



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

Step 2

Step 2 document – to be released for comment

Date: 29 September 2022

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Background

- ICH Q5A(R1) was finalised in 1999. This guideline considers testing and evaluation of the viral safety of biotechnology products derived from characterised cell lines of human or animal origin.
- ICH Q5A(R2) Concept Paper and Business Plan were endorsed in Singapore in November 2019.
- This revision was signed off as a *Step 2* Document 29 September 2022 to be issued by the ICH Regulatory Members for public consultation.
- Anticipating finalisation as a *Step 4* document to be implemented in the local regulatory system in November 2023.

Background Continued

- Original document is still referred to actively and considered quite useful
- However, recognised that a revision was necessary to reflect current scientific knowledge and biotechnology advances:
 - Manufacturing (both maturation of the industry and the emergence of continuous)
 - New product types that are amenable to viral clearance (including genetically engineered viral vectors and viral vector derived products)
 - Potential Analytical technologies (e.g., Next Generation Sequencing [NGS])
 - Alternative Virus clearance validation strategies (including prior knowledge)

Key Principles

- Desire to retain the usefulness and key principles in the original version that still provide value
- Retain original organisation of the document for continuity as layout continues to serve purpose
- Reflect in revision what is necessary for marketing authorisation not consideration for clinical development (unchanged)
- Highlight key scientific principles and allow flexibility for evolution of the science and understanding, including risk-based approaches
- Reflect EWG desire to describe where scientific consensus already exists specifically in detail

Key Principles Continued

- Defines what's new with respect to viral safety
 - Describes key aspects to new products and manufacturing processes in scope of viral safety
 - Describes specific considerations about viral safety for Continuous Manufacturing (CM)
- Continues to be used in conjunction with existing guidelines
- Supports and encourages new methodologies to align with Alternative testing principles (Replacement, Reduction and Refinement [3Rs])
 - Not just allows, but highlights specific instance that they would be appropriate
 - Not eliminate alternative testing that still is used by some
- Gives a framework for qualifying methods, or replacing a current method with a new technique

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 Processes	New
Section 8	Summary	Minor Changes
Section 9	Glossary	Major Changes

Annexes

Annex	Title	Comment
Annex 1	<u>PRODUCTS DERIVED FROM CHARACTERISED CELL BANKS WHICH WERE SUBSEQUENTLY GROWN <i>IN VIVO</i></u>	No Changes
Annex 2	<u>THE CHOICE OF VIRUSES FOR VIRAL CLEARANCE STUDIES</u>	Minor Changes
Annex 3	<u>STATISTICAL CONSIDERATIONS FOR ASSESSING VIRUS AND VIRUS REDUCTION FACTORS</u>	Minor Changes
Annex 4	<u>CALCULATION OF REDUCTION FACTORS IN STUDIES TO DETERMINE VIRAL CLEARANCE</u>	Minor Changes
Annex 5	<u>APPENDIX 5 CALCULATION OF ESTIMATED PARTICLES PER DOSE</u>	Minor Changes
Annex 6	<u>EXAMPLES OF PRIOR KNOWLEDGE INCLUDING IN-HOUSE EXPERIENCE TO REDUCE PRODUCT-SPECIFIC VALIDATION EFFORT</u>	New
Annex 7	<u>GENETICALLY-ENGINEERED VIRAL VECTORS AND VIRAL VECTOR-DERIVED PRODUCTS</u>	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
- This includes genetically-engineered viral vectors and viral vector-derived products, which can undergo virus clearance
- This may also include
 - viral vectors where a helper virus is not required to produce them
 - recombinant proteins that are expressed using a helper virus such as baculovirus, herpes-simplex virus or adenovirus
- This also includes viral vector derived products such as virus-like particles (VLPs), protein subunits and nanoparticle-based vaccines and therapeutics

Summary of Guideline Content

Key Update 1 – 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 helper 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 7 - 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 2 – Continuous Manufacturing

- Created a New Section (Section 7 POINTS TO CONSIDER FOR CONTINUOUS MANUFACTURING PROCESSES)
- Limited to Viral Safety Considerations specific to CM
- Designed to be read in parallel with ICH Q13
- Describes when “batch” process evaluation could be considered sufficient as a scale down model

Summary of Guideline Content

Key Update 2 – Continuous Manufacturing

- Designed to highlight aspects specific for CM
 - 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 3 – New Test Methods

- Guideline encourages use of new alternative tests (includes Next Generation Sequencing and Polymerase Chain Reaction [PCR] in discussion)
 - Aligns with initiative to reduce animal use for testing (3Rs)
- Highlights that direct head-to-head comparison with existing methods is generally not expected
- Molecular Methods (with subsections for nucleic acid amplification techniques and NGS) added to Cell line qualification section (Section 3)
- Limited description of method qualification expectations included in Section 3 as well

Summary of Guideline Content

Key Update 3 – New Test Methods

- Specific opportunities to replace existing methods with targeted or broad molecular methods highlighted
 - Antibody Production Tests
 - *In Vivo* Assays
 - *In Vitro* Assay
- Recommendations are described throughout the body of the text and specifically highlighted in table footnotes

Summary of Guideline Content

Key Update 4 – 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 5)

Summary of Guideline Content

Key Update 5 – Prior Knowledge

- New section F added to Section 6 to outline principles to apply prior knowledge
- New Annex 6 created to provide specific examples of prior knowledge
 - “PRIOR KNOWLEDGE INCLUDING IN-HOUSE EXPERIENCE TO REDUCE PRODUCT-SPECIFIC VALIDATION EFFORT”
 - Highlights that Prior Knowledge should reflect literature and marketing application holder specific experience
- Glossary includes new definitions on prior knowledge and platform validation to support how they are used in this guideline
- Confirms, that to establish robust virus clearance and use prior knowledge:
 - should be demonstrated across similar products
 - the composition of the product intermediate is comparable to the intermediates used in virus clearance studies (or demonstrated not to play an impact)

Summary of Guideline Content

Key Update 5 – Prior Knowledge

- 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 (parvovirus evaluation only for nanofiltration)
 - Confirmatory run expected for viral filtration
 - Clear understanding of process conditions

Summary of Guideline Content

Key Update 6 – Flexible Approach for Well Characterised Rodent Cell Substrates

- Several testing flexibilities described for well characterised cell lines
- Specific examples including and mention in particular in Chinese Hamster Ovary (CHO) cell substrates
 - Annex 5 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 experiments
 - There is no infectivity assay for these particles and the detection assay (e.g., molecular or biochemical) should be qualified for its use
- *In vivo* testing may be excluded based on risk assessment
 - Specific statement “However, *in vivo* testing is not necessary for well characterised cell lines such as CHO, NS0, and SP2/0, based on risk-based considerations”

Summary of Guideline Content

Key Update 7 - Glossary

- New definitions added to reflect revision
- Definitions to aid in describing expectations for new products
 - Helper Virus
 - Viral Vector
 - Viral Vector Derived Product
 - Master Virus Seed
 - Working Virus Seed
- Definitions to aid in describing expectations for prior knowledge
 - Platform Validation of Virus Clearance
 - Process Robustness of Virus Clearance
 - Prior Knowledge
- Definitions to align terminology
 - End of Production Cells (EOPC)

Considerations

- The ICH Q5A(R2) Guideline should be applied in conjunction with ICH Q13 for considerations specific to continuous manufacturing.
- The ICH Q5A(R2) Guideline should be applied in conjunction with other ICH “Q” Guidelines, including ICH Q8 - ICH Q12.

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
- The ICH Q5A(R2) Guideline revision retains 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;
 - Assessing the capacity of the production process to clear infectious viruses;
 - Testing the product at appropriate steps of production.

Contact

- For any questions please contact the ICH Secretariat:

admin@ich.org

Work Plan: Expected Future Key Milestones

Estimated Future Completion Date	Milestone
September 2022	<i>Step 1</i> sign off and <i>Step 2 a/b</i> endorsement Initiate regional public consultation period
November 2022	Virtual meeting to discuss communication strategy and public engagement
Summer 2023	Face to Face meeting to resolve comments
November 2023	Final resolution of comments <i>Step 3</i> Sign-off and <i>Step 4</i> Adoption



Thank you!

ICH Secretariat
Route Pré-Bois 20
1215 Geneva
Switzerland

E-mail: admin@ich.org

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