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

Arifa S. Khan, Ph.D.
Supervisory Microbiologist
Division of Viral Products
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

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History and Background

- ICH **Q5A(R1**) was finalized in **1999**. The guideline details testing and evaluation of the viral safety of biotechnology products derived from characterised cell lines of human or animal origin.

➢ ICH recognized that **a revision was necessary** to reflect current scientific knowledge and biotechnology advances related to:

  - Manufacturing
  - Emerging product types
  - Analytical technologies
  - Virus clearance validation strategies

➢ ICH Q5A(R2) Concept Paper **Outline** was endorsed in Amsterdam in **June 2019**.

➢ ICH Q5A(R2) **Concept Paper and Business Plan** was endorsed in Singapore in **November 2019 (F2F).**

- https://www.ich.org/page/formal-ich-procedure

ICH Q5A(R2) Meeting Highlights (Administrative)

- **Nov. 2019 Singapore: <u>F2F</u>**
  - Agreement on final topics/themes for revision
  - Creation of sub-Teams and strategy for drafting technical document
  - Creation of material for presentations to external stakeholders
    - Recognition of need for early engagement with stakeholders
- **May 2020 Vancouver: <u>Virtual</u>**
  - Potential for Step 1 signoff being delayed until November 2021, delayed from May 2021 due to slower progress (COVID-19!)
  - Continue sub-Team and EWG virtual meetings
- **Nov. 2020 Athens: <u>Virtual</u>**
  - Continue sub-Team and EWG virtual meetings
- **June 2021 Incheon: <u>Virtual</u>**
  - Continue sub-Team and EWG virtual meetings

Topics for Updating ICH Q5A(R2)

1. New classes of biotechnology products
   - *e.g., virus-like particles (VLPs), subunit proteins, and viral-vectored products*
2. Additional validation approaches for virus clearance
   - *e.g., using prior knowledge*
3. New virus assays and alternative analytical methods
   - *e.g., PCR, NGS/HTS*
4. Virus clearance validation and risk mitigation strategies for advanced manufacturing
   - *e.g., continuous manufacturing*
5. Aspects of virus clearance validation that have emerged or evolved

1. New classes of biotechnology products

- In the past twenty years, there has been an emergence of advanced biotechnology products based on the development of new production technologies and biomanufacturing platforms.
- Specifically, virus-like particles (VLPs), subunit proteins, and viral-vectored products have been developed for vaccines and gene therapies using novel mammalian and insect-based vector/cell expression systems.
- For some of these products, clearance of virus vector and adventitious agents may need to be demonstrated.
  - *May include: baculovirus-expressed VLPs and proteins; AAV vectors; helper-dependent (adenovirus, HSV) viral vector products*
- The physicochemical properties of known and potential viruses for the species of cell line origin need to be considered in selection of appropriate viruses for the clearance studies.

1. New classes of biotechnology products (cont.)

Discussions on placement of new product types in the current guideline

- Describe new product types in an Annex
  - A consensus on their similarities to conventional products as well as risk factors (e.g., cell substrate and raw materials)
  - Outline of testing approaches
  - General expectations for virus clearance

2. Additional validation approaches for virus clearance

- Flexibility in validation approaches should be allowed in order to effectively leverage knowledge gained during development of manufacturing processes with extensive experience to support virus clearance.
  - *For example: dedicated virus clearance steps applied during purification of monoclonal antibodies*
- It is necessary to discuss expectations and limitations for the use of data from a purification step for related products or product classes that follow the same virus removal/inactivation unit operation purification step or conditions.
  - *For example: matrix composition and interference with virus clearance*
- Additionally, opportunities to use alternative approaches for virus clearance validation based on experience with well-characterized cell substrates and manufacturing processes should be discussed.
  - *For example: CHO derived RVLPs for validation of virus clearance steps*

3. New virus assays and alternative analytical methods

- Technological advances since the publication of the original ICH Q5A(R1) guideline have occurred that require additional discussion.
- Specifically, nucleic acid-based assays such as Polymerase Chain Reaction (PCR) and High-Throughput Sequencing (HTS) may provide rapid and sensitive detection of adventitious and endogenous viruses in the starting and harvest materials.
- Additionally, quantitative PCR assays may be considered for assessment of the virus clearance capability of the manufacturing process.
  - *For example: validation of virus removal during protein A column chromatography using PCR; investigation of virus partitioning at chromatographic steps where the virus may be inactivated by buffers*
- However, these nucleic acid-based assays have limitations as they cannot distinguish between infectious and noninfectious particles and therefore detection of a signal may need a confirmatory test with an infectivity assay for risk-assessment.
- Additional justification describing the use of these methodologies should be provided.
- General principles for the inclusion of new assays and potential replacement/supplement of existing assays should be presented in order to continue to support future development of new technology.

3. New virus assays and alternative analytical methods (cont.)

Discussions

- Retention, elimination, or substitution/replacement of *in vivo* tests by PCR or a broad screen molecular method (e.g., HTS)
  - HAP, MAP, and RAP
  - *In vivo* adventitious virus assays
- Level of detail for HTS
- Testing at certain points in the manufacturing process relative to risk (MCB, WCB, LIVCA, etc.)
- Incorporating HTS into the existing testing section

4. Virus clearance validation and risk mitigation strategies for advanced manufacturing

- The principles of viral safety described in the ICH Q5A(R1) guideline apply to emerging or advanced manufacturing approaches beyond traditional unit and batch process operations.
- However, specific challenges associated with viral safety in advanced manufacturing are not addressed in the original guideline, and would benefit from additional discussion and clarification. These challenges may include:
  - Screening for and detection of adventitious and endogenous viruses during continuous manufacturing
  - Validation of virus clearance strategies adapted from traditional unit operations
  - Suitability of small-scale models designed for traditional virus clearance spiking studies to represent advanced manufacturing systems
  - Potential considerations for the role of facility design and manufacturing processes (open versus closed systems) in viral safety evaluation (ICH Q7)

4. **Virus clearance validation and risk mitigation strategies for advanced manufacturing (cont.)**

Discussions

- Acknowledgement that **Continuous Manufacturing (CM)** is an evolving field
- Aspects of virus clearance validation that have emerged or evolved, specifically end of lifetime studies for chromatographic resin
  - Progress on where specific recommendations are made and where principles will be described, including the use of prior knowledge/platform experience
- Scope of Advanced Manufacturing/Continuous Manufacturing
  - Considerations where general principles can be applied with CM systems
  - Important to include both a framing of how different types of CM approaches may be considered (e.g., full end-to-end CM vs. Semi-continuous)
  - Potential where “batch mode” evaluation would be appropriate
  - Format for how these unique considerations should be incorporated into guideline text
- Drafting of a new section is ongoing
  - Incorporating feedback from ongoing ICH Q13 EWG on specific viral safety considerations
  - Desire to include additional detail on specific considerations that are unique to certain viral clearance steps

5. Aspects of virus clearance validation that have emerged or evolved

- Some aspects of virus clearance validation have emerged or evolved since the publication of the ICH Q5A(R1) Guideline. For example:
  - The recommended evaluation of chromatographic resin at the end of its lifetime for Protein A resin and potentially other resins
  - Additional relevant model viruses for virus clearance studies

- Selection of appropriate model viruses for validation of nanofilters

- Risk mitigation technologies for treatment of raw materials.
  - For example: Virus inactivation of raw materials

5. Aspects of virus clearance validation that have emerged or evolved (cont.)

Discussions

- Where specific recommendations are made and where principles will be described, including the use of prior knowledge/platform experience

- Additional discussions on the virus clearance safety margin, including calculation of clearance factors.
  - Virus clearance safety margin
    - Whether or not the described virus clearance safety margin could depend on the product type (e.g., well-characterized cell lines)
    - Situations where using alternative approaches (e.g., averaging log reduction value [LRV]) may be considered in lieu of using the lower LRV from duplicate determinations

Work Plan: Expected Future Key Milestones

Estimated Future Completion Date	Milestone	
August 2021	First Draft of Technical Document	For internal consultation
Dec 2021	Engagement of PWP	
May 2022	Step 1 sign off and Step 2 a/b endorsement	For public comments
Nov 2023	Step 3 Sign-off and Step 4 Adoption	

Plenary Working Party (PWP): A type of technical group associated with a Working Group (WG) following the formal ICH Procedure (further to approval of its Concept Paper), the membership of which would include that of the WG as well as up to one expert per ICH Member or Observer who is either unable to participate in the WG due to size limitations, or who is unable to devote the necessary level of effort to participate actively in WG activities, but still wants to follow the progress of the WG

ICH Q5A(R2) Expert Working Group Membership

Dr. Joel Welch, *Rapporteur* (FDA, United States)	Dr. Johannes Blümel, *Regulatory Chair* (EC, Europe)	Ms. Grace Gnall, *Rapporteur Supporter* (FDA, United States)

ANVISA, Brazil
- Ms. Silmara Cristiane da Silveira Andreoli

EC, Europe
- Dr. Johannes Blumel
- Mr. Mats Jernberg

EDQM
- Dr. Laurent Mallet

EFPIA
- Dr. Marie Murphy

FDA, United States
- Dr. Arifa Khan
- Dr. Kathryn King

Health Canada, Canada
- Dr. Christopher Storbeck

HSA, Singapore
- Dr. Zhang Wei

IFPMA
- Ms. Wei Gong

IGBA
- Dr. Andrej Francky
- Dr. Parag Goyal

JPMA
- Dr. Nao Nakamura
- Mr. Kazuhisa Uchida

MFDS, Republic of Korea
- Dr. Daehyun Baek

MHLW/PMDA, Japan
- Dr. Akira Sakurai
- Dr. Yoji Sato

NMPA, China
- Mr. Wenbo Sai

PhRMA
- Lianchun Fan
- Anne Stokes

Roszdravnadzor, Russia
- Ms. Evgeniya Postnova

Swissmedic, Switzerland
- Dr. Regula Johner

TFDA, Chinese Taipei
- Dr. Fong-Chun Huang

TGA, Australia
- Mr. Dennis Dowhan

USP
- Dr. Fouad Atouf

WHO
- Dr. Ivana Knezevic

Presentations Topics in Today's Session

1. New classes of biotechnology products
2. Additional validation approaches for virus clearance
3. New virus assays and alternative analytical methods
4. Virus clearance validation and risk mitigation strategies for advanced manufacturing
5. Aspects of virus clearance validation that have emerged or evolved