Making Medicines Affordable

EBG's Perspective on the Draft Guideline on the Non-clinical/Clinical Issues

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Overview

1. Biosimilar specific clinical models and endpoints
2. Extrapolation of indications

3. Excellent guidance – high scientific concepts greatly appreciated

Biosimilar development foundation is technical development and analytical characterization

Description

Comparability approach

- Highly analogous structure and function (via robust analytical characterization)
- Same scientific approach as for manufacturing changes

Clinical

- Role in development program is to confirm similarity, not re-demonstrate safety and efficacy

Clinical designs

- Targeted clinical programs with indication and endpoints most sensitive to detect differences
- Extrapolation possible

Foundation:characterization

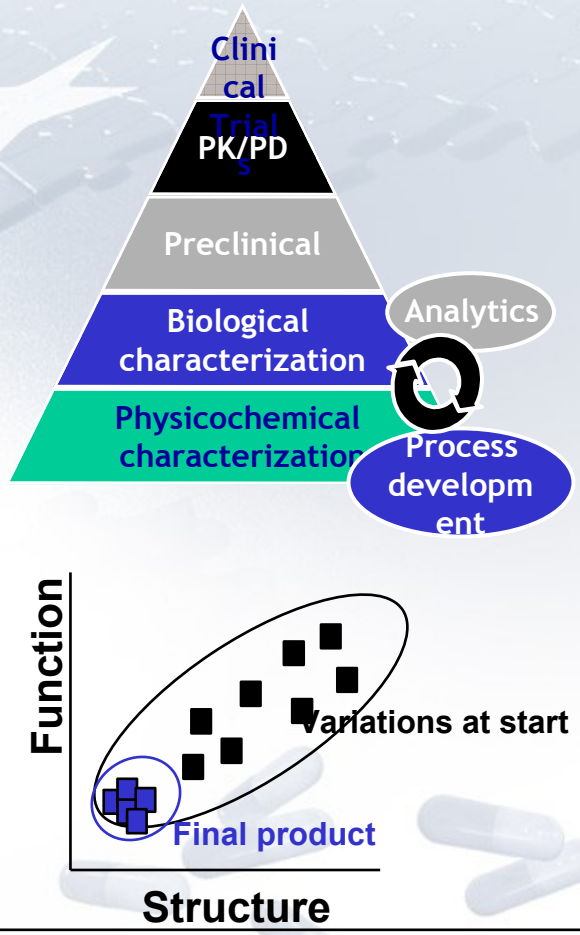


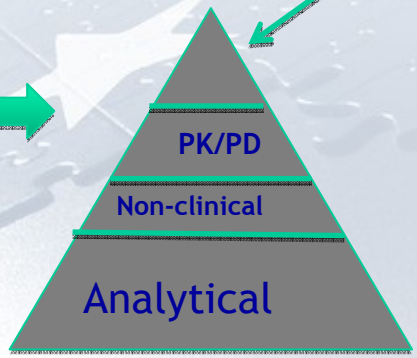
Illustration of the difference between originator and biosimilar development

Originator development

The world turned upside down....

Biosimilar development

Additional clinical studies



Comparison with the reference product

- Several trials >1000 pat , replication needed
- Primary endpoint: ACR20 – 6 m min
- Secondary: ACR50, ACR70, DAS28, Remission, HAQ
- Structural damage (6-12 m with 12 month F/U)

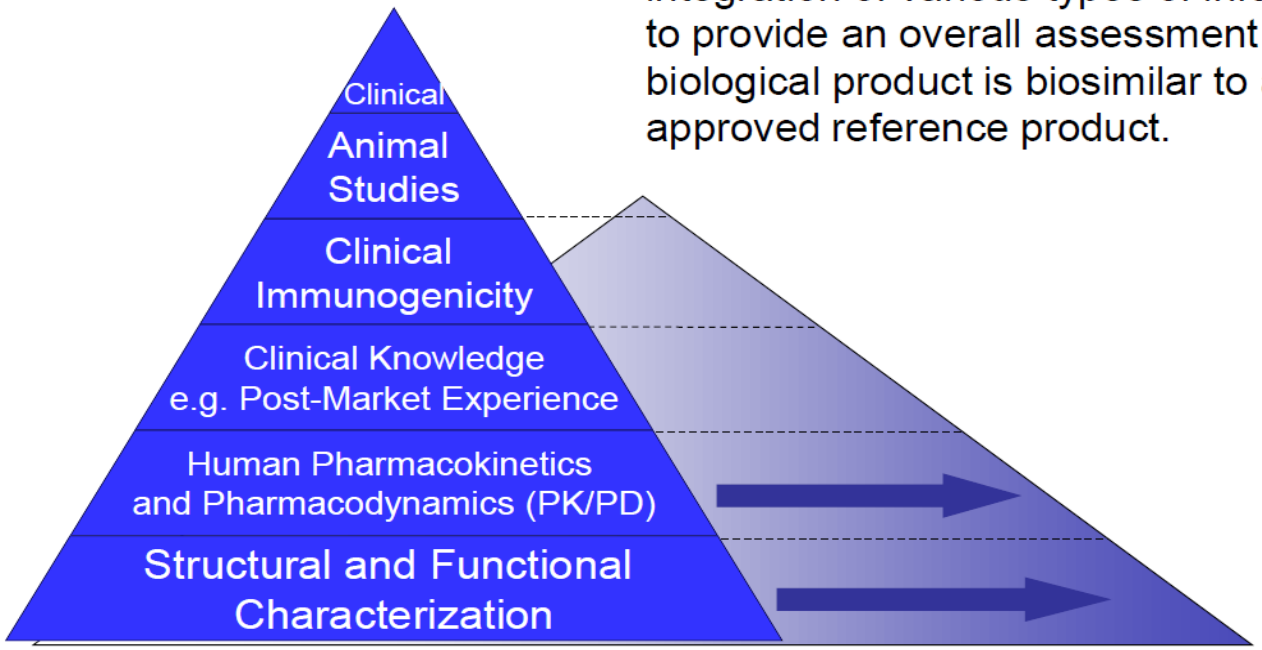
- One study 200-600 pat
- Primary endpoint at 3-6 months: DAS28
  Secondary: averaged score over time, ACR20, 50, etc
- Immunogenicity key

Figure inspired by Judith Macdonald, APEC conference, Seoul Sept 2013

Totality of Evidence

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Totality of Evidence

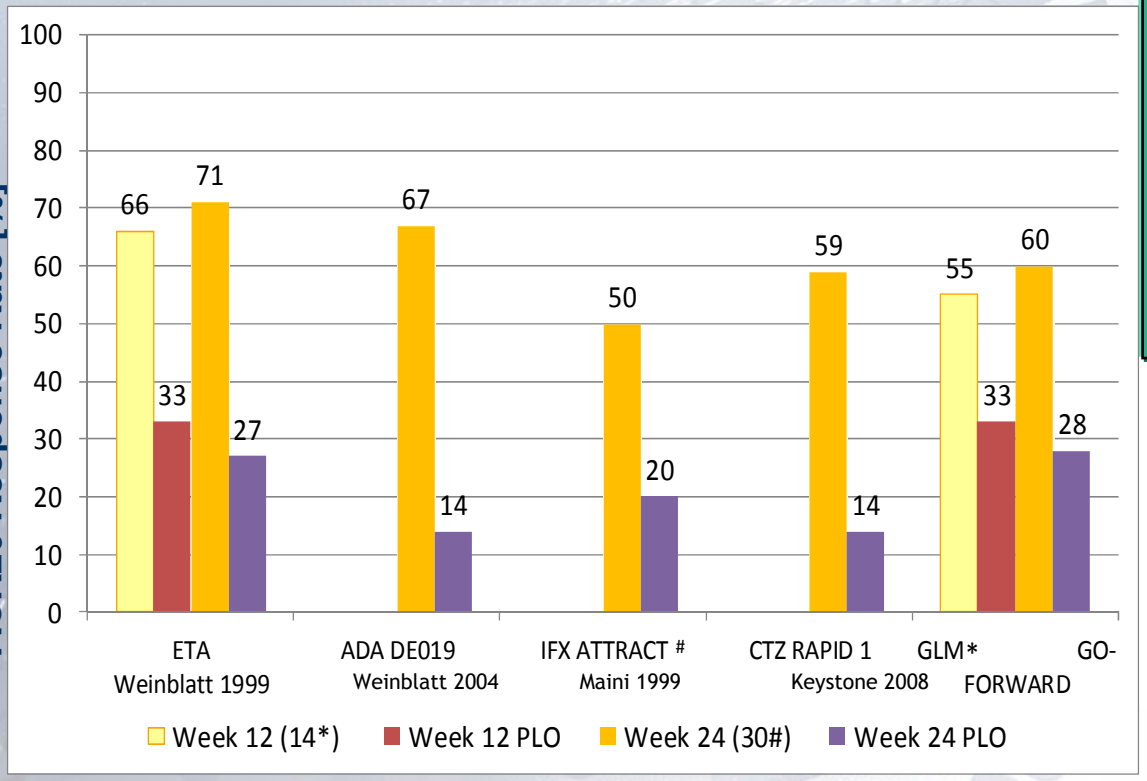


No “one size fits all” assessment :

FDA scientists will evaluate the applicant’s integration of various types of information to provide an overall assessment that a biological product is biosimilar to an approved reference product.

Clinical trials are less sensitive than analytical tools to detect differences between molecules

Response Rates of anti-TNFs vary depending on study protocols



Kaymakcalen, et al: Clinical Immunology, (2009) 131, 308-316

Expectations for Biosimilar efficacy/safety clinical trials

- **The clinical trial is the last step in confirming biosimilarity and potentially the least sensitive one to detect differences should any exist**
  - Exceptions when sensitive PD surrogates are available (e.g. G-CSF and insulin)
- **Margins and confidence intervals drive sample size**
  - If no sensitive endpoint is available, stringent requirements may lead to prohibitive sample size
- **Right balance is needed for efficient biosimilar studies**
  - Retain scientific rigor and design options
  - Feasibility (development cost, duration)

Key features of Biosimilar Clinical Trials

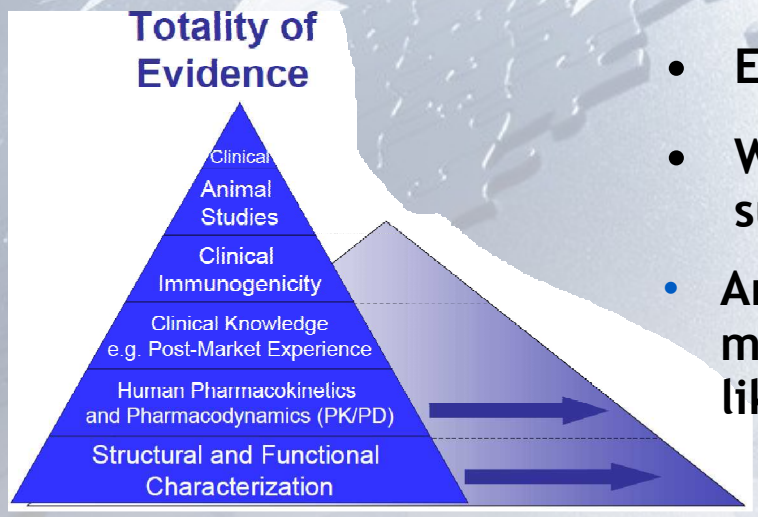
- Confirmation rather than demonstration of similar efficacy and safety in the most sensitive patient population
- Assessment of immunogenicity
- Selection criteria for sensitive clinical trial population
  - Immunocompetence (immunogenicity)
  - Large effect size (precision of efficacy assessment)
  - Feasibility
- Flexibility to tailor in the context of the overall similarity package

PK/PD studies may be sufficient in certain cases

- The way the section is worded, suggests that “confirmatory efficacy clinical trial(s)” will always be needed. However, as stated in section 218-221, confirmatory PK/PD trials may also be sufficient in certain cases. Therefore, we suggest to revise the wording to allow for more flexibility in the clinical program.
- The selected PD marker may not need to be a validated surrogate for patient benefit
- Sensitive markers reflecting the biologic effect(s) of the drug may be most sensitive and appropriate to confirm similarity

“Fingerprinting“ a prerequisite for a tailored clinical approach

A greater degree of comparability approaching finger print like comparability should result in a tailored clinical approach



Fingerprinting or Super-characterization
(S. Kozlowski)

- Need to score characterization for attribute coverage, sensitivity & orthogonality
- Evaluate combinations of attributes; algorithm
- What fraction of all potential attributes is sufficient (in addition to critical attributes)?
- Are some subsets of attributes more meaningful than others (e.g., better predict likely impact of process on product)?

Extrapolation of indications

- Highly appreciated that extrapolation of safety and efficacy from one therapeutic indication to others of the reference product is possible based on appropriate justification
- Currently, the same mode of action is given as the ultimate reasoning for an extrapolation – this seems to be overstated
- The revised draft GL also requests that “the totality of evidence derived from the comparability exercise and the potential remaining uncertainties” should be considered

Extrapolation of indications

Should be justified based on the demonstration of:

- a high level of structural (as demonstrated by physicochemical characterization) and functional (as demonstrated by in vitro biological assays) similarity;
- similarity regarding pharmacokinetics in humans;
- similar efficacy and safety in a single, most sensitive indication (immunogenicity)

The totality of evidence derived from the biosimilar comparability exercise and the proven safety and efficacy in the most sensitive indication are the key factors for the extrapolation of indications.

Summary

- Biosimilar development is unique and innovative
  - Requires extensive characterization of originator
  - Requires foundational comparability exercise
  - Preclinical and clinical studies are less sensitive than biologic and functional characterization
  - Clinical trials should address residual uncertainty that will vary depending on analytical comparability
  - Fingerprint-like data leaves little residual uncertainty such as clinical PK/PD or immunogenicity
  - Extrapolation aided by fingerprint-like comparability

Non-clinical program: reduction of animal studies still required at national level

- Stepwise, risk based approach (3Rs) highly welcome
- In-vitro assays are often more sensitive than animal studies
- Animal data useful for PK evaluations when formulations different from the originator are used
- Specific non-clinical disease models are useful for demonstrating similar responses
- Animal data do not address residual uncertainty (e.g. no extrapolation of immunogenicity data)
- Animal data have shown to be more acceptable for ethics committees (EC) - education of national regulators and ECs on Biosimilars crucial for avoiding unnecessary studies