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Session 2: Non-Clinical Issues
Innovator Industry Presentation

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Role of non-clinical assessment of biosimilar mAbs

- **Non-clinical pharmacology, pharmacokinetic and toxicology studies are key components of integrated assessment of comparability between the innovator and biosimilar products.**
- **Comparative Pharmacology**
  - **Equivalence of biological endpoints** in response to both products needs to be demonstrated (*in vitro* potency assays at functional level)
    - Ligand binding (ELISA, Biacore)
    - Fc receptor binding
    - Cell based assays (mitogenesis, flow cytometry, apoptosis)
    - Bioassays / *in vivo* animal models (e.g., murine xenografts, transgenics)
  - Assay formats should be based on current state-of-the-art considerations
- **Comparative Pharmacokinetics**
  - **Equivalence of PK** parameters for both products in relevant animal species needs to be demonstrated
- **Comparative Toxicology**
  - **Lack of toxicologically meaningful differences** between the toxicity observed for the biosimilar and the toxicity profile of the innovator needs to be demonstrated

Q2.1: To what extent do we ask for non-clinical studies in relevant species, given that the relevant species is often non-human primates (NHP) and thus the number of animals per group is limited?

- As for other biosimilar products, comparative data (PK/PD) obtained in a relevant species should be mandatory
  - PK and PD are critical factors for demonstration of similarity, in particular given the complexity of these large molecules
  - Where possible, PK, PK/PD (including dose response) studies should be combined to reduce the number of animals used
    - **A head-to-head comparative PK/PD evaluation in adequate animal model** (if feasable) to understand how *in vitro* PD results translate into *in vivo*
- The extent and design of toxicology studies
  - Should include **one repeat dose study** of minimal but sufficient duration to evaluate the toxicity profile in relationship to that known for the innovator
  - **Need for head-to-head comparative toxicity** studies ?
    - In principle, comparator arm should be included unless the exclusion is justified
    - Need to balance the extensive (terminal) animal use in comparative studies (e.g., 54 NHPs/study**)** and the ability to detect potential unexpected toxicity of a biosimilar based on the described toxicity (or lack of) for the innovator product

Q2.1: To what extent do we ask for non-clinical studies in relevant species, given that the relevant species is often NHP and thus the number of animals per group is limited? *cont'd*

- Repeat dose toxicity study (typically in NHP) including PD markers (if feasable)
  - Treatment duration
    - Adequate to detect potential differences between the biosimilar and the established toxicity profile for the innovator
  - Recovery groups
    - Generally should be included (control and high dose recovery groups generally sufficient); however, where the toxicity is known to be reversible, not need to evaluate
  - Immunogenicity
    - Should be included to explain potential unexpected PK/PD profile and/or toxicity
  - Safety Pharmacology
    - Case-by-case, e.g. CV endpoints to be included in repeat dose toxicology
  - Local tolerance
    - To evaluate injection sites – see Q2.4

Q2.2: How could PD measures ("fingerprinting") be supplementary to quality development

- PD markers for biosimilar should be chosen appropriately to demonstrate equivalent target binding/capture and other relevant functional endpoints
  - Important to consider the analytical format for characterisation of PK, PD and immunogenicity and how these inter-relate to each other
  - PK-PD characterisation may utilise downstream markers from primary target binding (mechanism of action) based on known relevant biology
    - Either single or multiple PD markers (fingerprint) may be relevant to profile the biosimilar; however, broad spectrum –omics approaches should only be considered as exploratory

Q2.3: For anti-tumoural mAbs, to what level would a comparison of the functional activity beside ADCC/CDC (if relevant) be required? What level is feasible (e.g., signalling events)?

- Comprehensive comparative (head-to-head) functional (anti-tumour) activity *in vitro* characterisation is needed
- Need for comparative (head-to-head) *in vivo* anti-tumour activity (in animal tumour models) should be considered based on results of *in vitro* characterisation and PK profile of biosimilar mAbs
  - When ADCC/CDC comparison results in significant differences and/or the impact of the differences is not understood
  - PK profiles and *in vivo* findings in non-tumour animal models are significantly different
- Feasibility of the evaluation of anti-tumour MOA-related endpoints, e.g., target dependent signaling pathways, is product dependent
- Any relevant endpoints in pharmacology studies generated with newly emerging methodology should be considered to enhance comparative evaluation

Q2.4: What is the impact of formulation on in vivo behaviour (injection site and infusion rate comparability)? How could it best be studied?

- Pivotal non-clinical study for a biosimilar should mimic injection site and infusion rate* intended to be used in clinical studies

  * - NB infusion rate used in non-clinical studies is often much greater than that used clinically. The converse should be carefully justified.

- If injection site and/or infusion rate for biosimilar is different from innovator then this should be studied clinically

Summary – Non-Clinical Issues

- Non-clinical pharmacology, pharmacokinetic and toxicology studies for biosimilar mAbs need to be adequately designed to detect potential relevant differences in therapeutic and safety profiles
- Assessment criteria should be product specific and formulated in context of full understanding of its structural, biochemical and bioactivity attributes (potency, PK/PD relationship, safety)
- The extent of the non-clinical studies will be dependent on the nature of the pharmacology as well as the nature of (severity, reversibility and monitorability) and dose-response relationship for (known) adverse effects
- Some aspects of biosimilarity (e.g., product label statements regarding immunogenicity) can currently only be addressed in properly designed clinical studies

Back up Slides

Q2.5: Is there any rationale for conducting reproductive and developmental toxicity studies with biosimilar mAbs, given the existing human experience and that the relevant species is often NHP?

- It is not appropriate to conduct repro-toxicology studies for biosimilar mAbs if expected PK/PD and toxicity profiles in early non-clinical and clinical development are confirmed
  - Comparable biological activity in pharmacology studies
  - No unique toxicity detectable in adequate toxicity studies supporting clinical trials
- The same principle should apply even when some structural differences (e.g., glycosylation) but no biological differences (PK/PD, toxicity profile) in biosimilar mAbs are described
  - No evidence that potential small differences in the quality and/or biological activity of a product could result in a detectable difference in risk of reproductive, developmental and/or embryo-fetal toxicity (unlike risk of immunogenicity)
  - There is negligible IgG placental transfer during the period of organogenesis
  - These studies require significant animal use to generate data and yet data for biologicals are not robust
  - It is unlikely that new data from animal studies with biosimilar mAbs would change the warnings established for their original products