

# Q6B- Quo Vadis?

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Disclaimer: The opinions expressed are my own and do not necessarily represent those of the MPA or EMA

# ICH Q6B

- Adopted September 1999
- Scope includes well characterised proteins and polypeptides from recombinant or non-recombinant cell-culture expression systems, their derivatives, and products of which they are components (e.g., conjugates).
- Principles outlined may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids.
- Does not cover antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components.

## Q6B cont.

- Still a good guideline and general principles apply ( at least in most cases)
- Acknowledges that the specification is only a part of the overall control strategy and should work together with IPC's, GMP, raw material testing etc. and that IPC's may allow certain attributes to be left out in DS testing.
- Considerable part is on characterisation covering what attributes should be considered for setting the final specifications. Definitions- product/ process related substances/ impurities & contaminants have been widely accepted.
- In addition sections on attributes to be captured in specifications and different methods to be used in characterisation ( appendix). Smaller part, 1 page, on how to justify the specification including the acceptance criteria.

# Importance of an updated Q6B

- Global business with world wide activities and contacts with multiple regulatory Agencies.
- Harmonisation of the understanding a) how to select attributes to be included, b) justify the absence of others and c) on what principles the acceptance criteria should be set, is of key importance
- Guideline 20 + years old, a lot has happened since September 1999
  - ICH Q8-12: process and product understanding including criticality & other risk assessments, RTTR, quality systems
  - New analytical techniques developed both for monitoring during production and routine batch testing.
  - Incredible development of biotech molecules ( Mabs, other rec. proteins, ADC, ATMPs etc.) and a considerably better understanding of product characteristics.

# ICH Q8

- "Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B."
- My interpretation: You can build your control strategy differently ( RTRT, IPCs vs batch analysis, no test for nonCQAs, no routine test if acceptable levels always found- DNA, HCPs- etc.) taking Q8 principles into account BUT there is no opening saying that when using QbD you don't have to justify that your acceptance criteria are clinically meaningful.

# Confusion/ Split messages

- “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.”

# But also

- “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.”

# Problem

These different statements are not always possible to combine:

- Normally few batches are used in clinical studies and their variation may not be sufficient to assign acceptance criteria which will be acceptable for routine testing without a risk of having multiple future OOS's and rejections.
- Setting specification based on statistical calculations of routine batch results will not by itself guarantee that the levels can be considered clinically meaningful
  - Common use of Tolerance intervals- applied on few batches will result in wide limits, often far from what has been used clinically.
  - Products with good process control and low batch to batch variability will be "punished" with tighter limits compared to those under less control and wider variability



# Results

- Companies often claim acceptance criteria based on batch consistency statistics ( e.g. TI from limited number of batches) + adding a factor due to these limited data and experience without justifying the resulting limits from a safety and efficacy perspective.
- Even when companies can justify the limits from a clinical perspective, regulators may ask for tightening of the limits if the batch results are tighter than the limits. This tightening may be a prerequisite for approval or requested to be done after a specified number of batches have been produced even if the limits can be considered to have no negative effect on safety or efficiency.

# Personal reflections on "Quo vadis?"

- Revisit and modernize the guideline:
  - A lot is still applicable
  - Add aspects introduced via Q8-12 which have impact on setting specifications
  - Update the characterisation section and the appendix as appropriate taking new methodologies and product understanding into account.
  - Consider if the scope should be widened to some of the products now excluded, taking the added complexity in mind (methods & characterisation ATMP ≠ Monoclonals)
- Avoid a too high level document allowing for considerable regional interpretation
  - Global harmonisation of specifications will not be possible during an application process but more likely to be reached if the principles for selecting attributes to be tested and how to set acceptance criteria are agreed.

# Quo vadis cont.

- Expand the section on Justification of specification to clarify the principles in more detail and avoid the split message now conveyed
  - **Outcome EMA- industry workshop 2011:** "Clinical qualification is considered the most important aspect when setting the acceptance criteria." - Not only linked to levels in batches used in clinical trials
  - Consistency is important to verify that the process is under control but can be handled by other means, e.g. PQS through trending and internal action plans.
  - Include options beyond the levels seen in the actual clinical trials to justify limits- e.g prior knowledge from relevant products, criticality assignment, experience from dose finding studies, use of in vitro methods and non-clinical data
  - The principles of setting specification would also be applicable for those biologicals not included as such in the scope.



Thank you !