DESIGN OF BIOSIMILAR BIOANALYTICAL PROGRAMS: STRATEGIES, PERSPECTIVES

JANKA RYDING, EBF 2019

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Introduction

- Currently >20 biosimilar medicines have been approved by the FDA, and >60 have been approved by the EMA

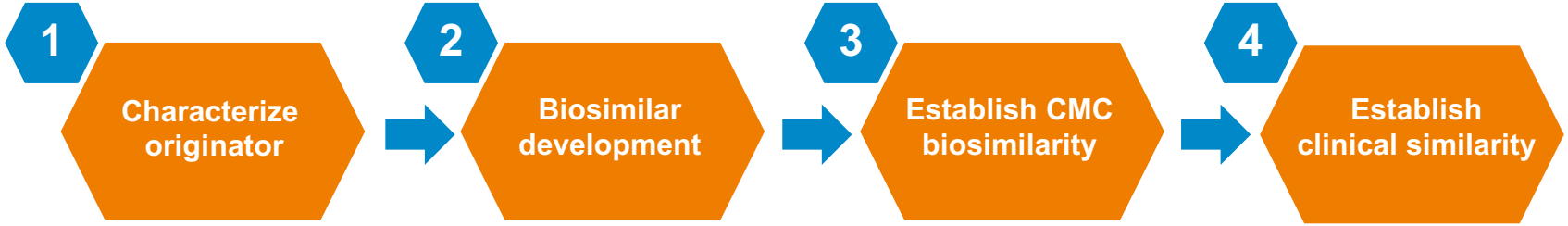
- Biosimilars are developed under the "totality of evidence" principle, which can be defined as the sum of data from analytical, preclinical, and clinical studies.

  *"There is no one size fits all approach to biosimilar product development"**

- Let's look into what bioanalytical considerations are relevant for biosimilar drug development.

*FDA: Biosimilar development, review, and approval (2017). Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess.

Biosimilar Development ≠ Originator Development



Assess variability of originator characteristics

Understand critical quality attributes (CQAs) of originator

Develop cell line and manufacturing process

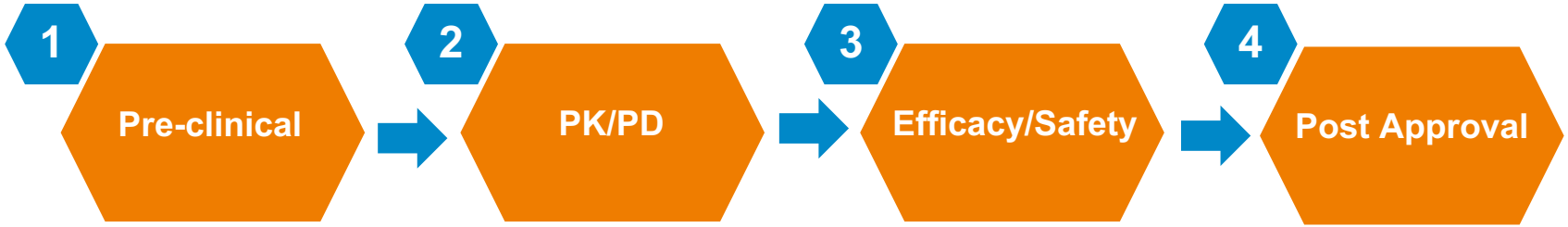
Physicochemical, biological and functional characterization

Confirm CQAs are similar to originator

Non-clinical, PK/PD studies

Clinical trials to confirm comparability and eliminate any uncertainty

Goal is to Confirm Biosimilarity and Not to Prove de Novo Efficacy or Safety



Toxicology

Demonstrate PK/PD equivalence in a sensitive human population

Demonstrate similarity, not safety and efficacy *de novo*

Additional data to meet regulatory needs, e.g. long-term immunogenicity

Bioanalytical Program Strategy Considerations 1

- How good is your analytical package?
- Review available documentation (e.g. EPARs) for originator
- How many originator compounds will be compared with the biosimilar?

  When will originator(s) material be available for assay testing?
- What are the populations/indications?

  Matrix sourcing
- Which target regulatory body/bodies?

  Consider regulatory interactions, any critical bioanalytical questions?

Bioanalytical Program Strategy Considerations 2

- Evaluate trial design e.g. arms/switching, stratifications, sampling,blinding, sample availability, timelines
- Clinical endpoints, in particular early on define comparability for IMG
- Evaluate follow-up requirements e.g. immunogenicity
- Evaluate timeline of critical reagents including originator(s)/biosimilar material, positive control(s) (immunization?) and availability of protein concentration data
- Plan for banking your samples
- Plan for in-study cut-point (ensure sample availability/volume aspects)
- Any expected interference/pre-dose positivity/drug tolerance issues?

Role of Bioanalytics

- Develop and validate comparative PK/IMG assays
  a) Design assay strategy (one-assay, two assays etc)
  b) Demonstrate drug comparability
  c) Provide documentation (including assay strategy justifications)

- Sample Analysis
  a) Design sample analysis strategy
  b) Provide documentation (link to one-assay justification)

PK – Regulatory Guidance

- FDA: “The same assay should be used for measuring concentrations of the proposed biosimilar product and the reference product and validated for use with both products”

- FDA: ..”in submissions to the FDA, the sponsor should provide a rationale for the choice of assay and the relevance of the assay to drug activity”

Source: FDA Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, 2016

ADA – Regulatory Guidance

- FDA: no specific biosimilar related text just “validate per guidance”
- EMA: “The assays should preferably be capable of detecting antibodies against all epitopes of both biosimilar and reference molecule“
  a) If two-assay approach: “If separate assays are used for the biosimilar and the reference product, this two antigen assay approach requires careful validation to exclude any bias due to differences in sensitivity and drug tolerance.
  b) If one-assay approach: “The Applicant may use a single assay approach in which the biosimilar molecule is used as antigen. In principle, this assay format should be able to detect all antibodies to the biosimilar product but not necessarily all antibodies to the reference product”

Source: FDA Bioanalytical Method Validation 2019
FDA Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products Draft, 2016
EMEA/CHMP/BMWP/14327/2006 2017

PK Assay Considerations 1

- Testing paradigm per e.g. Marini et al 2014, Colbert et al 2014
  a) One-assay approach i.e. biosimilar is used for CALs/QCs
  b) Demonstrate drug comparability in development and validation
  c) Documentation

- Pre-requisites for starting bioanalytical comparability testing (best-case)
  a) Confirmation of analytical similarity between biosimilar/originator(s)
  b) Reagent availability (biosimilar/originator(s), capture/detection, matrix etc)
  c) Drug concentration

     Biosimilar drug concentration CoA

     Originator(s) drug concentration CoA

     Do not use package concentration (nominal) but as determined (actual) by your CMC, ideally using the same method as the originator.

Marini JC *et al*, AAPS J 2014 Nov; 16(6): 1149–1158, Colbert A *et al*, MAbs. 2014 Sep-Oct; 6(5): 1178–1189.

PK Assay Considerations 2

- Pre-requisites for starting bioanalytical comparability testing (continued)
  - d) Use the drug lot(s) that are planned for the trial

    Applies for the comparability testing and also sample analysis
  - e) Make sure to have sufficient volume to cover trial(s) and mind the expiry date of the originator(s).
  - f) Define comparability acceptance criteria

    No consensus available. Examples:

    Standard VAL PK criteria

    Target TE ≤20%

    Minimal difference in %RE between biosimilar/originator QCs

    Apply statistical methods to evaluate bioanalytical equivalence in method

Source: Marini JC *et al*, AAPS J 2014 Nov; 16(6): 1149–1158

ADA Assay Considerations 1

- Pre-requisites for starting bioanalytical comparability testing (best-case)
  a) Confirmation of analytical similarity between biosimilar/originator(s)
  b) Originator(s) drug concentration CoA (not as critical as for PK)
  c) Use the drug lot(s) that are planned for the trial
  d) Make sure to have sufficient volume to cover trial(s) and mind the expiry date of the originator(s)
  e) Screening assay: Labelled biosimilar
  f) Confirmatory assay: Biosimilar and/or Originator(s)
  g) Define comparability acceptance criteria

ADA Assay Considerations 2

- Pre-requisites for starting bioanalytical comparability testing (continued)
  - g) Positive control(s), use of anti-biosimilar and/or anti-originator

    Ideal to generate Ab(s) by immunization

    Commercial Ab may also be a viable option

    Caution: use of anti-biosimilar and anti-originator may add imbalance in comparability due to differences in e.g. affinity.
  - h) Adequate critical reagent characterization
  - i) Basic development parameters should be established e.g. MRD, estimate of CP, low PC concentration, confirmatory drug concentration

What To Do If Bioanalytical Drug Similarity <u>Cannot</u> be Demonstrated

- Issue an Investigation: confirm root cause for bioanalytical non-similarity
  Things to consider:
  Assay design
  Reagents (e.g. capture/detection)
  Human factor (e.g. errors in dilution)
  Matrix
  Verify protein concentration
  Has it worked before e.g. in development, previous studies e.g. non-clinical?
  Could it be for real?...then go back and evaluate your analytical data
- Consider Two-assay approach - Plan for blinding and time constraints

Documentation Recommendations 1

- **Development:**

  Generate a development report including a dedicated “one-assay suitability”-section.

  - Compile or link relevant results with a clear assessment and conclusion
  - Critical experiments should be documented (e.g. data/lab notebooks) Critical reagents generation e.g. PC should be documented in report/CoA

- **Validation:**

  Results supporting the suitability of the one-assay approach from validation should be summarized in the validation report under its own heading.

  - May include reference to supportive development report data
  - If comparability data is not spot on, a discussion section is needed to highlight relevance and potential impact of any observed differences.

Documentation and Recommendations 2

- **Sample analysis report:**

  Sample analysis report should include statement on suitability/justification of the “one-assay approach”

- **Submission modules:**

  e.g. Integrated Summary of Immunogenicity (ISI in 5.3.5.3), 2.7.1, 2.7.2

  Summarize comparability data from validation with justification.

  Include statement(s) on assay(s) suitability

THANK YOU FOR LISTENING

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