Report to SAGE
November 2013

WHO Expert Committee on Biological Standardization
Geneva
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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

Pathogenesis: Change in Prion protein

WHO Expert Committee on Biological Standardization

Forty-ninth Report

World Health Organization
Geneva
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 worldwide
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 e.g. 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