

Biosimilars in the US: Progress and Promise

DIA Biosimilars 2016

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BPCIA 2009 Created an Abbreviated Licensure Pathway for Biological Products



- A biological product that is demonstrated to be “**highly similar**” to an FDA-licensed biological product (the **reference product**) may rely for licensure on, among other things, publicly-available information regarding FDA’s previous determination that the reference product is safe, pure and potent.
- This new licensure pathway under section 351(k) of the PHS Act permits a biosimilar biological product to be licensed based on **less than a full complement of product-specific preclinical and clinical data** → **abbreviated licensure pathway**.

Definition

Biosimilar or Biosimilarity means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; **and**
- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.



Biosimilar Program at FDA

Implementation Committees

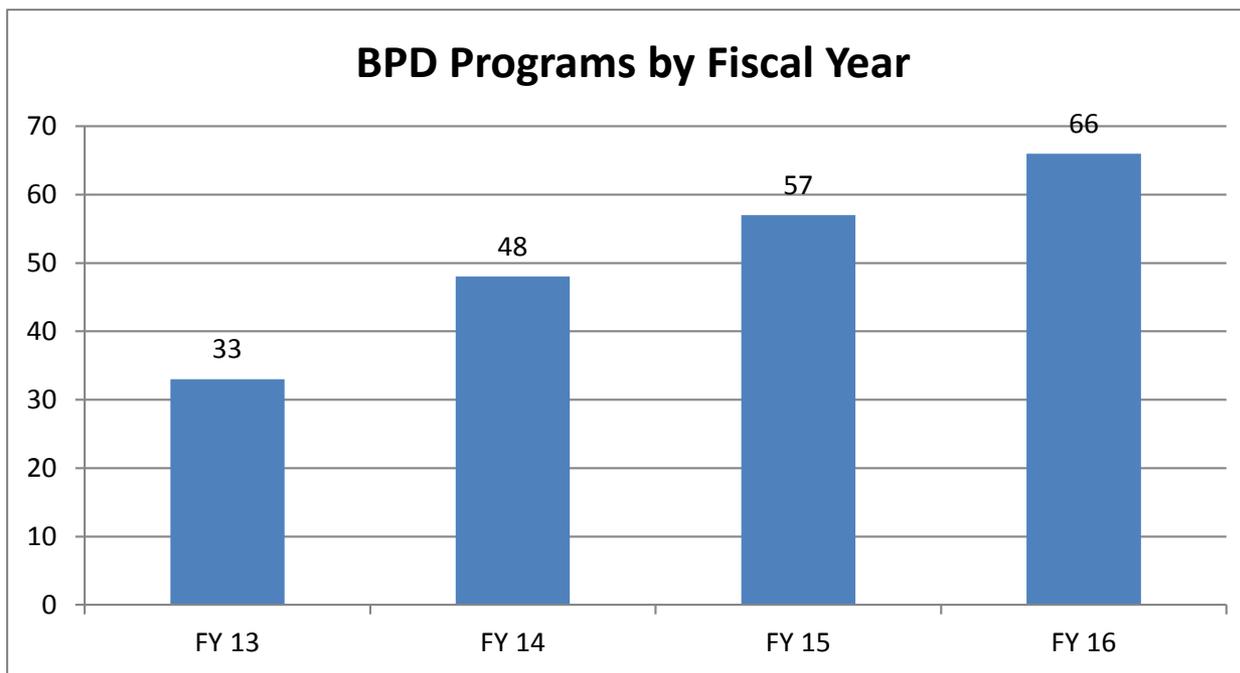
- FDA established three committees to ensure consistency in FDA's regulatory approach and guidance to sponsors regarding development programs for
 - proposed biosimilar biological products intended for submission under section 351(k) of the PHS Act, and
 - related issues.
- The committees are charged with developing policy and coordinating activities related to biosimilars:
 - CDER/CBER Biosimilar Implementation Committee
 - CDER Biosimilar Review Committee
 - CBER Biosimilar Review Committee

OND Therapeutic Biologics and Biosimilars Staff (TBBS)



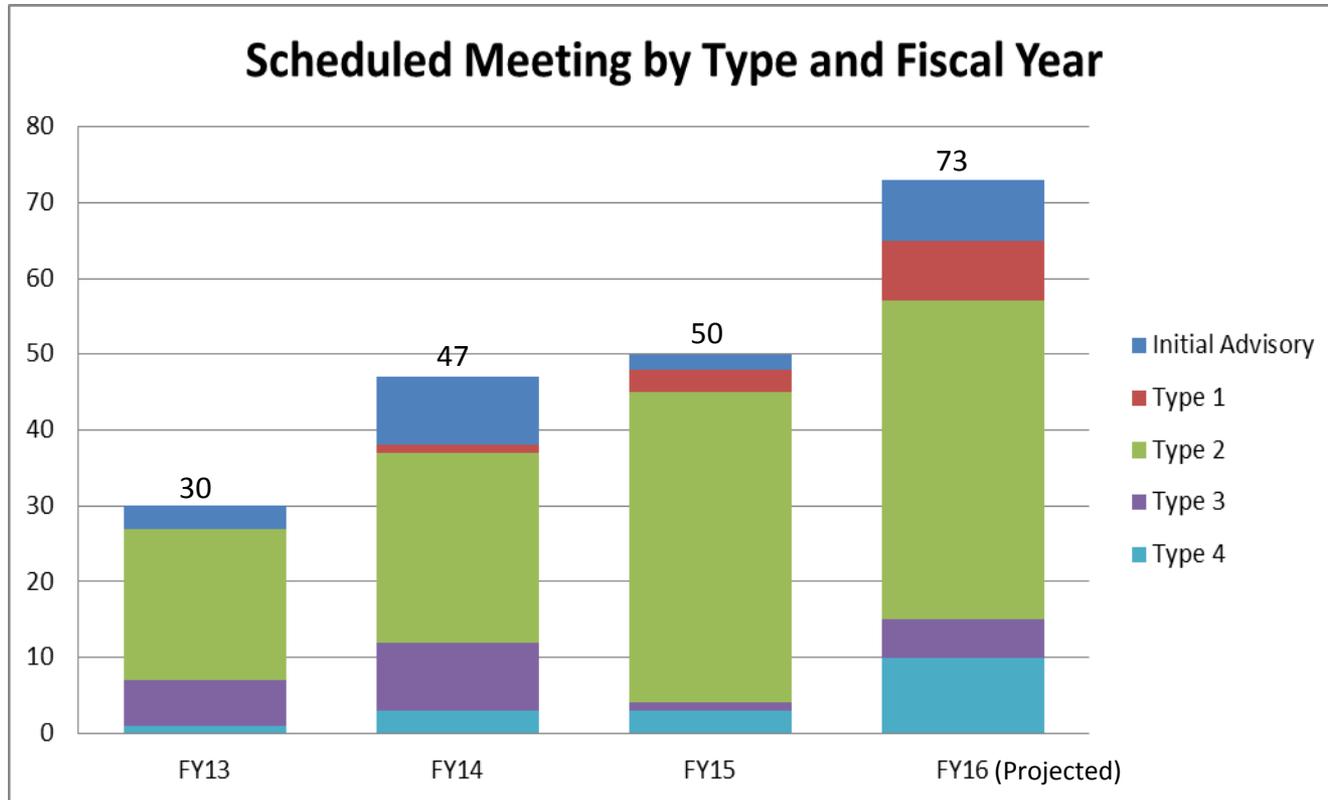
- Housed in the Office of New Drugs (OND) Immediate Office
- Ensures consistency in regulatory approach and in advice provided to sponsors regarding development programs for proposed biosimilar products, review of applications submitted under 351(k) of the PHS Act, and issues related to the implementation of the BPCI Act of 2009
- Central point of contact for OND and other CDER staff for biosimilars, therapeutic biologics, and follow-on versions of complex protein products and other complex products
- Develop policy, procedures, and staff training to consistently implement the BPCI Act
- Manage CDER's Biosimilar Review Committee
- Led by Leah Christl, Ph.D.

Growth in Enrollment in Biosimilar Product Development (BPD) Program



- A biosimilar product is no longer in the BPD program after a 351(k) BLA is accepted for review (i.e., filed)
- CDER has received meeting requests to discuss the development of biosimilars to 20 different reference products.

Growth in BSUFA Development-Phase Meetings for Proposed Biosimilars



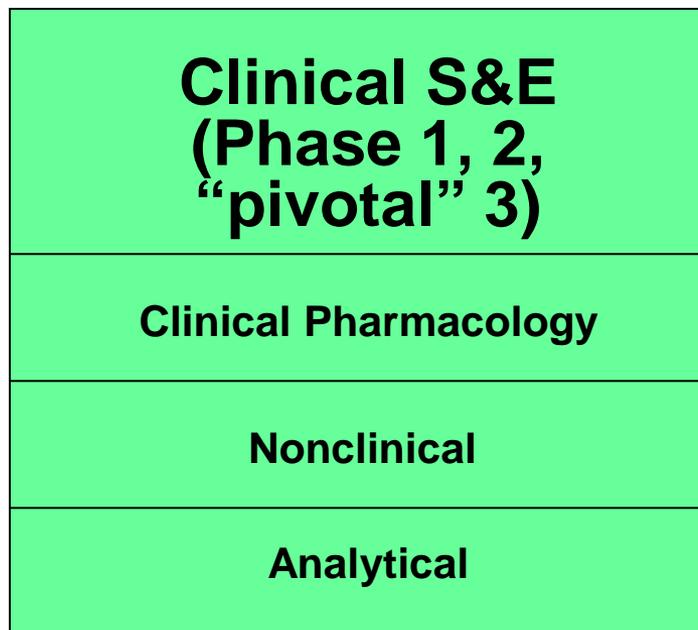
Biosimilars: Key Concepts and Lessons Learned



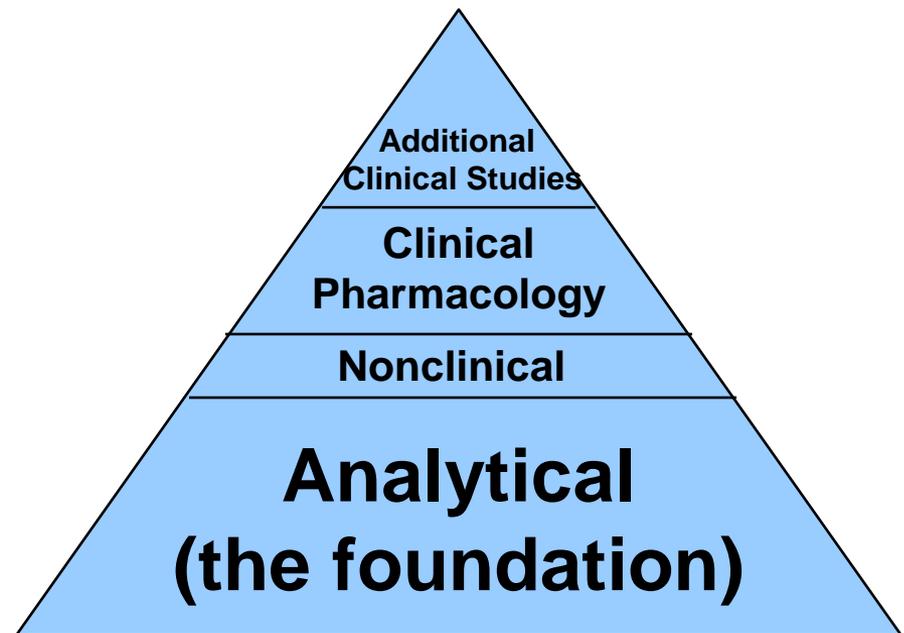
Key Concept 1: Goals of “Stand-alone” and Biosimilar Development are Different



“Stand-alone” Development Program, 351(a)
Goal: To establish safety and effectiveness of a new product



“Abbreviated” Development Program, 351(k)
Goal: To demonstrate biosimilarity (or interchangeability)



Lesson #1: The “cultural and cognitive transformation” is challenging



- “Biosimilars represent a paradigm shift in the way we make a finding of safety and efficacy.” This requires a “cultural and cognitive transformation” ¹
- Significant progress made within FDA, still a work in progress for many clinicians, patients, and other stakeholders
- Example: ODAC discussion of Zarxio (filgrastim-sndz)
 - FDA focused on analytics, PK, PD as most sensitive
 - Committee members focused on comparative clinical trial in breast cancer patients and foreign marketing

¹2012 DIA/FDA Biosimilars Conference: Dr. Janet Woodcock’s keynote address

Lesson #2: Biosimilar Development

Concepts are Novel and Often Complex



- FDA encourages the use of novel methods and study designs (e.g., endpoints, populations) to increase sensitivity to detect potential differences to support a demonstration of biosimilarity
 - Program may be very different from program that supported reference product approval; e.g., PK/PD in normal volunteers rather than Phase 3 clinical trial
- Novel approaches must be justified and supported by adequate data and information
- Extensive internal FDA scientific, regulatory, and legal discussions often required to support novel approaches
 - Very resource and time consuming process

Lesson #3: Extrapolation is a novel and challenging concept

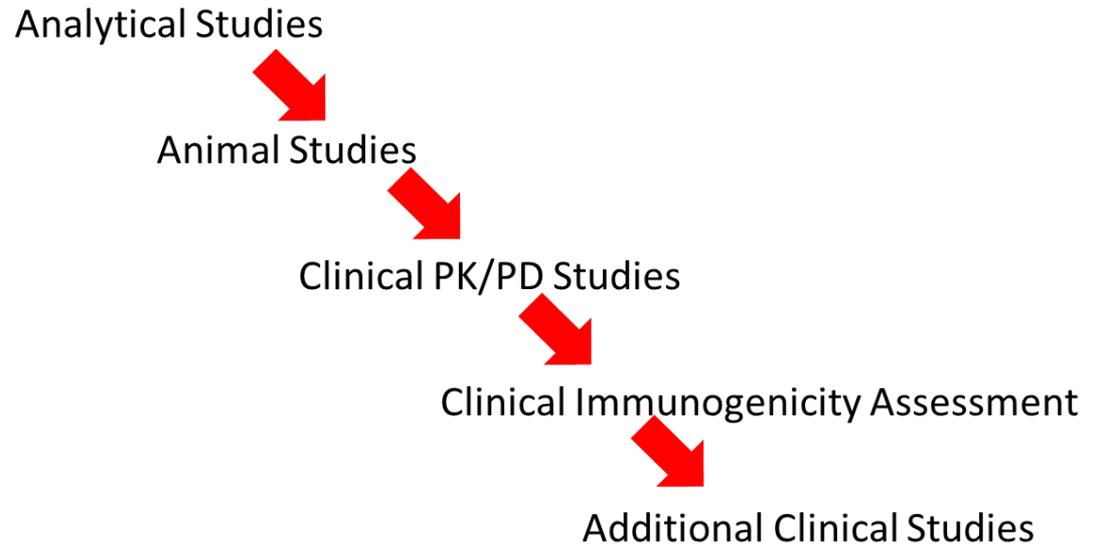


- Novel concept that can be challenging for some to accept
 - Biosimilar extrapolation is from reference product to biosimilar product based on all available data, **not** from indication studied for biosimilar to other indications
 - For products where the approved uses are in patient populations/diseases that are very different, extrapolation raises significant concern among prescribers and patients
 - Lack of direct evidence, i.e., no comparative clinical trial
 - Fear of the unknown, “don’t know what we don’t know”
- Consequences of lack of understanding of extrapolation
 - Sponsors may conduct additional clinical studies that are not necessary for biosimilar approval
 - Defeats the intent of the **abbreviated** pathway
 - Potential for reduced uptake and acceptance of biosimilars by prescribers and patients
 - Reduces cost savings anticipated through use of biosimilars

Key Concept 2: Stepwise Evidence Development



- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
 - Evaluation of residual uncertainty at each step
- **Totality-of-the-evidence** approach in evaluating biosimilarity



* The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, in its discretion, that certain studies are unnecessary in a 351(k) application.

Lesson #4: Legal Rationale for Stepwise Development Program



- “Highly similar” and “No clinically meaningful differences” are related but distinct statutory requirements for a biosimilar
 - Cannot “overcome” lack of ability to demonstrate *highly similar* with a demonstration of *no clinically meaningful differences*
- Risk of not proceeding in a stepwise fashion is wasted time and resources for industry and FDA
 - Using a product that is not reflective of the final commercial process to conduct PK/PD and clinical studies may necessitate repeating some/all studies

Best Practices

Best Practice #1: Support Education Regarding the “paradigm shift”



- Need to change the focus and the conversation:
 - The goal of a biosimilar development program is to **demonstrate biosimilarity** between the proposed product and a reference product, not to independently establish safety and effectiveness of the proposed product.
 - Move away from concept of “pivotal Phase 3” safety and efficacy study paradigm to more sensitive measures
- Need to better explain and educate stakeholders about:
 - Analytical similarity data (structural and functional analysis)
 - PK and PD (if relevant) endpoints are generally more sensitive to product differences than traditional clinical efficacy endpoints
 - Extrapolation

Best Practice #2: Choose and use your BPD Meetings Wisely



- Refer to FDA guidance for industry on Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants at
 - <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm345649.pdf>
- Choose a meeting type that meets your needs, and submit a meeting package that will support that objective
 - e.g., BIA meeting is not intended to provide in depth, highly detailed advice on clinical development
- Timelines with the different meeting types can impact development - anticipate the type of interaction you will want and prepare in advance

Best Practice #3: Submit a Complete Application



- Incomplete applications and submissions are not a good use of FDA (or industry) time and resources
- FDA strongly recommends requesting a BPD Type 4 meeting **and** ensuring adequate time to address the advice provided prior to submitting the 351(k) BLA accordingly
- Ensure totality of the evidence, including scientific justification for extrapolation, supports approval
 - Present data in the step-wise framework – tell the “biosimilarity story”
- Ensure facilities are **ready for inspection** within the necessary timeframes
- Concepts are captured in draft BSUFA II goals letters regarding “Program” for biosimilar BLA review



Thank you

