# Current Issues in Biosimilar Regulatory Submission in US

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# Disclaimer

*This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.*

# Outline

- Development of regulatory approval pathway in US
  - US FDA guidance on biosimilar product development
- Current issues
  - Totality-of-the-evidence
  - Similarity (non-inferiority) margin selection
  - Analytical similarity assessment
  - Interchangeability
  - Switching design
  - Extrapolation

# US FDA guidance on biosimilar product development

- FDA has developed several guidance to assist sponsors in biosimilar drug product development in the past few years, e.g.,
  - Guidance on scientific considerations (2015)
  - Guidance on quality considerations (2015)
  - Guidance on Q&A (2015)
  - Guidance on pharmacology (2016)
  - Guidance on interchangeability (draft, 2017)
  - Guidance on analytical similarity assessment (draft, 2017)

# Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

## Guidance for Industry

*Additional copies are available from:*

*Office of Communications, Division of Drug Information*
*Center for Drug Evaluation and Research*
*Food and Drug Administration*
*10001 New Hampshire Ave., Hillandale Bldg., 4th Floor*
*Silver Spring, MD 20993-0002*
*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353*
*Email: druginfo@fda.hhs.gov*
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

*and/or*

*Office of Communication, Outreach and Development*
*Center for Biologics Evaluation and Research*
*Food and Drug Administration*
*10903 New Hampshire Ave., Bldg. 71, Room 3128*
*Silver Spring, MD 20993-0002*
*Phone: 800-835-4709 or 240-402-7800*
*Email: ocod@fda.hhs.gov*
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

# Stepwise approach

- Analytical studies
  - Critical quality attributes at various stages of manufacturing process
- Animal studies
  - Include the assessment of toxicity
- Clinical pharmacology
  - Include pharmacokinetics (PK) or pharmacodynamics (PD)
- Additional clinical studies
  - The assessment of immunogenicity
  - Safety/tolerability
  - Efficacy

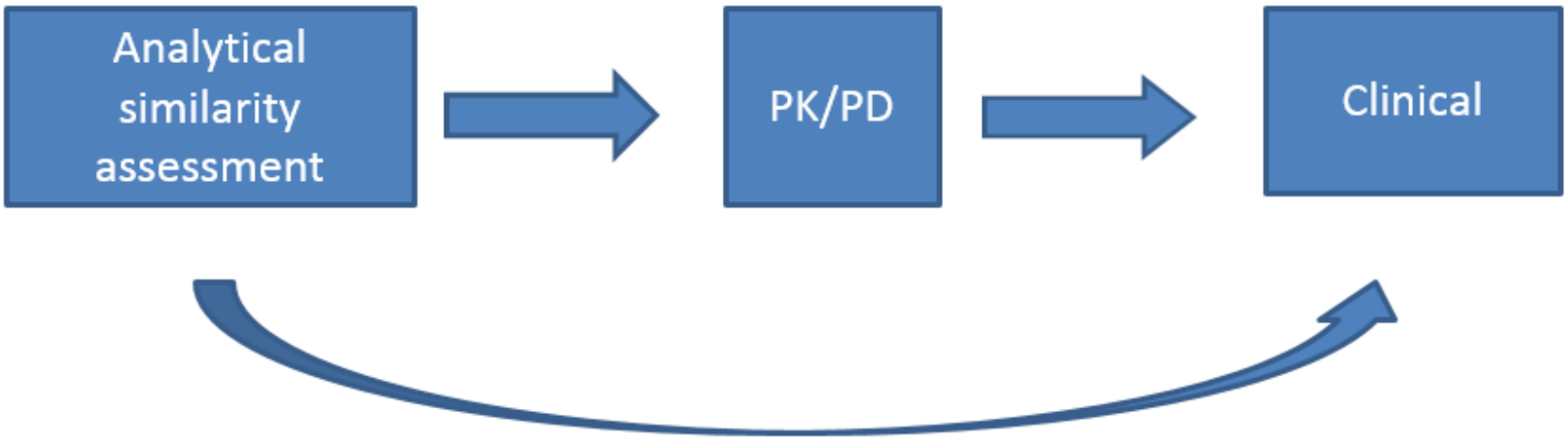
FDA 2015 Guidance

# Totality-of-the-evidence

- Approach in evaluating biosimilarity
- No one-size fits all assessment
- Analytical, PK/PD, and clinical similarity
  - Analytical data
  - PK/PD data
  - Clinical outcomes

# Totality-of-the-evidence

Fundamental Biosimilarity Assumption?



# Similarity (non-inferiority) margin selection

- US FDA 2016 revised guidance on non-inferiority clinical trials
- Major concerns
  - False positive
  - Sample size
- Strategy for similarity margin selection
  - Flexibility
  - Scientific validity

# Non-Inferiority Clinical Trials to Establish Effectiveness

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**November 2016**
**Clinical/Medical**

# Similarity (non-inferiority) margin selection

- US FDA 2016 revised guidance for selection of non-inferiority margin
- Current issues
  - Often, different margins are proposed by the sponsor and the US FDA
  - Current practice for margin selection is data-driven.

# Statistical Approaches to Evaluate Analytical Similarity

## Guidance for Industry

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**September 2017**
**Biosimilars**

# Analytical similarity assessment

- Scientific justification for selection of $1.5\sigma_R$
  - Fixed margin versus random margin
- A mean shift of $\frac{1}{8}\sigma_R$ is considered of clinically importance
- Concern of Tier 2 quality range approach
- Potential issue of tolerable interval approach
- Sample size recommendation of a minimum of 10 lots per product

# Interchangeable or interchangeability

- The term interchangeable or interchangeability means that the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product

Section 351 (i)(3) of PHS Act

# Interchangeability

- An interchangeable product is biosimilar to the reference product
- It can be expected to produce the same clinical result as the reference in any given patient
- For a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the product and the reference product is not greater than the risk of using the reference product without such alternation or switch

Section 351 (k)(4) of the PHS Act

# Switching designs

- FDA recommended switching design
  - (RTRT, RRRR) with three switches
- Criteria
  - Interchangeability assessment
- Sample size
  - Under the FDA recommended switching design

# Extrapolation

- Scientific justification for extrapolation across indications should be provided
  - PK/PD profile
  - Mechanism of action (MOA)