

2018 ASCPT Symposium

Demonstrating Biosimilarity with Clinical PK and PD Data in Lieu of Comparative Efficacy

Co-Chairs:

John Davis, Ph.D.

Yow-Ming Wang, Ph.D.

Speakers:

Penny Zhu, Ph.D.

Gary Fanjiang, M.D.

Wojciech Krzyzanski, Ph.D.

Yow-Ming Wang, Ph.D.



Biosimilars Program

- As of December 1, 2017, 60 programs were enrolled in the Biosimilar Product Development (BPD) Program. CDER has received meeting requests to discuss the development of biosimilars for 27 different reference products.
 - Since program inception and as of December 1, 2017, 11 companies have publicly announced submission of 20 351(k) BLAs to FDA.
 - As of December 1, 2017, eight 351(k) BLAs for biosimilar products have been approved.
 - Zarxio (filgrastim-sndz)
 - Erelzi (etanercept-szzs)
 - Renflexis (infliximab-abda)
 - Mvasi (bevacizumab-awwb)
 - Inflectra (infliximab-dyyb)
 - Amjetiva (adalimumab-atto)
 - Cyltezo (adalimumab-adbm)
 - Ogivri (trastuzumab-dkst)
- * Ixifi (infliximab-qbtx) approved on 12/13/17

Clinical Data Supported Biosimilarity



Biosimilar product	PK similarity	PD similarity	Comparative Efficacy (+ safety)	
Zarxio (filgrastim-sndz)	X	X	X	(DSN)
Inflectra (infliximab-dyyb)	X		X	(ACR20)
Erelzi (etanercept-szzs)#	X		X	(PASI)
Amjetiva (adalimumab-atto)	X		X	(ACR20, PASI)
Renflexis (infliximab-abda)	X		X	(ACR20)
Cyltezo (adalimumab-adbm)	X		X	(ACR20)
Mvasi (bevacizumab-awwb)	X		X	(ORR)
Ogivri (trastuzumab-dkst)	X		X	(ORR)
Ixifi (infliximab-qbtx)	X		X	(ACR20)



Primary endpoint(s) same as in confirmatory studies of reference product



Primary endpoint, measures a direct therapeutic effect; were secondary endpoint in confirmatory studies of reference product



Endpoint(s) correlates with efficacy measure(s) in confirmatory studies of reference product



Takeaways from Current Experience

- Biosimilar programs more frequently rely on comparative efficacy data than PD similarity data to demonstrate biosimilarity to the reference products.
- Would the use of PD similarity data to support the demonstration of biosimilarity be beneficial to biosimilar development programs with respect to efficiency?
- How to implement PK-PD similarity approach?



The Role of PK and PD in The Regulatory Framework for Biosimilars Approval

Symposium Title:

***Demonstrating biosimilarity with clinical PK and PD data in lieu of comparative efficacy
(2018 ASCPT Annual Meeting)***

Yow-Ming C Wang, Ph.D.

Co-Director, Therapeutic Biologics Program

Office of Clinical Pharmacology

Office of Translational Sciences

CDER

Disclaimer



- The presentation today should not be considered, in whole or in part as being statements of policy or recommendation by the United States Food and Drug Administration. (Exception – **Overview of FDA’s Approach to the Development of Biosimilars**)
- Throughout the talk, representative examples of commercial products may be given to illustrate a methodology or approach to problem solving. No commercial endorsement is implied or intended.

Overview



- Overview of FDA's Approach to the Development of Biosimilars
- Experience with Approved Biosimilars
- Practical Considerations for PD Biomarkers
- Summary

Overview of FDA's Approach to the Development of Biosimilars

Key Development Concepts



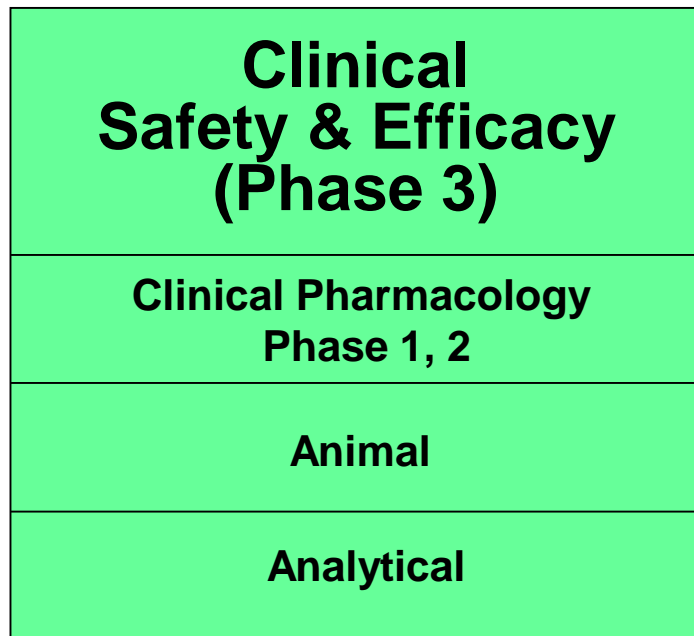
(Source: Division of Drug Information Webinars, posted on 12/5/2017)

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



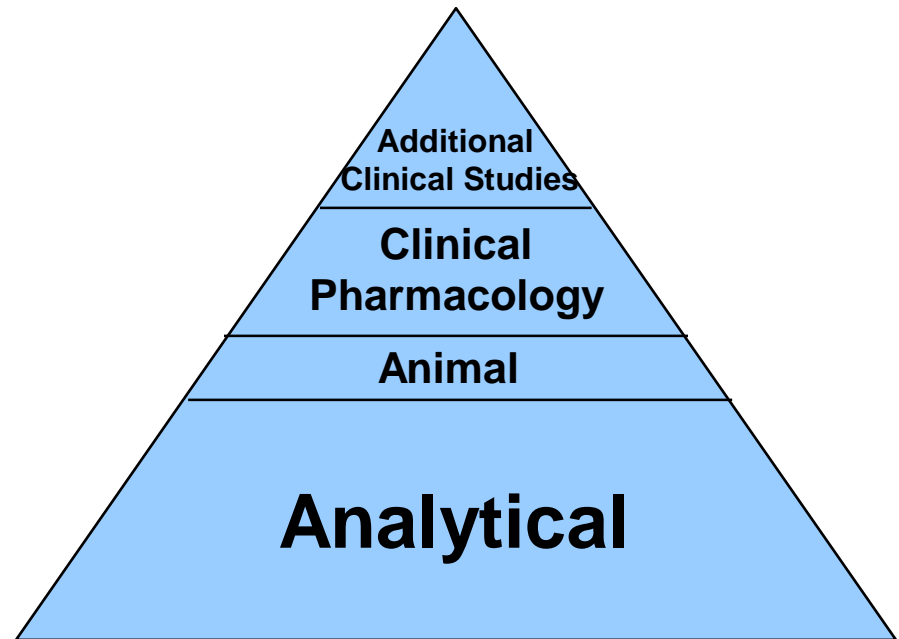
“Stand-alone” Development Program, 351(a)

Goal: To establish safety and efficacy of a new product



“Abbreviated” Development Program, 351(k)

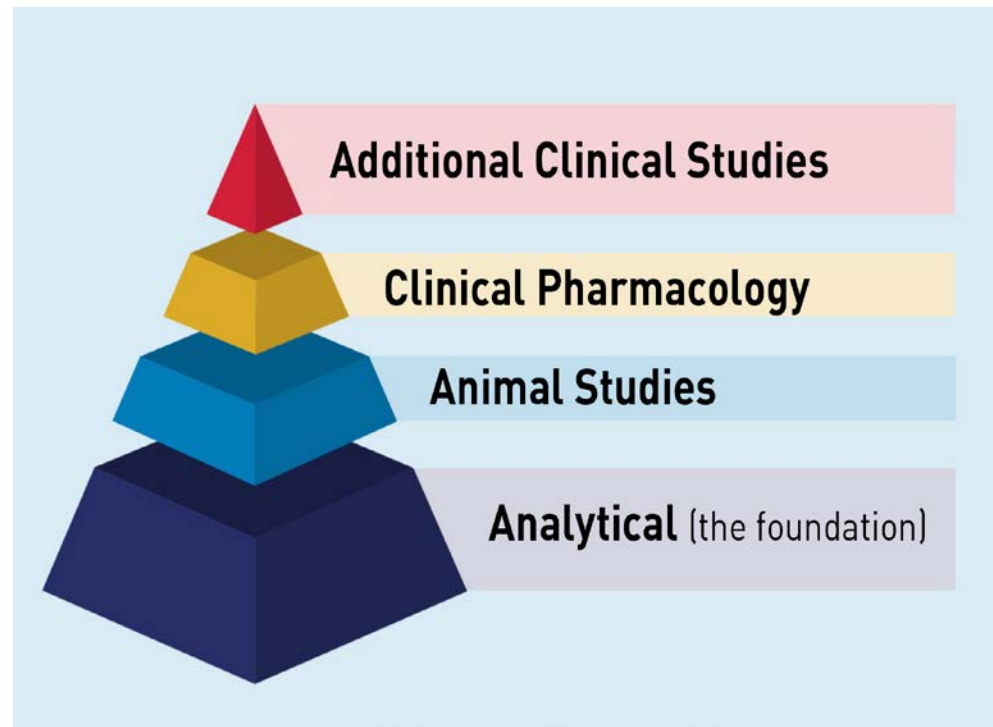
Goal: To demonstrate biosimilarity (or interchangeability) to a reference product



What does this difference mean from a development perspective?

#2: Stepwise Evidence Development

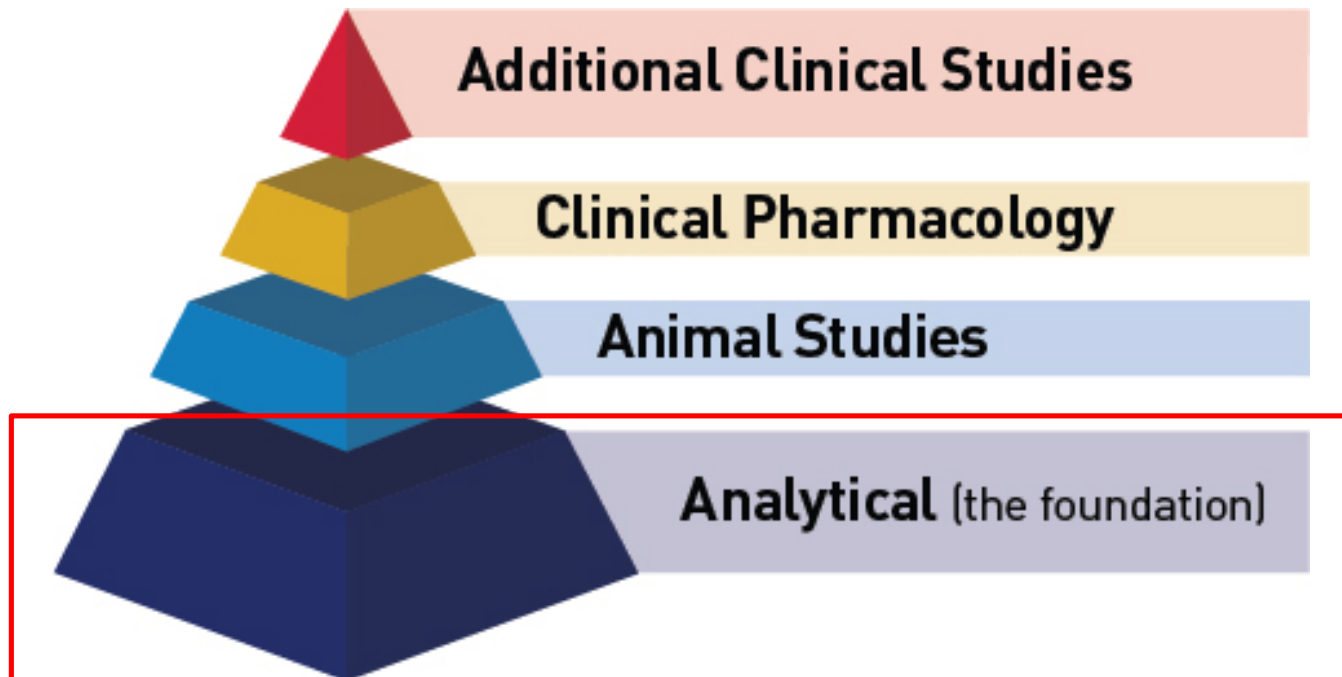
- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
- Evaluation of residual uncertainty at each step of data generation
- *Totality-of-the-evidence* approach in evaluating biosimilarity – no “one-size fits all” assessment
- **There is no one “pivotal” study that demonstrates biosimilarity**



#3: Analytical Similarity Data - The Foundation of a Biosimilar Program

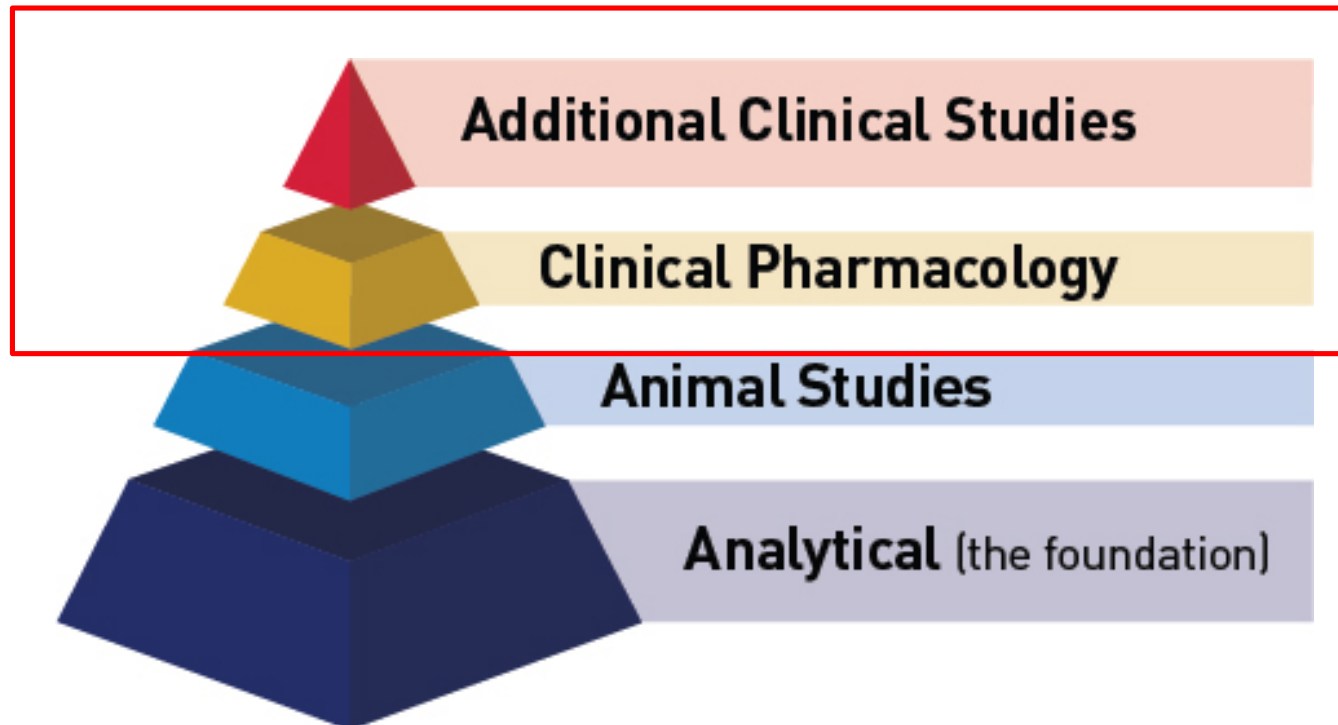


- Extensive structural and functional characterization



4: Role of Clinical Studies

- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting structural and functional characterization and, where relevant, animal studies.



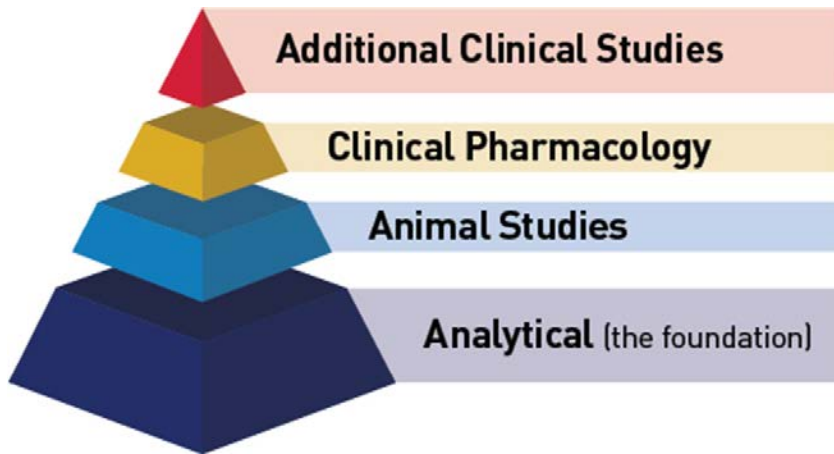
5: Extrapolation

- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation
- Sufficient scientific justification for extrapolation is necessary
- Differences between conditions of use (e.g., indications) do not necessarily preclude extrapolation
- FDA guidance outlines factors to consider, including:
 - MoA in each condition of use
 - PK and biodistribution in different patient populations
 - Immunogenicity in different patient populations
 - Differences in expected toxicities in each condition of use and patient population

Type of Comparative Clinical Data

As a scientific matter, FDA expects ...

(2)
at least 1 clinical study that includes a
assessment of the immunogenicity

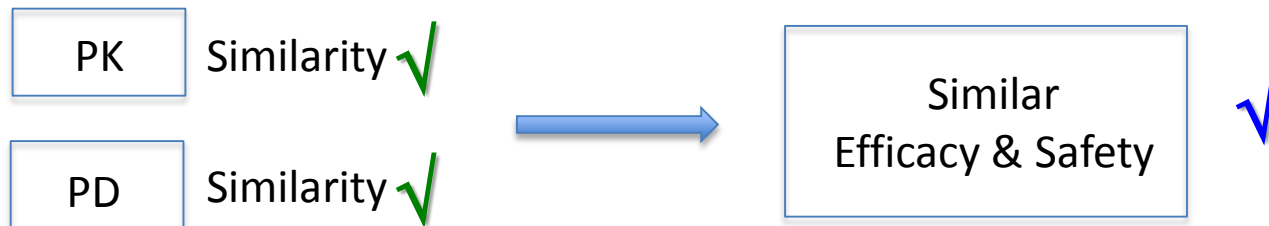


if there are residual uncertainties ...
a comparative clinical study will be necessary to support a demonstration of biosimilarity

(1)
an adequate comparison of clinical PK, and PD if relevant

Comparative Human PK and PD Data

- PK and/or PD is generally considered the most sensitive measure for assessing differences between products, should they exist
- PK similarity - in an adequately sensitive population
- PD similarity - using PD measure(s) that reflects the mechanism of action (MOA) or reflects the biological effect(s) of the drug
- **PK and PD similarity** data support a demonstration of biosimilarity with the assumption that similar exposure (and pharmacodynamic response, if applicable) will provide **similar efficacy and safety** (i.e., an exposure-response relationship exists)





Experience with Approved Biosimilars

Clinical Data Supported Biosimilarity



Approved Biosimilar product	PK similarity	PD similarity	Comparative clinical study	
Zarxio (filgrastim-sndz)	X	X	X	(DSN)
Inflectra (infliximab-dyyb)	X		X	(ACR20)
Erelzi (etanercept-szzs) [#]	X		X	(PASI)
Amjevita (adalimumab-atto)	X		X	(ACR20, PASI*)
Renflexis (infliximab-abda)	X		X	(ACR20)
Cyltezo (adalimumab-adbm)	X*		X	(ACR20)
Mvasi (bevacizumab-awwb)	X		X	(ORR)
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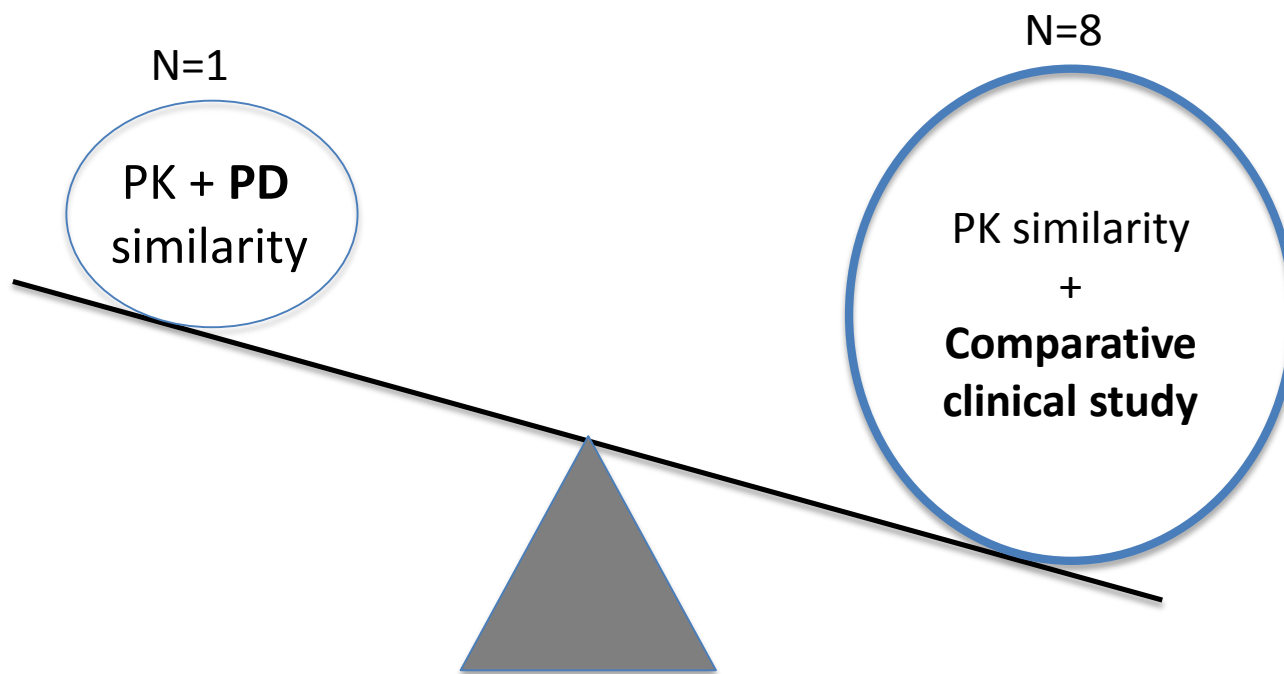
N ~ 30 (crossover PK, PD study)
 N ~ 100 / arm (clinical study)

↓
 N ≤ 70 / arm (except #)

↓
 N ~ 300 / arm (except *)

Current State

- By number of approved biosimilar products – N=1 with PK-PD
- By sample size – larger with comparative clinical study
- By study duration – longer with comparative clinical study
- ...



PK & PD Similarity Data vs. Comparative Clinical Data - Potential Decision Drivers



- Feasibility & challenge to conduct comparative clinical studies
 - Availability of patient population, sample size, study duration, ...
- Sensitivity of study endpoints (clinical efficacy vs. PD) for detecting differences between two products
 - Experience with PD endpoints may be less
- Availability of relevant PD biomarkers
- Scientific understanding & justifications for PD biomarkers
- Factors beyond scientific considerations, e.g.,
 - Business decisions, return of the investment on PD biomarkers
 - Public perception/receptivity of PD endpoints
 - ...

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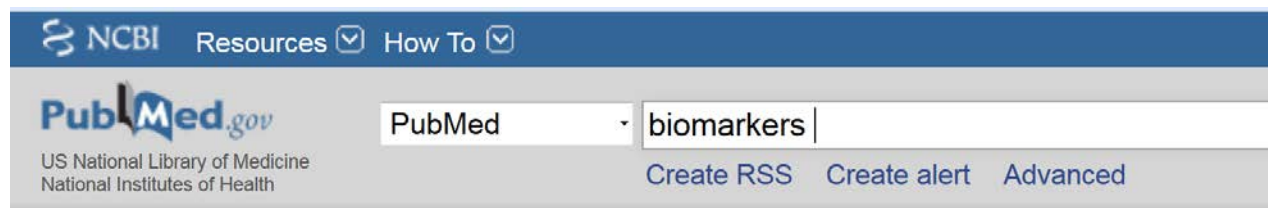
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OFFICE OF CLINICAL PHARMACOLOGY

Practical Considerations for PD Biomarkers

Looking for PD Biomarkers? (Leverage Available Resources)



- Scientific knowledgebases



Home > Drug Databases > Drugs@FDA

Drugs@FDA: FDA Approved Drug Products



Review documents
Product labeling

Search by Drug Name, Active Ingredient, or Application Number

- New understanding of old products
 - Technologies for assessing PD responses
 - Tools for translational sciences

How to Select PD Biomarkers?



(Source: FDA, biosimilars clinical pharmacology guidance)

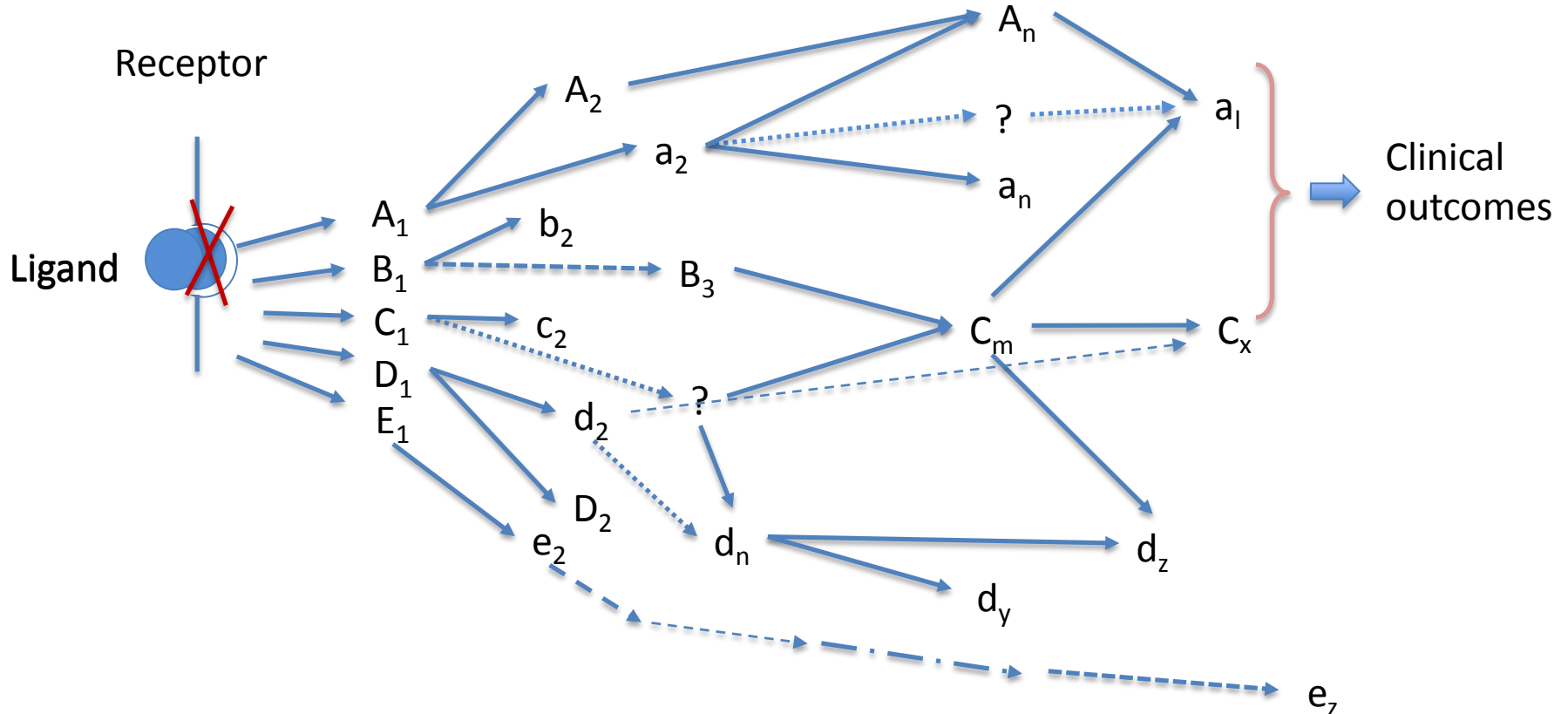
Five Characteristics to Consider

1. The time of onset of change in the PD biomarker relative to dosing and its return to baseline with discontinuation of dosing
2. The dynamic range of the PD biomarker over the exposure range to the biological product
3. The sensitivity of the PD biomarker to differences between the proposed biosimilar product and the reference product.
4. The relevance of the PD biomarker to the mechanism of action of the drug (to the extent that the mechanism of action is known for the reference product)
5. The analytical validity of the PD biomarker assay

Understanding The Pharmacological Mechanisms of Action (MOA)



The PD biomarker(s) used to measure PD response should be a single biomarker or a composite of biomarkers that effectively demonstrate the characteristics of the product's target effects.



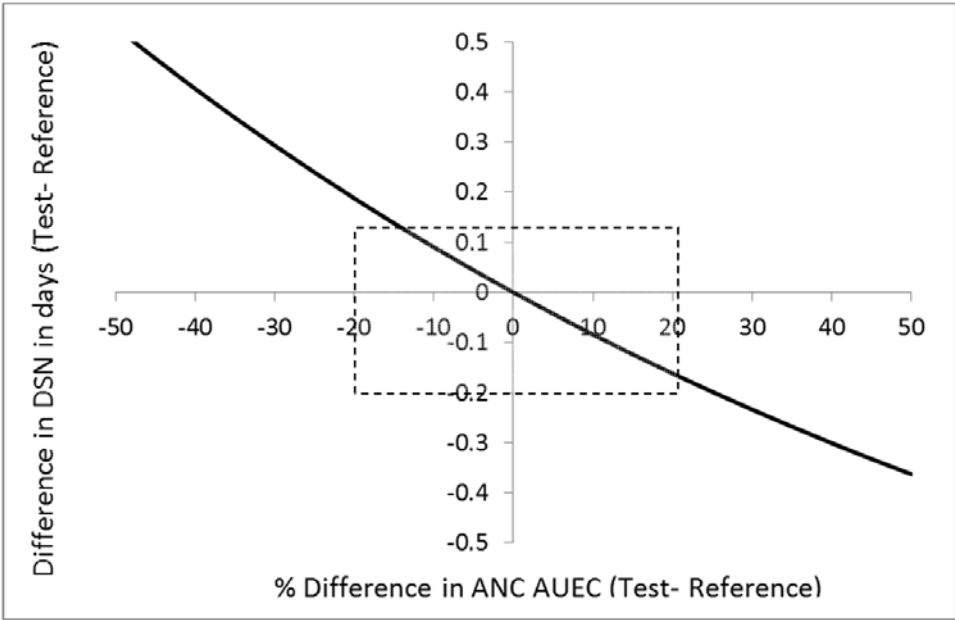
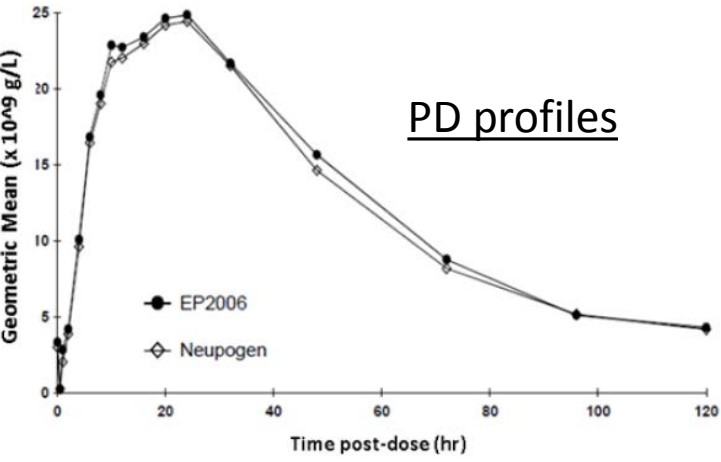
About The Relevance of PD Biomarkers to The Mechanism of Action



- Indicators of target engagement?
 - Soluble ligand concentration for drugs that inhibit target ligand binding to its receptor
 - Receptor occupancy level for drugs that bind to receptor to stimulate or block the receptor function.
- Consequences of target engagement?
 - Cellular responses upon drug binding to its target
 - Tissue responses upon drug binding to its target
 - Physiological responses upon drug binding to its target
- Do these two classes of PD biomarkers provide similar weight of evidence?

About The Sensitivity of PD Biomarkers (Absolute Neutrophil Count, ANC for Filgrastim)

- The temporal profile of PD response reflects the effect of drug.
- ANC correlates to a clinical outcome measure, duration of severe neutropenia (DSN). → relevant biomarker
- PD similarity criteria (90% CI within 80-125%) are associated with DSN changes (≤ 0.2 days) smaller than ± 1 day, not a clinically meaningful difference . → sensitive biomarker

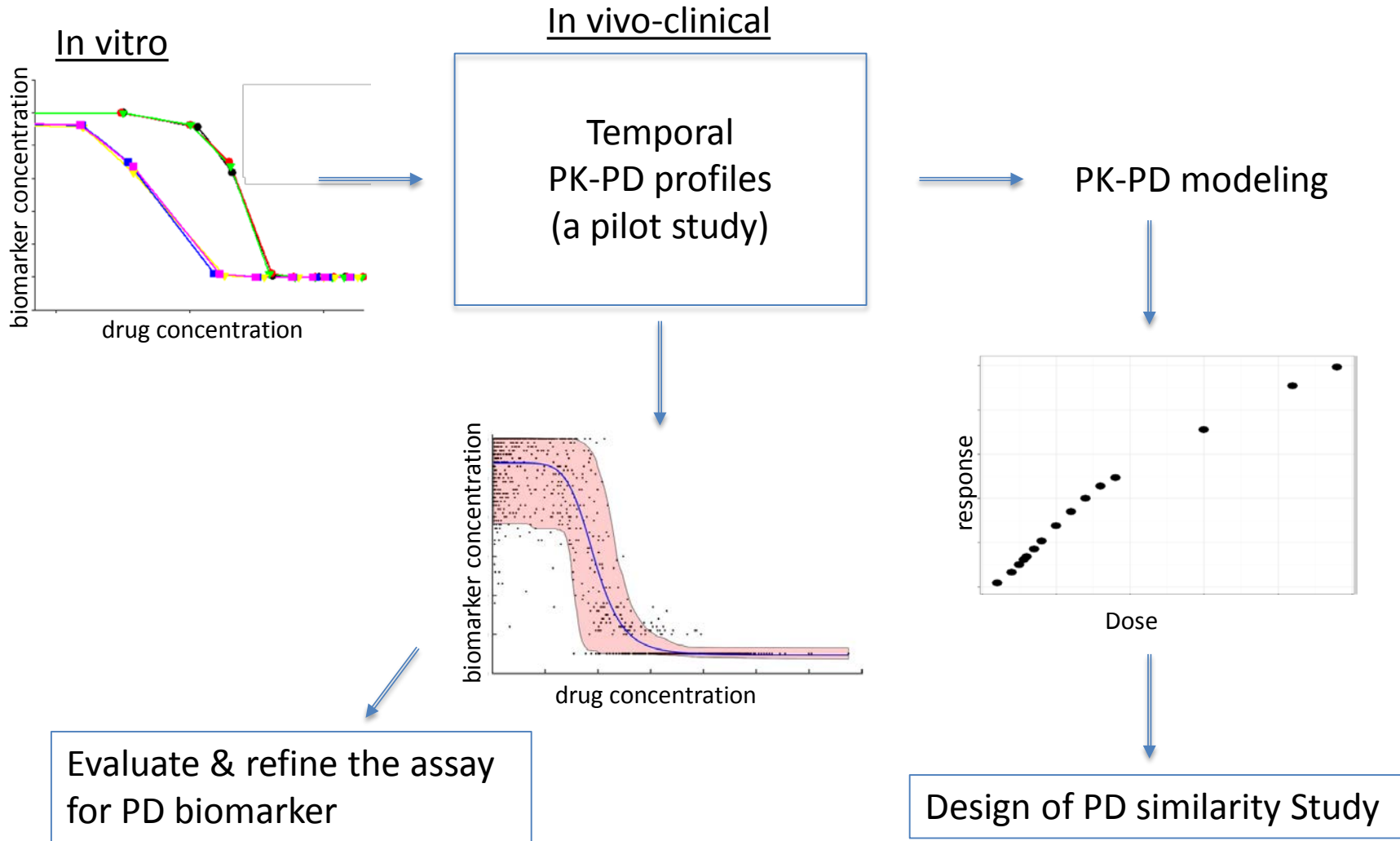


Source: FDA review of filgrastim-sndz BLA

Pilot Study to Evaluate PD Biomarkers



– An Example From Biosimilar INDs



About Bioanalytical Assays for PD Biomarkers



Guidance for Industry

Bioanalytical Method Validation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (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) Brian Booth, 301-796-1508 or (CVM) John Kadavil, John.Kadavil@fda.hhs.gov

Revision 2 will be
available in 2018.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

September 2013
Biopharmaceutics

Revision 1

More About Bioanalytical Assays for PD Biomarkers



- BMV guidance: “When biomarker data will be used to support a regulatory action, such as..., the assay should be fully validated.
- It is applicable to PD similarity studies to support a demonstration of no clinically meaningful differences in biosimilar development programs.
- Consult the BMV guidance for regulatory expectations.
- Evaluate adaptation needed to use assays for diagnostic tests or other commercially available assays in drug development.
- Consider assay suitability for PD similarity assessment, e.g.,
 - Appropriateness of ULOQ, LLOQ for the range of PD data
 - Sample handling protocol in line with established stability
- Provide adequate documentation in BLA submissions.

Summary



- For certain products, the use of PK and PD similarity data in lieu of comparative clinical data to support a demonstration of no clinically meaningful differences and biosimilarity **is** within the regulatory framework for biosimilars approval.
- Selected PD biomarkers should be relevant to the mechanism of action(s) of the drugs.
- Pilot study(ies) may be necessary to inform the design of a definitive PD similarity study that is powered for statistical testing.
- The bioanalytical method validation guidance is applicable to PD biomarker assays.

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