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ICH Q5A(R2) – Viral Safety of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

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Presentation Outline

- Background
- Key Principles
- Key Updates to ICH Q5A
- Conclusions

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Background

- ICHQ5A(R1) was introduced in 1999
- Developed based on a Concept Paper and Business Plan in November 2019
- Signed off as Step 4 document in November 2023

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Key Principles

- Retention of basic organization and scientific principles
- Recognition of key scientific principles
- Allows flexibility for scientific advancement
- New technologies align with replacement, reduction and refinement of animal testing
- Introduces viral safety advances
  - Introduces virus detection using NGS
  - Introduces platform approaches to viral clearance
  - Describes new products
  - Presents viral safety considerations for Continuous Manufacturing

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Guideline Objectives

- Key scientific and regulatory considerations
- Three principle, complementary approaches
  - Selecting and testing of cell lines and raw materials
  - Assessing virus clearance capacity of process
  - Testing for infectious viruses at appropriate steps
- Q5A(R2) used in conjunction with:
  - ICH Q2
  - ICH Q5D
  - ICH Q13

Results of Public Consultation

- New products
- New definitions
- Clarification of terms Limit of *In Vitro* Cell Age (LIVCA) and End of Production Cells (EOPC)
- Implementation of Next Generation Sequencing
- Removal of Annex I

Table of Contents

Section 1 - Introduction	Major Changes
Section 2 – Sources of Viral Contamination	Minor Changes
Section 3 – Cell Line Qualification	Major Changes
Section 4 – Testing for Viruses	
Section 5 – Action Plan for Clearance Studies	
Section 6 – Evaluation of Viral Clearance	
Section 7 - Continuous Manufacturing	New
Section 8 – Summary	Minor Changes
Section 9 – Glossary	Major Changes
Section 10 - References	New

Annexes

- **Annex 1** Choice of Viruses for Clearance Studies
- **Annex 2** Statistical Considerations For Virus Reduction Factors
- **Annex 3** Calculation of Reduction Factors
- **Annex 4** Estimated Particles Per Dose
- **Annex 5** Examples of Prior Knowledge
- **Annex 6** Genetically Engineered Viral Vectors

- Minor Changes
- New
- New

Summary of Guideline Content – Key Update 1 – New Product Types

- Scope expanded to include viral vectors
  - Must be amenable to viral clearance
- Genetically–engineered viral vectors and viral vector derived products
  - Recombinant proteins expressed using production virus
  - Viral vectors where helper virus may not be required for their production
- Viral-vector derived products

Summary of Guideline Content – Key Update 2 – Section Location

- Section 2 – additional reference to new products
- Section 5 – New case F for production or helper virus
  - Use of relevant model virus for clearance
  - Additional examples of viruses utilized in clearance studies (Table A-1)
- Annex 6 – specific considerations for new product types
  - New table (A5) detailing testing expectations

Summary of Guideline Content – Key Update - 3 - Continuous Manufacturing (CM)

- New Section
- Viral safety considerations for CM
- In parallel with ICH Q13
- Specific aspects of CM
  - Cell cultivation
  - Diversion/segregation
  - Integration of unit operations

Summary of Guideline Content –
Key Update - 3 - Continuous Manufacturing (CM) – cont-d

- Specific considerations for individual unit operations
  - Chromatography
  - Low pH/solvent
  - Viral filtration

Summary of Guideline Content – Key Update – 4 – New Test Methods

- New alternative methods (e.g., NGS)
- New section in Cell line characterization - molecular methods
- Head-to-head comparisons of NGS with existing methods
- NGS considered a limit test

Summary of Guideline Content – Key Update – 4 – New Test Methods (cont'd)

- NGS or Nucleic acid amplification techniques (NATs), or PCR, may be used as alternative to virus-specific detection such as antibody production tests
- Recommendations regarding use of NGS or NAT described throughout the document

Summary of Guideline Content – Key Update 5 – Resin reuse

- Guideline updated to reflect scientific advance
- Protein A affinity capture chromatography
  - Virus removal not impacted or slightly increases for used resin
  - Product-specific resin re-use not expected
- Guideline is open ended for the use of prior knowledge for other resin types
  - E.g., anion exchange chromatography or cation exchange chromatography
    - Equivalent prior knowledge should be provided in place of product-specific viral clearance studies

Summary of Guideline Content – Key Update 6 – Prior Knowledge

- New section (6.6) added to section 6 outlining specific principles required for use of prior knowledge
  - Well characterized platform process
  - Composition of process intermediates
  - Equivalence of upstream step
  - Robustness of critical parameters
- New Annex 5 created
  - Provides specific examples of prior knowledge

Summary of Guideline Content –
Key Update – 7 - Flexible Approach for Well Characterized Cell Substrates

- Testing flexibilities for well characterized cell lines
- Specific examples for CHO cell substrates
  - Annex 4 includes footnote in safety factor calculation
    - Safety margin of <10-4 particles/dose
- Use of CHO-derived endogenous virus particles
  - Molecular or biochemical detection method should be qualified
- In vivo testing may be excluded
  - “In vivo testing is not necessary for extensively used well-characterized cell lines such as CHO, NSO, and SP2/0, based on prior knowledge”

Summary of Guideline Content – Key Update – 8 - Glossary

- New definitions to reflect changes
  - Next Generation Sequencing
- Definitions regarding expectations for new products
  - Helper virus
  - Viral vector for protein expression
  - Viral vector-derived products
  - Master virus seed and working virus seed
  - Production virus

Summary of Guideline Content – Key Update – 8 – Glossary (cont'd)

- Definitions regarding expectations for prior knowledge
  - Platform validation and manufacturing
  - Process robustness of viral clearance
  - Prior knowledge
- Definitions to align terminology
  - End of Production Cells (EOPC), Extended Cell Bank (ECB), and Limit of In Vitro Cell Age (LIVCA) Cells

Guidelines for Implementation

- Products not in scope
- Validation of technology (e.g., Next Generation Sequencing) not described
- Should be read in concert with ICH Q2, ICH Q5D, and ICH Q13

Conclusions

- The ICH Q5A(R2) guideline establishes harmonized scientific and technical requirements for products derived from characterized cell lines of human or animal origin:
  - Regulatory expectations for:
    - Testing
    - Evaluation of virus safety
- The guideline retains:
  - original structure and principles
  - Provides additional recommendations on the three established approaches to control viral contamination
    - Selecting and testing of cell lines and raw materials
    - Assess virus clearance capacity of the process
    - Testing of the product at appropriate stage of manufacture

THANK YOU!

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