Concept of the ICH-Q5A second revision.

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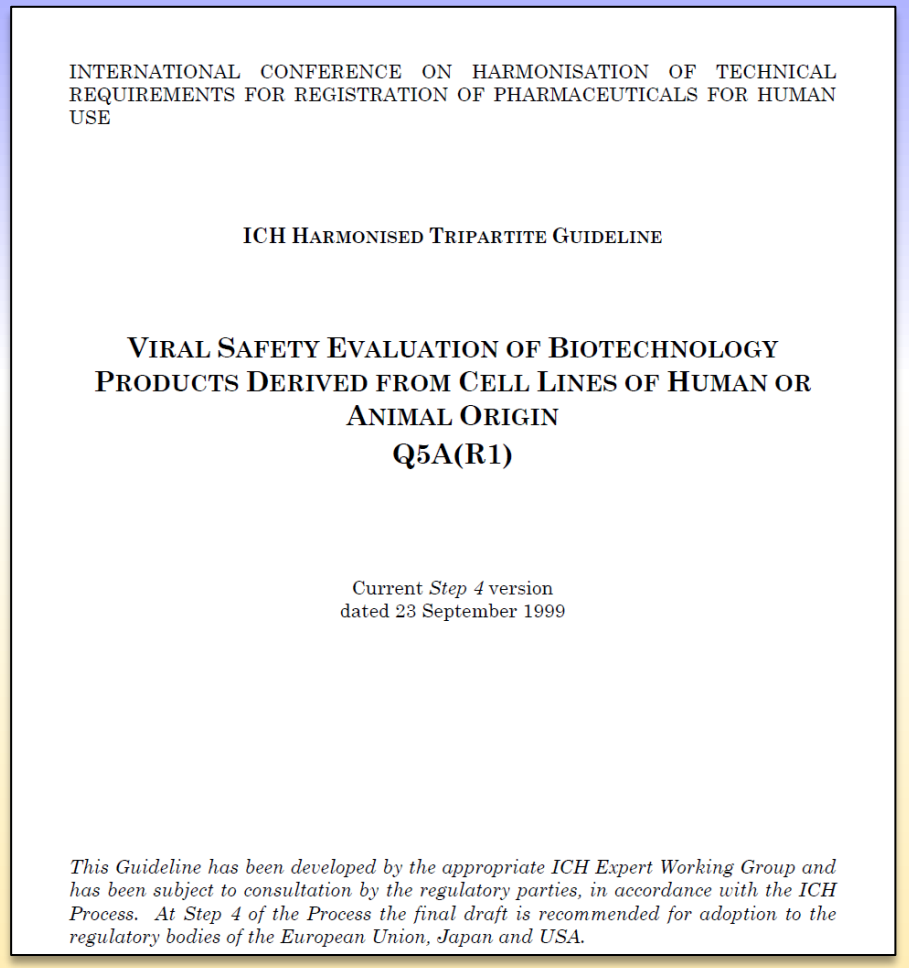
Background

- ICH Q5A(R1) was finalized 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.



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

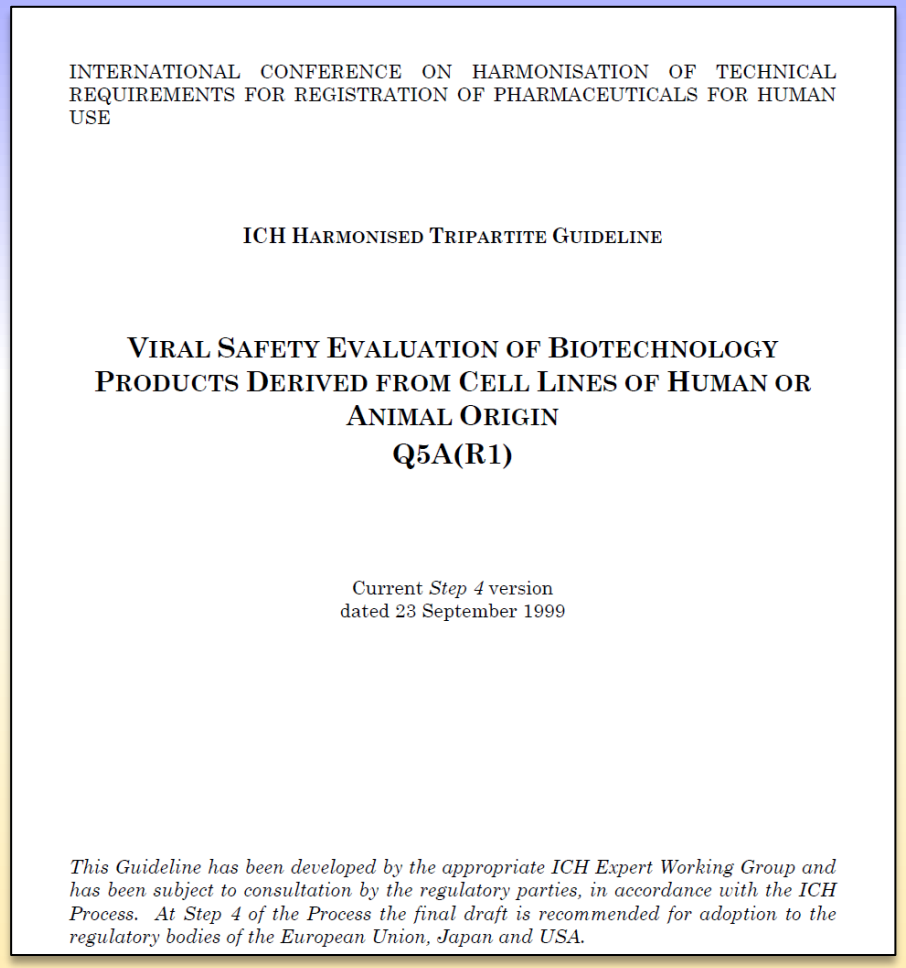
VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS DERIVED FROM CELL LINES OF HUMAN OR ANIMAL ORIGIN
Q5A(R1)

Current *Step 4* version
dated 23 September 1999

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Background Continued

- Original document is still referred to actively and considered quite useful
- However, recognized 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)



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ICH Q5A is one of the most critical guideline

Basic Requirements for Viral Safety of Biotechnological/Biological Products listed in Japanese Pharmacopoeia <*G3-13-141*>

Introduction

The primary role of specification of biotechnological/biological products listed in the Japanese Pharmacopoeia (JP) is not only for securing quality control or consistency of the quality but also for assuring their efficacy and safety. In the meantime, the requirements to assure quality and safety of drugs have come to be quite strict recently, and a rigid attitude addressing safety assurance is expected for biotechnological/biological products. The key points for quality and safety assurance of biotechnological/biological products are selection and appropriate evaluation of source material, appropriate evaluation of manufacturing process and maintenance of manufacturing consistency, and control of specific physical properties of the products. Now, how to assure quality and safety of such drugs within a scope of the JP has come to be questioned. This General Information describes what sorts of approaches are available to overcome these issues.

It is desired that quality and safety assurance of JP listed products are achieved by state-of-the-art methods and concepts which reflect progress of science and accumulation of experiences. This General Information challenges to show the highest level of current scientific speculation. It is expected that this information will contribute to promotion of scientific understanding of quality and safety assurance of not only JP listed products but also the other biotechnological/biological products and to promotion of active discussion of each Official Monograph in JP.

nature biotechnology PERSPECTIVE
https://doi.org/10.1038/s41587-020-0507-2

Viral contamination in biologic manufacture and implications for emerging therapies

ble 1 | Virus contaminations of mammalian cell culture produce proteins and vaccines, segregated by year, both blicly reported and contained in the CAACB study

ar of contamination	Contaminations (virus / host cell)	Total
1985–1989	Blue tongue / CHO EHDV / CHO[18,19]	2
1990–1994	Herpesvirus / primary monkey Herpesvirus / Vero MVM / CHO (x2)[20–22] Parainfluenza 3 / MRC5 Reo3 / MRC5 Simian adenovirus / primary monkey	7
1995–1999	CVV / CHO Reovirus / human primary kidney[23] Vesivirus 2117 / CHO[24]	3
2000–2004	CVV / unknown (x2)[25] Human adenovirus / HEK293[26]	3
2005–2010	CVV / CHO MVM / CHO (x2) Vesivirus 2117 / CHO (x3)[27–29]	6
2010–present	MVM / CHO[30] MVM / BHK-21[35] PCV-1 / Vero[31,32]	3
Unknown	MVM / BHK-21[33] Reovirus / Unknown[34]	2

Contaminating virus and host cell line are indicated where known. Note: some contamination events were reported publicly and in more detail to the CAACB. CVV, Cache Valley virus; EHDV, epizootic hemorrhagic disease virus; MVM, minute virus of mice; PCV-1, porcine circovirus type 1; Reo3, reovirus type 3.

Desire to retain the usefulness and key principles in the original version that still provide value

Key Principles

- 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 allow, 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 Characterization 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	PRODUCTS DERIVED FROM CHARACTERIZED CELL BANKS WHICH WERE SUBSEQUENTLY GROWN *IN VIVO*	No Changes
Annex 2	THE CHOICE OF VIRUSES FOR VIRAL CLEARANCE STUDIES	Minor Changes
Annex 3	STATISTICAL CONSIDERATIONS FOR ASSESSING VIRUS AND VIRUS REDUCTION FACTORS	Minor Changes
Annex 4	CALCULATION OF REDUCTION FACTORS IN STUDIES TO DETERMINE VIRAL CLEARANCE	Minor Changes
Annex 5	APPENDIX 5 CALCULATION OF ESTIMATED PARTICLES PER DOSE	Minor Changes
Annex 6	EXAMPLES OF PRIOR KNOWLEDGE INCLUDING IN-HOUSE EXPERIENCE TO REDUCE PRODUCT-SPECIFIC VALIDATION EFFORT	New
Annex 7	GENETICALLY-ENGINEERED VIRAL VECTORS AND VIRAL VECTOR-DERIVED PRODUCTS	New

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

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

New Annex 7

ICH Q5A(R2) Guideline

ANNEX 7: GENETICALLY-ENGINEERED VIRAL VECTORS AND VIRAL VECTOR-DERIVED PRODUCTS

7.1 Introduction

Advances in biotechnology have led to an emergence of new and advanced production platforms expressing new product types manufactured using characterised cell banks of human or animal origin (i.e., avian, mammalian, or insect). The scope of Annex 7 includes helper-virus dependent and helper-virus independent genetically-engineered viral vectors and viral vector-derived products that are amenable to virus clearance based on considerations of the physicochemical properties of the product. These products include Virus-Like Particles (VLPs) and protein subunits that are produced using baculovirus/insect cells, nanoparticle-based vaccines, and viral-vector products such as AAV. These medicinal products may be applied *in vivo* or *ex vivo*.

Table A-5: Tests that Should Be Performed at Applicable Manufacturing Stages

Test	*MCB, WCB, Cells at the LIVCA*	*Virus Seed* [k]	*Unprocessed Bulk (Harvest)*	*Drug Substance*
Test for adventitious or endogenous viruses				
[a, b] *In vitro* assays or NGS	[i] See Table 1 of main guideline	+[h]	+[h]	-
[b] *In vivo* assays or NGS		+[h]	-[h,l]	-
[c] other virus specific tests		1	1	-
[d] Antibody production assays or specific molecular assay		+[j,l]	-	-
Tests for Endogenous, Helper and Replication Competent Viruses, as applicable				
[e]retroviruses	[i] See Table 1 of main guideline	+	+[l]	-
[f]residual helper Viruses	NA	-	+	+[l]
[g]replication competent viruses	+	+	(+)	(+)

[a]Testing should be performed on permissive cell lines, based on risk assessment. The indicator cells cultures should be observed for at least 2 weeks, with a further secondary passage of 2 weeks of observation. Include testing for haemadsorbing and

New Annex 7 Continued

ICH Q5A(R2) Guideline

ANNEX 7: GENETICALLY-ENGINEERED VIRAL VECTORS AND VIRAL VECTOR-DERIVED PRODUCTS

7.1 Introduction

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Examples include:

- Subunit proteins and VLPs produced using baculovirus/insect cells can be purified and high levels of virus log reduction factors can be achieved through the manufacturing process and are validated by viral clearance studies; and
- Some viral-vector products such as AAV are amenable to robust viral clearance steps, ensuring adventitious and helper virus clearance inactivation or removal.

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
- 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


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harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Draft version

Endorsed on 27 July 2021

Currently under public consultation

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
- 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

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)

Prior Knowledge Continued

- 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

New Annex 6

ANNEX 6: EXAMPLES OF PRIOR KNOWLEDGE INCLUDING IN-HOUSE EXPERIENCE TO REDUCE PRODUCT-SPECIFIC VALIDATION EFFORT

According to the general principles for a platform validation approach, robust virus clearance should be demonstrated across products from the same platform and the procedure for virus clearance should follow established and well-characterised conditions. In addition, it should be shown that the composition of the product intermediate is comparable to the intermediates used in virus clearance studies unless prior knowledge indicates robustness of virus clearance with respect to product intermediate composition.

In this context, platform validation is defined as the use of prior knowledge including in-house (applicant-owned data) experience with viral reduction data from other products, to claim a reduction factor for a new similar product. In general, a virus clearance claim for a new product based on prior knowledge including in-house experience should include a discussion of all the data available and the rationale to support the platform validation approach (see Section 6.6). Part of the prior knowledge and in-house data used to reduce product-specific validation could be provided as a comparison of the new product and its manufacturing process with other in-house products, related process conditions, and product intermediates.

Table A-2: Summary of Process Parameters and Their Potential Impact for Detergent Inactivation

Process parameter	*Potential Impact*	*Rationale*
SD or Triton X-100 concentration	High	Inactivating agent
Incubation time	High	Mechanism of inactivation is time-dependent
Temperature	High	Impact on inactivation kinetics
Pre-treatment by 0.2 µm filtration	High	Removal from the starting intermediate of aggregates potentially entrapping and protecting viral particles from detergent access
Total lipid content or surrogate parameter in HCCF	Low	Low impact observed with worse-case HCCF
Type of product	Low	No impact on inactivation observed for MAb, half antibody, fusion protein or recombinant protein
Total protein content in HCCF	Low	Low impact observed with worse-case HCCF
pH	Low	Triton X-100 is a non-ionic detergent
Ionic strength	Low	See above
Buffer salt in HCCF	Low	See above
Potential interaction between virus particle and product	Low	No impact on inactivation observed and disruption of lipid envelope lowers probability of interaction with product

Flexible Approach for Well Characterized Rodent Cell Substrates

- Several testing flexibilities described for well characterized 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 characterized cell lines such as CHO, NS0, and SP2/0,based on risk-based considerations”

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 characterized 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