Workshop on Global Harmonization of Specification:
Implementing A Patient-Centric, Enhanced Control Strategy

June 23, 2025 Tokyo

# ICH Q6 (R1) review status

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https://events.iabs.org/GHSW-2025

# Outline

1. Overview of the topic : Q6 (R1) Specifications

2. Current status of discussion in Q6 (R1) EWG

3. Enhanced approach for setting specifications

This presentation is a personal view and not representing the organization or ICH EWG.

# History from ICH Q6A/B to Q6 (R1)

1999 Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: **Chemical Substances**

Q6B Specifications: Test Procedures and Acceptance Criteria for **Biotechnological/Biological Products**

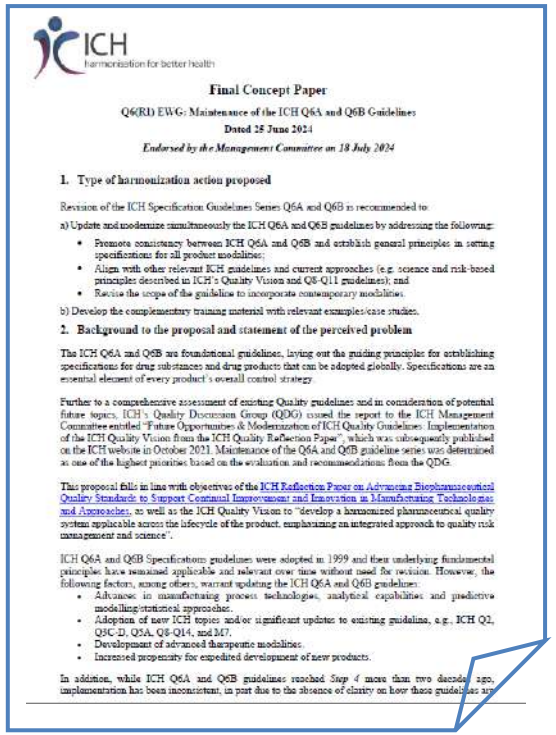
2020 **Q**uality **D**iscussion **G**roup Q6(R1) Concept Paper Outline

2024.3 Q6(R1) Informal Working Group

2024.6 **Fukuoka** meeting
Final Concept Paper endorsement
⇒ Q6(R1) Expert Working Group

2024.11 **Montreal** meeting

2025.5 **Madrid** meeting



ICH
harmonisation for better health

**Final Concept Paper**

**Q6(R1) EWG: Maintenance of the ICH Q6A and Q6B Guidelines**

**Dated 25 June 2024**

***Endorsed by the Management Committee on 18 July 2024***

**1. Type of harmonization action proposed**

Revision of the ICH Specification Guidelines Series Q6A and Q6B is recommended to:

a) Update and modernize simultaneously the ICH Q6A and Q6B guidelines by addressing the following:

- Promote consistency between ICH Q6A and Q6B and establish general principles in setting specifications for all product modalities;
- Align with other relevant ICH guidelines and current approaches (e.g. science and risk-based principles described in ICH's Quality Vision and Q8-Q11 guidelines); and
- Revise the scope of the guideline to incorporate contemporary modalities.

b) Develop the complementary training material with relevant examples/case studies.

**2. Background to the proposal and statement of the perceived problem**

The ICH Q6A and Q6B are foundational guidelines, laying out the guiding principles for establishing specifications for drug substances and drug products that can be adopted globally. Specifications are an essential element of every product's overall control strategy.

Further to a comprehensive assessment of existing Quality guidelines and in consideration of potential future topics, ICH's Quality Discussion Group (QDG) issued the report to the ICH Management Committee entitled "Future Opportunities & Modernization of ICH Quality Guidelines: Implementation of the ICH Quality Vision from the ICH Quality Reflection Paper", which was subsequently published on the ICH website in October 2021. Maintenance of the Q6A and Q6B guideline series was determined as one of the highest priorities based on the evaluation and recommendations from the QDG.

This proposal falls in line with objectives of the ICH Reflection Paper on Advancing Biopharmaceutical Quality Standards to Support Continual Improvement and Innovation in Manufacturing Technologies and Approaches, as well as the ICH Quality Vision to "develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product, emphasizing an integrated approach to quality risk management and science".

ICH Q6A and Q6B Specifications guidelines were adopted in 1999 and their underlying fundamental principles have remained applicable and relevant over time without need for revision. However, the following factors, among others, warrant updating the ICH Q6A and Q6B guidelines:

- Advances in manufacturing process technologies, analytical capabilities and predictive modelling/statistical approaches.
- Adoption of new ICH topics and/or significant updates to existing guideline, e.g., ICH Q2, Q3C-D, Q5A, Q8-Q14, and M7.
- Development of advanced therapeutic modalities.
- Increased propensity for expedited development of new products.

In addition, while ICH Q6A and Q6B guidelines reached *Step 4* more than two decades ago, implementation has been inconsistent, in part due to the absence of clarity on how these guidelines are

# Drivers for the revision

- New therapeutic modalities (e.g., ATMPs, oligonucleotides, etc.)
- New manufacturing process technologies (e.g., continuous mfg.) and analytical capabilities (e.g., RTRT)
- Adoption of new ICH topics and/or significant updates to existing guidelines (Q2(R2)/Q14, Q1/Q5C -> Q1, Q8-Q13)
- Introduction of Quality by Design, Control Strategy and risk/science-based concepts (Q8-Q11)
- Incorporating prior knowledge
- Increased need for expedited product development to address unmet medical needs

Cited and arranged from the presentation of Dr. Ingrid Marcovik
https://www.casss.org/docs/default-source/cmc-strategy-forum-japan/2024-speaker-presentations/markovic-ingrid-cber-fda-2024-session-iii-.pdf?sfvrsn=97a0d33_8

# Q6 (R1) Expert Working Group

## Regulatory Members (14)

ANVISA, Brazil
COFEPRIS, Mexico
EC, Europe
EDA, Egypt
FDA, United States
Health Canada, Canada
JFDA, Jordan
MFDS, Republic of Korea
MHLW/PMDA, Japan
MHRA, UK
NMPA, China
SFDA, Saudi Arabia
Swissmedic, Switzerland
TFDA, Chinese Taipei

## Industry Members (5)

BIO
EFPIA
IGBA
JPMA
PhRMA

## Observers (7)

ANPP, Algeria
APIC
EAC
EDQM
IFPMA
SAHPRA, South Africa
USP

https://www.ich.org/page/quality-guidelines

**Rapporteur** Ms. Silmara Cristiane da Silveira Andreoli (ANVISA, Brazil), Dr. Olivier Dirat (PhRMA)
**Regulatory Chair** Dr. Robin Levis (FDA, United States)

# Recommendations from Quality Discussion Group (QDG)

QDG, as part of their purview, recommended revision of Q6A and Q6B to reflect current scientific advances and address the following:

① ➢ Cover contemporary modalities and complex biological products
– considerable scope increase

② ➢ Expand scope to cover marketing authorization and commercial phase of product lifecycle

➢ Align with relevant ICH guidelines (Q1, Q2, Q8-Q14, M7, and others)

➢ Include science and risk-based approaches and not only reliance on batch data

③ ➢ Clarify pharmacopeial role in setting specification

①

# Scope of Q6A and Q6B

| Current | Q6A (1999) | Q6B (1999) |
|---|---|---|
| In scope | - Synthetic and semi-synthetic antibiotics<br>- Synthetic peptides of low molecular weight | - Proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates)… produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures<br>- Proteins and polypeptides isolated from tissues and body fluids |
| Out of scope | - Higher molecular weight peptides and polypeptides<br>- Radiopharmaceuticals<br>- Products of fermentation<br>- Oligonucleotides<br>- Herbal products<br>- Crude products of animal or plant origin | - Antibiotics<br>- Synthetic peptides and polypeptides<br>- Heparins<br>- Vitamins<br>- Cell metabolites<br>- DNA products<br>- Allergenic extracts<br>- Conventional vaccines<br>- Cells<br>- Whole blood<br>- Cellular blood components |

①

# Scope of Q6(R1)

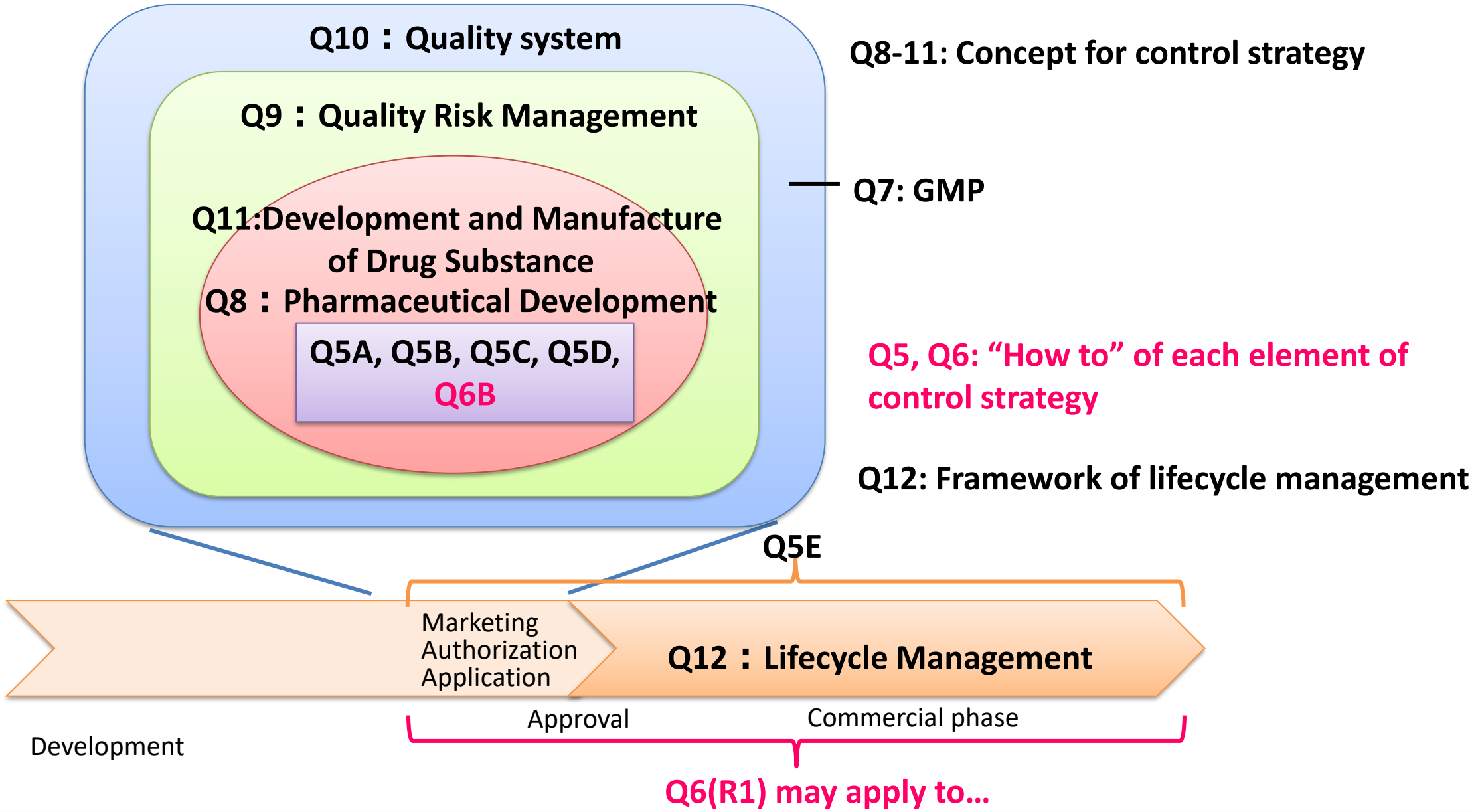
Update the scope to also include classes of drug substances and products both chemical entities and biologicals which were not sufficiently covered in ICH Q6A and Q6B

- (e.g. cell and gene therapies, vaccines, oligonucleotides, antibody-drug conjugates (ADCs), etc.);

- drug/biologic-device combination products that meet the definition of a pharmaceutical or biological product.

https://database.ich.org/sites/default/files/ICH_Q6%28R1%29_Final_**ConceptPaper**_2024_0625.pdf

# ② ICH Quality guidelines and product lifecycle



③

# Role of Pharmacopoeias in Setting Specifications

- Acknowledge the legal requirements where applicable
- Defer to existing pharmacopoeial recommendations regarding applicability of alternative analytical methods in setting specifications

# ③ Harmonisation of Pharmacopoeia is a different activity from Q6

**Q4B** "Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions"

| | |
|---|---|
| Q4B | Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions |
| Q4B(R1) | Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions |
| Q4B Annex 1(R1) | Residue on Ignition/Sulphated Ash General Chapter |
| Q4B Annex 2(R1) | Test for Extractable Volume of Parenteral Preparations General Chapter |
| Q4B Annex 3(R1) | Test for Particulate Contamination: Sub-Visible Particles General Chapter |
| Q4B Annex 4A(R1) | Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests General Chapter |
| Q4B Annex 4B(R1) | Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms General Chapter |
| Q4B Annex 4C(R1) | Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter |

| | |
|---|---|
| Q4B Annex 5(R1) | Disintegration Test General Chapter |
| Q4B Annex 6 | Uniformity of Dosage Units General Chapter |
| Q4B Annex 7(R2) | Dissolution Test General Chapter |
| Q4B Annex 8(R1) | Sterility Test General Chapter |
| Q4B Annex 9(R1) | Tablet Friability General Chapter |
| Q4B Annex 10(R1) | Polyacrylamide Gel Electrophoresis General Chapter |
| Q4B Annex 11 | Capillary Electrophoresis General Chapter |
| Q4B Annex 12 | Analytical Sieving General Chapter |
| Q4B Annex 13 | Bulk Density and Tapped Density of Powders General Chapter |
| Q4B Annex 14 | Bacterial Endotoxins Test General Chapter |

https://www.ich.org/page/quality-guidelines

Harmonisation of analytical procedures for general tests deeply contributes to the global harmonization of specifications.

# ③ Q4B Maintenance Procedure (Revised version as of May 2024)

- Because the inputs to the Q4B process were from the **Pharmacopoeial Discussion Group (PDG)** harmonisation process, it is recognised that the pharmacopoeial texts could be updated as technology and requirements change, or for other reasons.
- In November 2018, ICH and the **PDG** agreed to collaborate in the **maintenance** of the current ICH Q4B Annexes.

https://database.ich.org/sites/default/files/Annex%205%20-%20Maintenance%20of%20Q4B_Revised.pdf

**Pharmacopoeial Discussion Group**

| European Pharmacopoeia | US Pharmacopeia | Japanese Pharmacopoeia | Indian Pharmacopoeia |
|---|---|---|---|

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# Q6(R1) Guideline Structure

1. Introduction
2. General Principles
3. Considerations for Chemicals
4. Considerations for Biologicals
5. Glossary
6. References
7. Appendixes (if needed)

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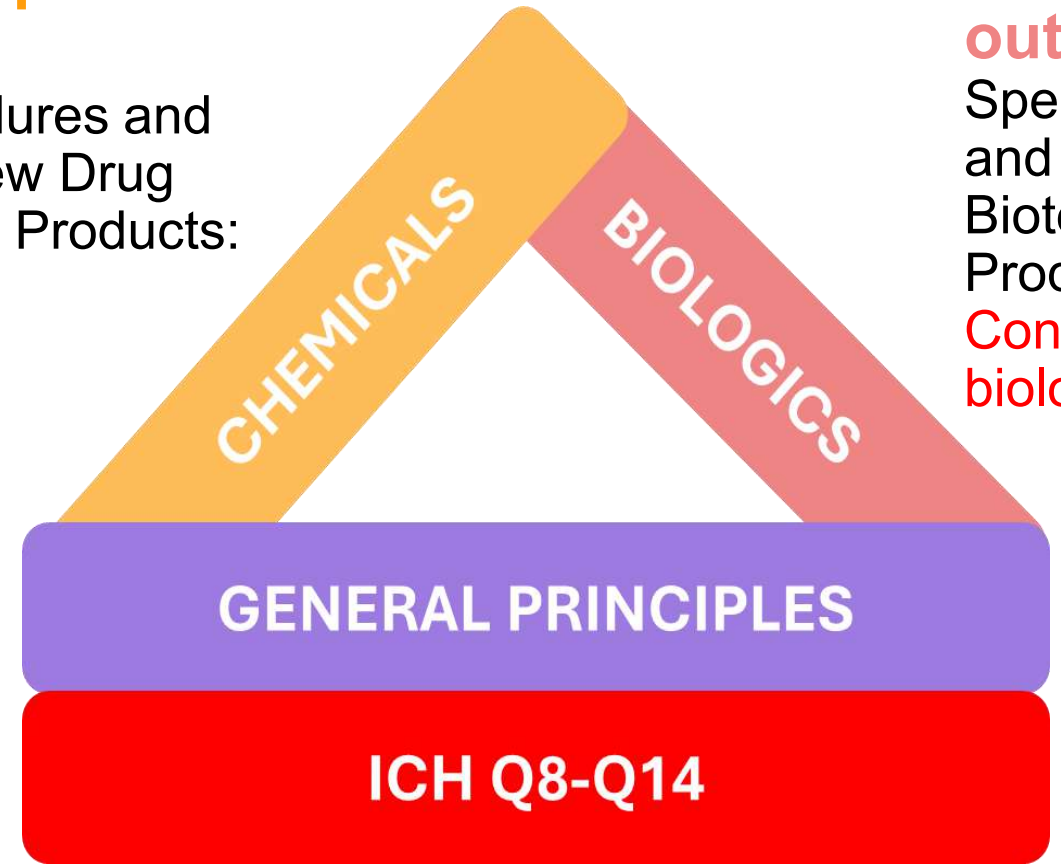
Annexes (if needed)

# Q6(R1) Strategy

**Leveraging the principles outlined in Q6A:**

Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances




**Leveraging the principles outlined in Q6B:**

Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Considerable expansion of biological modalities in scope

**Identifying common unifying principles applicable to all product types**

**Traditional and Enhanced approaches**

# Q6 EWG meetings with other ICH Groups

**Q6:Specifications**
Revision of Q6A/B

**Q1:Stability**
Revision of Q1/Q5C

- ✓ Meeting with Q1/Q5C members to align on expectations for shelf-life/stability specifications

**CGTDG:**
Cell and Gene Therapies Discussion Group

- ✓ Initial contact with CGTDG and Q6 leadership after Fukuoka meeting
- ✓ Montreal meeting - A formal in-person meeting with broader membership for alignment on expectations and ways of working together

# Q6(R1) : Current status of each section

## ◆General principles section

- Scientific approaches – Proposed how to apply the concept of science and risk-based approaches to specifications

## ◆Chemical and Biologics sections

- High level organisation of Chemicals and Biologics sections retain the Q6A and Q6B flow
- Chemicals: Significant expansion of dosage forms included and contemporising of Q6A contents
- Biologicals: Significant expansion of modalities covered and contemporising of Q6B contents

# Draft document review status of Q6(R1)

EWG reviewed the draft document before the Madrid meeting in May 2025.

- First time all 3 sections were reviewed together by the EWG
- 1110 comments received from EWG

**Topics identified for discussion in Madrid:**

- Role of specifications in control strategy
- Manufacturing consistency role in setting acceptance criteria
- Description of traditional and enhanced approaches to setting specifications
- Drug-device combination products considerations in Q6
- Decision criteria for annexes to be included
- Flow, redundancies and interplay between sections

# Decisions to include Annexes for Vaccine and ATMPs

Because,

- Products submitted globally
- Products have significant numbers of unique aspects that are not covered by the core guideline
- Fast evolving landscape for these products (Annexes can be updated independently from the core guideline)

1. Introduction
2. General Principles
3. Considerations for Chemicals
4. Considerations for Biologicals
5. Glossary
6. References

Appendixes (if needed)

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Annexes (Vaccine, ATMPs)

# Product type specific issues in setting specifications

EWG to perform a gap analysis for other products with unique aspects to determine if additional information is needed and where to place it, or if they should be excluded from the scope

For example,

- Synthetic peptides
- Oligonucleotides
- ADCs
- Plasma derived products
- Radiopharmaceuticals
- Fermentation products
- Herbal medicinal products
- Allergens, etc…

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# Modernisation of Q6 guidelines

The modern regulatory perspective emphasizes a science and risk-based approach for establishing specifications.
Therefore, updating ICH Q6A and Q6B introduces an opportunity to set specification based on holistic approaches that would include e.g.:

- Appropriate use of prior knowledge;
- Appropriate use of pharmaceutical development data;
- Prospective process and product (CQA and CPP) understanding;
- Considerations of the overall control strategy;
- Appropriate use of modelling tools and statistical evaluations;
- Non-clinical and clinical relevance;
- Impact to the safety and efficacy of the drug product.

https://database.ich.org/sites/default/files/ICH_Q6%28R1%29_Final_**ConceptPaper**_2024_0625.pdf

# Principles for consideration in setting specifications (Q6B)

## Process Controls

manufacturing variability

- ✓ Process-related considerations
- ✓ In-process acceptance criteria and action limits
- ✓ Raw materials and excipient specifications

## Characterisation

- ✓ Physicochemical properties
- ✓ Biological activity
- ✓ Immunochemical properties
- ✓ Purity, impurities and contaminants
- ✓ Quantity

## Analytical Considerations

- ✓ Reference standards / materials
- ✓ Validation of analytical procedures

analytical variability

## Statistical Concepts

Safety and Efficacy

## Batch data

used in non-clinical and/or clinical studies

## Specifications

- attribute requiring testing
- analytical procedure
- acceptance criteria

## Release Limits vs. Shelf-life Limits

stability

**Pharmacopoeial Specifications** (if applicable)

# Approaches for development and manufacturing of drug substance (Q11)

## Traditional approach

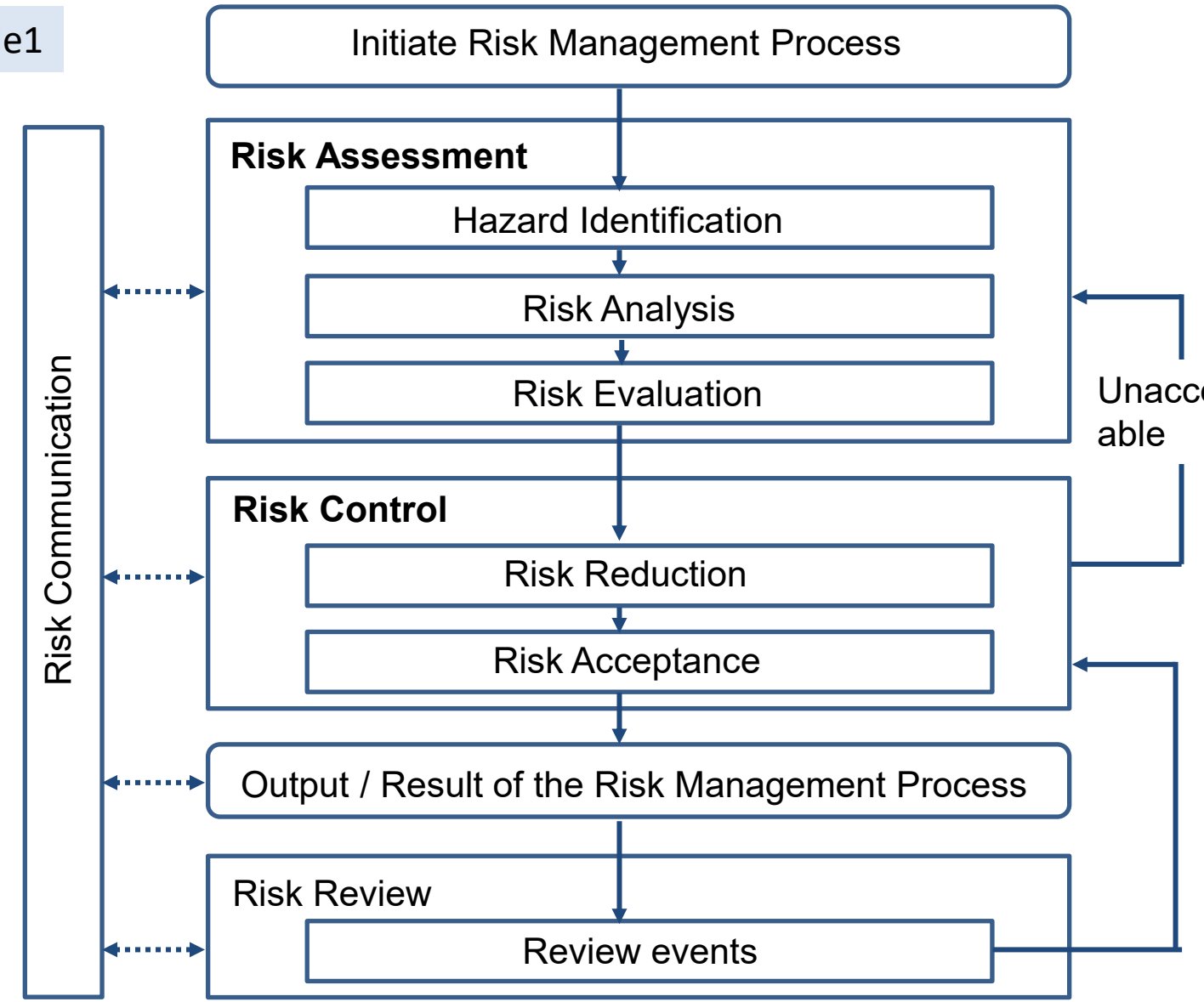
- ✓ Set points and operating ranges for process parameters are defined
- ✓ The drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria.

## Enhanced approach

- ✓ Risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs)
- ✓ Develop appropriate control strategies applicable over the lifecycle of the drug substance which may include the establishment of design space(s).

# Overview of typical risk management process

ICH Q9(R1) Table1




QTPP

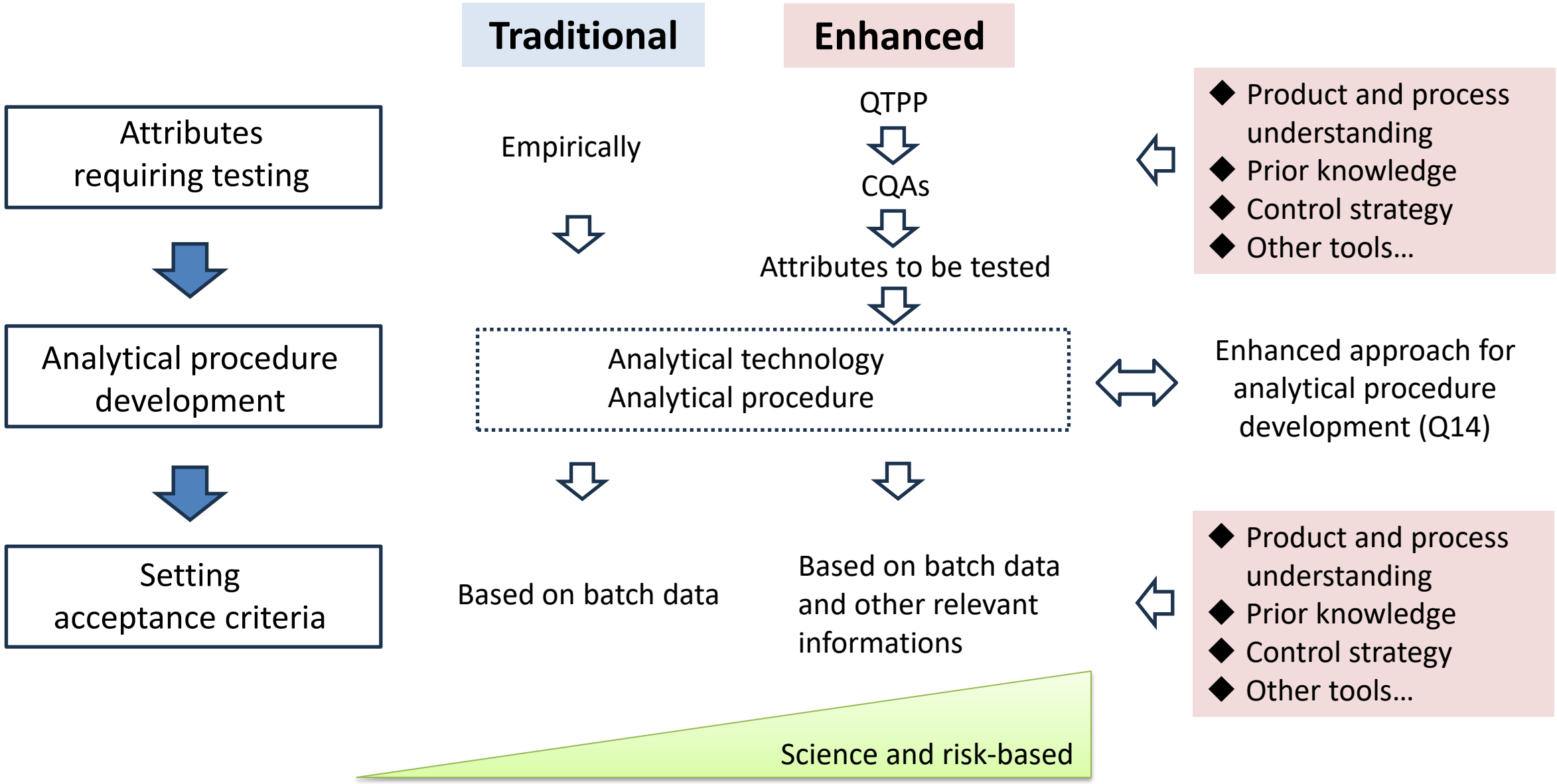
CQA

Acceptable range

Control strategy

- Process control
- Specifications
- Other items

# Approaches for setting specifications



# Terminology: *Patient Centric Specifications*

Is there any needs to introduce new terminologies for ICH Q6(R1)?

**Consensus by EWG**:

- Not to introduce new terminologies in ICH Q6(R1) unless it is necessary
- Support use of science- and risk-based concept/tools developed in Q8-Q14

**Rationale**

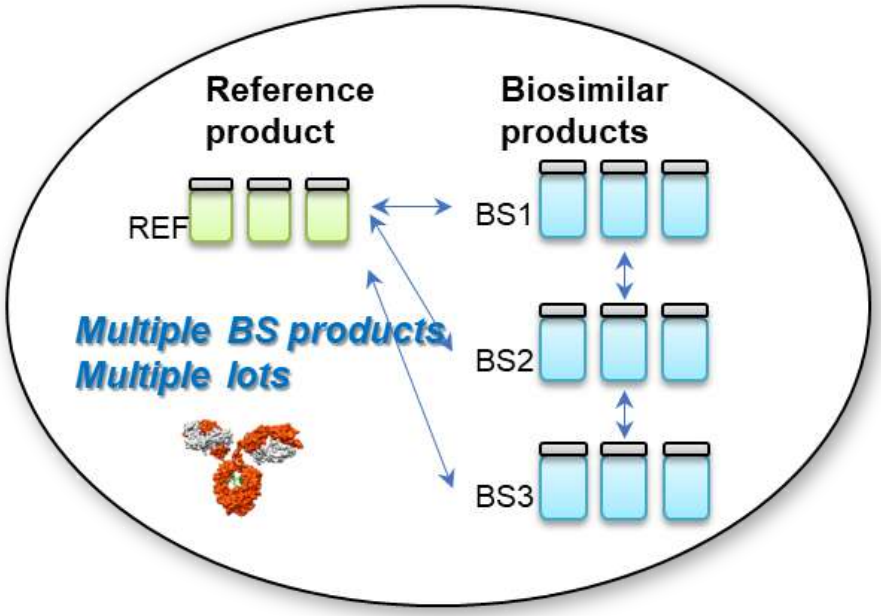
- New terminology could mislead readers and increase complexity.

  Both "**traditional**" and "**enhanced**" approaches are **patient centric and relevant to patients.**

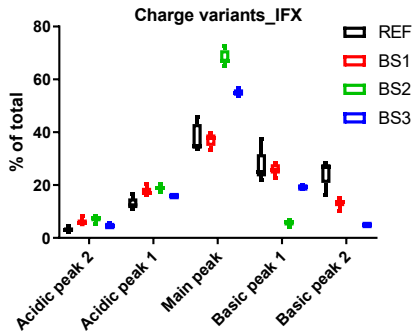
- Science- and risk-based approaches used in Q-guidelines, e.g.,Q8-14 already covered patient relevant concept
- One of the objectives for Q6(R1) is to modernize in line other Q-guidelines.

# Additional information for discussion
# Examples: Characterisation of innovator and biosimilar mAbs approved in Japan

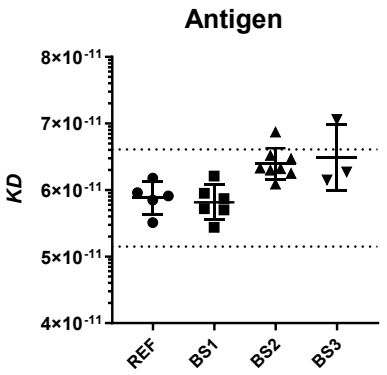
Infliximab
Trastuzumab
Rituximab
Bevacizumab
Etanercept

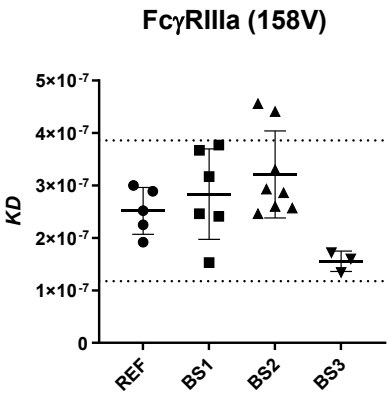



## Charge heterogeneity

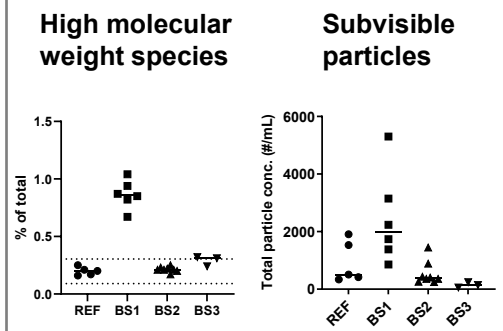



## Binding affinity

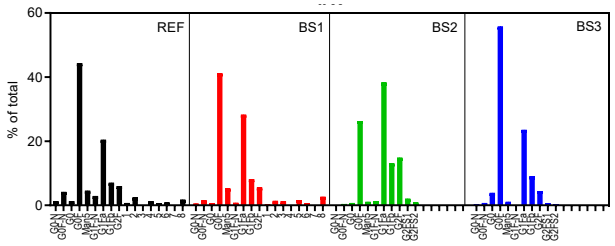


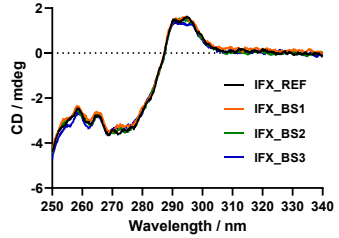

## Aggregates & Subvisible particles




## Glycan profile



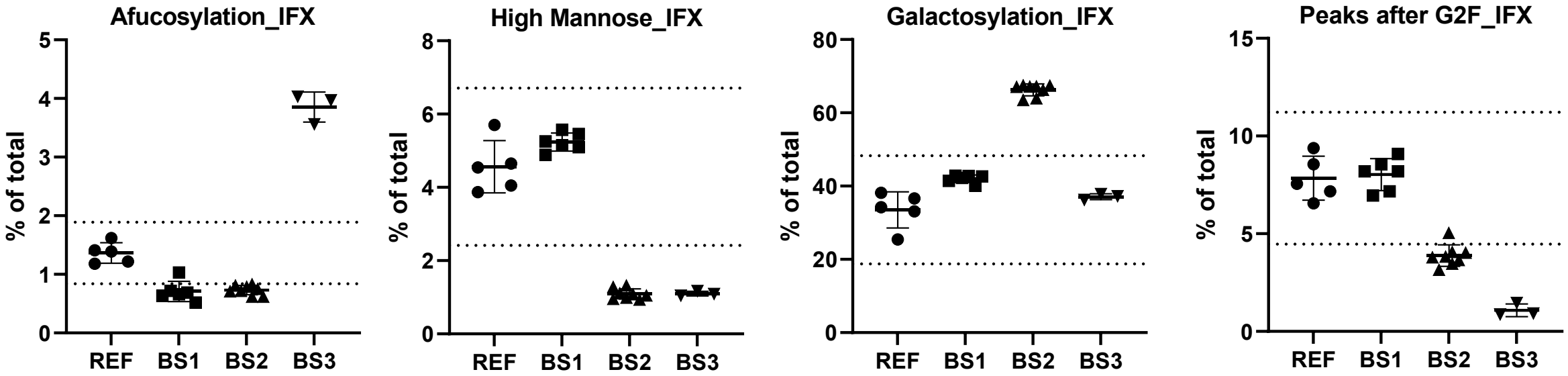

## Higher order structure




Shibata H. et al. BioDrugs. 2025. doi: 10.1007/s40259-025-00722-4.

# Additional information for discussion
# Examples: Glycan analysis of innovator and biosimilar mAbs

Four products (REF and BS1,2,3) approved via clinical studies, and meet the same efficacy and safety criteria. However, the glycan profile is different.




Infliximab

REF: reference product, BS: biosimilar

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Quality range (3SD)

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Can we use these data as prior knowledge for setting specification of glycan profile for other mAbs with related structure and indications?

- ✓ CQA or non-CQA
- ✓ Acceptance criteria setting



Shibata H. et al. BioDrugs. 2025. doi: 10.1007/s40259-025-00722-4.

# Key Takeaways

EWG acknowledges that the application of science and risk-based principles and a continuum of process and product knowledge are essential elements for modernization of specification setting.

EWG agreement on how to include science and risk-based approaches for specification setting

- Defined traditional and enhanced approaches to setting specifications
- Scientific knowledge applied to justify specifications according to enhanced and traditional approaches.
- Application of principles to different modalities was discussed with case studies

# Anticipated Benefits of Q6(R1)

Patient Access

Global Specification Standards

More efficient product development


More efficient & consistent assessment

Enhanced communication

- Enable access to high-quality, safe and effective medicines to patients world-wide
- Enable globally harmonized approach to setting specs using science- and risk-based principles and ensuring robust testing strategies to assure product quality
- Facilitate global development with globally harmonized approach to setting specs clarifying regulatory expectations
- Improve efficiency and consistency in regulatory assessment and decision-making
- Enhanced communication between industry and regulators by bringing everyone on the same page

Cited from the presentation of Dr. Ingrid Marcovik
https://www.casss.org/docs/default-source/cmc-strategy-forum-japan/2024-speaker-presentations/markovic-ingrid-cber-fda-2024-session-iii-.pdf?sfvrsn=97a0d33_8

# Work plan: Expected future Key Milestones

| Expected Completion date | Deliverable |
|---|---|
| **Jun. 2026** | • Step 1 and 2a/b Sign-off<br>• Step 2 presentation<br>• Initiate work on training material |
| **Jun. 2028** | • Step 3 and 4 Sign-off<br>• Step 4 presentation |

# Acknowledgements


**Q6(R1)EWG**

| | |
|---|---|
| IABS Workshop in Tokyo | Scientific Committee:<br>Dr. Cristiana Campa, Dr. Andrew Chang, Dr. Cecilia Tami, Dr. Robin Levis<br>Speakers and Panelists:<br>Dr. Emmanuelle Charton, Dr. Horacio Pappa, Dr. Takahiro Yamaguchi |
| MHLW/PMDA | Dr. Atsuko Oimura |
| Co-Rapporteur | Dr. Silmara Cristiane da Silveira Andreoli, Dr. Olivier Dirat |

**NIHS, JP**

Dr. Hiroko Shibata



## Thank you for your attention !