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Nonclinical and Clinical Considerations

Closed Workshop on Biosimilars

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Topics

1. **Stepwise approach to non-clinical program**
2. **Biosimilar-specific clinical model and endpoints**
3. **Extrapolation of indication(s)**

1. Stepwise approach to non-clinical program

- Drug development is generally ‘stepwise’ with analytic and pharmacologic characterization before in-vivo non-clinical and then clinical studies
- For biosimilars, the guideline recommends determination of need for in-vivo nonclinical studies based on sponsor evaluation of differences in quality attributes, differences in pharmacology/function, and/or new impurities
- We agree with the general outline and expectations as they are logical and scientifically sound, but…

1. Stepwise approach to non-clinical program

- Primary responsibility of Member States is to assess CTAs for safety rather than whether a product meets biosimilarity standards
- Challenge: No mechanism to determine adequacy of CMC results prior to decisions on in vivo studies until submission of MAA

➢ Recommend including language that reinforces other guidance encouraging applicants to seek scientific advice in order to maximize chance of success and maintain high standards of assessment

➢ Recommend including a statement that centralised scientific advice should be sought prior to clinical studies when the step-wise data recognise structural/functional differences between the biosimilar and reference product

2. Biosimilar-specific clinical model and endpoints – General Comments

- We understand this is general guidance and not class-specific, but should be more specific to what constitutes a sensitive population and a sensitive endpoint
- Sponsors and healthcare community will benefit from more specificity informing expectations and requirements

2. Biosimilar-specific clinical model and endpoints - PK

- PK informs about circulatory time for target availability
  - Does not inform about in-vivo efficacy
  - Limited information on safety and immunogenicity unless multiple exposures and adequate observation time
  - Equivalent PK to that of the reference product is a necessary requirement
  - Equivalent PK is not sufficient to confirm clinical equivalence
  - Agree with prespecifying the PK equivalence margin

➢ Recommend revising to make ‘necessary but not sufficient’ a clear statement

2. Biosimilar-specific clinical model and endpoints - PD

- Recommend adding additional discussion explaining limitations and providing specific criteria for use of (multiple) PD markers where none of them is an accepted surrogate for clinical efficacy
- PD markers must be clinically relevant and inform mechanism of action (MOA)
  - Multiple irrelevant biomarkers do not inform efficacy (eg. cytokine changes that do not have dose-response association or involved in MOA)
- PD markers must be sensitive to inform clinical efficacy (dose-response of PD markers relationship to clinical efficacy)
  - Multiple insensitive markers do not make a sensitive marker
- Recommend adding to statement that PD may be sufficient to conclude clinical comparability, but still need to assess clinical safety and immunogenicity

2. Biosimilar-specific clinical model and endpoints – Efficacy and Safety

- Sensitive population (model) ***and*** sensitive endpoint are needed to detect a difference in efficacy and safety if a difference exists
  - Confirmation of comparable efficacy requires assessment of a sensitive endpoint in a sensitive population to be informative
  - Efficacy equivalence margin depends on effect size of reference product and sensitivity of the study model in addition to potential uncertainty given analytical and nonclinical results
  - Study population should inform safety events of interest and evaluate for overt new biosimilar-specific findings
- Recommend more specificity to define a sensitive population and sensitive endpoint
  - Consider including examples of appropriate populations/endpoints

2. Biosimilar-specific clinical model and endpoints - Immunogenicity

- Request more specific expectations for population(s) to assess clinical immunogenicity
- Duration and number of exposures for appropriate assessment (chronic use)
  - Pre-approval immunogenicity detection depends on characteristics of reference product but also population studied (eg. concomitant immune-modulators or chemotherapy)
  - Therefore, sensitive population may differ from efficacy sensitive population
  - ➢ Recommend clarity as to populations/indications/classes of molecules requiring 12 months of data vs those with shorter duration or exposures appropriate
- ➢ If there is lower immunogenicity, must understand and explain the reason; though we agree with efficacy assessments by subgroups with and without anti-drug antibodies in such a circumstance

3. Extrapolation of indication(s)

- Scientific justification based on mechanism of action and pathophysiology
- Clinical study sensitive to confirm equivalent efficacy (population and endpoint) and inform efficacy in other indications
- Clinical study sensitive to inform safety and immunogenicity in other indications (no immune suppression) and chronic use if applicable

➢ Recommend specific language of appropriate pre-approval data requirements

  ➢ 'sensitive population and endpoints' to inform potential extrapolation of efficacy

  ➢ 'sensitive population and duration of exposure' to inform potential extrapolation of safety and immunogenicity

3. Extrapolation of indication(s) – Anti-CD20 Example

- Anti-CD20 (rituximab)
  - Efficacy evaluation in RA: Assessed with ACR 20 has limited discriminatory capability of two active molecules particularly when the study is conducted on the dose-response plateau (may confirm no clinical difference in RA but is it sensitive to inform other indications?)
  - Immunogenicity evaluation if also receiving methotrexate provides limited immunogenicity information if other indications do not include immune suppression (such as maintenance use in oncology)
  - How informative is the safety and immunogenicity assessments at 6 months (1 dose) or 12 months (2 doses) to inform other indications with more frequent dosing or chronic use?
  - Extrapolation to oncology (including curative setting)?
    - MOA of B-cell depletion but the disease pathophysiology is different from inflammation
    - Extrapolation for chronic use efficacy, safety, and immunogenicity to indications with monotherapy or curative settings - requires appropriate data to extrapolate to curative oncology setting with confidence

➢ Recommend requiring clinical evaluation (pre-approval with multiple doses) in both inflammation and oncology to inform efficacy, safety and immunogenicity

3. Extrapolation of indication(s)

- Extrapolation is important to biosimilar developers
- Needs to be scientifically supported based on evidence of similarity (efficacy, safety, and immunogenicity) to gain and maintain confidence of physicians and patients
- EU is global leader in guidelines and evaluation of biosimilars. Maintaining clear scientific pre-approval requirements is critical for long-term global success

➢ Recommend more clarity in guidelines on key aspects accompanied by full transparency in scientific decision making

Overall Approach to Biosimilars

- Resolving key Efficacy or Safety questions should never be a post-approval exercise
- Benefit of increased specificity of standards even for case-by-case evaluation
  - Benefit if same rapporteurs / co-rapporteur evaluates a molecule for same reference product for consistency and facilitate management of any safety issues in post approval setting
- Patient and physician confidence are key to biosimilar uptake (Tajani)
- Good communication of the science behind approval combined with post-approval data on immunogenicity or rarer safety events as appropriate, and ability for rapid detection of signals for individual products will benefit both originator and biosimilar(s)