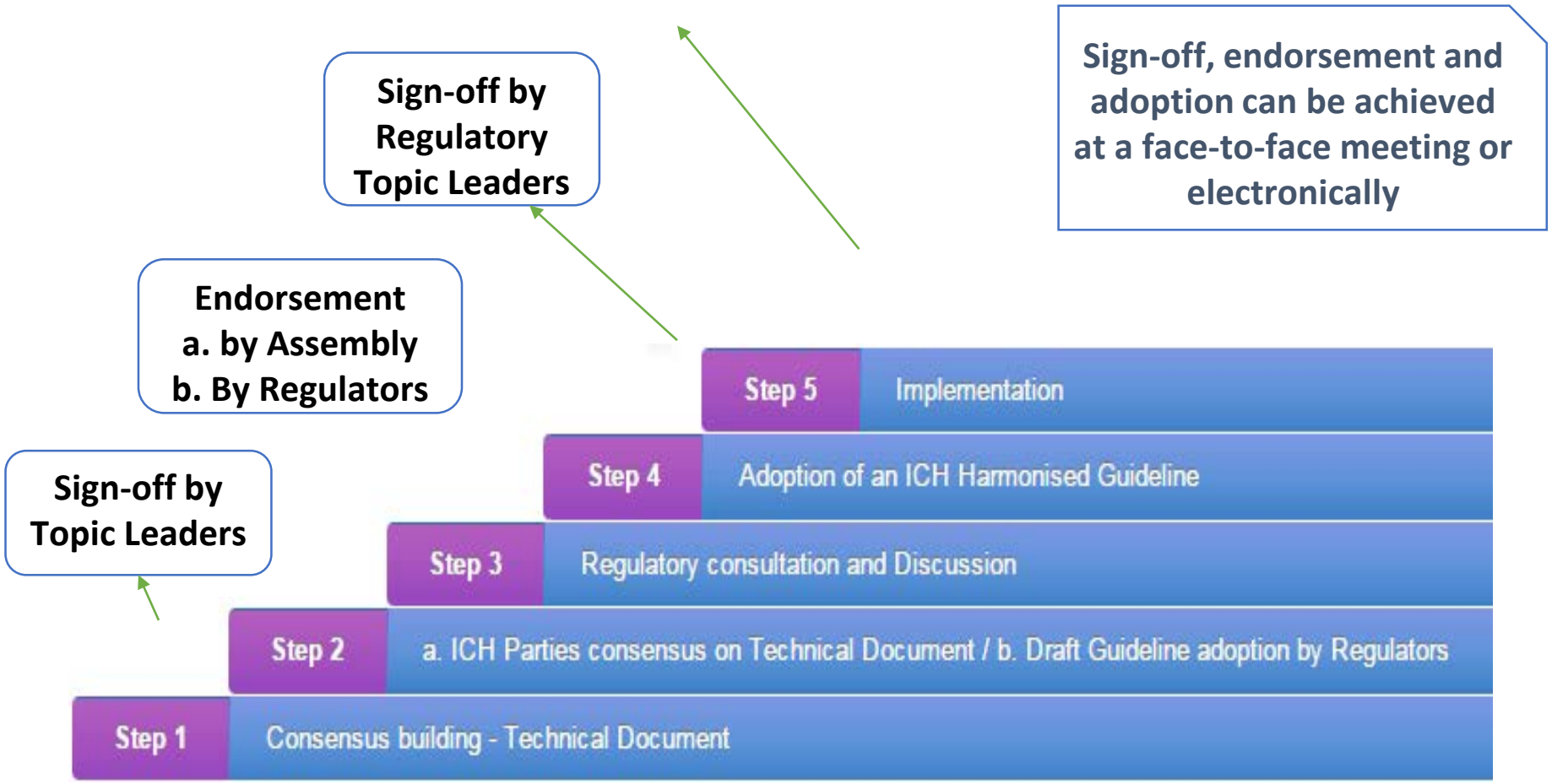
ICH Q5A(R2): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin Presentation for External Audience

Created November 2019

Disclaimer:

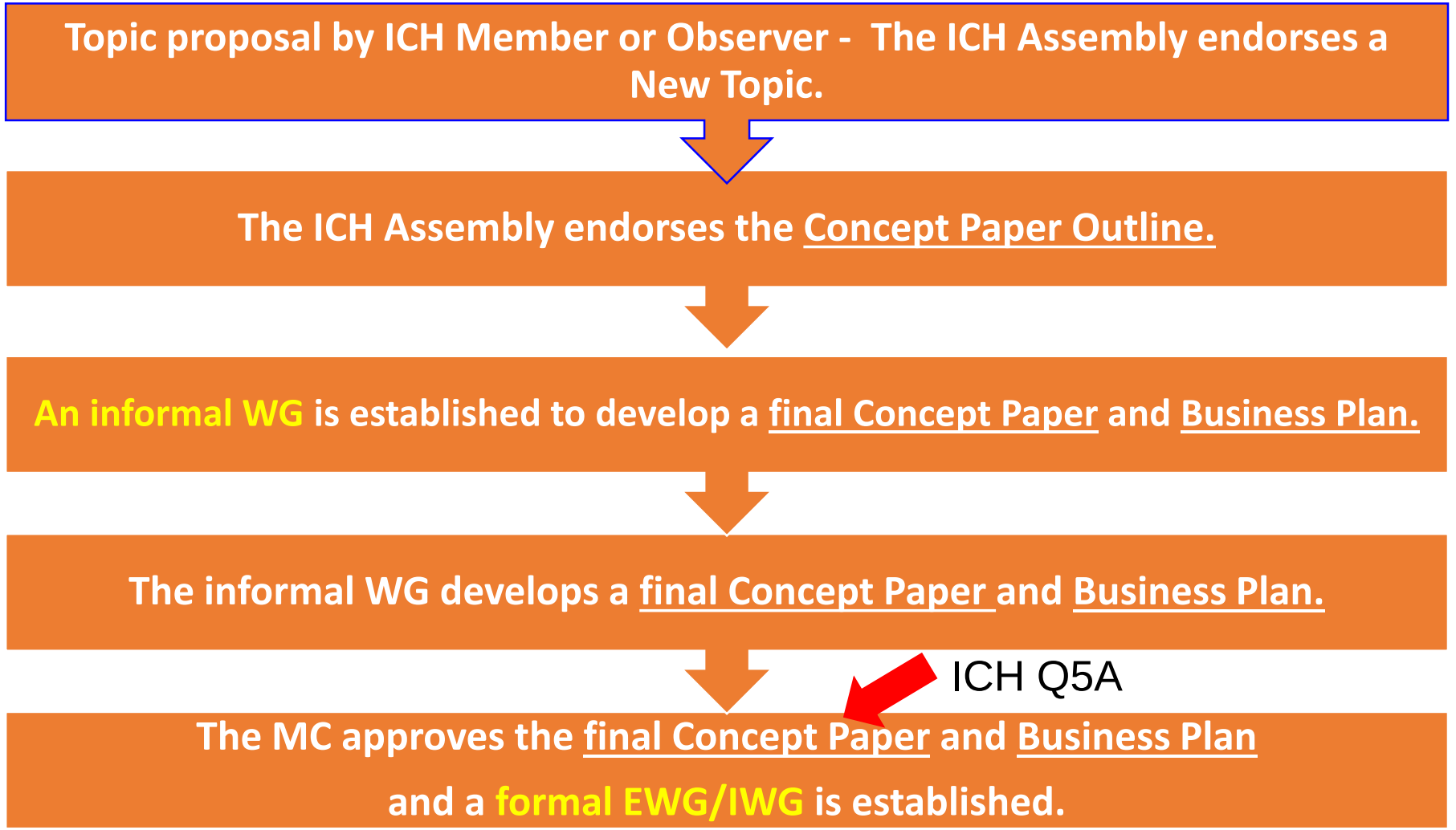
- Expert Working Group members are appointed by their nominating ICH Member or Observer party and are responsible for representing the views of that party, which may not necessarily reflect their personal views.
- Working Group experts do not respond personally to external inquires but are directed to forward any inquiries they receive to their nominating party or the ICH Secretariat for a response on behalf of either their ICH party or the ICH Association as appropriate.

Formal ICH Procedure



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

ICH Harmonisation Activities Before Step 1



Work Plan: Expected Future Key Milestones

Expected Future Completion Date	Milestones
Nov. 2019	Endorsement of Work Plan
Nov. 2019	Initiation of consensus building of work group
Nov. 2020	First draft of technical document
June 2021	Step 1 sign-off and Step 2 a/b endorsement
Nov. 2022	Step 3 sign-off and Step 4 adoption

ICH Q5A(R2) Expert Working Group Membership

Dr. Joel Welch, Rapporteur (FDA, United States)

Expert list

ANVISA, Brazil
Ms. Silmara Cristiane da Silveira Andreoli

EC, Europe
Johannes Blumel

EFPIA
Dr. Marie Murphy

FDA, United States
Dr. Arifa Khan
Dr. Cecilia Tami

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. Gi Hyun Kim

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

NMPA, China
Ms. Meng YANG

PhRMA
Lianchun Fan
Anne Stokes

Swissmedic, Switzerland
Dr. Christoph Berger

TFDA, Chinese Taipei
Mr. Hung Chang

TGA, Australia
Mr. Dennis Dowhan

USP
Dr. Fouad Atouf

WHO
Dr. Ivana Knezevic

History/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.
- Recognized that a revision was necessary to reflect current scientific knowledge and biotechnology advances:
  - manufacturing
  - emerging product types
  - analytical technologies
  - virus clearance validation strategies
- ICH Q5A(R2) Concept Paper Outline endorsed in Amsterdam in June 2019.
- ICH Q5A(R2) Concept Paper and Business Plan endorsed in Singapore in November 2019.

Progress Made at November 2019 Singapore Meeting

- Endorsement of Joel Welch, US FDA, as Rapporteur
- Discussion on the final language for the Concept Paper and Business Plan
  - Management Committee approval of the final versions
- Discussion and agreement on Work Plan
- Completion of initial outline of topics
- 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 via public scientific conferences

Progress made at Singapore Meeting (Cont'd)

- Agreed final themes for revision:
  - New classes of biotechnology products (e.g., virus-like particles (VLPs), subunit proteins, and viral-vectored products)
  - Additional validation approaches for virus clearance (e.g., modular validation)
  - New virus assays and alternative analytical methods (e.g., PCR, NGS)
  - Virus clearance validation and risk mitigation strategies for advanced manufacturing (e.g., continuous manufacturing)
  - Aspects of virus clearance validation that have emerged or evolved

New classes of biotechnology products

- 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.
  - May include: baculovirus-expressed VLPs and proteins; AAV vectors; adenovirus vectored 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.

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 processing of monoclonal antibodies
- 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.
  - 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

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.
  - 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.
- 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 (ICH Q7)
- Details for this topic will also support the ongoing development of ICH Q13, Continuous Manufacturing of Drug Substances and Drug Products.

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 discussions on the virus clearance safety margin, including calculation of clearance factors.
- Additionally, risk mitigation technologies for treatment of raw materials will be discussed.
  - For example: Virus inactivation of raw materials


WELL(C)HOME