Report to SAGE
November 2013

WHO Expert Committee on Biological Standardization

Geneva

October 21 – 25, 2013

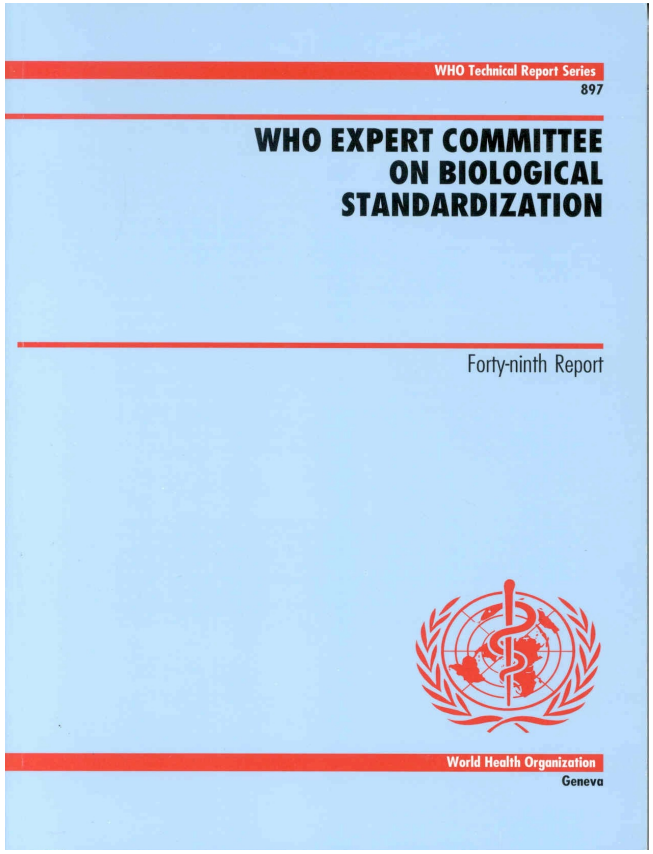
E. Griffiths, Chair ECBS

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

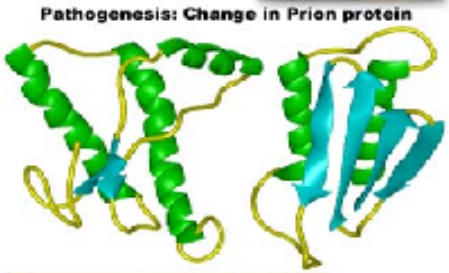
Biological standards – WHO products

Global written standards



Global measurement standards

Standards evidence base



WHO Biological Measurement Standards (Physical standards)

- Used for calibrating national , regional or manufacturers reference materials
- Mostly in International Units (IUs)
- **Form basis of quality control, regulation 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

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**

ECBS 2013: Key outcomes relevant to immunization

Written Standards adopted

- Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines **(New)**
- Guidelines on the Quality, Safety and Efficacy of Typhoid Conjugate Vaccines **(New)**
- Guidelines on Quality, Safety and Efficacy of Biotherapeutic Protein Products Prepared by rDNA Technology (Quality section applies also to vaccines) **(Replacement)**

Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines

- The number of novel adjuvants being evaluated in clinical trials has increased considerably – some already licensed
- Development and evaluation of adjuvants and adjuvanted vaccines presents regulatory challenges
- **Non-clinical evaluation** crucial for proceeding to clinical trials

Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines

- Vaccine manufacturers and regulators ask about type and extent of information required to proceed to clinical studies with novel adjuvants
- Existing WHO Guidelines on Non-clinical Evaluation of Vaccines (2005) provide valuable general guidance but only limited information on new adjuvants
- Internationally harmonized guidance was requested to facilitate development and licensure of adjuvanted vaccines

Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines

- Focus on vaccines **against infectious diseases**; therapeutic vaccines eg against cancer, excluded since different benefit /risk
- Testing of adjuvant alone is not mandatory but recommended
- Provide guidance on points to consider when transitioning from non-clinical to clinical testing (first in human studies)
- Acknowledge limitations of animal studies to predict human responses (local/systemic)

Guidelines on the Quality, Safety and Efficacy of Typhoid Conjugate Vaccines

- Address evaluation of typhoid vaccines based on Vi polysaccharide covalently linked to a carrier protein
- Based on experience gained with other conjugate vaccines - Hib, meningococcal and pneumococcal
- Also from experience with existing typhoid vaccines which have been available for many years but have a number of limitations
- No special safety issues to be addressed
- NRA expectations likely to change once Vi conjugate is approved in a country/region

Expected advantages of conjugated typhoid vaccines

- **From 2 years up**
  - Systemic T-cell-dependent immune response to Vi
  - Boostable, avoid hypo-responsiveness
  - Better and longer-lasting protection than oral or plain Vi
  - Should boost Vi-primed (natural or plain Vi vaccine)
- **Less than 2 years**
  - Plain Vi is not immunogenic; oral not approved (min 6 years)
  - T-cell-dependent response to conjugated polysaccharide

Typhoid conjugate vaccines- Expected Clinical Evaluation

- **Protective efficacy** study in subjects aged > 2 years **not necessary**. Anti-Vi IgG antibody associated with protection, but no standard assay and threshold levels are uncertain .
- **Aged > 2 years clear** : safety and immunogenicity vs plain Vi
- **Aged < 2 years less clear** : case by case, efficacy and safety or immunogenicity and safety with post approval effectiveness studies
- Human challenge studies (have been/are being done)

ECBS 2013: Physical Standards established / proposed new standards relevant to immunization

- Trivalent inactivated polio vaccine (TIPV) for D antigen assay – *3rd International Standard*
- **Proposed new work** : Typhoid Vi polysaccharide serum, human, *WHO 1st International Standard.* Noted the extension of the collaborative study to include NIH Standard (Vi IgG9R1) serum already used in evaluation of clinical materials
- **Proposed new work** :Typhoid Vi polysaccharide *WHO 1st International Standard*

ECBS 2013: Physical Standards established /proposed new standards relevant to immunization

- **Proposed new work** - Diphtheria toxoid for flocculation assay, *WHO 3rd International Standard*
- **Proposed new work-** Meningococcal serogroup A polysaccharide , *WHO 1st International Standard*
- **Proposed new work -** High and low mutant reference virus for MAPREC assay for poliovirus type 2 , *WHO 2nd International Standard*
- **Proposed new work -** Respiratory syncytial virus serum, human , *WHO 1st International Standard*

Proposed new /updated Recommendations or Guidelines

- **2014** – IPV (contingent on completion and approval of GAPIII for bio-containment aspects) :

  Regulatory evaluation of post-approval changes;

  Regulatory Risk Assessment in case of Adventitious Agents discovered in already licensed vaccines

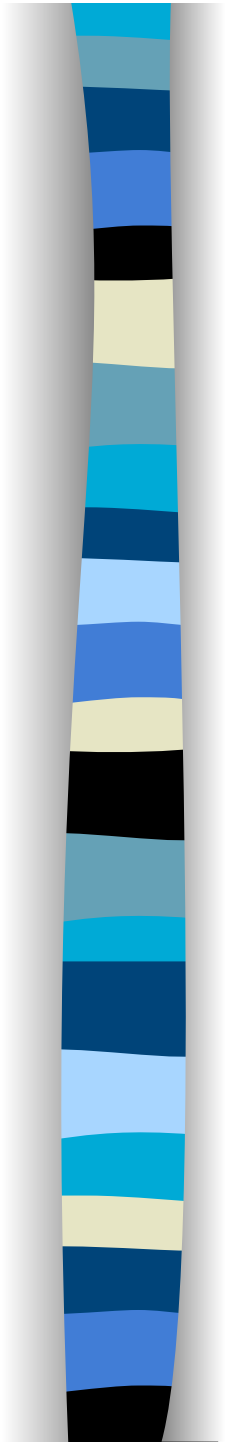
- **2015** – HPV, GMP for biologicals and Regulatory expectations for CTC,

Other ECBS business - Developments re Controlled Temperature Chain (CTC)

- Progress made in developing regulatory framework for the stability evaluation of vaccines under a CTC
- Taking advantage of the true heat stability of vaccines can we move from practice of “off-label “ CTC use to regulatory approved evidence based **ON-LABEL** use?
- Two consultations (Ottawa Dec 2012 and Langen 2013) have set scene for moving forward.
- Agreed it can be done for certain vaccines and need for WHO guidance on stability evaluation in CTC
- Clear labelling was critical
- Time lines agreed – guideline development and consultation 2014: consultation and to ECBS 2015

Other ECBS Business

- Noted that **implementation workshops** , which include case studies , particularly helpful in translating WHO guidance into practice. ECBS recommended such activities should be expanded and given a high priority
- Recent implementation workshops – on stability evaluation of vaccines: evaluation of cell substrates
- ECBS agreed to consider proposals to revise existing **labelling requirements** for vaccines. Currently under development: ECBS 2015



Thank you for your attention