How to Connect Patient Centric Specifications with Immunogenicity of Biotherapeutics - A Regulator's Perspective

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Current ICH wording Q6B

- Current wording ICH Q6B: leads to confusion
  - “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.”

Problem

Understatement: 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 critera 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.

Patient centric specification

Working definition:

“A set of tests and acceptance ranges to which product quality attributes should conform for the product to be safe and effective when used as labeled. Justifications for acceptance ranges focus on risk-based assessment of the impact to patients.”

--by M Ruesh et al (“Strategies for Setting Patient-Centric Commercial Specifications for Biotherapeutic products,” J. Pharmaceutical Sciences 110 (2021) 771-784)

Still: 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

Options for justifying patient centric spec´s

- **Clinical trials in humans-** Obvious source, but often limited use due to few batches in the clinical program which will not cover the expected range in future commercial batches.
- **Dose finding studies** may be useful- recalculation of exposure based on actual levels seen. How many patients should have been exposed?
- **Prior knowledge-** Compare with similar products given to a similar patient population by similiar routes of administration to justify levels which can be considered safe and efficacious and to understand if the attribute is critical or not. Possible to extrapolate from other modalities, other groups of patients and other routes of administration?

Making use of in-vitro or animal models in justfying patient centric limits

There are two aspects which are relevant:

- Effects related to the intended substance itself
- Effects related to product related impurities/ substances

For small molecules, multiple mechanisms for side effects may be seen and which may be studied *in vitro* and *in vivo*. This in contrast to biotech products where the nature of side effects is mainly due to too high or too low activity or to immunogenicity.

This has until now limited the use of preclinical models, particularly in relation to immunogenicity, to justify limits which can be considered patient centric.

Two different scenarios

- Effects related to the intended molecule – this is mainly relevant at early development stages- if poor activity or expected immunogenicity, this may end the project before FIH. More rarely seen in files.
- Effect due to product related substance/ impurity- in vitro/animal studies can be useful here to justify the levels proposed for the product both during clinical trials and in setting commercial acceptance criteria.
  - Examples include determination of activity for fractions with 100 % of the product related substance/ impurity or preparations with a higher than normal fraction of such substances and calculating the effect on the activity taking the proposed limit into account; e.g. Form X has 50 % activity and the proposed limit is 6 % leading to a potential loss in activity of 3 %. Which may be negligible.

However…

- Until now we have seen very few, if any, examples in applications where *in-vitro* or animal models have been used to justify immunogenicity of product related substances/ impurities.
- Development of such models would be very welcomed as they may aid in the understanding of potential risk for immunogenicity of different product related substances/ impurities
- Aspects to consider:
  - Proof of the model to fully mimic the human immune response?
  - Will multiple variants need multiple studies, e.g. one study per variant?
  - Impact of route of administration?

Way forward ➡

- The evolvement of immunogenicity studies *in vitro* and in animals to predict immunogenicity in humans is highly welcomed and may be very useful in justifying acceptance criteria from a safety and efficacy point of view.
- The methods need to be shown to fit for their intended purpose.
- Companies are adviced to seek scientific advice through EMA or national agencies to discuss their plans for these studies.
- For the moment too early to put out guidance in writing, but will be helpful when more experience is gained.

Thank you for listening

Questions?

Wait for the panel