
- IPRF BWG (details will be provided by Dr Peter Richardson later)
- IPRF BWG - works with ICMRA (International Coalition of Medical Regulatory Authorities): 22 members, established in 2014
- WHO guidelines for similar biotherapeutic products: recognized by BWG as one of the main sources of guiding principles
- Main activities (WHO requested by ICDRA 2014):
  - “Common Public Assessment Information”
  - “Reflection paper on extrapolation of indications”
  - Develop training manual for “analytical comparability for biosimilar monoclonal antibodies”
**16th International Conference of Drug Regulatory Authorities (ICDRA)**

- Held every two years, have become a well established forum for regulatory authorities, WHO and interested stakeholders for regulation of medicines

- **16th ICDRA, Rio de Janeiro, Brazil**, 26-29 Aug 2014, attended by government officials and regulators from more than 100 WHO MS with pre-conference on “Ensuring Quality and Safety of Biosimilars for Patients Worldwide”, 24-25 Aug 2014

- Recommendations:
  1. Ensure regulatory oversight throughout the life cycle
  2. Improve efficiency of regulatory evaluation of BTPs
  3. Implementation of WHO GLs on BTPs/SBPs
  4. Collaboration between regulators and other relevant stakeholders
  5. Regulatory convergence as a tool to increase global access to SBPs

- Outcomes published in WHO Drug Information 28 (3), 2014
17th ICDRA in Nov 2016 in Cape Town

- Pre-ICDRA: 27 - 28 Nov 2016
- ICDRA: 29 Nov - 2 Dec 2016
- Selected topics:
  - Biosimilars, Good regulatory practices, Regulatory convergence initiatives, Regulators response to shortages of supplies, Regulators' role in addressing anti-microbial resistance, Regulatory challenges of medical products for maternal & child health
- Link for regular update: www.icdra.co.za
Points for discussion

• Access to biotherapeutics of assured quality, safety and efficacy at the affordable price is one of WHO goals:
  – What are the key elements for improving the access?
  – Are current standards too high?
• Building capacity and expertise was recognized as a critical element in promoting regulatory convergence as a way forward:
  – What should be done in terms of education and training of:
    • scientists, medical doctors, pharmacists and other experts involved in development, regulatory evaluation and use of biotherapeutic products including biosimilars?
    • What are the available tools?
    • What is missing?
Many thanks to

- My team (NSB/TSN/EMP/WHO)
- Members of WHO drafting and Working Groups
- Collaborating Centers
- Many individual experts
Thank you

Further information and contact

Biological standardization website:
www.who.int/biologicals

Contact details:
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