Regulatory harmonization and alliances to foster vaccination

Developing Country Vaccine Manufacturers Network 14th AGM
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WHO/HIS/EMP/TSN
Outline

- Regulatory harmonization - or regulatory convergence?
  - Platforms to promote regulatory convergence
  - AVAREF

- Common standards for vaccines
  - Development of WHO written and measurement standards
  - Implementation of recently adopted WHO standards

- Alliances to promote vaccination
  - Network of WHO Collaborating Centers for standardization and evaluation of vaccines
  - Regulatory science agenda for vaccines
Harmonization or convergence?

- Regulatory harmonization initiatives
  - European Medicines Agency
  - ASEAN
  - APEC
  - East African Community
  - Many others

- Regulatory convergence
  - Current direction of thinking by regulators
    - Soon to be published US Institute of Medicine report
  - Same decisions are reached without a legally-binding obligation to do so
Platforms to promote regulatory convergence

- Leveraging decisions of others
  - Expedited review procedure for prequalified vaccines
    - See Nora Dellepiane's presentation at this meeting

- Joint reviews
  - Article 58 process of EMA
  - Clinical trial applications for multi-country CTs
    - AVAREF

- Common standards
  - WHO standardization processes
  - WHO prequalification
AVAREF-African Vaccine Regulatory Forum
An informal network approach to regulation of clinical trials in Africa

Representation: 19 countries target for CT of HIV, Malaria, TB, meningitis vaccines

Scope

Regulation of medicines
Regulation of vaccines
Regulation of clinical trials

National Regulatory Authority
Ethics Committees

Support from USFDA, Health Canada, European regulators
New vaccines in clinical development presented by sponsors/Vaccine developers
Recognized and supported by donors as an efficient platform

Informal structure allows rapid and dynamic response as per needs identified
Currently working on formalization process
WHO norms and standards for biologicals

Global written standards

Global measurement standards

Regulatory science agenda

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

www.who.int/biologicals
WHO Written Standards for Vaccines

- Technical specifications that help define safe and efficacious vaccines
- Intended to be scientific and advisory in nature
- Starting point for setting national requirements as well as a basis for vaccine prequalification
- Guidance for NRAs and manufacturers on international regulatory expectations for the production and quality assurance of vaccines, stability, non-clinical and clinical evaluation of vaccines
- Facilitating international convergence of vaccine licensure
- Living documents revised in response to scientific advances

Evolving concept: from quality specifications to scientific principles for the entire regulatory oversight
Development of written standards
ECBS 2010 - 2014

- Cell substrates
  - YFV
  - Hep B
  - Vaccine lot release

- OPV (TRS 904, 910)
  - D, T (TRS 800) + Combo
  - Malaria (new)
  - JE LA

- IPV (TRS 926)
  - Manufacturing Changes
  - Regulatory Risk Assessment

- Dengue (TRS 932)
- BCG (TRS 745, 771)
- aP (TRS 878)

- Nonclinical evaluation of adjuvanted vaccines (new)
  - Biologicals derived by rDNA tech (TRS 814)
  - Typhoid conjugate vaccines (new)
New reference preparations from WHO

International Standards adopted by ECBS 2012

- Anti HPV -18 serum - 1st International Standard
- Diphtheria antitoxin, Human- 1st International Standard
- Antibody to influenza H1N1 pdm virus - 2nd International Standard
- BCG Moreau - Reference Reagent
- Endotoxin- 3rd International Standard

Proposed new International Standards for consideration by ECBS 2013

- Trivalent inactivated polio vaccine (TIPV) for D antigen assay

Proposed new projects for consideration by ECBS 2013

- Replacement standards for: Diphtheria toxoid for flocculation assay; High and Low Mutant Reference Virus for MAPREC assay of poliovirus type 2

New standards for Typhoid Vi polysaccharide; Meningococcal Serogroup A polysaccharide
Selected topics for implementation workshops

1. Stability evaluation of vaccines
2. Standardization of biotherapeutic products
3. Vaccine lot release
4. Combined vaccines based on DTP
5. Regulatory Risk Assessment
Implementation of selected written standards - 2008-2012

Implementation workshop on Rotavirus Vaccine Potency Testing Potters Bar, March 2007
4th Implementation workshop on Vaccine Lot Release Riga, Dec 2011
2nd Implementation workshop on Vaccine Lot Release Beijing, Dec 2009
1st Implementation workshop on SBPs, Seoul, Aug 2010
1st Implementation workshop on Vaccine Stability Seoul, April 2008
2nd Implementation workshop on SBPs, Xi’an, May 2012
3rd Implementation workshop on Vaccine Lot Release, Jordan, Nov 2010
1st Implementation workshop on Vaccine Lot Release Tunis, Oct 2008
Implementation workshop on SBPs in AM Region Bogotá, March 2012
Implementation workshop on Rotavirus Vaccine Potency Assays, Caracas, June 2006

Host Countries for Implementation Workshops
Data not available
Not applicable

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

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Stability evaluation of vaccines: WHO Guidelines

  

- Implementation workshops:
  - WHO/ IABS workshop - Oct 2008
  - Regional workshops
    - Hosted and co-organized by Korea FDA - April 08
    - Bi-regional workshop: Bangkok, 30 Jan - 1 Feb 2013

- Concept of regional implementation
  - NRAs and NCLs involved as well as manufacturers (DCVMN, IFPMA)
  - Case studies focused on the need in the region in question
  - Opportunity for further developments in specific areas
Constraints at NRAs in SEA & WP in Implementing Stability Guidelines

- Limited human resources dedicated to evaluating vaccine stability, there for lack of experts with comprehensive understanding and knowledge of stability issues
- Limited experiences in reviewing stability report based on statistical modeling
- Limited access to statistical experts (in-house or academic) who are knowledgeable to study design & analysis of vaccine stability
- Others
  - Lacking appropriate analytical assay methods
  - Complex decision making process
  - Rigidity in changing legislation
Emerging Issues Relating to Vaccine Stability Guidelines

- Regulatory consideration for evaluation of vaccines for use in a Controlled Temperature Chain (stand-alone or annexed to VacStabGLs?)
  - Definition of terms to be introduced: e.g. CTC, temperature cycling, stability budget, peak temperature indicator, VVMs
  - Algorithm to help assess the need for clinical trials
  - Standardized labeling

- Standardized format (or protocol) for stability report in filing Label Variations for shelf-life, lot release specifications, CTC studies, and others (can be annexed to VacStabGLs)
  - A Report Format is available in ASEAN guidelines for Drug Product
Scientific principles for evaluating risk in the case of an adventitious agent found in an already licensed vaccine

Case studies in preparation (PCV in rotavirus vaccine, RT in MMR, SV40 in polio vaccines, bacteriophage in live viral vaccines)
  - Narrative part
  - Table with step by step review of the evidence

Informal consultation with regulators, manufacturers and other experts: 30-31 May 2013, Lijiang, China

Review of examples for publication and/or Guidelines
Implementation workshops and next steps

- Opportunity to discuss all issues in a forum of regulators, manufacturers and other experts

- Outcomes:
  - Current: Meeting report with the summary of the lectures, case studies and the outcomes of the discussion
  - Future: E-learning tools to assist with the implementation of guiding principles into regulatory and manufacturers’ practice

- Technical support to NRAs and NCLs - identify areas where assistance is needed

- Challenges:
  - Timely nomination of the suitable participants (ie representatives of NRAs/NCs)
  - Funds
  - Organizational and technical support by the host institution
Network of CCs: 2013-2014

- Increasing demand for technical assistance from Member States
- Better coordination of WHO technical assistance
- Growing complexity of reviewing scientific evidence for regulatory purpose, especially for novel vaccines

Plan for additional CCs in 2013-2014:
- Division of Virology, Paul Erhlich Institute, Germany
- Thai NCL
- Indonesian NRA

- Link between CCs network and various expert groups, regional regulatory networks and other relevant bodies/associations
Regulatory science

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

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Examples of how regulatory science has contributed to improved access to vaccines

- MAPREC and transgenic mouse tests for evaluation of OPV
- Development and use of alternative potency evaluations for pandemic H1N1 vaccines
- Defining international consensus values for serological correlates of immunity for pneumococcal conjugate vaccines
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
Further information and contact

Biological standardization website:  
[www.who.int/biologicals](http://www.who.int/biologicals)

Immunization website:  [www.who.int/immunization](http://www.who.int/immunization)

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