ICH
harmonisation for better health

Q5A(R2)

Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Step 4

Step 4 document – To be implemented

6 November 2023

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

Legal Notice

Background

- This document has been signed off as *Step 4* document (1 November 2023) to be implemented by the ICH Regulatory Members.
- This document was developed based on a Concept Paper and Business Plan endorsed in Singapore (18 November 2019).

Key Principles

- Retains original organisation and scientific principles of ICH Q5A(R1) in the document
- Highlights key scientific principles and allows flexibility for evolution of science and knowledge, including risk-based approaches
- Supports and encourages use of new technologies to align with principles of replacement, reduction and refinement of animal testing
- Introduces new advances with respect to viral safety
  - Describes key aspects related to new products and manufacturing processes in scope of viral safety
  - Describes specific considerations about viral safety for Continuous Manufacturing (CM)
  - Introduces Next Generation Sequencing (NGS) for virus detection
  - Introduces platform approach for viral clearance evaluation

Guideline Objectives

- Capture key scientific and regulatory considerations that promote harmonization with respect to evaluation of viral clearance, characterisation, and testing
- To describe the three principal, complementary approaches to control potential viral contamination
  - Selecting and testing cell lines and other raw materials, including media components for ensuring the absence of undesirable infectious viruses
  - Assessing the capacity of the production processes to clear adventitious and endogenous viruses
  - Testing the product at appropriate steps of production for the absence of contaminating infectious viruses
- Intended to be used in conjunction with existing Guidelines, in particular ICH Q2, ICH Q5D, and ICH Q13

Results of Public Consultation

- Additional description of new products in scope
- Addition of definitions to glossary
- Additional description added to better clarify the relationship of Limit of *In Vitro* Cell Age (LIVCA) and End of Production Cells (EOPC)
- Better described new technologies, such as Next Generation Sequencing (NGS), and their implementation
- Removed previous Annex 1 Products derived from Characterised Cell Banks which Were Subsequently Grown *in vivo*

Table of Contents

Section	Title	Comment
Section 1	Introduction	Major Changes
Section 2	Potential Sources of Viral Contamination	Minor Changes
Section 3	Cell Line Qualification: Testing for Viruses	Major Changes
Section 4	Testing for Viruses for Unprocessed Bulk	Major Changes
Section 5	Rationale and Action Plan for Viral Clearance Studies and Virus Tests on Purified Bulk	Major Changes
Section 6	Evaluation and Characterisation of Viral Clearance Procedures	Major Changes
Section 7	Points to Consider for Continuous Manufacturing	New
Section 8	Summary	Minor Changes
Section 9	Glossary	Major Changes
Section 10	References	New

Annexes

Annex	Title	Comment
Annex 1	The Choice Of Viruses For Viral Clearance Studies	Minor Changes
Annex 2	Statistical Considerations For Assessing Virus And Virus Reduction Factors	Minor Changes
Annex 3	Calculation Of Reduction Factors In Studies To Determine Viral Clearance	Minor Changes
Annex 4	Calculation Of Estimated Particles Per Dose	Minor Changes
Annex 5	Examples Of Prior Knowledge Including In-house Experience To Reduce Product-specific Validation Effort	New
Annex 6	Genetically-engineered Viral Vectors And Viral Vector-Derived Products	New

Summary of Guideline Content

Key Update 1 – New Product Types

- Scope is defined as products that are amenable to viral clearance without negative impact on the product
- Includes some genetically-engineered viral vectors and viral vector-derived products
  - Recombinant proteins that are expressed using a production virus (e.g., using recombinant baculoviruses or helper viruses such as herpes-simplex virus or adenovirus)
  - Viral vectors where a helper virus is not required to produce them
- Now includes viral vector derived products such as virus-like particles (VLPs), protein subunits and nanoparticle-based protein vaccines

Product Categories/Types

ICH Q5A(R1)	ICH Q5A(R2)
Included: • Products derived from in vitro cell culture: • Interferons • Monoclonal antibodies • Recombinant DNA-derived products • Recombinant subunit vaccines • Products derived from hybridoma cells grown in vivo as ascites Excluded: • Inactivated vaccines • All live vaccines containing self-replicating agents • Genetically-engineered live vectors	Included: • Products derived from in vitro cell culture: • Cytokines • Monoclonal antibodies • Recombinant DNA-derived products • Recombinant subunit vaccines • Genetically-engineered viral vectors and viral vector derived products provided they are amenable to viral clearance ○ e.g., Virus Like Particles (VLPs) and protein subunits Excluded: • Inactivated vaccines • All live vaccines containing self-replicating agents • Products derived from hybridoma cells grown in vivo as ascites • Genetically-engineered viral vectors provided they are not amenable to virus clearance • Cell therapies

Examples

ICH Q5A(R1)	ICH Q5A(R2)
Included: • mAbs • Recombinant proteins • Recombinant subunit vaccines • Certain vaccines • Interferons Excluded: • Inactivated viral vaccines • Live attenuated vaccines: Measles, Mumps, Rubella • Lentivirus, Adeno-Associated Virus (AAV), and adenovirus vectors	Included: • mAbs • Recombinant proteins • Recombinant subunit vaccines • Certain vaccines • Cytokines • Helper-dependent AAV and AAV produced by transient or stable transfection • Baculovirus produced VLP vaccines and gene therapies e.g., baculovirus expressed AAV • Protein subunits expressed in baculovirus Excluded: • Inactivated viral vaccines • Live attenuated vaccines: Measles, Mumps, Rubella • Cell therapies • Viral vectors not amenable to viral clearance such as Retroviral vectors e.g., Lentivirus

Summary of Guideline Content

Key Update 2 – Section Location

- Introduction - Document includes expanded description of Scope
- Section 2 - Document includes additional reference to new products and their context
- Section 5 - Document includes a new case, “Case F” to describe when a production virus is used in the production of a product
- Describes the use of a relevant model virus for helper virus clearance in Table 4
  - Additional descriptive examples provided in Table A-1 Examples of Viruses Which Have Been Used in Viral Clearance Studies
- Annex 6 - New annex that includes specific considerations for these new product types
  - Includes new table of testing and associated steps during manufacture

Summary of Guideline Content

Key Update 3 – Continuous Manufacturing

- Created a New Section (Section 7: Points To Consider For Continuous Manufacturing)
- Limited to viral safety considerations specific to continuous manufacturing
- Designed to be read in parallel with ICH Q13
- Designed to highlight aspects specific for continuous manufacturing
  - Longer cell cultivation duration
  - Possible diversion/segregation impact
  - Integration of unit operations
  - Sampling considerations for cell culture (also Section 4)
- Describes specific considerations on a unit operation basis
  - Chromatography steps
  - Low pH / solvent detergent inactivation
  - Viral filtration

Summary of Guideline Content

Key Update 4 – New Test Methods

- Encourages use of new alternative tests (includes Next Generation Sequencing (NGS) and Polymerase Chain Reaction (PCR))
- Clarifies head-to-head comparison of NGS with existing methods is not recommended
- Describes that NGS is considered a limit test (ICH Q2)
- Added new section on Molecular Methods (with subsections for nucleic acid amplification techniques and NGS) added to cell line qualification section (Section 3)

Summary of Guideline Content

Key Update 4 – New Test Methods (cont.)

- Specific opportunities to replace existing methods with targeted or broad (non-targeted) NGS highlighted
  - Antibody production tests
  - *In Vivo* assays
  - *In Vitro* assays
- Nucleic Acid Amplification Techniques (NATs), such as PCR-based methods may be used as an alternative for virus-specific detection
  - Antibody production tests
- Recommendations are described throughout the body of the text and specifically highlighted in table footnotes

Summary of Guideline Content

Key Update 5 – Resin Reuse

- Desire to have guideline reflect key areas of scientific progress and understanding
- For Protein A affinity capture chromatography, prior knowledge indicates that virus removal is not impacted or slightly increases for used (e.g., end-of-life) chromatography media/resin
  - Explicit statement that product-specific studies with used resin are not expected
- Guideline is open ended that the use of prior knowledge might also apply to other chromatography types involved in viral clearance (e.g., Anion Exchange Chromatography (AEX) or Cation Exchange Chromatography (CEX) etc.)
  - Equivalent prior knowledge including in-house experience and a detailed justification should be provided *in lieu* of product-specific viral clearance studies with end of lifetime resin (See Key Update 6)

Summary of Guideline Content

Key Update 6 – Prior Knowledge

- New section 6.6 was added to Section 6 to outline specific principles needed to apply prior knowledge
- New Annex 5 created ("Prior Knowledge Including In-house Experience To Reduce Product-specific Validation Effort")
  - Provides specific examples of prior knowledge
  - Highlights that prior knowledge should reflect literature and marketing application holder specific experience
- Confirms that to establish robust virus clearance and use prior knowledge:
  - Operating conditions are similar and well understood
  - The composition of the product intermediate is representative of the intermediates used in virus clearance studies (or demonstrated not to have an impact)

Summary of Guideline Content

Key Update 6 – Prior Knowledge (cont.)

- Gives specific examples of using prior knowledge including the known criticality where already established for some parameters
  - Solvent detergent activation
  - Low pH incubation
  - Viral filtration
- Gives specific examples of how virus selection may be informed based on prior knowledge (e.g., parvovirus evaluation only for nanofiltration)
  - Confirmatory run expected for viral filtration
  - Clear understanding of process conditions

Summary of Guideline Content

Key Update 7 – Flexible Approach for Well Characterised Rodent Cell Substrates

- Several testing flexibilities described for well characterised cell lines
- Specific examples including, in particular, Chinese Hamster Ovary (CHO) cell substrates
  - Annex 4 includes footnote in safety factor calculation
    - A safety margin of $<10^{-4}$ particles/dose may be considered acceptable for CHO products
- For CHO cell-derived products, CHO-derived endogenous virus particles can also be used for viral clearance studies
  - There is no infectivity assay for these particles and the detection method (e.g., molecular or biochemical) should be qualified for its use
- *In vivo* testing may be excluded
  - Specific statement “However, *in vivo* testing is not necessary for extensively used well-characterised cell lines such as CHO, NS0, and SP2/0, based on prior knowledge”

Summary of Guideline Content

Key Update 8 - Glossary

- New definitions added to reflect revision
  - Next Generation Sequencing (NGS)
- Definitions to aid in describing expectations for new products
  - Helper Virus
  - Viral Vector for Protein Expression
  - Viral Vector Derived Product
  - Master Virus Seed and Working Virus Seed
  - Production Virus
- Definitions to aid in describing expectations for prior knowledge
  - Platform Validation and Platform 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

- For products not in scope of this guideline, general considerations and approaches can be applied
- Validation of technology such as next generation sequencing (NGS) is not described and should consider the general principles of ICH Q2
- This guideline should be read in conjunction with ICH Q2, ICH Q5D, and ICH Q13

Conclusions

- The ICH Q5A(R2) Guideline establishes harmonised scientific and technical requirements to fulfill regulatory expectations for testing and evaluation of the viral safety of biotechnology products derived from characterised cell lines of human or animal origin based on scientific progress made since the last revision
- The ICH Q5A(R2) Guideline retains original structure and principles and provides additional recommendations on the established and complementary approaches to control the potential viral contamination of biotechnology products:
  - Selecting and testing cell lines and other raw materials for the absence of undesirable infectious viruses
  - Assessing the capacity of the production processes to clear adventitious and endogenous viruses
  - Testing the product at appropriate steps of production for demonstrating the absence of contaminating infectious viruses

Contact

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