Final Concept Paper
Q5A(R2): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
Dated 17 November 2019
Endorsed by the Management Committee on 18 November 2019

Type of Harmonisation Action Proposed

It is proposed to revise the Q5A(R1) Guideline "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" to reflect new biotechnology product types, advances in manufacturing technology, analytical methods for virus testing, and scientific knowledge that have occurred since publication of the original document in 1999.

Statement of the Perceived Problem:

Since the publication of the Q5A(R1) Guideline in 1999, advances in biotechnology product development and manufacturing have occurred. The following advances are not reflected in the original guideline:

- New classes of biotechnology products have been developed, resulting in challenges for consistent regulation of these products across different health authorities.
- Only a limited number of validation approaches for virus clearance are described that can be currently applied. This has resulted in regulatory health authorities adopting different positions on the acceptability of these advances.
- New alternative analytical methods are available for use in virus testing but are not described. The techniques should be discussed, and additional detail included to support the inclusion of future analytical techniques.
- The development of advanced manufacturing (including, but not limited to continuous manufacturing processes) requires additional considerations for implementation of virus validation and risk mitigation strategies.

Issues to be Resolved

- <u>New classes of biotechnology products</u>

In the past twenty years, there has been an emergence of advanced biotechnology products due to 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. 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.

- Additional validation approaches for virus clearance

Where appropriate, 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. It is necessary to discuss expectations and limitations for the use of data of a purification step for related products or product classes that follow the same virus removal/inactivation unit operation purification step or conditions. Additionally, opportunities to use alternative approaches for virus clearance validation based on experience with well-characterized cell substrates and manufacturing processes should be discussed.

- 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 Next Generation Sequencing (NGS) 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. 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. For this reason, additional justification describing their use should be provided. Moreover, 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.

- 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

Details for this topic will also support the ongoing development of ICH Q13.

- 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 and will be discussed. 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
  - Additional discussion on the virus clearance safety margin, including calculation of clearance factors

Additionally, risk mitigation technologies for treatment of raw materials will be discussed.

Background to the Proposal

Consensus has emerged that ICH Q5A(R1), while still useful, requires revision to allow for a consistent global understanding of viral safety within the biopharmaceutical landscape. Moreover, to support both the development of new products and the use of state-of-the-art technologies, updating of viral safety approaches is essential. Implementation of updated assays and alternative validation approaches will benefit both industry and regulators by providing increased flexibility for viral safety assessment. Finally, the revised guideline will allow for a more harmonized approach for newer classes of biotechnology products and new developing technologies.

Type of Expert Working Group and Resources

It is proposed to establish an Expert Working Group with representatives with specialized knowledge on virus-detection technologies, virus clearance strategies, and manufacturing processes.

The Expert Working Group may also engage with external service providers who have experience with performing virus testing and virus clearance evaluations.

Timing

This working group had its first face-to-face meeting in November 2019. It is anticipated that this guideline may take 3 years to complete.