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

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2023-02-24

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Presentation Outline

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

Background

- ICH Q5A(R1) was finalized in 1999
- Concept paper and business plan endorsed in 2019
- Revision signed off in September 2022 (Step 2)
- Issued by the ICH Regulatory Members for public consultation
- Anticipating finalization to be implemented in November 2023 (Step 4)

Background – Key Principles

- Original document remains very useful
- Revision necessitated by advances in biotechnology and to reflect current scientific knowledge:
  - Manufacturing
  - New Product Types
  - Potential Analytical technologies
  - Alternative Virus clearance validation strategies

Background – Key Principles

- A recognition that the original structure and key principles be preserved
- Maintain focus on requirements for marketing authorization
- Highlight key scientific principles but retain flexibility to allow for scientific evolution
- Describe scientific consensus

Background (Cont'd)

- Key Updates introduced
  - New Product Types
  - Continuous Manufacturing
  - New Test Methods
  - Resin Reuse
  - Prior Knowledge
  - Flexible Approaches for Well Characterized Rodent Cell Substrates
  - Glossary

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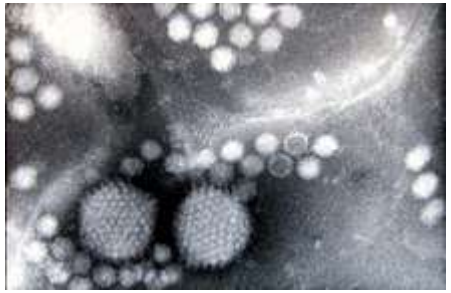
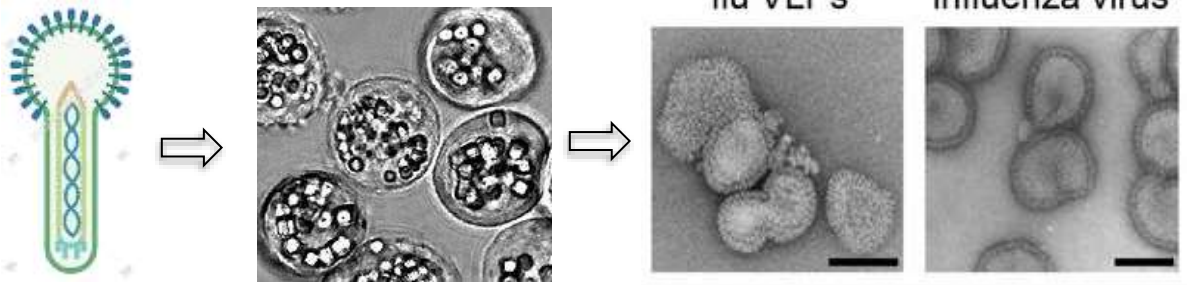
New Product Types

- Scope
  - Genetically engineered virus vectors
    - Amenable to virus clearance (Non-enveloped)
    - Helper virus
  - Virus-vector-derived products
    - Baculovirus and insect cells
  - Nanoparticle-based vaccines and therapeutic products
  - Annex 7 added





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Key Update 1 – Updated Sections

Section 2. Reference to new product types

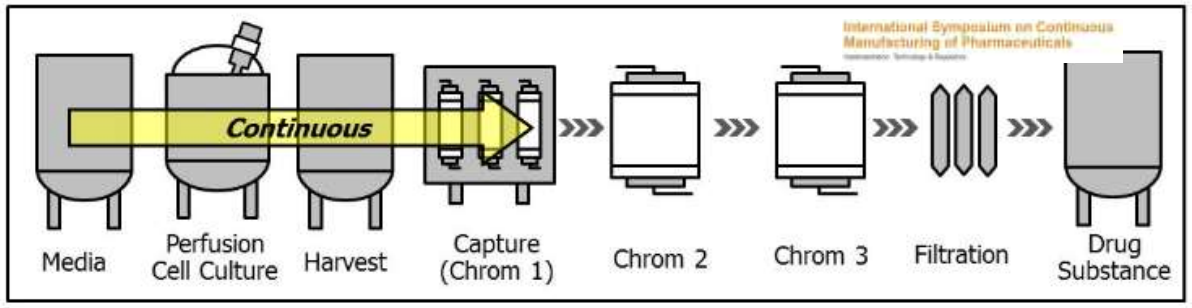
Section 3.2 Recommended Virus detection and Identification Assays

Section 5. Case F – Helper virus used in production (Table 4)

Annex 7: Genetically-Engineered Viral Vectors and Viral Vector-Derived Products

Continuous Manufacturing (CM)

- New Section 7
- Viral Safety Considerations specific to CM
- Considered in conjunction with Q13
- Describes when “batch” process evaluation is sufficient for scale down model



Continuous Manufacturing

- Highlights CM-specific aspects
  - Cultivation duration
  - Possible diversion/segregation impact
  - Integration of unit operations
  - Sampling considerations for cell culture

Continuous Manufacturing

- Describes specific considerations on a unit operation basis
  - Chromatography steps
  - Low pH/Solvent detergent inactivation
  - Viral filtration

New Test Methods

- Introduction of Next Generation Sequencing (NGS)
  - Broad detection
  - Highly sensitive
  - Used agnostically or targeted
- Encouraged to replace *in vivo* test
- May be used supplement or replace *in vitro* test
- Molecular methods encourage to replace HAP, MAP, and RAP

Resin Reuse

- Protein A affinity capture resin
  - No decline in virus clearance at end-of-life
  - Product-specific end-of-life studies not required
- May be applicable to other column types

Prior Knowledge

- Use of Platform virus clearance/inactivation data
  - Well characterized platform process
    - Understanding of mechanism of virus clearance/inactivation
    - Composition of process intermediate
    - Equivalence of upstream step
    - Robustness of critical parameters
- New Annex 6 added to provide examples of permitted steps
  - Detergent/solvent, low pH, nanofiltration

Flexible Approaches for Well Characterized Cell Lines

- Master Cell Bank *in vivo* test exemption
  - Risk based
  - CHO, NS0, SP2/0
  - Testing performed on parental line and multiple MCBs from same line
- Virus clearance log reduction value for CHO (10^{-4} vs 10^{-6})
- Use of CHO RVLP as specific model virus for virus clearance studies

Glossary

- New definitions added to reflect expectations for new product types
  - Helper virus
  - Viral vector
  - Viral vector derived product
  - Master virus seed
  - Working virus seed

Glossary (cont'd)

- New definitions to reflect expectations for prior knowledge
  - Platform validation of virus clearance
  - Process robustness of virus clearance
  - Prior knowledge
- New definitions to align terminology
  - End of production cells

Summary

- Original guideline
  - Overall layout
  - Flexibility to accommodate future scientific and technological advances
- Updates to ICH Q5A reflect advances in:
  - Science
  - Medicinal products
  - Manufacturing
  - Testing technologies

THANK YOU!