Report to SAGE 2015

WHO Expert Committee on Biological Standardization

Geneva

October 12 -16th , 2015

What is a WHO Expert Committee?

- Official Advisory Body to Director-General of WHO
- Established by World Health Assembly or Executive Board
- EC Reports presented to Executive Board
- Participation in Expert Committee meetings:

  - **Members** ("Experts") selected from WHO Expert Advisory Panels (2015:14)
  - **Technical advisers** and participants
  - **Observers**: - *international organizations*,
    - *NGOs*,
    - *professional associations*

WHO Expert Committee on Biological Standardization

- Established 1947. Previously under League of Nations – since 1920s
- Work of the ECBS enables WHO to fulfil its constitutional mandate in this area
- Biotherapeutics
- Blood and blood products
- *In vitro* diagnostics
- **Vaccines and immunization related issues**

Vaccines

- ECBS responsible for formally establishing International Standards and adopting global norms for vaccines / biologicals
- **Written Standards** – Guidelines and Recommendations (global perspective)
- **Physical Standards** – used to calibrate national , regional and manufacturers reference materials – used in research, quality control and regulation
- Based on scientific consensus and extensive global consultation – NRAs, NCLs, manufacturers, other standard setting bodies, WHO Collaborating Centres

WHO Guidelines and Recommendations

- WHO **"Guidelines"** allow greater flexibility than **"Recommendations"** but both deal with manufacturing, non-clinical and clinical aspects.
- Usually, product **Guidelines** appear before products are licensed after which firmer **Recommendations** are developed (eg acellular pertussis, malaria, dengue , HPV, conjugate typhoid vaccines)
- WHO Prequalified **vaccines** must meet WHO specifications

ECBS 2015: Key outcomes relevant to immunization

- 3 Written Standards Adopted
- New guidelines under development
- Physical Standards Established and work on development of New International Standards Relevant to Immunization
- Ebola Issues
- Evaluation of new technologies

ECBS 2015: Three Written Standards Adopted

- WHO Guidelines on Good Manufacturing Practices (GMP) for Biological Products **(Revised)**
- WHO Guidelines on Stability Evaluation of Vaccines for use under Extended Controlled Temperature Conditions **(New)**
- WHO Recommendations to assure the Quality, Safety and Efficacy of Recombinant Human Papilloma Virus-like Particle Vaccines **(Revised / New)**

WHO Guidelines on Good Manufacturing Practices (GMPs) for Biological Products

- Complementary to and forms an annex of GMP for Pharmaceuticals (Main Principles).
- Major revision of 1991 version
- Revision reflects the developments in science and technologies for the manufacture and control of biologicals / vaccines
- Emphasizes the inherent variability of biologicals and their production, including the risks in manipulating pathogenic organisms

WHO Guidelines on GMP for Biologicals

- Biocontainment now included recognizing different biosafety risk groups
- Mentions containment requirements for products like polio vaccines , referring to specific WHO Guidelines
- Makes clear containment procedures (cover safety of operator and environment) should not conflict with those for the product

WHO Guidelines on Stability Evaluation of Vaccines under Extended Controlled Temperature Conditions (ECTC)

- Term ECTC developed to distinguish **Regulatory requirements** from Programmatic requirements (Controlled Temperature Chain (CTC)
- ECTC is independent of specific programmatic needs, such current WHO CTC programme (single exposure for three days at 40 C) . Offers greater flexibility
- Developed with wide consultation

WHO Guidelines on ECTC

- Describe stability evaluation of a specific vaccine when exposed to a single short term temperature change immediately prior to administration
- Vaccines licensed for use under ECTC will have sufficient information regarding the approval conditions (max temperature and time) on the package insert.
- Will require formal procedures for monitoring (eg peak threshold indicator) / time
- Regulatory approval of ECTC avoids off-label vaccine use - consistent with best practice

Recommendations on the quality, safety and efficacy of recombinant HPV virus-like particle vaccines

- Replacement of 2006 **Guidelines.** Now firmer **Recommendations**
- Development due to considerable experience of vaccine use, development of HPV vaccines with extended valency, likely entry of new manufacturers into the market.
- Scope still restricted to L1 capsid proteins
- Now includes bacteria as cell substrates

WHO Recommendations for HPV Vaccines

- Considerable experience accumulated of HPV L1 VLP type 16 and 18 vaccines
- Led to important changes to future clinical trial design and endpoint recommendations
- Difficulties in using histological endpoints to establish efficacy for new 16/18 vaccines due to impact of HPV vaccines / lower prevalence of other oncogenic HPV types
- Recommendation to use immunological and viral persistence data as endpoints in support potential efficacy. Non inferiority with comparator

Written Standards under development

- Guidelines on clinical evaluation of vaccines (update of 2001) (2016)
- Guidelines on influenza vaccines for non-producing countries (2016)
- Maternal immunization - Guidelines on labelling influenza vaccines for use in pregnant women (2016)
- **Ebola vaccines (2016)**
- Guidelines on safe production and quality control of inactivated polio vaccines (2017)

Guidelines on the quality, safety and efficacy of Ebola vaccines

- Under development but considerable work already done
- Lots of challenges: rapidly moving situation
- How to provide guidance in the event of vaccine need during public health emergency
- Scope – focused on viral vectored vaccines since no WHO guidance on this type of vaccine available; also most advanced candidates. For other types of products reference made to existing WHO guidelines eg for rDNA antigens

Guidelines on the quality, safety and efficacy of Ebola vaccines

- Draft follows traditional style , quality , non clinical and clinical aspects.
- Where development may be accelerated during a public health emergency, context specific examples given in small print.
- Need to update text in light of expected new data.
- Separate document under consideration dealing with regulatory pathways for making unapproved vaccines available in a public health emergency.

ECBS 2015: Physical Standards established

- 3rd International Standard for Diphtheria Toxoid for Flocculation Test
- 1st International Standards for Meningococcal serogroup A and X polysaccharides
- 1st International Reference Reagent for Ebola antibodies
- 1st International Reference Reagent for Ebola NAT (Ebola virus RNA)
- **New Work agreed –** IS for meningococcal serogroup W and Y polysaccharides : antibodies (human) to *Clostridium difficile*

ECBS 2015: Physical Standards established

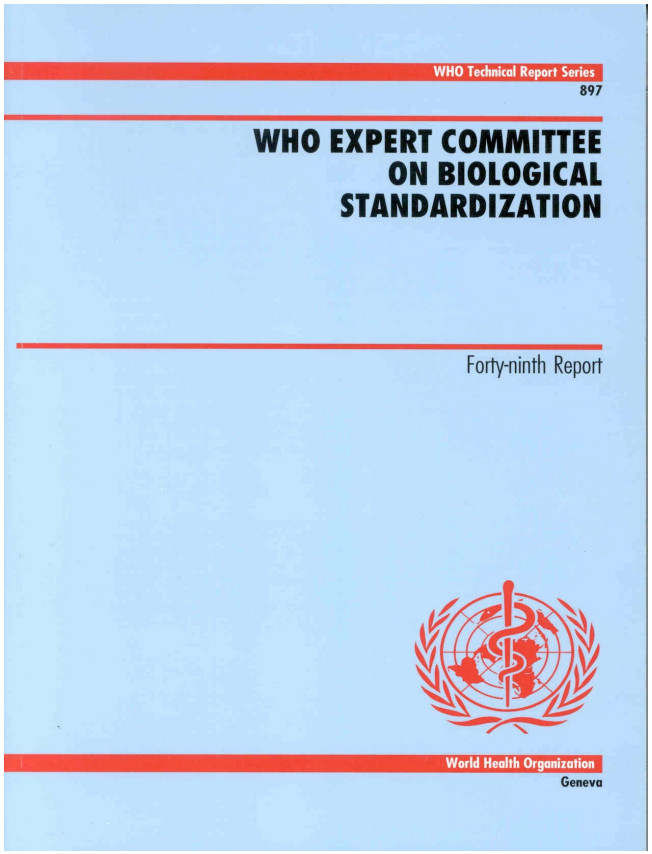
- 1st International Standard for anti-EV71 antibodies.
- Quantification of anti-EV71 neutralizing antibodies in human sera important marker for evaluation of immunogenicity of EV71 vaccines under development. May lead to international use of EV71 vaccines licensed in China
- Result of close collaborative work between NIBSC (UK) and NIFDC (China)

New Technologies

- ECBS considered evaluation of massively parallel (deep) sequencing as tool for assessing genetic consistency of polio strains used in vaccine production
- Collaborative study showed promising data – maybe will lead to replacement of the MAPREC test
- Whole genome sequence analysis will also be considered in the future
- Candidate control material (reference panel) for detection of adventitious viruses by deep sequencing also now available as interim reference from NIBSC

Biological standards – WHO products

Global written standards



Global measurement standards

Standards evidence base