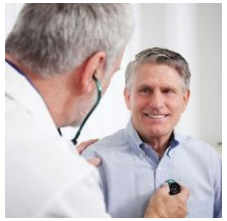
European Federation of Pharmaceutical Industries and Associations

ICH Q5A(R2) - Viral Safety Evaluation of Biotechnology Products

New Products and Virus Detection Assays



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Disclaimer

Expert Working Group (EWG) members are appointed by their nominating ICH Member or Observer party and are responsible for representing the views of that party, which may not necessarily reflect their personal views nor those of the ICH EWG.

Background & EFPIA Representation

- The decision to revise ICH Q5A(R1) - *Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* → ICH Q5A(R2) was made at the ICH Assembly 2019
- EFPIA as well as other industry groups have welcomed the plan for guideline revision
- Summer 2020 CMC Forum included wider stakeholder feedback for topic development

- **EFPIA Industry Expertise Assembled June 2019**
  - EFPIA nominated their ICH EWG representatives & accompanying taskforce
  - Virus Safety SMEs nominated from across EFPIA industry members (c. 23 members)
  - EFPIA consensus feedback represented within EWG alongside other ICH members
  - Utilise team TCs and Q&A's to collect feedback on each of the topics under development for revision
  - Ongoing feedback loop & for progress updates
  - Active engagement and debate for each topic in development

Brief Outline of Main ICH Q5A (R2) Revision Topics

- **Guidance revision is considered necessary to reflect current scientific knowledge and biotechnology advances:**
  - Manufacturing, emerging product types, analytical technologies & virus clearance validation strategies

- **Structured into 5 main themes for revision:**
  - Address new classes of biotechnology products
  - Address new & alternative virus detection test methods
  - Include additional validation approaches for virus clearance
  - Address aspects of virus clearance that had emerged or evolved
  - Include general expectations for advanced manufacturing – virus clearance validation and risk mitigation strategies

Inclusion of New Product Types

- **The (R2) Concept Paper Describes the Emergence of Advanced Biotechnology Products**
  - This is due to the development of new production technologies & biomanufacturing platforms
- Specifically, virus-like particles (VLPs), protein subunits, and viral-vector products have been developed for vaccines and gene therapies using mammalian and insect-based cell expression systems.
  - E.g., baculovirus-expressed VLPs and proteins; AAV vectors; adenovirus vectored products
- 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.

EFPIA Topic Development & Prioritisation of Objectives

The inclusion of new product types within the revised guideline is welcomed. The technology and their applications continue to develop within the emerging ATMP category.

The industry perspective prior to COVID-19; expect to prepare for ~25 new ATMP MAA submissions over these 2yr. Therefore, the revised guideline represents a significant opportunity for harmonisation of expectations for overall virus safety, for future global product supply.

Feedback from the EFPIA Topic Development:

Since there is a broad cohort of ATMPs and emerging technologies, determining which of the product types are to be included in scope of the revised guideline has been central to the industry feedback. Products could be categorised based upon any or all the following considerations:

Their additional risk factors?	➢ expect platform-specific risk factors to apply
The potential capacity (or not) for virus clearance?	➢ ICHQ5A considers the three elements for overall virus safety. Virus clearance expectations is one of those three key elements
The additional virus testing & characterisation approaches across the product lifecycle	➢ platform-specific testing approaches may apply

ICH Q5A(R2) - VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS

SUMMARY POINTS FROM EFPIA CONSENSUS BUILDING

- The products to be included in scope needs to be unambiguous, with clear expectations for industry.
- Ensure general guidance and expectations to adapt with emerging technological advances
  - Highlighting the main risk factors and the appropriate control measures
  - Avoiding exclusionary narrative, to reflect the emerging platforms
  - Relevant examples would be beneficial

- Virus vector products that are physically amenable to virus clearance:
  - Guidance should clearly recommend that clearance is provided to as reasonable a level as possible
  - High level guidance to reflect the evolving platforms and clearance technologies

- General guidance for adventitious agent characterization (e.g., cell substrate, virus seed testing) is considered as significant opportunity for harmonization.

- Holistic virus safety would apply through a risk-based assessment - based on therapeutic dose, number of administrations, risk level for specific helper virus and overall benefit/risk assessment

- To also consider the existing regional guidance and pharmacopoeia references

ICH Q5A(R2) - VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS

REFLECTING ON APPLICABLE EXISTING REGULATIONS

Existing regional guidance for emerging products + vaccine regulations should be considered in developing the harmonised expectations for virus safety for the new products.

US Vaccine	•US FDA Guidance for Industry; Characterization and Qualification of Cell Substrates and other Biological Materials used in the Production of Viral Vaccines for Infectious Disease Indications (2010)
WHO	•Annex 3 Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for characterisation of cell banks TRS978 (replacement for Annex 1 of TRS 878)
EMA Guidance and Ph.Eur. Chapters	•Ph. Eur. 2.6.16 Tests for Extraneous Agents in Viral Vaccines for Human use •EMA/CAT/80183/2014 (2018) Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products •Ph. Eur. 5.2.3 Cell Substrates for the Production of Vaccines for Human Use •Ph. Eur. 5.1.7 Viral Safety •Ph. Eur. 5.14 Gene Transfer Medicinal Products for Human Use •CHMP/BWP/2458/03 (2005) Guideline on Development and Manufacture of Lentiviral Vectors
US GT Guidance	•Chemistry, Manufacturing and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) •US FDA Guidance for Industry; Testing of Retroviral Vector-based Human Gene Therapy Products for Replication Competent Retrovirus During Product manufacture and Patient Follow-up

ICH Q5A(R2) - VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS

Summary of Changes to Scope of the Guideline from EWG

Section	[1]ICHQ5A(R1) scope	[1]ICH Q5A(R1) out of scope	[2]ICH Q5A(R2) added to scope
Definition of Scope	This document is concerned with testing and evaluation of the viral safety of biotechnology products derived from cell lines of human or animal origin (i.e., mammalian, avian, insect). Scope covers products derived from cell cultures initiated from characterized cell banks	Non-conventional transmissible agents like those associated with BSE and scrapie	

Product Categories/Types	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.
		• Inactivated vaccines
		• All live vaccines containing self replicating agents
		• Genetically Engineered live vectors
			• Genetically-engineered viral vectors that are amenable to viral clearance
			• Viral Vector-Derived Products (Virus Like Particles (VLPs) and Protein subunits)

Examples	• Mabs • Recombinant proteins • Recombinant subunit vaccines • cytokines	• Inactivated viral vaccines • Live attenuated vaccines: Measles, Mumps, Rubella. • Lentivirus, AAV, and adenovirus vectors	- AAV and adenovirus helper AAV - Baculovirus produced VLP vaccines and gene therapies e.g. baculovirus expressed AAV - Protein subunit expressed in baculovirus

[1]Wording taken directly from ICH Q5A R1; [2]Consistent with concept paper. Deliberations are ongoing

ICH Q5A(R2) - VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS

Expectations for Virus Testing & Characterisation

- Apply risk-based principles and considerations for applicable testing across the product lifecycle
- Cell substrate characterisation would broadly align with traditional Mab processes.
  - Guidance for testing for specialised risk factors would be beneficial
- Harmonised guidance for virus vector seed lots will also benefit the industry.
- Address the potential for replication competent viruses & residual helper virus testing
- To avoid overlap/contradictions with existing guidance
- Consider including how advanced molecular methods apply & to replace legacy *in vivo* testing, where applicable

Expectations for Virus Clearance

- Capacity for clearance associated with the physicochemical compatibility of the vector/ product and clearance technologies in a purification scheme
  - Guidance for helper virus clearance.
  - Whether cell substrate and manufacturing risk factors influence the virus clearance approach
  - Examples would be helpful.
- Where no/limited clearance is possible, virus safety would be assured through prevention controls and virus testing/characterisation.

ICH Q5A(R2) - VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS

- **Inclusion of Advanced Methods for Virus Detection and Characterisation**

The Forward-Looking Approach within ICH Q5A(R1)

- ICHQ5A(R1) already describes how advances in analytical testing are expected with scientific progress.
  - ……*proposals for alternative techniques, when accompanied by adequate supporting data, may be acceptable. Manufacturers are encouraged to discuss these alternatives with the regulatory authorities*…. (from Section III.B).

- Example of emerging technology since 1999 revision:
  - ….*The Polymerase Chain Reaction (PCR) may be appropriate for detection of sequences of these human viruses as well as for other specific viruses*……(from Section III.B)

The (R2) Concept Paper Describes the Technological Advances in Virus Detection

- Specifically, nucleic acid-based assays such as Polymerase Chain Reaction (PCR) and High Throughput Sequencing (HTS)/Next Generation Sequencing (NGS) may provide rapid and sensitive detection of adventitious and endogenous viruses in the starting and harvest materials

- 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.

EFPIA Topic Development & Prioritisation of Objectives

The inclusion of new and alternative analytical methods is welcomed for the guideline revision.

Objectives:

1. Elaborate on PCR methodology, due to commonplace application since R1. Consider the increasing capacity of these methods for detection of viruses within closely-related virus families.

2. Introduce new HTS/NGS methodology. Recognizing that HTS platforms are emerging, and the potential future benefits and applications are wide-ranging.

3. Strong endorsement for the application of molecular methods in addressing 3R's substitutes for:
    i. Broad screen *in vivo* methods
    ii. Specific screening for species specific viruses (e.g., MAP, HAP, RAP)

Guidance should encourage the substitution of *in vivo* methods.
ICH guidance should provide a perspective on the level of harmonised regulatory acceptance of substitution and substitution approaches.

4. Include the need for a follow-up strategy for positive signal due to reliance on molecular method.

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Current & Forward-Looking Expectations for Cell Line Qualification

- Comprehensive safety assessment of cell substrates.
- Traditional biotechnology products generally utilize well-characterized cell lines (e.g., CHO).
- The accumulated satisfactory cell line qualification data within industry exemplifies their consistent safety profile.

- Rapid acceleration of new products to clinic.
- Emerging methods with equivalent/ enhanced specificity
- Prior knowledge from platform-based manufacturing using parental lines.
- Less reliance on animal-origin materials.
- Vaccine manufacture progress with HTS evaluations.

- Comprehensive & risk-based testing strategy
  - Reflecting cell line history and susceptibilities, prior knowledge from parental cells & AO-free processes.
- Level of characterization of WCBs/replacement WCBs commensurate with risk assessment.
- Obviating, refining or replacing the *in vivo* testing, where appropriate
- New methods are fit for purpose, with aligned expectations for their qualification

- Since cell substrate testing generally applies at early phase, a need for consensus regulatory acceptance of cell substrate testing for a global market applies.

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Application of *in vivo* testing:

- Available repeated *in vivo* and adventitious agent testing of well-characterized cell substrates across product lifecycles were reviewed within the group to determine whether the *in vivo* testing identified a contaminant and if not already identified by the orthogonal tests.
- Gombold *et al* (2014) as well as ongoing equivalency work with HTS help identify the comparative specificities and sensitivities of *in vivo* to *in vitro* or molecular methods.
- Risk & cost/benefit-based justification for the obviating/reducing/refining of *in vivo* testing for what are considered well-characterized cell substrates.
- If alternative molecular method apply, substitute the *in vivo* testing as priority.
  - Equivalency studies for *in vivo* testing would be considered contrary to 3R's principle.
- New and advanced methods for virus detection in cell substrate characterization need to be fit for purpose (i.e., sensitive, specific) and appropriately controlled to mitigate the risk of false positive results.
- A perspective on the harmonization of expectations for both HTS method suitability and qualification will help progress their application, particularly if used to substitute legacy methods.

Potential Applications of New Virus Assays

Advanced methods may complement existing tests but should also be advanced as potential alternatives to existing methods, where appropriate.

- PCR method substitutes for targeted virus detection in scope (e.g., Antibody Production Tests)
- PCR Quantitation of Virus-like Particles
- HTS Detection Assay Substitute for the Detection of Unknown Viruses *in vivo*
- HTS or Broad Range PCR Detection Assay Substitutes for the Detection of Viruses *in vitro*

Table 1: Virus Tests to Be Performed Once at Various Cell Levels

	MCB	WCB[a]	Cell at the limit[b]
Tests for Retroviruses and other Endogenous Viruses			
Infectivity	+	-	+
Electron microscopy[c]	+[c]	-	+[c]
Reverse transcriptase[d]	+[d]	-	+[d]
Other virus-specific tests[e]	as appropriate[e]	-	as appropriate[e]
Tests for Non-endogenous or adventitious Virus Test			
In vitro assays	+	-[f]	+
In vivo assays	+	-[f]	+
Antibody production tests[g]	+[g]	-	-
Other virus-specific tests[h]	+[h]	-	-

[a] See text - Section 3.1.2

[b] Cells at the limit; Cells at the limit of in vitro cell age used for production (See text - Section 3.1.3).

[c] May also detect other agents.

[d] Not necessary if positive by retrovirus infectivity test.

[e] As appropriate for cell lines which are known to have been infected by such agents.

[f] For the first WCB, this test should be performed on cells at the limit of in vitro cell age, generated from that WCB; for WCBs subsequent to the first WCB, a single in vitro and in vivo test can be done either directly on the WCB or on cells at the limit of in vitro cell age.

[g] e.g., MAP, RAP, HAP - Usually applicable for rodent cell lines.

[h] e.g., Tests for cell lines derived from human, non-human primate or other cell lines as appropriate.

Extract from Current Effective ICH Q5A Guideline

Suggestions from EFPIA members on the Inclusion of Advanced Molecular Methods

- Expecting the inclusion of general assay details, in alignment with existing methods.
  - Non-hierarchical nor mandatory. Part of a toolbox of analytical measures. Provide options and guidance on method suitability & focus on where these methods may play a significant role in virus safety testing/characterisation.
  - ICHQ5A is not expected to provide significant level of detail for new method qualification & could complement ongoing technical discussions within Advanced Methods Implementation Groups.

- However, further conceptual details on the application and expectations for assay standarisation may help set the direction for HTS. Also to encourage further industry and regulatory harmonisation and confidence in the expected and varied approaches.
  - Differentiation between targeted and agnostic approaches, viromic and transcriptomic approaches & analysis since pipeline/database and controls adapt accordingly.
  - A system validation approach is recommended, since HTS is based on combination of main elements.
  - Inclusion of virus families likely detected by existing methods may help with determining baseline expectations for NGS.
- As a rapidly emerging technology, allow for continuous improvement and phase-appropriate implementation akin to existing guidance narrative approaches within R1.

Summary

The ICHQ5A(R2) revision will change to reflect current scientific knowledge and biotechnology advances

- including the emergence of new product categories and analytical technologies

Acknowledgments

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