WHO regulatory standards for vaccines and biotherapeutics: challenges and opportunities

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Outlines of presentation

- Setting Norms and Standards in WHO context
- WHO Norms and Standards for biologicals
  - Written standards
  - Measurement standards
  - Regulatory science
  - Implementation
  - Way forward: Regulatory convergence
- Challenges and opportunities
Setting Norms and Standards in WHO context

- WHO is the directing and coordinating authority for health within the United Nations system on behalf of its 194 Member States (MS).

- **Setting norms & standards** and promoting & monitoring their implementation are affirmed as a core function of WHO for the 6-year period from 2014 to 2019.

- WHO is not a regulatory authority but mandated to provide supports to national regulatory authorities.

- 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
Setting Norms and Standards in WHO context

- Implement this mandate in at least 2 ways
  - WHO acts as a global standards setting body; or
  - WHO collaborates with other standards setting bodies that can be used globally.

- WHO works on
  - Development and establishment of norms and standards; and
  - Support their implementation into regional and national regulatory practices.

WHO N&S Define International regulation, policy, expectations Implement Assured Q, S, E of biologicals
WHO Regulatory standards for biologicals

- WHO has played a key role for over 50 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.

- These activities are to facilitate the exchange of the products between countries, and to ensure the availability of vaccines of appropriate quality for use in international immunization programmes.

- WHO accomplishes the 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 International Laboratory and WHO **Collaborating Centres** for Biological Standardization.
WHO Expert Committee on Biological Standardization

- Established in 1947, met before the 1st meeting of the World Health Assembly in 1948
- Indicating the urgency and importance of resuming international biological standardization activities after the disruption of the 2nd WW.
- Original responsibilities
  - Establishment of measurement standards, since 1946
  - Reviewing and approving sets of requirements for biological products, since the early 1960s.
- Expanded responsibilities and activities
  - Provide best scientific advice to the Organization
  - Evaluate and promote regulatory research involving new bioassays based on noble and highly sophisticated biotechnologies
  - Nomenclature of vaccines
- Meets once per year – next meeting 17-21 Oct 2016
Biologicals (vaccines and biotherapeutics) What are the issues?

Differ from Chemical Drugs in many ways:

- Biological starting materials
- Standardization of manufacturing process essential
- Highly complex products, e.g. large protein molecules: 200 to 1000 times the size of small molecule drugs
- Test methods needed to characterize batches of the product
- Clinical performance cannot be fully predicted from physicochemical characteristics alone
67th World Health Assembly

- 67th World Health Assembly, 19-24 May 2014

- First-ever & New Resolution on biotherapeutics (BTPs)
  - WHA 67.21
    - “Access to BTPs including similar biotherapeutic products (SBPs) and ensuring their Q, S, and E”
    - Sponsored by Australia and Colombia on behalf of the Union of South American Nations (UNASUR) countries.
    - Supported by Mozambique (on behalf of AFRO countries); Indonesia; Vietnam; Ethiopia; Tanzania; USA; Philippines; Colombia; Malaysia; South Africa; Brazil; China; Australia; Panama; Thailand; Papua New Guinea; India; Suriname.
    - Four NGOs (IABS, IFPMA, Doctors Without Borders (Médecins Sans Frontières (MSF)) and Medicus Mundi International – Network Health for All (MMI)) also spoke in support of the resolution.
WHO Norms and Standards for Biologicals

Current paradigm

Global written standards
A tool for harmonization of specifications worldwide

Global measurement standards
A tool for comparison of results worldwide

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

Their implementation
into country practices

Essential elements for development, licensing and lot/batch release
Concept of WHO Written Standards (1)

- Provide key principles related to the manufacturer, quality control and licensing of biologicals
- Safeguard recipients and populations against unacceptable risks of adverse events
- Take a global perspective, facilitating international alignment of licensure of biologicals
- Be used as the basis for licensing and on-going regulatory oversight and meet the original intention of facilitating the international exchange of biologicals
- Essential for clarity, consistency, predictability and transparency
- Contribute for countries to adopt international regulation
- Be a basis of review for WHO vaccine prequalification programme
Consider guidance issued by other bodies – intention to complement them, not to create a conflict.

The use of WHO written standards as a basis for national requirements also promotes regulatory convergence.

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

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

Assist with the implementation of the guidelines into regulatory and manufacturers practice;

**Recommendations**

- “requirements” were renamed to better reflect their nature
- For biologicals already gone through efficacy studies or already licensed

**Guidelines**

- Allow greater flexibility than “recommendations”
- For biologicals in early stage of development to give guidance for further development
Concept of WHO Measurement Standards (1)

- **WHO role**: To define an internationally agreed unit to allow comparison of biological measurements worldwide.

- **Reference materials** required to standardize potency, purity, and identity measurements for complex biological materials.

- **Biologicals** cannot be completely characterized by physico-chemical means alone so require use of some form of bioassay:
  - Bioassay: comparison of response of test substance with that of reference material.

- Using well-characterized preparations as references:
  - Fundamental to ensuring the quality of biological products as well as the consistency of production; and
  - Essential for the establishment of appropriate clinical dosing.
Concept of WHO Measurement Standards (2)

- WHO international reference materials provide global standard against which experimental values can be compared and expressed.
- Direct comparisons between products and measurements across different methodologies and assays in use around the world.
- Established as primary standards and used to calibrate secondary standards, i.e. regional or national pharmacopoeial standards, and in-house working standards.
- Defined the **International Unit (IU)** of biological activity.
- Made for use in laboratory assays only and should not be administered to humans.
- Distribution: through one of the WHO Collaborating Centers.
Lifecycle of Standards

1. Identify need/gap
2. Endorsement by ECBS
3. Development/Replacement/Establishment of standards
4. Adoption by ECBS
5. Implementation
6. Monitoring
A Global Regulatory Science Agenda for Vaccines

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- Laboratory-based regulatory science
  - correlates of immunity
  - correlates of safety
  - improved product characterization
  - improved potency assays

- Science to develop regulatory processes
  - innovative clinical trial designs;
  - tools to assist the benefit-risk decision-making process;
  - novel pharmacovigilance methodologies
Expected outcomes from a regulatory science agenda

- New regulatory tools are developed to improve access to products of assured quality
- Linkages are established with science and technology communities to nurture regulatory innovations
- Spread of regulatory science expertise and the benefits of regulatory science to the less-well-resourced countries
Implementation of standards: Potential Tools

- **Implementation workshop** on the guidelines has become an increasingly important tool in achieving regulatory convergence.
  - Organized by WHO HQ with the support of a national regulatory authority and Regional Office
  - Promote the WHO recommendations/guidelines in question
  - Share experience among countries
  - Obtain information from countries about their use of WHO documents and their ability to follow WHO guidance as well on interpreting difficult aspects of the guidance given in the documents
  - Practice some of evaluation principles through case studies

- **Publications** of meeting reports and case studies from implementation workshops

- **E-learning tools**: 1) Courses, modules, or webinars on selected topics; 2) Videos of key presentations; 3) Q&A on specific aspects; 4) Information sharing via WHO website
Impact in supporting world health
- Biological standardization plays a key role in facilitating the transfer of laboratory science into world-wide regulatory and clinical practice.
- It facilitates research and development as well as industrial exploration of scientific advances and global access to critical biologicals.

Portfolio in 2015
- Approximately 78 written standards
- Approximately 300 international Biological Reference Substances

Way forward
- Promoting regulatory and policy convergence to improve access to assured quality and affordable biologicals
Opportunities for regulatory convergence

- Convergence goes beyond the development of common standards and processes to take into account implementation by regulatory authorities
  - Aim; regulatory decisions across economies or countries become more aligned
  - does not require the harmonization of different countries’ laws and regulations
  - Same decisions are reached without a legally-binding obligation to do so
  - is becoming a more widely used term

*From: “Strategic directions in biological standardization”, Dr D. Wood in ECBS 2013*

- WHO standards as common tools for regulatory evaluation of biologicals – science based standards for science based regulation
Opportunities for regulatory convergence

- 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
    - Written & Measurement
- 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 and industry networks:
  - DCVRN, PANDRH, AVAREF, ASEAN, APEC Harmonization Center, IPRF,
  - IFPMA, IGPA, EGA, DCVMN, BIO, DIA
- Important to map out all initiatives and prioritize WHO activities
- Collaboration with Universities in the context of regulatory science
Challenges & Opportunities

- Complex multinational supply chains – convergence of standards will be critical.
- Support innovation to enable scientific advances in production and control of biologicals to be translated into quality and affordable products.
- Regulatory science requires increased levels of international collaboration.
- Expectations are growing to reduce regulatory and policy burden while expectations for more transparency is increasing.
- A new standard needs to fit into existing laws and regulatory frameworks.
- Regulators may need training on the new standard & Insufficient expertise and resources in MS.
- Industry may not be prepared to respond to it.
- **Stronger regulatory systems will be essential** to successful implementation of the guidelines and the convergence of regulatory assessments globally.
- Convergence of international norms and standards will be increasingly recognized as a key driver to address all these needs.
Further information and contact

Website: Standardization of Biologicals

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

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