Report to SAGE 2014

WHO Expert Committee on Biological Standardization

Geneva

October 13 – 17th , 2014

WHO ECBS

- Biotherapeutics
- Blood and blood products
- *In vitro* diagnostics
- **Vaccines and immunization related issues**

Vaccines

- The availability of vaccines of **consistent** safety and efficacy , and of assured quality, is key to the success of any immunization program
- **The work of the WHO and the ECBS in developing global norms and standards and in promoting their implementation underpins this need**
- ECBS body responsible for establishing International Standards and adopting global norms for biologicals

WHO Written Standards- Recommendations / Guidelines

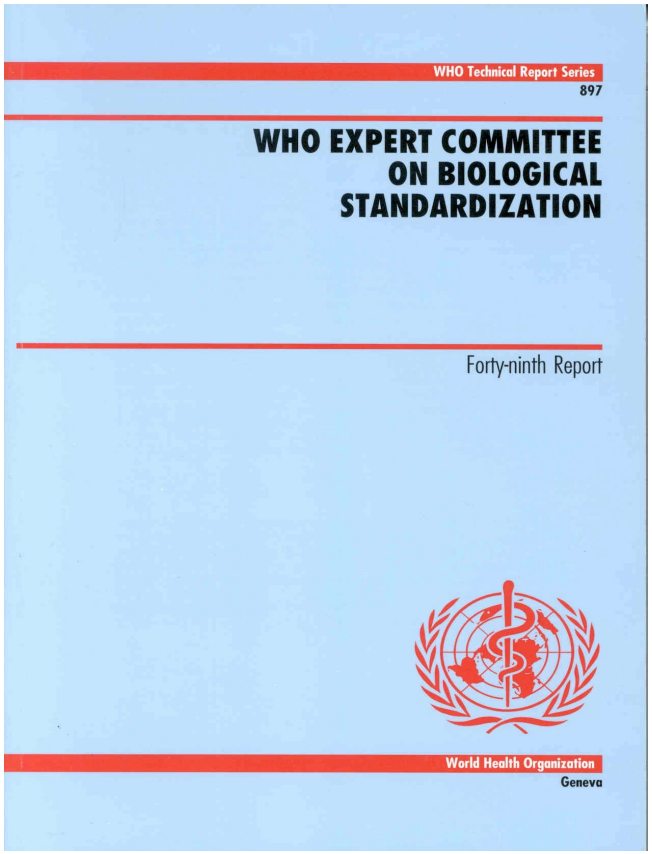
- Guidance for NRAs and manufacturers on international regulatory expectations for quality, non-clinical and clinical aspects
- **Take a global perspective** : Promote regulatory convergence/ accelerate licensing
- Based on scientific consensus and considerable global consultation – NRAs, manufacturers, other standard setting bodies, WHO Collaborating Centres
- **WHO Prequalified vaccines must meet WHO specifications**

WHO Biological Measurement Standards (Physical standards)

- Used for calibrating national , regional or manufacturers reference materials
- **Form basis of quality control, regulation, research and clinical dosing of biological medicines globally (also filling of vials)**
- Support the reliability of *in vitro* diagnostics
- Their development involves collaborative studies in numerous laboratories world wide

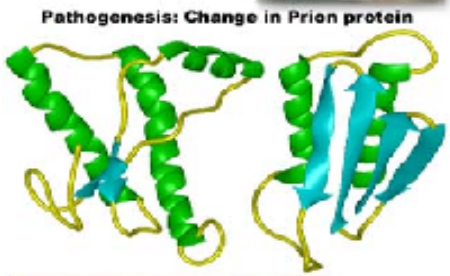
Biological standards – WHO products

Global written standards



Global measurement standards

Standards evidence base



ECBS 2014: Key outcomes relevant to immunization

- Ebola Issues
- 3 Written Standards Adopted
- Physical Standards Established and work on development of New International Standards Relevant to Immunization agreed

Ebola Issues

- ECBS recognized the urgent need for interventions , including vaccines
- Noted that the two candidate vaccines were currently under clinical evaluation
- Recognized that **regulatory preparedness is critical** for rapid access to licensed vaccines (with less than usual data package – lessons learnt from pandemic influenza vaccine)
- Recommended an ECBS sub group to assist WHO on regulatory issues
- Need for additional physical standards

ECBS 2014: Three Written Standards Adopted

- Recommendations to Assure the Quality Safety and Efficacy of Inactivated Polio Vaccine **(Revised)**
- Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines **(New)**
- Guidance on Scientific Principles for Regulatory Risk Evaluation on finding an Adventitious Agent in a Marketed Vaccine **(New)**

Recommendations to Assure the Quality, Safety and Efficacy of Inactivated Poliomyelitis vaccine

- Last revised in 2000 with addendum 2003
- Revision needed in light of advances in scientific knowledge, vaccine production and QC technologies, including use of Sabin Strains and the use of IPV in the Polio Endgame Strategic Plan 2013 -2018.
- Revised document developed following considerable global consultations with experts from academia, industry, NRAs / NCLs, Polio programme staff

Revised IPV Recommendations

- Scope includes IPV derived from wild type strains, attenuated Sabin strains used to produce OPV, and attenuated strains derived by rDNA technology (under development)
- New sections on non-clinical and clinical evaluation: Appendix – history of all virus seeds for IPV production.
- Updated in line with the revision of other WHO documents published since last revision
- Addendum 2003 (deals with production of wIPV) may need slight revision following finalization of GAP III requirements

Key issues addressed during revision of IPV document

- Characterization of Sabin IPV seeds and monovalent pools prior to inactivation to justify appropriate containment in the light of GAP III
- Regulatory approval based on comparative assessment of safety and immunogenicity.
- Human immunogenicity studies of new sIPV using a licensed IPV as comparator. Where such an IPV not available, OPV may be acceptable to NRA - only in regions where high sero conversion well established

Guidelines on Procedures and Data Requirements for Changes to Approved Vaccines (New)

- Refer to changes made after a vaccine has been approved (licensed) (variations)
- Changes in product composition, manufacturing process, quality control, equipment , facilities or labelling are very common in the life of a product.
- Important to recognize that such changes may impact the quality, safety or efficacy of a vaccine.

Guidelines on how to deal with Changes to an Approved Vaccine

- Requested by regulators from WHO Member States
- Facing difficulties due to

  - different approaches to similar changes in different NRAs,

  -different data requirements to demonstrate comparability of product after change

Guidelines on how to deal with Changes to an Approved Vaccine

- Document intended to serve as a guide for establishing national requirements for regulating post approval changes
- Categories of changes (major, moderate, minor) and reporting procedures are provided in the main body of the text and detailed data requirements to support proposed changes provided in appendices

Guidance on Scientific Principles for Regulatory Risk Evaluation on finding an Adventitious Agent in a Marketed Vaccine (New)

- Discovery of porcine circovirus sequences and infectious circovirus in rotavirus vaccines in 2010 renewed concern for finding an adventitious agent in a marketed vaccine
- An issue discussed by SAGE 2010
- New detection technologies are powerful tools

Background

- A broad framework exists with regard to adventitious agents and viral safety pre-licensure
- Aspects associated with discoveries post licensure are less well covered in the sense of regulatory actions and decision making
- ICDRA (2010) recommended WHO assist countries in developing regulatory risk management strategies in response to the detection of an adventitious agent in licensed vaccine.

Purpose of the Document

- To provide guidance to regulators on the **principles of regulatory risk evaluation** when a signal for a potential adventitious agent is detected in an already licensed vaccine
- Covers: how was the signal detected: what is already known about the product: where was the signal detected: what exactly was detected; new benefit – risk assessment
- Recognises may be a need for immediate action before answers to Qs available

The Risk Evaluation Guidance Document

- Underwent considerable international consultation
- Supported by a paper published in 2014 that reviews 4 case studies to illustrate how such situations were addressed and what lessons were learnt.
- SV40 (1960), bacteriophages in live viral vaccines (1973), reverse transcriptase in measles and mumps vaccines (1995), PCV in rotavirus vaccines (2010)
- Petricciani et al, Biologicals 42,(5) 223- 236

The Risk Evaluation Guidance Document

- Recognises benefit-risk assessment depends not only on science but also regional and other considerations (epidemiology and availability of alternative vaccines)
- Considers **close cooperation** between regulatory and public health officials **crucial**
- Emphasises the importance of communications and transparency-understanding the basis of decisions made
- Emphasises the importance of WHO in global co-ordination of responses

ECBS 2014: Physical Standards established

- 1st International Reference Reagent of anti-malaria (*Plasmodium falciparum*) human serum
- 2nd International Standard for *H influenza b* polyribosyl phosphate polysaccharide
- **Continuation of work** on 1st International Standard for human anti-Vi serum . Work to date shows considerable variability in ELISA assay results possibly due to quality of the Vi antigen and presence of anti LPS antibodies in candidate serum.

Proposed new standards relevant to immunization agreed

- 1st International Standard for Pertussis Toxin (replacement for JNIH5 - running out)
- 3rd International Standard for Tetanus Toxoid for flocculation assay
- 1st International Standard for Meningococcal serogroup X polysaccharide
- 1st International Standard for antibody to A (H7N9) Influenza virus
- 7th International Standard for Rabies Vaccine
- MERS corona virus serum panel (diagnostic)

Written Standards under development

2015

- GMP for biologicals
- HPV
- Regulatory expectations for vaccines in Controlled Temperature Chain (CTC)

2016

- Guidelines on clinical evaluation of vaccines (update)
- Guidelines on influenza vaccines for non-producing countries

Thank you for your attention