Setting Specifications: Impact of Regulatory Harmonization

Bénédicte Mouterde & Patrice Riou
Global Analytical Sciences, Sanofi Vaccine, Marcy l'Etoile, France

IABS Workshop on Global Harmonization of Specification: Implementing A Patient-Centric Control Strategy - June 23-25th 2025 Tokyo, Japan

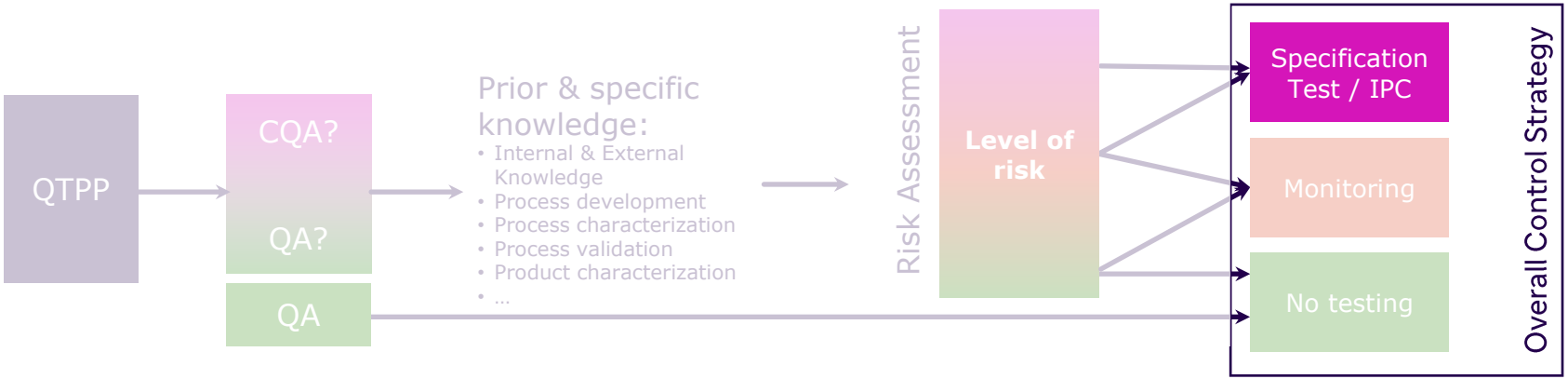
Agenda

- Regulatory landscape
- How we set specifications: challenges
- Regulatory harmonization efforts
- Regulatory harmonization challenges
- Impact of lack of harmonization in regulatory standards
- Conclusion and Suggestions

Regulatory landscape for setting specifications

	ICH	WHO	Europe	Japan	China	USA
Law, regulation						21CFR610
Pharmaco-poeia		(Int. Ph.)	Ph. Eur.	JP	ChP	USP
Guidelines	ICH Q6A/B	TRSXXX	EMA			FDA
Other standards				MRBP		
Reviewers			EMA	PMDA	CDE	FDA

Setting Specifications within an Overall Control Strategy



Specifications definition is one part of the Overall Control Strategy

- Step(s) where the CQA should be controlled (raw material, starting material, DS, DP)
- Choice of the analytical method(s):
  - Compendial method(s) in Pharmacopoeias? If yes, are they harmonized?
  - Possibility to use an alternative method?
- Definition of the acceptance criterion (product knowledge, risk assessment, regulatory standard)

Only CQAs should be tested in specifications, but not all CQAs should be in the specifications

Specifications definition (based on QbD): Staged approach during clinical development

Specifications evolve based on product knowledge

Potential CQAs

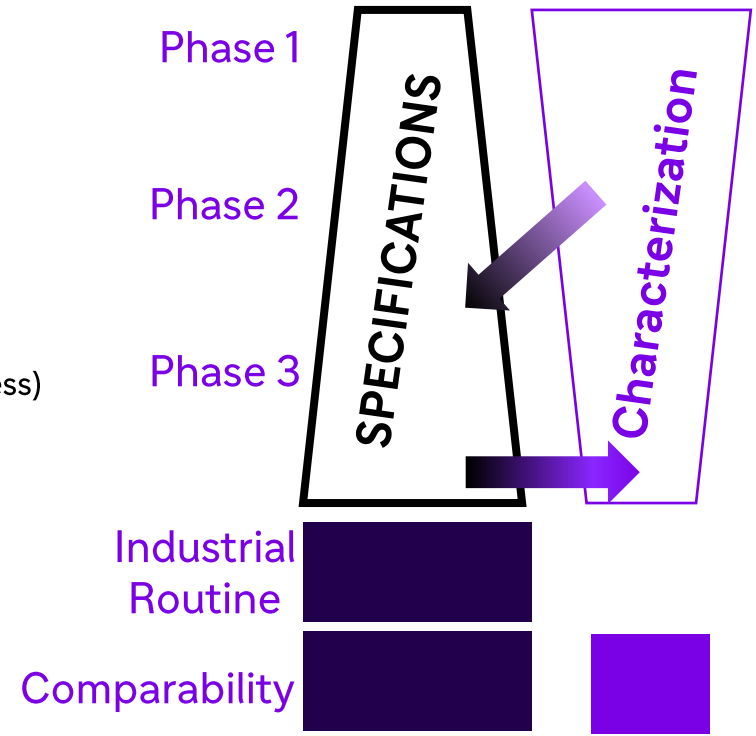
- Characterization test in phase 1
- Specification in phase 3 if confirmed as CQA

CQAs

- Within Specifications
- Removed from specification by risk analysis (if fully controlled by process)

Specific CQAs (e.g., antigenicity for recomb protein vaccines)

- In specifications for phase 1 **but without defined acceptance criteria**
- Acceptance criteria defined with tangible data for phase 3



Important Regulatory alignments
In vivo assay replacement/substitution

Global path across pharmacopoeias to move away from *in vivo* assays with guidelines to replace/substitute *in vivo* assays

Ph. Eur. 5,2,14
Substitution of in vivo method(s) by *in vitro* method(s) for the quality control of vaccines

Indian Ph 2022 addendum
Substitution of in vivo method(s) by *in vitro* method(s) for the quality control of vaccines

WHO 2024 DRAFT guideline on removal or replacement of animal tests for the quality control of biological products

CPC specification improvement project: guideline on in vivo potency assay replacement

In vivo adventitious agent tests replacement by High Throughput Sequencing

Ph. Eur. 5.2.3
Ph. Eur. 2.6.16
Ph. Eur. 2.6.41

ICH Q5AR2

Requirements for bact. and viral strains/seeds used for production of Biologics

Abnormal Toxicity Test/General Safety Test removal

Removal based on risk assessment (with periodic re-testing and testing for product life-cycle management)

Important Regulatory alignments
In vivo assay replacement/substitution

Global path across pharmacopoeias to move away from *in vivo* assays with guidelines to replace/substitute *in vivo* assays

- Ph. Eur. 5.2.14. "Substitution of in vivo method(s) by *in vitro* method(s) for the quality control of vaccines"
- Indian Ph 2022 addendum "Substitution of in-vivo Method(s) by *in-vitro* Method(s) for the Quality Control of vaccines"
- WHO 2024 DRAFT guideline on removal or replacement of animal tests for the quality control of biological products
- ChP: Ongoing CPC specification improvement project: guideline on *in vivo* potency assay replacement

***In vivo* adventitious agents tests replacement by High Throughput Sequencing**

- Ph. Eur. 5.2.3 (cell substrate – vaccines) and Ph. Eur. 2.6.16 (viral vaccines) and Ph. Eur. 2.6.41 (HTS)
- ICH Q5A (R2)
- ChP 2025 evolution of requirements for bact. and viral strains/seeds used for production of Biologics

Abnormal Toxicity Test/General Safety Test removal

- WHO, US, EU
- ChP 2025: possible removal based on risk assessment (with periodic re-testing and testing for product life-cycle management)

Important Regulatory alignments
Pyrogenicity

Ph. Eur. 5.1.13 Pyrogenicity
Risk assessment to define the method to be used:
Monocyte Activation Test (MAT)
and/or Bacterial Endotoxin Test (BET)

BET recombinant reagents alternatives to LAL/TAL

Korea General information (endotoxin test using recombinant factor C)

JP guideline G4-4-180 (BET and alternative methods using recombinant protein-reagent)

Ph. Eur. 2.6.32 (rFC)
Ph. Eur. 2.6.14 (LAL)

USP <86> (rFC & rCR are alternative to LAL)

ChP 2025
Guideline 925
rFC is an alternative to TAL

Monocyte Activation Test (MAT)
Alternative to Rabbit Pyrogen Test (RPT)

JP draft MAT chapter G4-13-190

Ph. Eur. 2.6.30 Method 1&2
Ph. Eur. 2.6.40 Vaccine Pyr

Chapter 5.5.2.7.1
(MAT method 1 &2)

ChP 2025
9301 Guideline for Application of Safety Tests for Injections: appendix MAT (method 1)

Korea
MAT method 1&2

USP <84> on MAT to come)
<151> Pyrogen Test

Important Regulatory alignments
Pyrogenicity

Pyrogenicity strategy Ph. Eur. 5.1.13

- Removal of RPT: risk assessment to define the method to be used (Monocyte Activation Test (MAT) and/or the Bacterial Endotoxin Test (BET))

BET alternatives to LAL/TAL (animal origin) by recombinant reagent

- Ph. Eur. 2.6.32 (rFC) and 2.6.14 (LAL)
- ChP Guideline 9251 (rFC is an alternative to TAL)
- JP guideline G4-4-180 (BET and alternative methods using recombinant protein-reagent)
- Korea General information (endotoxin test using recombinant factor C) very close to 2.6.32
- USP <86> (rFC & rCR are alternative to LAL)

Monocyte Activation Test (MAT) as an alternative to Rabbit Pyrogen Test (RPT)

- Ph. Eur. 2.6.30 (MAT with method 1 (semi-quantitative) and method 2 (quantitative) & 2.6.40 (MAT for inherently pyrogenic vaccines)
- Brazil 5.5.2.7.1 (MAT method 1 &2)
- ChP 2025 9301 Guideline for Application of Safety Tests for Injections: appendix describing MAT (method 1)
- JP draft G4-13-190 (refers to Ph. Eur. 2.6.30 & Ph Eur 2.6.40)
- Korea (MAT method 1&2)
- USP <84> on MAT to come, <151> Pyrogen Test "A validated, equivalent in vitro pyrogen or bacterial endotoxin test may be used in place of the in vivo rabbit pyrogen test, where appropriate."

Regulatory harmonization challenges
Bacterial and fungal contamination test on DS for biologics

Vaccine legacy of sterility test/bacterial and fungal contamination test on DS

- Ph. Eur. Vaccines monographs and WHO TRS guidelines (test procedure aligned worldwide 2009 ICH Q4B annex 8)
- **Most of vaccine DSs are not claimed sterile**: Sterility method is used as bacterial and fungal contamination test

The bioburden approach is in place for mAbs DS and accepted worldwide

- mAbs DSs **are not claimed sterile** (unlike DPs)

“Low” bioburden in vaccine regulation

- “Low” bioburden mentioned in Ph. Eur. 0153 Vaccine for human use
- Bioburden on vaccine DS accepted by US FDA but not referenced in any document
- Low bioburden not accepted as per ChP specific monographs

Bioburden test method is not standardized for DS & “Low” bioburden not defined

- Sample volume, culture conditions, bioburden limits?

Remaining Regulatory Alignments

Subvisible particles (not considered as CQA for vaccines)

- Vaccine can be exempted as per Ph. Eur. 0520 monograph preamble
- Not requested in USP for vaccines
- *Required by other regulations for vaccines*
- More and more questions from Reviewers

Uniformity of dosage units (CQA controlled by process)

- Compendial test of **content uniformity**, and **mass variation**, are not requested on vaccine DPs by some regulations but requested by others
- CQA controlled by the process and other specification tests

Impact of lack of harmonization in regulatory standards

Multiple different specifications and CTDs in different countries for the same product

Several test methods to measure the same CQA

- Test A implemented to comply with regulation 1
- Test B implemented to comply with regulation 2

Different acceptance criteria for the same test and product

- Product conforms to specifications for country A
- Product Out of specification for country B

Product pharmacovigilance may be biased in different countries

Vaccine supply difficulties

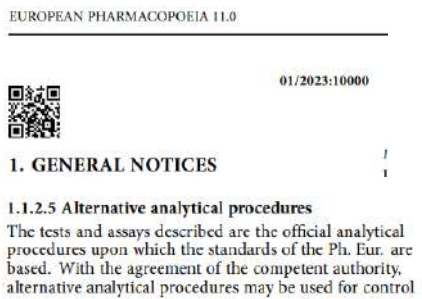
Regulatory alignment conclusions & suggestions

Efforts for international regulatory harmonization is a fact, even if there is still room for further alignment

Implementation of Enhanced approach for product specifications setting is an opportunity for regulations harmonization, here below some suggestions:

Monographs for identification of CQA per product type/modality

- Recombinant protein used as biotherapeutic, and Recombinant protein used as vaccine
- Viral vectors for gene therapy and live attenuated/ viral vectored vaccine


EUROPEAN PHARMACOPOEIA 11.0

01/2023:10000

1. GENERAL NOTICES

1.1.2.5 Alternative analytical procedures

The tests and assays described are the official analytical procedures upon which the standards of the Ph. Eur. are based. With the agreement of the competent authority, alternative analytical procedures may be used for control

General chapter for how to manage the CQAs

- Risk assessment for CQA management
- Technologies/compendial methods to monitor CQAs
- Open the door for alternative methods/strategies supported by data, scientific rationale and risk assessment

Acknowledgements

Thierry Bonnevay
Emmanuelle Coppens
Bruce Carpick
Marie-Gaëlle Roger

This work was funded by Sanofi. Bénédicte Mouterde & Patrice Riou are Sanofi employees and may hold shares and/or stock options in the company

sanofi