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How to use prior knowledge in defining a control strategy? – Some Regulatory Reflections

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Disclaimers apply

Critical Quality Attributes

- Critical Quality Attribute:
  - A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- Control Strategy:
  - A planned set of controls (..) that ensures (..) product quality.
- Which properties (quality attributes)?
  - CQA identification, product characterisation
- What limit (acceptance criterion)?
  - ICH Q6A/B
- How to ensure this?
  - Specification vs control strategy

Specifications – which acceptance criteria?

- ICH Q6A: Fairly detailed guidance
  - See decision tree #1
  - Supported by Ph. Eur. concept of identification/qualification limits (typically 0.1%)
  - Ph.Eur. 5.10 ('Control of impurities'): ***Qualification****: the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.*
- ICH Q6B: *based on 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*
  - Reflects that biologicals are complex mixtures

Regulatory concerns (biologicals)

- Outcome EMA - Industry workshop 2011:
- *Specifications should ensure that the product is safe and efficacious and representative of batches used in clinical trials*
- *Clinical qualification are considered the most important aspect when setting the acceptance criteria.*
  - *Acceptance criteria applied for critical attributes should normally not be wider than what has been clinically qualified.*
    - *Note added: Not necessarily restricted to levels used in clinical trials*
  - *Acceptance criteria for non-critical attributes can be based on process capability allowing wider limits than what have been used in the clinical trial*

Clinical relevance (focus biologicals)

- Clinical qualification of specifications/acceptance criteria for biologicals is desired goal
- However, this goal is elusive, lack of (product-specific) evidence-based data:
  - Actual number of patients really subjected to a certain level of impurities; *vis a vis*
  - The sensitivity to pick up rare (like immunogenicity) or small (minor shifts in PK/PD) clinical effects.
  - Actual Product Quality may be 'too good', but it is difficult to be sure -remember Eprex.
- Prior knowledge to the rescue!

Clinical relevance (focus biologicals)

- Keep in mind the pharmacovigilance findings of Thijs Giezen *et al.*:*'The safety of biologicals is mainly determined by exaggerated pharmacology; additionally immunogenicity*.'
- Evidence based proof will be difficult to obtain
  - Not feasible to produce/use impaired (artificially degraded) batches (aged?).
  - Sufficiently powered studies (number of patients/subjects, duration)
  - Animal models rarely predictive
  - Which standard of proof is feasible/acceptable?

A real life example

- "For monomeric IgG, the lower tolerance limit at the drug substance end of shelf life is ≥97.75%. This tolerance limit supports the proposed acceptance criterion of ≥96.0% for drug product release. Taking into account the expected decrease in monomeric IgG over 2 years from the date of manufacture yields an adjusted lower tolerance limit of ≥97.35%. This tolerance limit and the limited data set support the proposed acceptance criterion of ≥95.0% at the end of drug product shelf life."
- Clinical batches at release ≥ 98,7 % monomers, following 36 M storage all results ≥ 98,3%

Table 3.2.P.5.6.11-2 Statistical Analysis Summary – Purity and Potency [a]

Parameter		DS Substance End of Shelf-life and DP Starting Tolerance Limits Tolerance Limits (%) [a]	Proposed Drug Product Release Acceptance Criteria	Drug Product		Proposed Drug Product End of Shelf-life Acceptance Criteria
				Change on Stability [b]	Adjusted Tolerance Limits	
Size Exclusion HPLC	% Monomeric IgG	≥97.75	≥96.0	-0.407	≥97.35	≥95.0
	% HMWS	≤1.06	≤2.0	0.046	≤1.10	≤2.0
	% LMWS	≤1.39	≤2.0	0.344	≤1.73	≤3.0

A real life example –Prior Knowledge issues

- Why is this (purity, presence of dimers/fragments) a CQA? Why is it routinely tested for all MAbs?
  - Immunogenicity? How big (or small?) is the risk?
  - Common industry practice.
- What is an acceptable limit?
  - Prior knowledge: 95-99% ballpark?
  - Clinical qualification based on broad prior knowledge (broad experience, many Mabs)?
  - Cf. Ph. Eur. <0918> (Igiv); SE-HPLC purity: '*sum of monomer and dimer not less than 90%; sum of polymers and aggregates not more than 3%*' (dose: 0.2 - 2.0 g/kg)

There's more than MAbs…

- Enzyme Replacement Therapy
  - Importance of cellular uptake, mannose-6-phosphate glycosylation levels
- Coagulation factor analogues
  - Issues related to standardisation of biological activity testing
- Host Cell Proteins (process related impurity)
  - Observed specification levels vary two orders of magnitude

Where we are now

- Broad prior knowledge database crucial for robust (regulatory) decision making
- Prior knowledge provides additional reassurance beyond product specific data
- Prior knowledge often used implicitly
  - What's a CQA?
  - What to test?
  - Which acceptance criterion/limit?
- Necessary to identify the prior knowledge more explicitly
  - Transparency
  - Codification? How?
  - Open literature?

Questions to address

- *What is (and isn't) prior knowledge in the context of defining a control strategy?*
- *How can it be used for defining a control strategy?*
- *How to justify its use when defining a control strategy?*
- *How and where to present it in the dossier to support a control strategy?*
- *(How) can prior knowledge be used for justification of specifications exceeding clinical exposure and in support of safety threshold (across families of products)*

Four case studies

- Nancy Cauwenberghs (MSD)
  - Multivalent vaccines using prior knowledge from monovalent vaccines
- Rachel Orr (GSK)
  - Oligonucleotides as a specific class with associated prior knowledge
- Darrin Cowley (Amgen)
  - Monoclonal Antibodies
- Thomas Stangler (Novartis)
  - Monoclonal Antibodies/biosimilars


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