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AsahiKASEI

ICH Q6 Revision towards globally harmonized specifications

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Outlines

1. Introduction
   - Advancement from endorsement of Q6
   - Reasons for Q6 revision

2. Expectations and challenges for Q6 revision
   - Principles for specification setting
   - Prior knowledge
   - Holistic control strategy

Biological Product Growth

Red: recombinant protein

Global Sales in 2000		
Rank	**Brand Name**	**Sales (USD M)**
1	Prilosec/Losec	6,260
2	Zocor/Lipovas	5,280
3	Lipitor	5,031
4	Norvasc	3,362
5	Pravachol/Mevalotin	3,348
6	Claritin	3,011
7	Prevacid/Takepron	2,956
8	Procrit	2,709
9	Celebrex	2,641
10	Prozac	2,574

Source: *Uto Brain News Release (https://www.utobrain.co.jp/news-release/2001/070600/ubrelease200107.pdf)*

Global Sales in 2023		
Rank	**Brand Name**	**Sales (USD M)**
1	Keytruda	25,011
2	Comirnaty	15,305
3	Humira	14,404
4	Ozempic	13,892
5	Eylea	12,876
6	Eliquis	12,206
7	Biktarvy	11,850
8	Dupixent	11,590
9	Stelara	10,858
10	Darzalex	9,744

Source: *Drug Discovery and Development (https://www.drugdiscoverytrends.com/best-selling-pharmaceuticals-2023/)*

Advancements in Biological Field

- Manufacturing technology
  - Engineering: in-silico design, developability evaluation, machine learning
  - Expression system: target integration, rapid clone selection, host cell engineering
  - Manufacturing process: chemical-defined media, high-capacity resin, platform technology
  - Equipment: single-use technology

- Analytical technology
  - Mass spectrometry, multiple attribute method
  - Next generation sequencing
  - Analytical kit, automation

These advancements lead to:

- deep product and process understanding
- development biopharmaceutical product with enhanced quality, safety, and efficacy
- accelerated development of therapeutic biologics and availability to patients

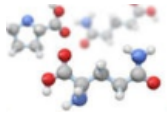
ICH Q6 Guidelines

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

Q6A

Current *Step 4* version

dated 6 October 1999



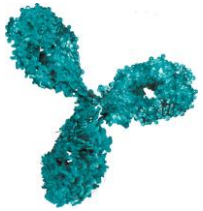
Scope:
Chemical new drug substance and products

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS

Q6B

Current *Step 4* version

dated 10 March 1999



Scope:
Proteins and polypeptides produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized

ICH Q6A and Q6B were finalized in 1999. These guidelines address setting specifications for chemicals and some specific biological products, respectively.

Relevant Guideline Updates

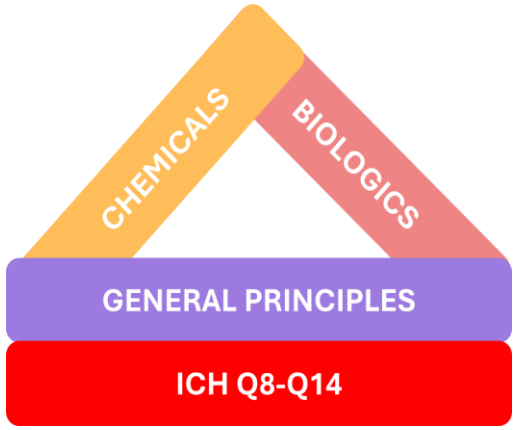
1999	Q6 Specifications	Quality by Testing
2005	Q8 Pharmaceutical Development	Quality by Design Science and risk-based approach
	Q9 Quality Risk Management	
2008	Q10 Pharmaceutical Quality System	
2011	Q11 Development and Manufacture of Drug Substances	
2014	M7 Mutagenic Impurities	
2014	Q3D Elemental Impurity	
2019	Q12 Lifecycle Management	
2022	Q13 Continuous Manufacturing	
2023	Q2(R2) Analytical Validation	
	Q14 Analytical Procedure Development	

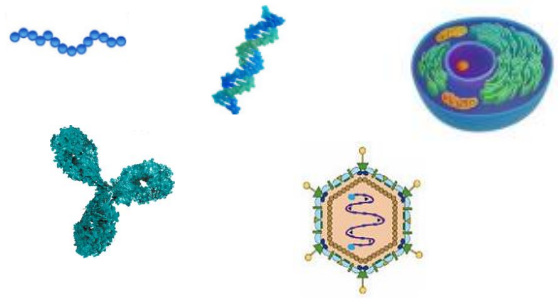
Need for Q6A and B update

- Promote consistency between ICH Q6A and Q6B and establish general principles
- Align with relevant ICH guidelines and science and risk-based approaches
- Revise the scope to incorporate contemporary modalities
- Include science and risk-based approaches and not only reliance on batch data
- Include considerations on lifecycle management of specifications
- Develop the complementary training material with relevant examples/case studies.

etc.

From Q6(R1) Concept paper with small modifications





Principles for Specification Setting per Q6B

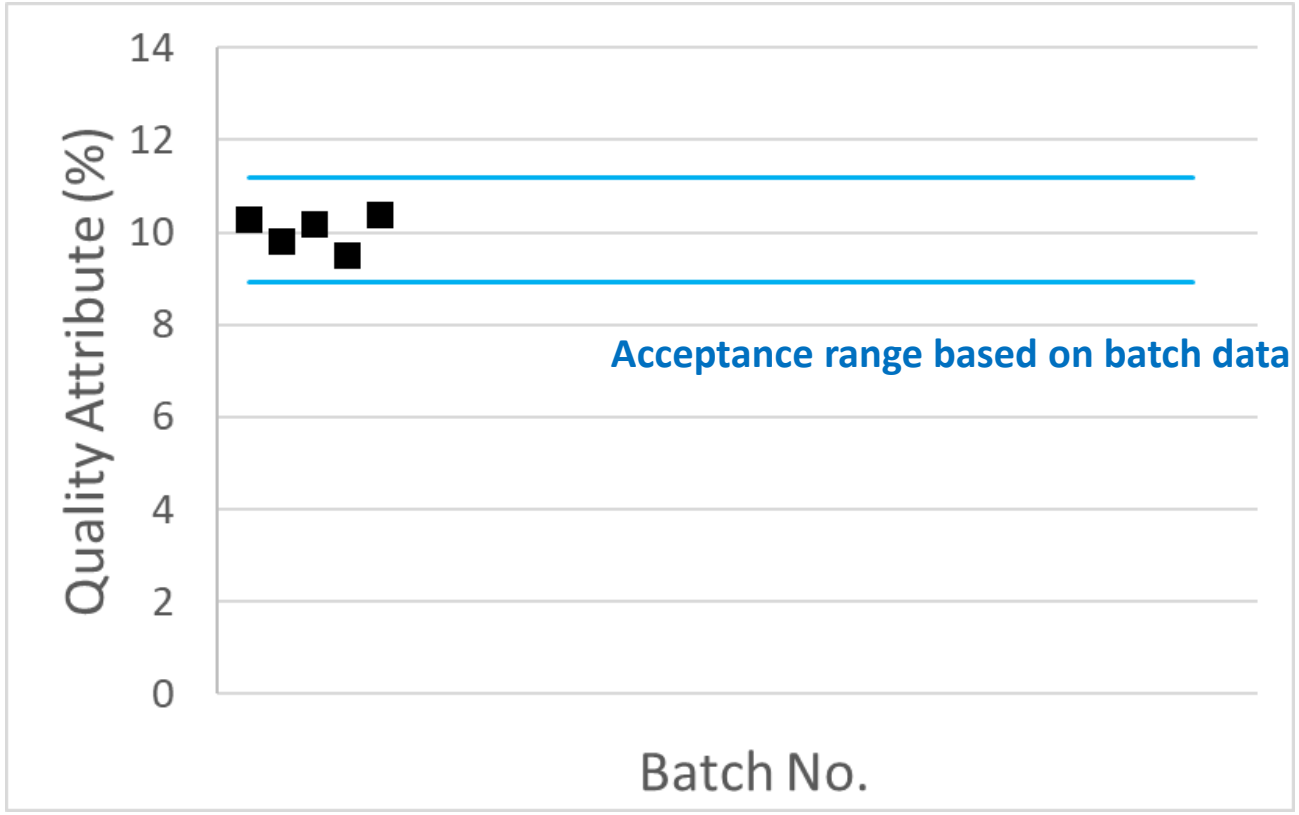
Q6B says

- Specifications […] should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.
- Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, and data from stability studies, and relevant development data.
- Further, the acceptance criteria for impurities should be based on data obtained from lots used in preclinical and clinical studies and manufacturing consistency lots.
- Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency.
- Specifications should be based on data obtained for lots used in pre-clinical and clinical studies. The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies.

But …

- Available data is limited at the marketing authorization application
- Difficult to predict manufacturing variability occurred in commercial stage

Possible scenario 1

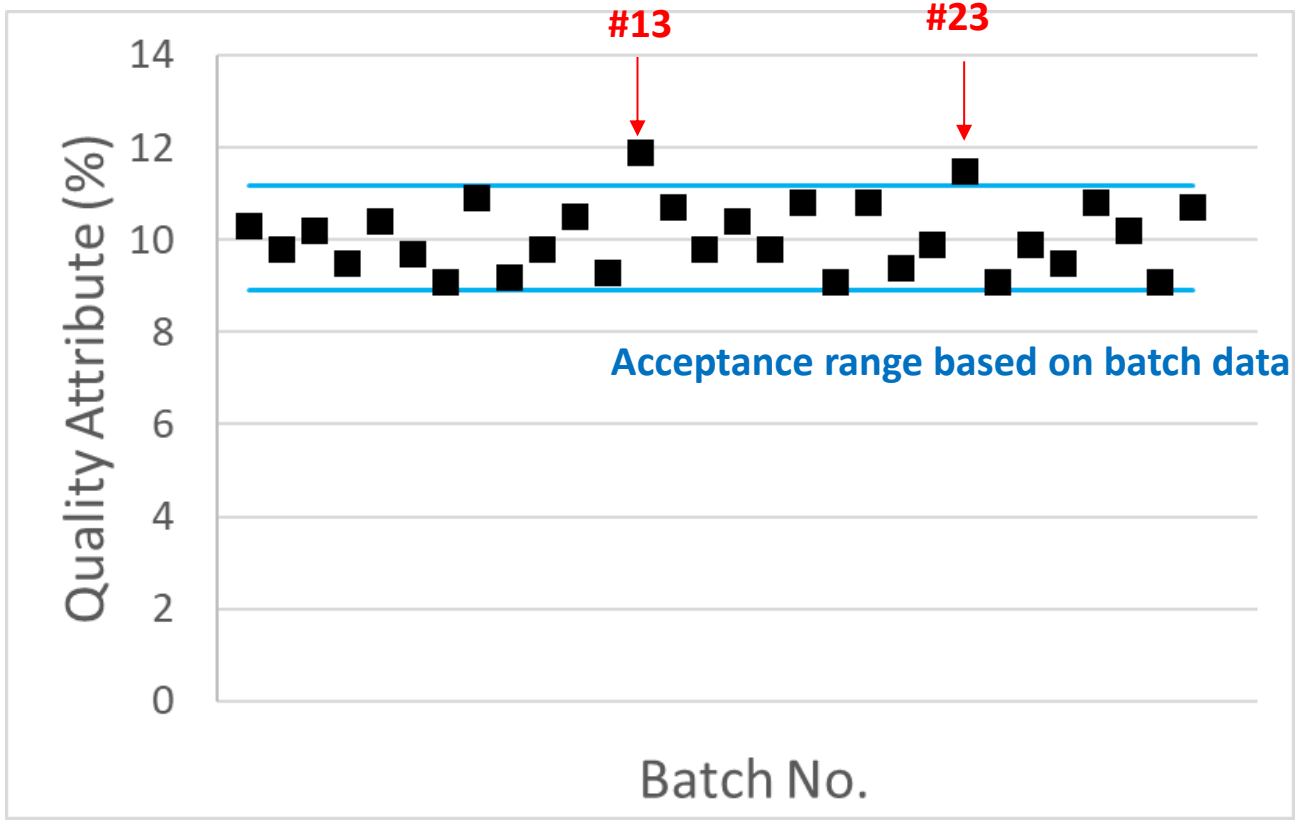


At the marketing authorization application

- Acceptance criteria is set based on the batch data available at the marketing authorization application.
- Batch data shows less variable, leading to narrow acceptable range.

What happens in commercial stage?

Possible scenario 1

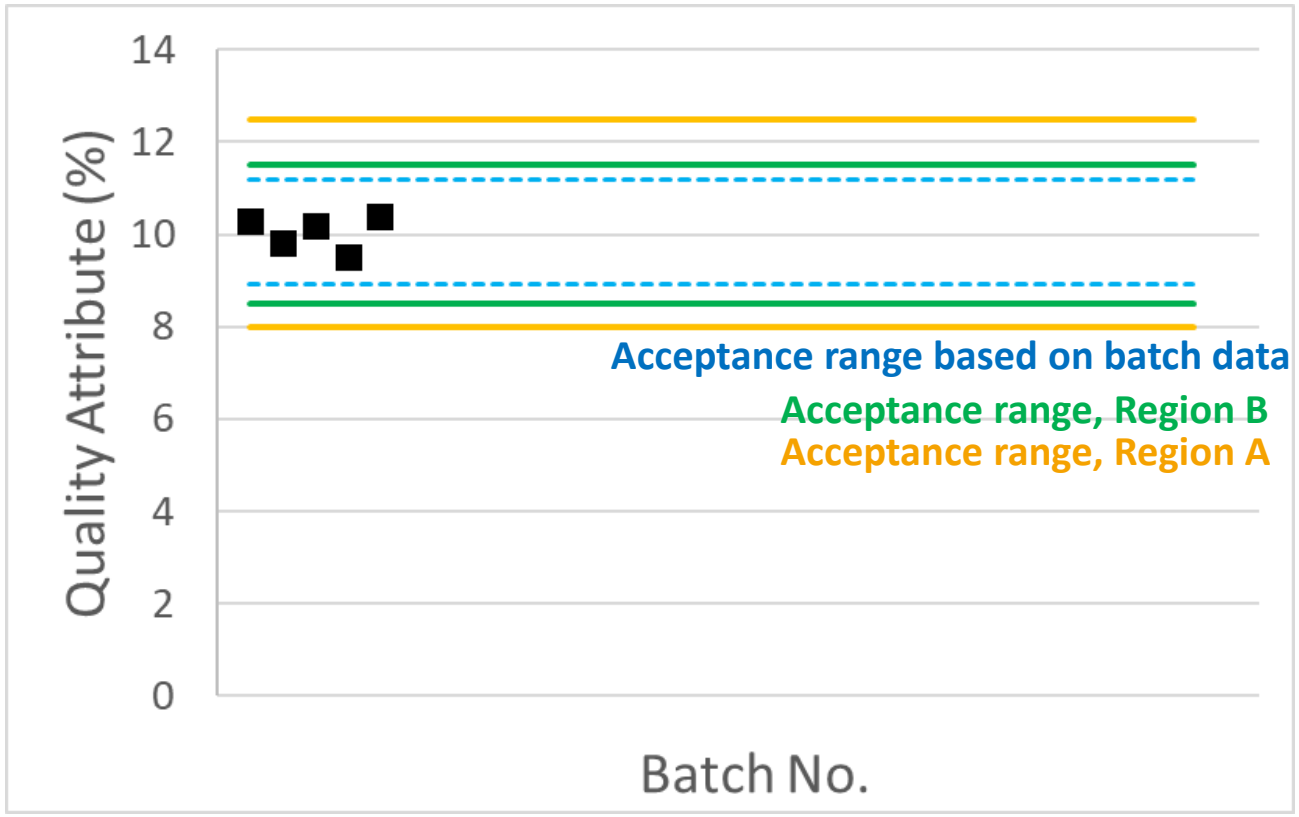


Commercial stage

- Larger variations are observed, due to raw material lot change, equipment change, etc.
- Manufacturer needs to alleviate variability to meet the acceptance range, e.g. select appropriate raw material lots, change manufacturing process.
- If the original acceptable range is inappropriate, regulatory procedure is initiated to change it.

- This leads to lot failures, cost increases, and regulatory interactions.
- High hurdle exists to widen acceptance criteria in post-approval phase.
- Acceptance criteria is sometimes burden to further improvements.

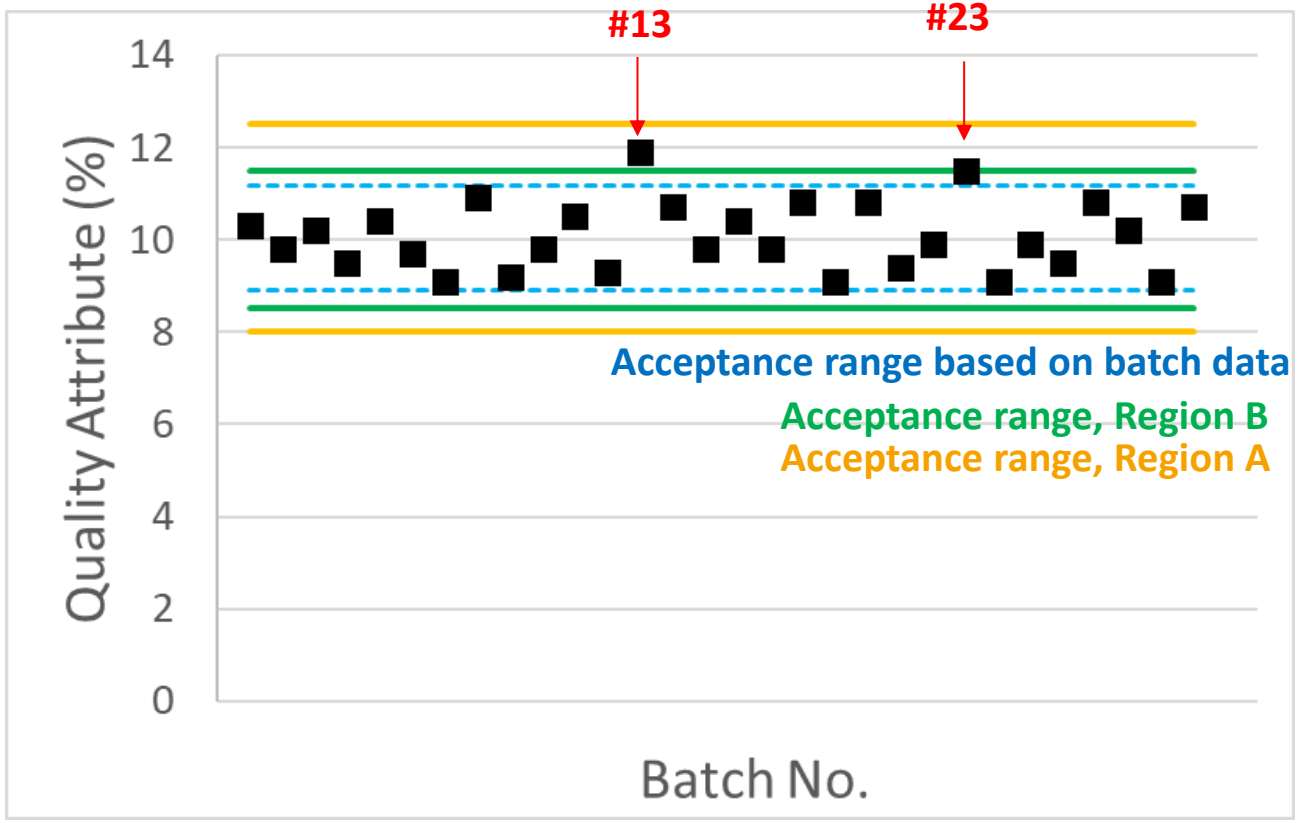
Possible scenario 2



At the marketing authorization application

- Acceptance criteria is set based on the batch data available at the marketing authorization application.
- Manufacturer negotiates a wider acceptance range by utilizing development data, but the approved acceptance range is different among the registration regions.

Possible scenario 2

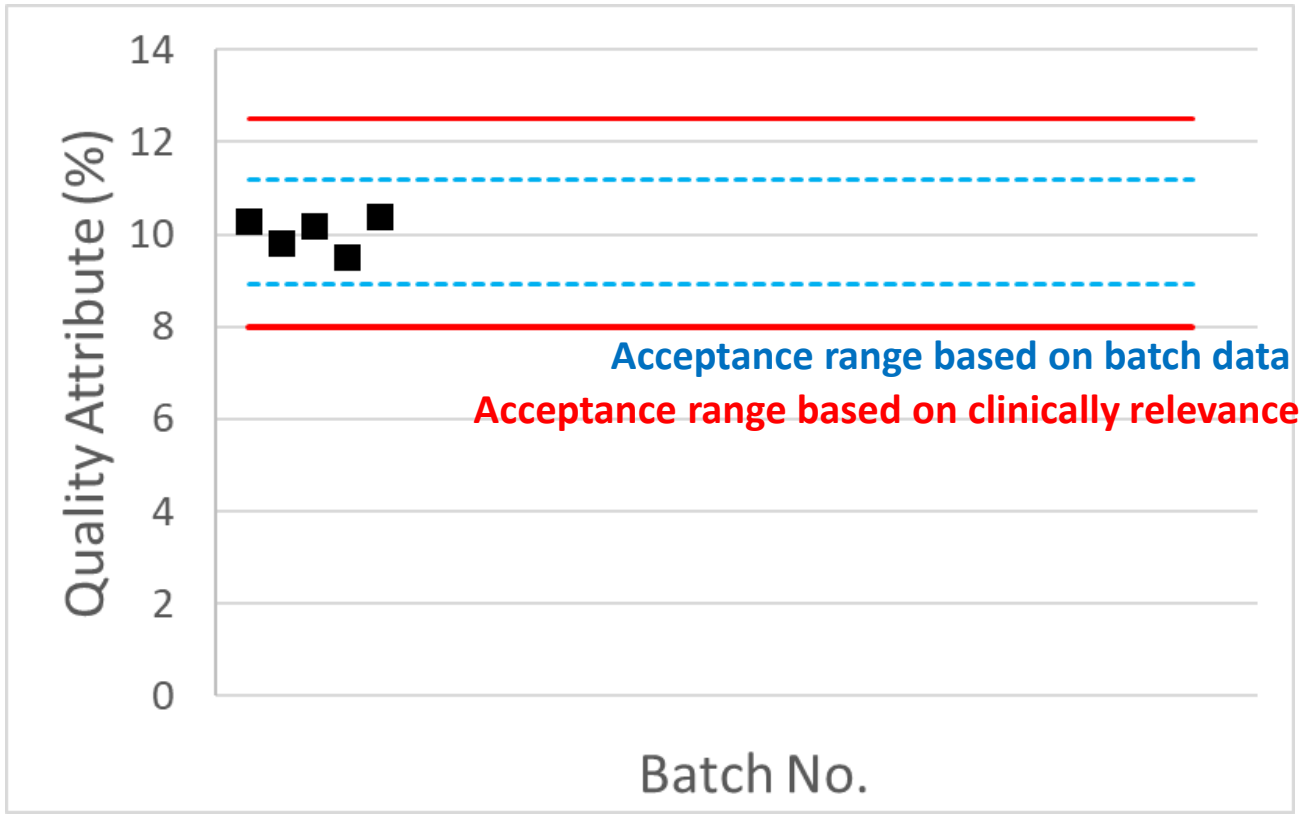


Commercial stage

- Larger variations are observed, due to raw material lot change, equipment change, etc.
- Batch#23 meets acceptable range of region A and B, but batch#13 meets only that of region A.
- Manufacturer needs to manage drug supply according to specifications in each region.

- This leads to lot failures in some regions and tricky supply management.
- High hurdle exists to widen acceptance criteria in post-approval phase.
- Acceptance criteria is sometimes burden to further improvements.

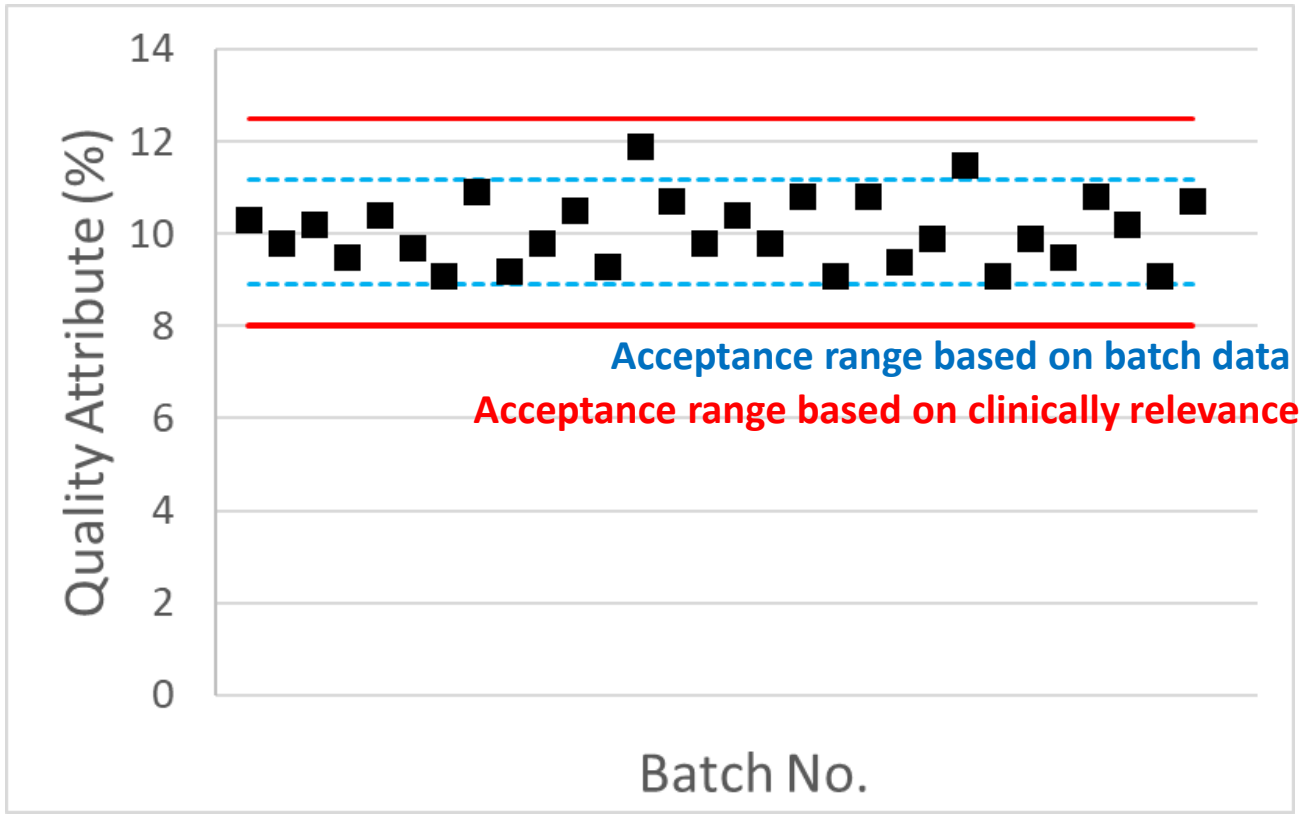
Possible scenario 3



At the marketing authorization application

- Acceptance criteria is set based on clinical relevance, e.g. safety and efficacy.
- Proposed range is wider than that based on the batch data but fully justified and accepted in every region.

Possible scenario 3



Commercial stage

- Manufacturer can supply all drug that meets the clinically relevant specifications.
- OOT/OOE lot is investigated according to GMP system.
- Manufacturer has flexibilities for further process improvement.

- This leads to stable drug supply and to improve patient access in global market.
- Manufacturer has a chance for further process improvement within the approved range.

Modernization of Specification Setting

Essential elements for modernization of specification setting:
- Application of science and risk-based principles
- Continuum of process and product knowledge

Possible solutions
- Characterization data
- Structure-function relationship
- Nonclinical and clinical data
- Prior knowledge

> Process and product understanding

Further discussion is needed by EWG.

Prior knowledge

Ex) Monoclonal antibody

- Platform: host cell, manufacturing process, analytical methods
- Prior knowledge: internal data, scientific literature
  - process related impurities, e.g. host cell protein, host cell DNA, residual Protein A
  - product related impurities, e.g. charge variant, C-term Lys, aggregate
  - stability prediction

Benefit

- Accelerate development
- Improve process/product understanding

Challenge

- Amount and quality of prior knowledge

Holistic control strategy

Some attributes may not need to be included into specifications based on results of suitable studies, or could be controlled by in-process parameter, in-process monitoring/control instead of release testing.

Ex)

- Process-related impurities, e.g. host cell protein, host cell DNA, residual protein
- General properties, e.g. pH, osmolarity
- Glycan
- Surfactant content

Benefits

- Shorten release testing period
- Increase the amount of release product
- Facilitate the use of RTRT

Further discussion is needed by EWG.

mAb Drug Substance specification example

Quality Attribute		Analytical method
Description		Visual inspection
Identification		Peptide map: HPLC-US, HPLC-MS Ion exchange: HPLC
pH		Compendial
Osmolarity		Compendial
Glycan profile		HILIC-UV
Product-related impurities	Charge variant	Ion exchange HPLC, icIEF
	Size variant	Size exclusion chromatography, Capillary SDS electrophoresis
Process-related impurities	Host cell protein	ELISA
	Host cell DNA	qPCR
	Residual protein A	ELISA
Endotoxin		Compendial
Microbial limit		Compendial
Potency		Cell-based assay, Binding
Assay (Protein content)		UV
Excipient or surfactant		HPLC

- Process-related impurities could be dropped off from specifications considering manufacturing process performance.
- Some attributes duplicated for DS and DP might be abbreviated considering quality change between DS and DP.

Expectations and Challenges for Q6 revision

Science and risk-based approach

- Align with Q8-Q11
- Establish general principles for globally harmonized specifications
- Establish general principles for setting clinically relevant specifications and manufacturing-based specifications
- Utilize prior knowledge for specification setting

Lifecycle management and continuous improvement

- Align with Q12 principles
- Facilitate the implementation of new manufacturing process and analytical method (link with Q13, Q14)

Modality

- Generalize principles applicable various modalities
- Annexes and/or training materials to supplement high level guideline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