WHO Recommendations for Evaluation of Animal Cell Cultures as Substrates for the Manufacture of Biological Medicinal Products and for the Characterization of Cell Banks (TRS 978, Annex 3)

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Outline of presentation

- Historical background
- Development chronology
- Scope and content of the document
- What is covered and what is not?
- What is new in the document versus the previous one(s)?
- Main messages to regulators and manufacturers
WHO Guideline Development Activities for Vaccines and Other Biologicals

- Norms and Standards Team: Systematic development of written standards, guidance documents

- Expert Committee on Biological Standardization (ECBS): publication of written standards / guidance documents (WHO Technical Report Series) – scientific in nature, advisory in content, quasi starting points for setting national requirements

- Implementation of standards into regulatory and manufacturing practice

- Step towards harmonization of national regulatory requirements

- Main driver in updating regulatory and manufacturing practices

- Living document to be revised in response to scientific advances
Cell Substrates and Cell Banks

- Cell substrates and cell banks play crucial role in the production of countless licensed and under development biologicals, preventive or therapeutic alike.

- They affect the characteristics and the safety of the end product biologicals.

- Understanding of their characteristics is essential for:
  - identifying points of concern, and
  - developing quality control systems to address these concerns.

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History-1

- Motto: Cells, vaccines and the pursuit of precedent (M. Hilleman - 1968)
- Known vs. unknown and the possible presence of harmful entities
- 1950's: normal vs. abnormal – primary cell cultures (PCC) vs. tumour cell lines, i.e. monkey kidney and HeLa cells, respectively
- Requirements for poliomyelitis vaccine (inactivated) – 1959 (TRS 178), revised in 1966 - Primatus of the primates for polio vaccines, but other PCCs contributed to the first golden age of vaccines, i.e. chick embryo cells
History-2

- All "normals" are normal, however some normals are more normal.
- 1960's: Human diploid cell lines (HDC) - concept of master / working cell banks and baselines of cell substrates' characterization developed.
- The ill defined "normality" criterion has become obsolete.
- 1970's: Continuous cell lines (CCL) – rapid growth, higher product yields.
- Requirements for the use of animal cells as in vitro substrates for the production of biologicals -1998 (TRS 878, Annex 1).
Replacement of TRS 878 (Annex 1)

- The need for revision / amendment of the 1998 guidance document emerged in the mid 2000's through advancement in use and quality control of new CCLs and insect cells.

- Study group was established to facilitate the resolution of regulatory and scientific issues related to their use.

- The actual outcome of the exercise was the production of a new, much extended guidance document: in reality the old document was replaced.
Road to TRS 978 (Annex 3)

- Study group established (2005)
- Consultations (Geneva 2006, 2007 and 2010, Beijing 2008, and Bethesda 2009) with academia, regulators, industry (IFPMA, DCVMN) and other experts
- Consideration of relevant guidance and other documents from the field – NRAs, ICH, pharmacopoeias
- Draft document placed for public comments
- ECBS discussion and approval (2010)
- Publication
Tasks Assigned to the Study Group

- Review scientific evidence for WHO recommendations
- Recommend studies to answer specific questions related to the risk associated with residual cell DNA
- Provide an authoritative and credible analysis of the risks and benefits of using CCLs for vaccine production (main task)
- Propose revision of TRS 878 (Annex 1)
- Consider new types of cell substrates from regulatory perspective
- Recommend development of appropriate reference preparations / reagents
Scope of the Document


- Besides generic issues, which apply genetically manipulated and other cell substrates, specific considerations to cells modified by rDNA technologies are not covered in the document.

- The guideline specifically excludes all products manufactured in embryonated hen's eggs, microbial cells (bacteria or yeast) and plant cells.

- Albeit some of the given general recommendations are relevant to PCCs, the guideline does not supersedes TRS 178 (1959) and TRS 323 (1966) targeting vaccine production in primary monkey kidney cells.
General considerations

- Types of animal cell substrates and their advantages and disadvantages
  - PCCs, DCLs, CCLs, insect cells, stem cell lines (for stem cells production of growth factors and vaccines are included into the document but not direct therapeutic use)

- Potential risks and risk mitigations associated with biologicals propagated in animal cell cultures
  - viruses and other transmissible agents
  - cellular nucleic acids (DNA and RNA)
  - growth promoting proteins
Part A: General Recommendations

- Good manufacturing practices
- Principles of good cell culture practice
- Selection of source material
- Certification of cell banks by the manufacturer
- Cryopreservation and cell banking
Part B: Recommendations for the Characterization of Cell Banks

- Identity
- Stability
- Sterility
- Viability
- Growth characteristics
- Homogeneity
- Tumorigenicity
- Oncogenicity
- Cytogenetics
- Microbial agents
Key Issues Established During the Consultation Process

- Microbial agents
- Tumorigenicity (in vivo and in vitro methods to measure)
- Oncogenicity and infectivity of cell DNA
- Determination of residual cell DNA (rcDNA)
- New cell substrates
- Evaluation of cell substrates in the context of new vaccines and other biologicals
- Characterization of cell banks

Changes/Additions-1

- Manufacturing recommendations applicable to all types of cell culture based production – general update

- Some consideration for the evaluation of novel cell substrates were added: insect cells and in a more limited way stem cells

- Updated and extended definitions and abbreviations list

- New section on risk-reduction strategies during manufacture
Changes/Additions-2

- A section on good cell culture practice was added
- Updated recommendations for microbial agents testing
- Acceptable rcDNA levels were not specified as they were considered as product specific. For acceptable product specific limit one has to consider:
  - Characteristics of the cell substrate
  - Intended use of the product
  - Effect of the manufacturing process on DNA fragments:
    1) size (reduction), 2) quantity (reduction), and 3) biological activity (inactivation)
Changes/Additions-3

- Source material section has been updated and the detailed methods used to test on bovine viruses in serum has been added in Appendix 1.

- Tumorigenicity section has been updated and a model protocol for the mouse model has been added in Appendix 2.

- Oncogenicity testing of tumorigenic cell lysates has been added and complemented with a model protocol in Annex 3.
Philosophy to Guide the Regulatory Decision Making Process

- Acceptability of a particular cell type (primary, diploid, continuous, stem cell or insect origin) as a substrate for the production of biologicals depends on the in-depth knowledge of its characteristics.

- The starting point for assuring safe products is the characterization of the starting materials, including the cell substrate, because if the risk factors are unknown or poorly determined, how one can address them during manufacture.

- Considering the extent to which the manufacturing process reduces or eliminates factors of cellular origin that may be of concern.

- An assessment of the totality of the available data is needed for determining whether a product propagated in a particular cell substrate is potentially approvable.
Message to Manufacturers

- Novel cells (CCLs, insect, avian, stem cells) have fundamental differences in cell biology which must be taken into account regarding characterization, cryo-preservation, stability, etc.

- In the field of cell culture research the ever expanding new technologies are broadening the armamentarium for safety, however sometimes it is difficult to choose the most appropriate ones for testing relevance. One must identify the most valuable systems, qualify them and provide them with suitable controls.

- Good cell culture practice principle: Know your cell culture system and what affects it! (Coecke et al. 2005)

- Characterization data, even the most relevant and detailed, do not protect against consequences of poor cell culture practices.
Summary of Additions

- Insect and stem cell considerations introduced
- More detailed background information throughout
- Risk reduction strategies discussed
- New section: good cell culture practice
- Detailed methods for bovine viruses in serum
- Model protocol for nude mouse test for tumorigenicity
- New section: oncogenicity testing with a model protocol
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Thank you!
Back-up slide
WHO Collaborative Centers for Standardization and Evaluation of Vaccines

- National Institute for Biological Standards and Control (NIBSC) – United Kingdom of Great Britain and Northern Ireland (1954)
- Department of Bacterial Pathogenesis and Infection Control, National Institute of Infectious Diseases (NIID) – Japan (1971)
- Immunobiology and Biochemistry Group, Office of Laboratories & Scientific Services, Therapeutic Goods Administration (TGA) - Australia (1983)
- Center for Biologics Evaluation and Research (CBER) - USA (1998)
- National Institute of Food and Drug Safety Evaluation (NIFDS) – Republic of Korea (2011)
- Biologics and Genetic Therapies Directorate, Health Canada – Canada (2011)
- Institute for Biological Product Control – PR China (2013)
- Division of Virology, Paul Ehrlich Institute (PER) – Germany (2013)