Quality, safety and standards for poliomyelitis vaccines

7th WHO/UNICEF consultation
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Expert Committee on Biological Standardization

- The ECBS is commissioned by WHO to establish detailed recommendations and guidelines for the manufacturing, licensing, and control of blood products, cell regulators, vaccines and related in vitro diagnostic tests.

- Members of the ECBS are scientists from national control agencies, academia, research institutes, public health bodies and the pharmaceutical industry acting as individual experts and not as representatives of their respective organizations or employers. The decisions and recommendations of the Committee are based entirely on scientific principles and considerations of public health.

- The ECBS meets on an annual basis since 1947 and is responsible for the establishment of the WHO International Biological Reference Preparations and for the adoption of the WHO Recommendations and Guidelines. The Expert Committee directly reports to the Executive Board, which is the executive arm of the World Health Assembly.
WHO recommendations intended to be scientific and advisory

Guidance for national control authority and manufacturers of biological products

Recommendations adopted as definitive national requirements or amended, provided that changes ensure that the vaccine is at least as safe and efficacious as that prepared in accordance with the WHO recommendations

http://www.who.int/biologicals/expert_committee
Oral Poliomyelitis Vaccine (OPV)
OPV WHO TRS

- TRS 904, 2002 Annex 1: recommendations for the production and control of poliomyelitis vaccine (oral)
- Update of TRS 800, 1990 and addendum adopted in TRS 897, 2000 to improve quality control tests of OPV
- MAPREC test to replace the RCT-40 test kept as optional or additional test
- Neurovirulence test in transgenic mice as an alternative to the current monkey neurovirulence test
- Test for retrovirus for vaccine produced in primary monkey kidney cells
MAPREC assay

- Molecular biological test, Mutant Analysis by PCR and Restriction Enzyme Cleavage, developed by CBER to quantify reversion at molecular level
- MAPREC assay validated for use with type 3
- MAPREC assay and materials available for type 2, use of the test needs to be approved by the ECBS
- For type 1, candidate reference materials under evaluation in a collaborative study; if validated, use of MAPREC needs to be approved by the ECBS
- Need of consultation / expert group to formulate P1/P2 MAPREC release criteria and replace RCT-40
TgPVR mice developed by introducing into genome the human gene encoding the cellular receptor of poliovirus

When infected with poliovirus, TgPVR mice develop flaccid paralysis and then death in some cases with histological lesions in central nervous system similar to those observed in monkey

Since 1992, studies carried out initially with type 3 monovalent vaccine to evaluate suitability of NVT on Tg mice

TRS 910, 2002: addendum to confirm the murine model provides a suitable alternative to monkey for the NVT of types 1, 2 and 3. However, the monkey NVT remains the "gold standard" test to requalify vaccine production
NVT on Transgenic Mice (TgPVR)

- Standard Operating Procedure for the transgenic mouse (TgPVR21) neurovirulence test
  - Series of workshops with manufacturers and NRAs held at NIBSC
  - Standardized method for inoculation, scoring, and statistical analysis
  - Procedures for qualification of new institutions and training/qualification of operators
  - Harmonized text utilized by EU and WHO; no evident interest in assay outside of EU
  - Publication of SOP by WHO and posting of ‘recommended materials’ on www.who.int/biologicals
NVT on Transgenic Mice (TgPVR)

Qualification of NIBSC as authorized reference center

- NIBSC tgpVR21 tests documented
- US FDA / CBER as external reviewer
- Assistance of GSK Biologicals for statistical analyses
- P1 and P3 completed; P2 underway
NVT on monkey

- Neurohistology workshop with manufacturers and NRAs held at NIBSC
- Standard set of scored histology slides established to train and calibrate readers / use as historical archive
- Need to review statistical section
Revision of OPV TRS

- “Equality” of monkey and TgPVR21 NVT
- MAPREC 1-2-3 replacement of RCT-40 test
- Any particulars for monovalent / bivalent / stockpile preparations
- OPV cessation: impact on TRS and timing of changes
- “Restart” provisions following OPV cessation
Inactivated Poliomyelitis Vaccine (IPV)
IPV TRS

- TRS 910, 2002 Annex 2: recommendations for the production and control of poliomyelitis vaccine (inactivated): update of TRS 673, 1982 and addendum adopted in TRS 745, 1987 to reflect the introduction of continuous cells, secondary or tertiary monkey kidney cells, or human diploid cells and standardize the control of products manufactured in these cell lines.

Revision of IPV TRS

Proposal for the removal of the test for effective inactivation on the trivalent bulk
- Inactivation carried out on the concentrated purified viral suspension in order to obtain the inactivated monovalent bulk.
- Test for effective inactivation is performed to check for the absence of residual infectious polioviruses at two production stages:
  - Inactivated monovalent bulk
  - Concentrated trivalent bulk
- Based on the extensive experience of IPV vaccine manufacturing, the removal of the test for effective inactivation on concentrated trivalent was proposed to:
  - European Pharmacopeia: modification accepted by group 15 and amended monograph published in July 2008
  - WHO: modification to be considered

Use of attenuated viral seed strains
- WHO Sabin-IPV development project
- Antigenicity and immunogenicity assay standardization
- Altered inactivation procedures and assays?
- Need for new “sabin-like” attenuated SO+2 seed stock? New OPV SO+2?

Post-eradication biosafety requirements
- Current TRS covers period from last case to OPV cessation
- Need requirements from OPV cessation onwards
- Decision on large-scale amplification of wild poliovirus strains
- Decision on attenuation status of Sabin strains (NVT on IPV bulks?)
- Development of IPV not dependent on replicating poliovirus?
Material preparation
Reference preparations

- **Poliomyelitis vaccine (inactivated):** lyophilized, Type 1 antigen: 430 D-antigen units/ml, Type 2 antigen: 95 D-antigen units/ml, Type 3 antigen: 285 D-antigen units/ml

- **Poliomyelitis vaccine (oral):** 7.51 log10 TCID 50/ml poliovirus type 1. 6.51 log10 TCID 50/ml poliovirus type 2. 6.87 log10 TCID 50/ml poliovirus type 3. 7.66 log10 TCID 50/ml total poliovirus content

- **Anti-poliovirus serum (types 1, 2, 3)**

- **MAPREC analysis of poliovirus types 3 and 2 (Sabin)**

- [http://www.who.int/biologicals/reference_preparations](http://www.who.int/biologicals/reference_preparations)
Reference preparations

Under development by NIBSC:

- Preparation of a new international reference for the determination by ELISA of D-ag content in IPV: ongoing collaborative study

- Development of reagents and references to be used in the determination by ELISA of D-ag content in S-IPV
Seed materials available from WHO

- Master and working seed lots of Sabin strains for vaccine production
- Vero 10-87 cell bank for vaccine production- Project to develop a replacement for this cell bank endorsed by the ECBS
- MRC-5 cell bank for vaccine production
ECBS endorsement

- Number of polio vaccine standards, both written and reference preparations, are in the pipeline or need to be developed

- Provision and maintenance of these standards remain a high priority for WHO
THANK YOU