Agenda

Sarah Yim
U.S. Food and Drug Administration

Yow-Ming Wang
U.S. Food and Drug Administration

Leah Christl
Amgen Inc.

Abhijit Barve
Viatris Inc.

David Strauss
U.S. Food and Drug Administration

Jeffry Florian
U.S. Food and Drug Administration

Salaheldin Hamed
U.S. Food and Drug Administration

Andrej Skerjanec
Sandoz Inc.

Wojciech Krzyzanski
State University of New York at Buffalo

Qin Sun
U.S. Food and Drug Administration

Paula Hyland
U.S. Food and Drug Administration

R. Donald Harvey III
Emory University

Bernd Meibohm
University of Tennessee

Peter Stein
U.S. Food and Drug Administration

Jian Wang
Health Canada

Elena Wolff-Holz
European Medicines Agency

Pharmacodynamic Biomarkers for Biosimilar Development and Approval

September 20, 2021 | 10:00 am – 2:30 pm ET

September 21, 2021 | 10:00 am – 2:30 pm ET

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome and Opening Remarks | Day 1

Mark McClellan

Duke-Margolis Center for Health Policy

Agenda

Session 1

Biosimilar Development Paradigms—Current and Future Perspectives

Session 2

Leveraging Pharmacology to Advance PD Biomarkers for Biosimilar Development

Session 3

Emerging Experiences and Approaches Using PD Biomarkers in Biosimilar Development

Session 4

Extending PD Biomarker Opportunities Across Therapeutic Areas & Advancing PD Biomarker Use in Future Biosimilar Development

Session 5

Regulatory Perspectives and Efforts to Advance PD Biomarkers for Biosimilars

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The Robert J. Margolis, MD, Center for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

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- Company-specific prices, pricing methods, pricing policies, pricing plans
- Sensitive cost information, including reimbursement rates or methods, pharmacy costs, and salaries/compensation information
- Marketing and strategic plans, market or competitive evaluations
- Identity and other information about present or potential customers, healthcare providers or payers, including costs, prices, profitability, marketing plans, and product development plans
- Research & development plans
- Other confidential or proprietary activities, strategies, processes or procedures
- Refusals to deal with any company or supplier
- Strategies or plans to award business or remove business from a specific company, to participate or not participate in any particular business opportunity or type of business opportunity
- Status of negotiations with present or potential customers, suppliers, payers or healthcare providers
- Any other confidential business information that could be used to reduce competition

Virtual Meeting Reminders

- Attendees are encouraged to contribute through the meeting with questions in the Zoom Q&A function.
- Panelists should go on video during the panel discussion
- Presenters should provide a verbal indicator when they'd like to advance the slides

Welcome and Opening Remarks

Janet Woodcock

U.S. Food and Drug Administration

Session 1: Biosimilar Development Paradigms—Current and Future Perspectives

10:20 am – 12:00 pm

Sarah Yim

U.S. Food and Drug Administration

Current and Future Perspectives on Biosimilar Development

Duke-Margolis/FDA PD Biomarkers for Biosimilars Workshop
September 20, 2021

Sarah Yim, M.D.
Director
Office of Therapeutic Biologics and Biosimilars
OND/CDER/FDA/DHHS

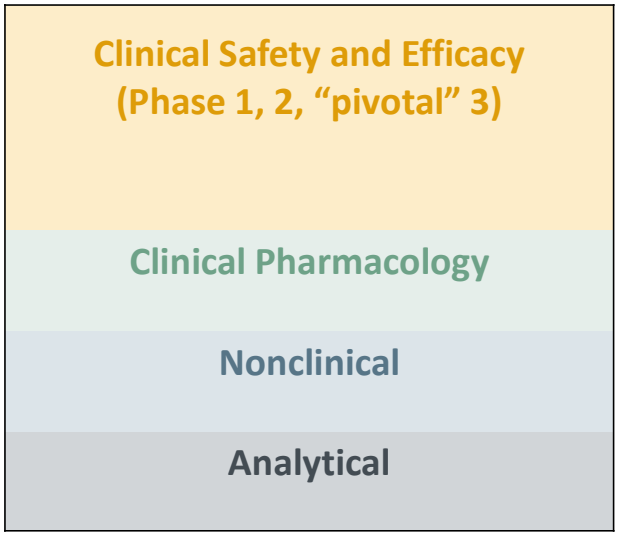
FDA U.S. FOOD & DRUG ADMINISTRATION

	Generic (Orange Book)	Biosimilar (Purple Book)
Comparative Assessment Standards	• **Therapeutic Equivalence** = Pharmaceutical Equivalence + Bioequivalence	• **Biosimilarity** = Highly Similar + No Clinically Meaningful Differences • **Interchangeability** = 1) biosimilar to the RP; 2) can be expected to produce the same clinical result as the RP in any given patient; 3) risk of switching between product and RP is not greater than using the RP without switching
Comparative pharmaceutical assessment	• Same active ingredient(s) • Same strength • Same dosage form • Same route of administration	• Analytically highly similar, notwithstanding minor differences in clinically inactive components • Same strength • Same dosage form • Same route of administration
Comparative therapeutical assessment	**Bioequivalence** = • Absence of sig diff in rate and extent of absorption • Similar availability at site of drug action at same molar dose under similar conditions	• Same mechanism of action (to the extent it is known for RP) • Condition(s) of use previously approved for RP • Assessment of toxicity (e.g., animal studies), immunogenicity, pharmacokinetics, pharmacodynamics (e.g., clinical studies) sufficient to demonstrate safety, purity, potency
Substitution	**Therapeutic Equivalence** = Can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling	**Interchangeability** = may be substituted for the RP without the intervention of the health care provider who prescribed the RP

Different Goals for "Stand-alone" vs. Biosimilar Development

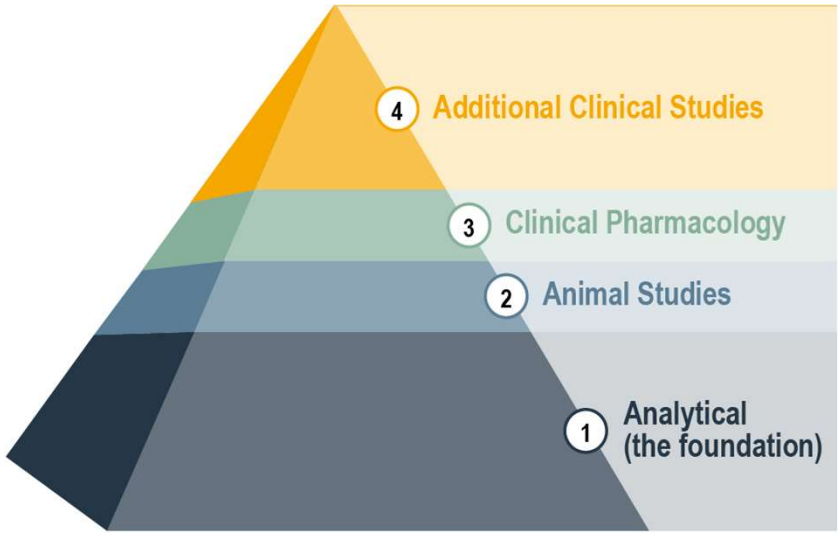
"Stand-alone": 351(a) BLA

Goal: To establish *de novo* safety and efficacy of a new product



"Abbreviated": 351(k) BLA

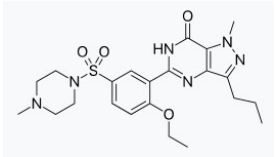
Goal: To demonstrate biosimilarity (or interchangeability) to a reference product

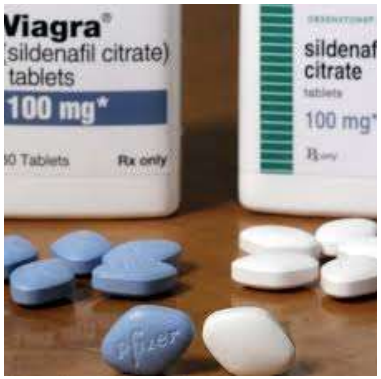


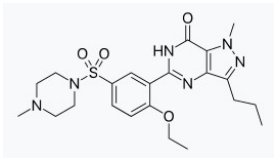
A typical small molecule drug: millions of identical molecules

Brand

Generic







A pill

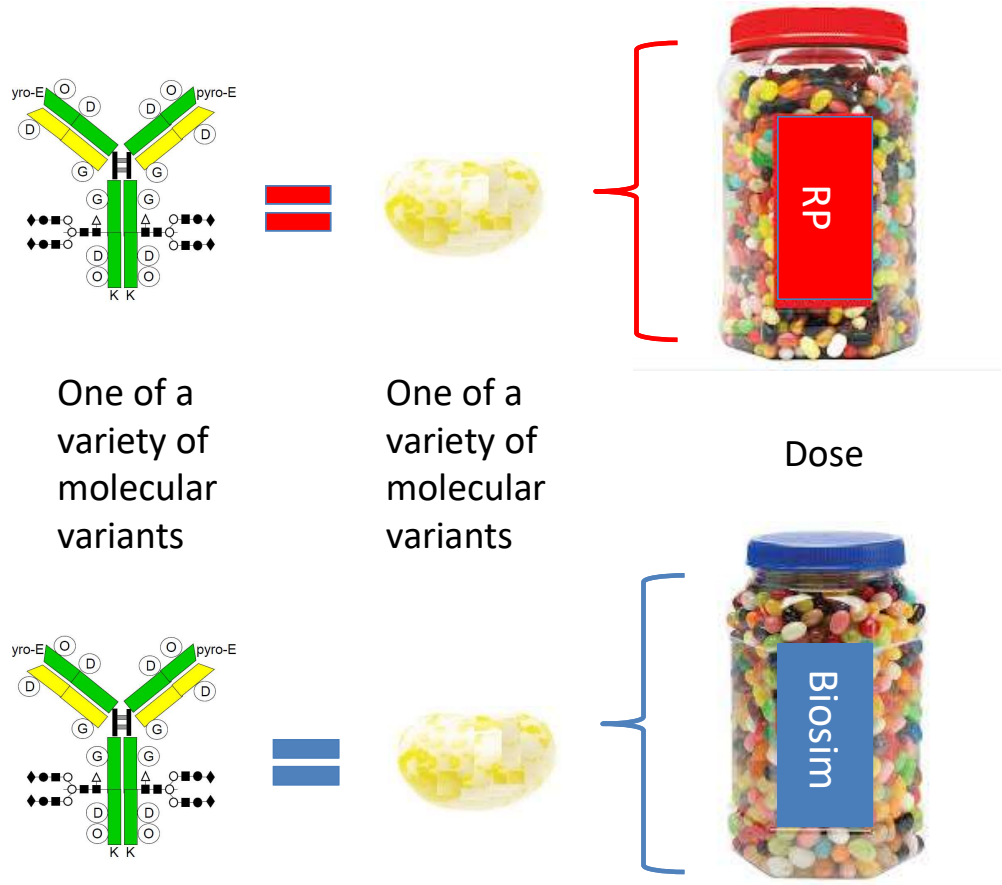
A molecule

A molecule

A pill

Biologics: the same protein with many variations

- Post-translational modifications result in millions of slightly different versions of the same protein per dose or batch
- **Both reference products and biosimilars contain these variations**
- Reference products try to keep a consistent mix of variants within a certain range, over time
- Biosimilars try to match the patterns and variations of the reference product



Approved Biosimilars in the U.S.A.

Reference Product	Approved Biosimilars					
Humira (adalimumab)	**Amjevita** *adalimumab-atto* *Amgen 2016*	**Cyltezo** *adalimumab-adbm* *Boehringer Ingelheim 2017*	**Hyrimoz** *adalimumab-adaz* *Sandoz 2018*	**Hadlima** *adalimumab-bwwd* *Samsung Bioepis 2019*	**Abrilada** *adalimumab-afzb* *Pfizer 2019*	**Hulio** *adalimumab-fkjp* *Mylan 2020*
Avastin (bevacizumab)	**Mvasi** *bevacizumab-awwb* *Amgen 2017*	**Zirabev** *bevacizumab-bvzr* *Pfizer 2019*				
Epogen (epoetin-alfa)	**Retacrit** *epoetin alfa-epbx* *Hospira/Pfizer 2018*					
Enbrel (etanercept)	**Erelzi** *etanercept-szzs* *Sandoz 2016*	**Eticovo** *etanercept-ykro* *Samsung Bioepis 2019*				
Neupogen (filgrastim)	**Zarxio** *filgrastim-sndz* *Sandoz 2015*	**Nivestym** *filgrastim-aafi* *Hospira/Pfizer 2018*				
Remicade (infliximab)	**Inflectra** *infliximab-dyyb* *Celltrion/Pfizer 2016*	**Renflexis** *infliximab-abda* *Samsung Bioepis/Organon 2017*	**Ixifi** *infliximab-qbtx* *Pfizer 2017*	**Avsola** *infliximab-axxq* *Amgen 2019*		
Lantus (insulin glargine)	**Semglee** *insulin glargine-yfgn* *Mylan/Viatris 2021,* *interchangeable*					
Neulasta (pegfilgrastim)	**Fulphila** *pegfilgrastim-jmdb* *Mylan/Viatris 2018*	**Udenyca** *pegfilgrastim-cbqv* *Coherus 2018*	**Ziextenzo** *pegfilgrastim-bmez* *Sandoz 2019*	**Nyvepria** *pegfilgrastim-apgf* *Hospira/Pfizer 2020*		
Rituxan (rituximab)	**Truxima** *rituximab-abbs* *Celltrion/Teva 2018*	**Ruxience** *rituximab-pvvr* *Pfizer 2019*	**Riabni** *rituximab-arrx* *Amgen 2020*			
Herceptin (trastuzumab)	**Ogivri** *trastuzumab-dkst* *Mylan/Viatris 2017*	**Herzuma** *trastuzumab-pkrb* *Celltrion/Teva 2018*	**Ontruzant** *trastuzumab-dttb* *Samsung Bioepis/Organon 2019*	**Trazimera** *trastuzumab-qyyp* *Pfizer 2019*	**Kanjinti** *trastuzumab-anns* *Amgen 2019*	

Purple = Marketed

Perspectives On Where We Are ~10 years after BPCIA

Public Health Goal: Make high quality, safe and effective biologic therapies accessible for more patients

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process

2. Maximizing scientific and regulatory clarity for the biosimilar product development community

3. Developing effective communications to improve understanding of biosimilars among patients, clinicians and payors

4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition

Public Health Goal: Make high quality, safe and effective biologic therapies accessible for more patients

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process
   - Review templates specific for 351(k) BLAs
   - Organizational changes to facilitate efficient review
   - Information resources and development tools
     - Index of critical quality attributes for use in comparing proposed biosimilars to certain reference products
     - Develop and validate pharmacodynamic (PD) markers tailored to biosimilar development and in silico modeling and simulation to evaluate pharmacokinetic (PK) and PD response vs. clinical response relationships using existing clinical data

Public Health Goal: Make high quality, safe and effective biologic therapies accessible for more patients

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process

2. Maximizing scientific and regulatory clarity for the biosimilar product development community
   - Dialogue with the public via public meetings and dockets
   - Guidance publication/finalization
   - Searchable, modernized Purple Book database of biologics
   - Update rules and regulations
   - Strengthen FDA's partnerships with international regulatory authorities
   - Real World Evidence to support safety and prescribing

Public Health Goal: Make high quality, safe and effective biologic therapies accessible for more patients

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process

2. Maximizing scientific and regulatory clarity for the biosimilar product development community

3. Developing effective communications to improve understanding of biosimilars among patients, clinicians and payors
   - More educational materials and media for patients, prescribers, other stakeholders
   - Educational curriculum for use in health professional schools
   - Stakeholder engagement

Public Health Goal: Make high quality, safe and effective biologic therapies accessible for more patients

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process

2. Maximizing scientific and regulatory clarity for the biosimilar product development community

3. Developing effective communications to improve understanding of biosimilars among patients, clinicians and payors

4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition
   - FDA/FTC coordination
   - Evaluate/address statutory and regulatory requirements/loopholes

“The confidence that individuals have in their beliefs depends mostly on the quality of the story they can tell about what they see, even if they see little”

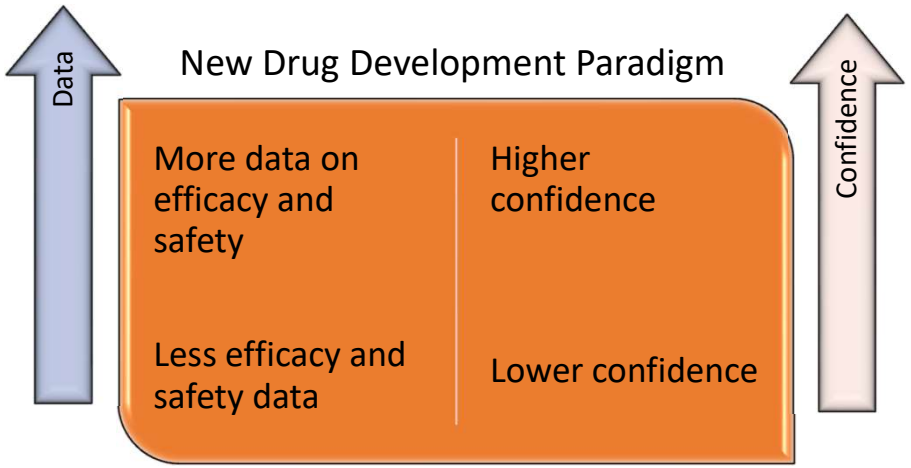
Daniel Kahneman, Thinking, Fast and Slow

Perspectives on Where We Want to go and How to Get There

Challenges

- US healthcare ecosystem and economic structure
- New drug development paradigm predominates thinking and is more intuitive
- Skepticism in what “experts” say – e.g., pandemic

Default Mental Model

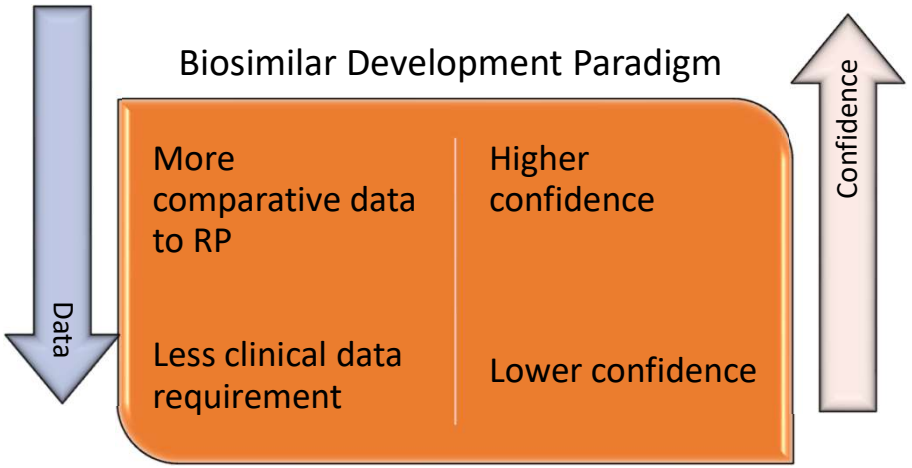


Perspectives on Where We Want to go and How to Get There

Challenges

- US healthcare ecosystem and economic structure
- Make biosimilar development feel more familiar and comfortable
- Make biosimilars feel more familiar and comfortable

Adapted Mental Model



The Rationale Supporting Abbreviation is Not Really Understood or Believed by Many Stakeholders

Reference Product

Clinical Safety and Efficacy (Phase 1, 2, "pivotal" 3)

Biosimilar

Education is Necessary but not Sufficient

- Effects of Educational or Regulatory Policies Targeting Prescribers
  - Single, controlled before-after study in the USA of an educational program +/- an intervention to regulate drug reimbursement at 4 different HMOs encompassing a total of 970,000 members

Share of prescribing	HMO A: Interventions to regulate drug reimbursement	HMO B: Education for Physicians and HMO members	HMO C: Education for Physicians	HMO D: No educational intervention
Preferred drug increase (95% CI)	↑ 45.6% (42.3%, 48.9%)	↑ 9.5% (7.9%, 11.1%)	↑ 2.3% (0.6%, 4%)	↑ 1.6% (0.4%, 2.8%)
Less preferred drug decrease (95% CI)	↓ -54.4% (-57.7%, -51%)	↓ -12.5% (-14.6%, -10.4%)	↓ -5% (-7.0%, -3.0%)	↓ -3.6% (-5.2%, -2.0%)

Suleman F, Movik E. Pharmaceutical Policies: Effects of Educational or Regulatory Policies Targeting Prescribers. Cochrane Database of Systematic Reviews, 2019, Issue 11, Art # CD013478. DOI: 10.1002/14651858.CD013478

Education is Necessary but not Sufficient

- Kaiser Permanente
  - Involvement of prescribers and pharmacists in the decision-making process
  - Peer to peer sharing of experience
  - Review of available evidence, including post-market data
  - Clinical guidelines and educational materials to support caregivers
  - Pharmacist drug education coordinators to educate patients and the care team and to answer questions/counteract misinformation

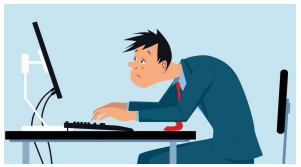
Awsare S et al. The case for letting biosimilars compete. Health Affairs. Dec 19, 2019. DOI: 10.1377/hblog20191212.286621

Advancing Public Health Goals: Efficient Development AND Increasing Confidence/Uptake

- Typically, healthcare providers are most familiar with and reassured by clinical efficacy and safety data
- Biosimilar and interchangeable scientific and regulatory concepts are not easy to convey in sound bites
- Efficient development won't help if it makes prescribers less confident in and less likely to use the products
- Education is necessary but not sufficient—changing feelings, beliefs and behaviors is a complex issue but critical in achieving public health goals

Resources

- Visit www.fda.gov/biosimilars for access to FDA education materials and information about biosimilar and interchangeable products
- Visit the www.fda.gov/purplebook for information on biological products, including if products are biosimilar to a reference product
- Visit www.fda.gov/drugsatfda (**Drugs@FDA**) for information on all CDER approved drug products, including labeling and review information



Yow-Ming Wang

U.S. Food and Drug Administration

Public Workshop

Pharmacodynamic Biomarkers for Biosimilar Development and Approval SEPTEMBER 20 - 21, 2021

FDA U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Applying Clinical Pharmacology Principles to Selecting Pharmacodynamic Biomarkers for Biosimilar Development

Yow-Ming Wang, PhD

Therapeutic Biologics Program

Office of Clinical Pharmacology/OTS/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.

- 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

- Biomarkers and context of use – pharmacodynamic (PD) biomarkers
- The role of PD biomarkers in biologics and biosimilars development
- Five characteristics of PD biomarkers to support biosimilarity – practical examples
- Opportunities to increase utilization of PD biomarkers
- Summary

Definition of Biomarker Is Context-Dependent

- Diagnostic Biomarker
- Monitoring Biomarker
- Pharmacodynamic (PD)/Response Biomarker
- Predictive Biomarker
- Prognostic Biomarker
- Safety Biomarker
- Susceptibility/Risk Biomarker
- Understanding Prognostic versus Predictive Biomarkers
- Reasonably Likely Surrogate Endpoint
- Validated Surrogate Endpoint
- Validation

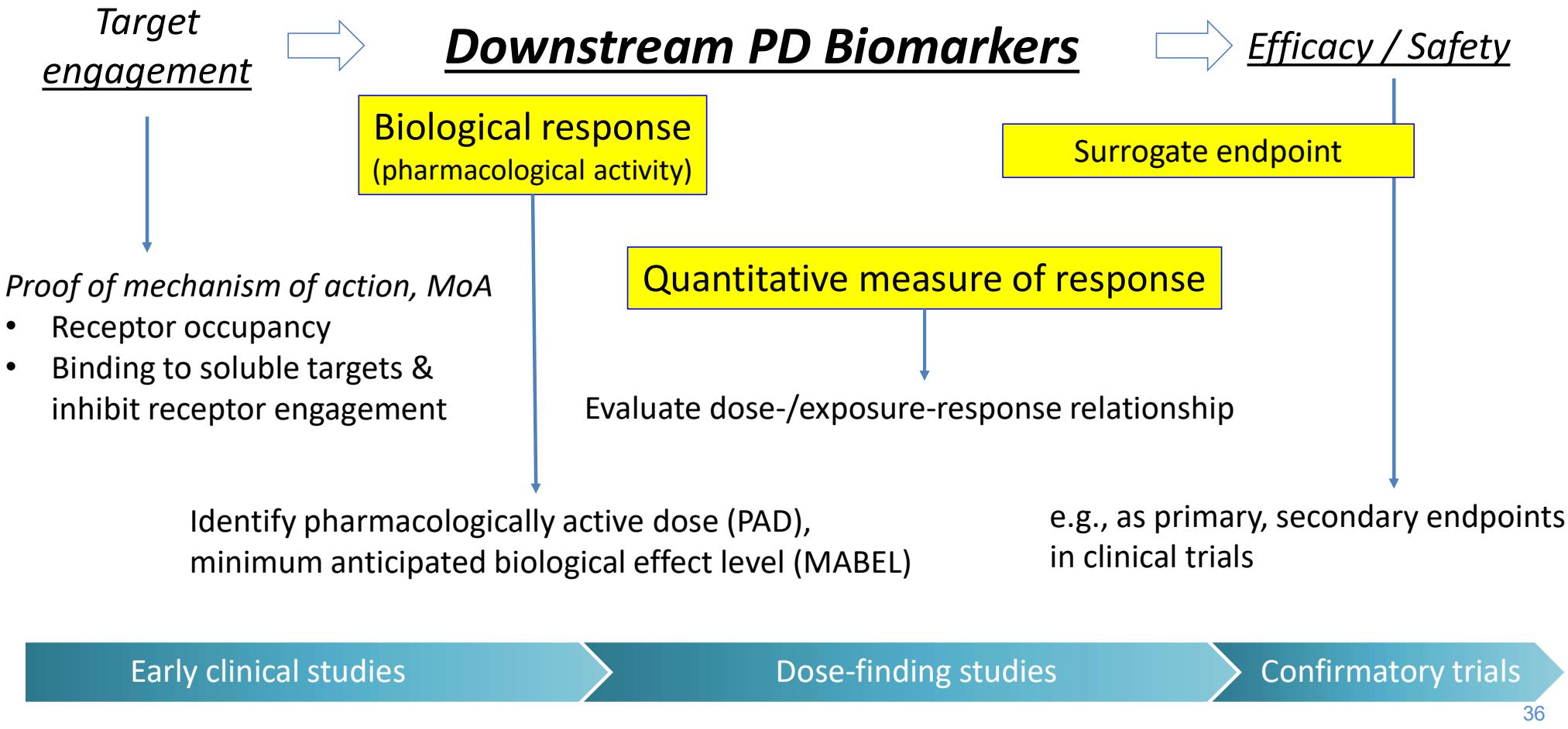
"used to show that a biological response has occurred after exposure to a medical product…"

Focus of this presentation

Potential use of PD biomarker

Last Updated: December 28, 2020

Prior Experience with Biomarkers in Drug Development
(PDUFA programs: goal – to establish safety & efficacy)



Role of Clinical Pharmacology Data

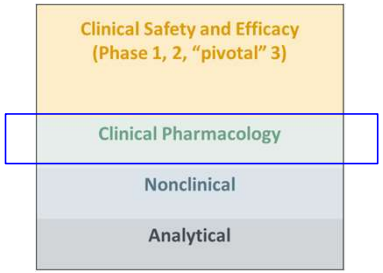
351(a) "stand-alone" BLA

- Goal: To establish safety and efficacy of the product
- Characterize PK and PD to evaluate

→ Dose-exposure relationship

→ Dose- / exposure-response relationship

→ Doses to study in clinical trials & dose(s) for the labeling



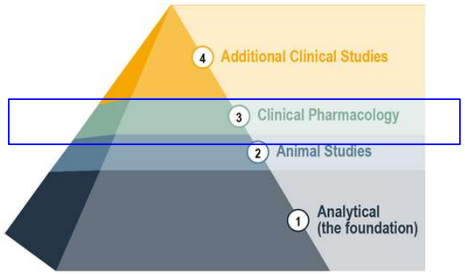
351(k) biosimilar BLA

- Goal: To demonstrate biosimilarity to a reference product
- Compare PK (and PD) between products

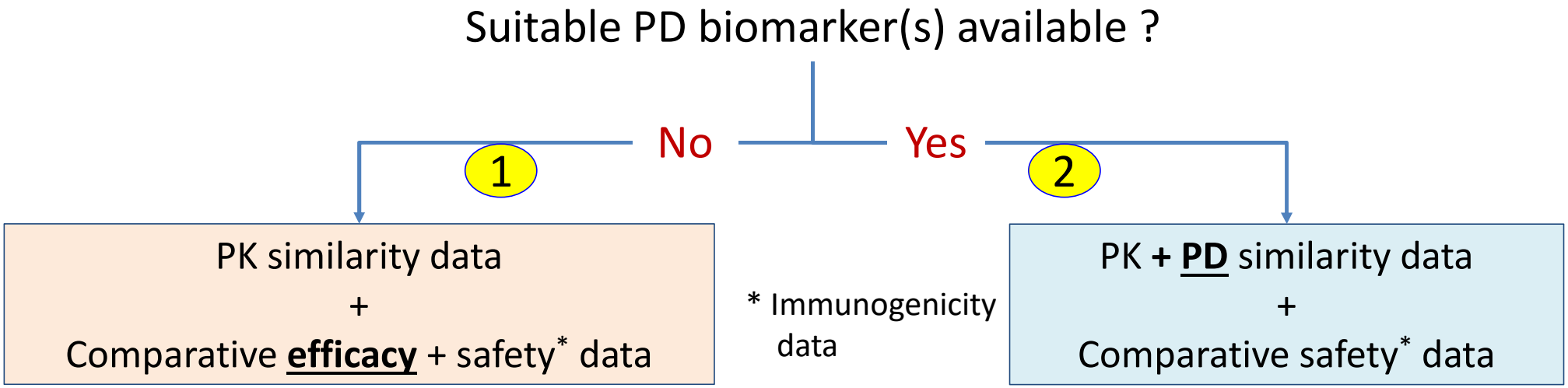
→ Similar exposure (PK)

→ Similar response (PD), if applicable

With the foundation of analytical similarity, similar PK and PD can support biosimilarity without a comparative clinical efficacy study



Two Approaches Supported Biosimilar Approvals
(when systemic PK is available)



i.e., PD similarity data ***in lieu of*** comparative efficacy data

22 BLAs (6 Reference Products)	8 BLAs (4 Reference Products)

Two Approaches Supported Biosimilar Approvals
(when systemic PK is available)

Suitable PD biomarker(s) available ?

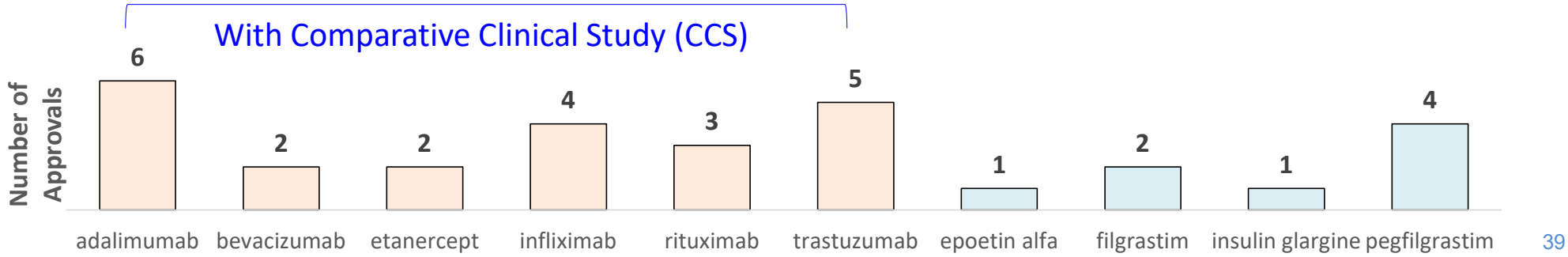
No → 1

PK similarity data
+
Comparative **efficacy** + safety* data

Yes → 2

PK **+ PD** similarity data
+
Comparative safety* data

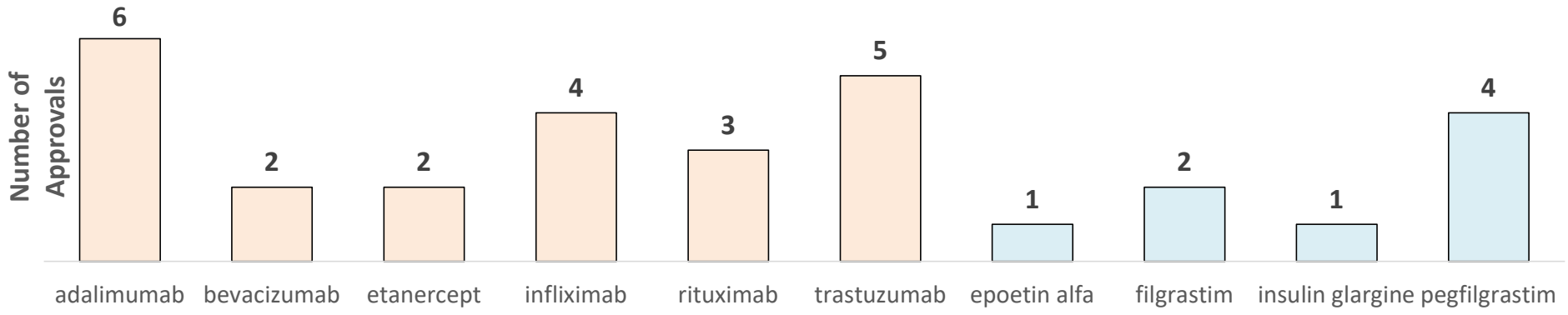
* Immunogenicity data



Biosimilar Programs with PK and PD Studies Are More Efficient

- Sample size — Comparative Clinical Study (CCS) > PK and PD similarity study
- Study duration — Longer for CCS than PK and PD study

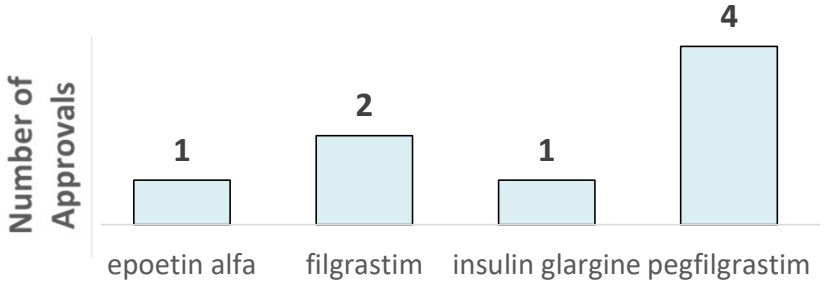
Study Sample Size (total number of subjects)										
PK + CCS Approach (1)						PK + PD approach (2)				
Comparative Clinical Study (CCS)						PK + PD study				
~600	~700	~500	~600	~300	~700	80-130	25-60	95	~270	

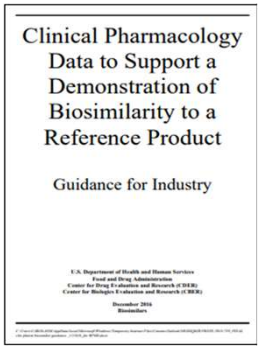


Biosimilar Programs with PK and PD Studies Are More Efficient

- Sample size — Comparative Clinical Study (CCS) > PK and PD similarity study
- Study duration — Longer for CCS than PK and PD study

Study Sample Size (total number of subjects)				
	2 PK + PD approach			
PK + PD study	80-130	25-60	95	~270
Comparative Clinical Study (CCS, not required for BLA)	~400	~200	~600	~300





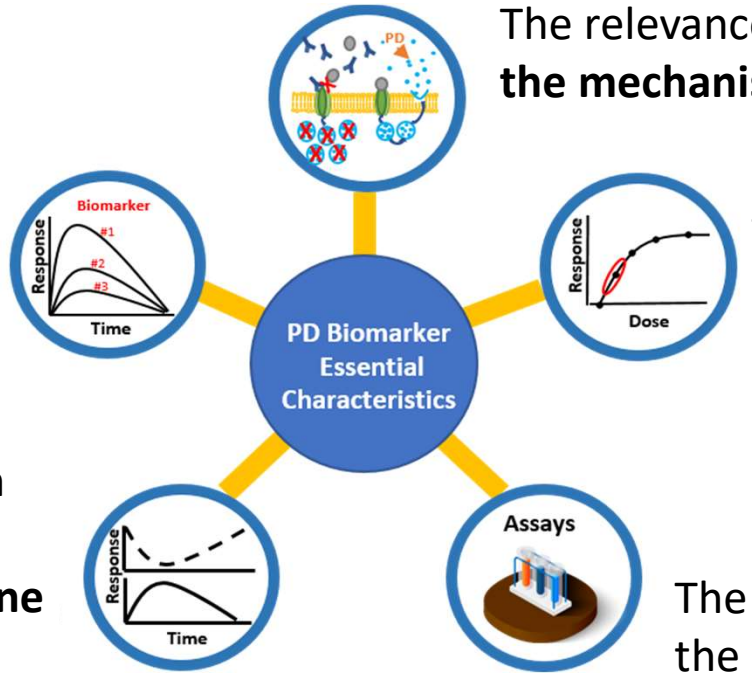
Five Essential Characteristics of PD Biomarkers for Biosimilar Programs

2

The **dynamic range** of the PD biomarker over the exposure range to the biological product

1

The **time of onset** of change in the PD biomarker relative to dosing and **its return to baseline** with discontinuation of dosing



4

The relevance of the PD biomarker to **the mechanism of action** of the drug

3

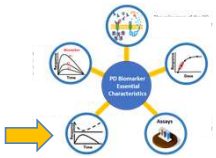
The **sensitivity** of the PD biomarker to differences between the proposed biosimilar product and the reference product

5

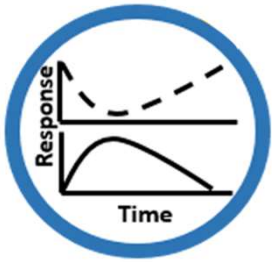
The **analytical validity** of the PD biomarker assay

Bioanalytical Method Validation
Guidance for Industry

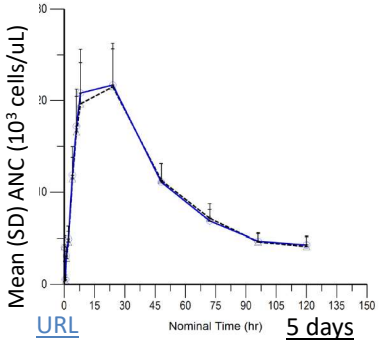
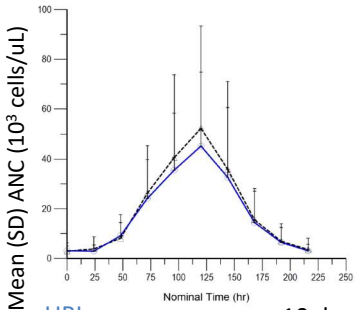
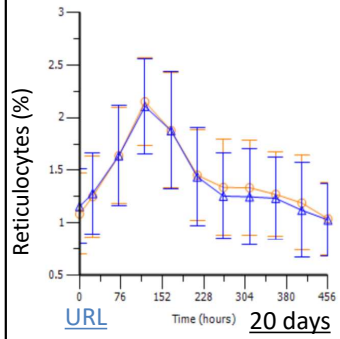
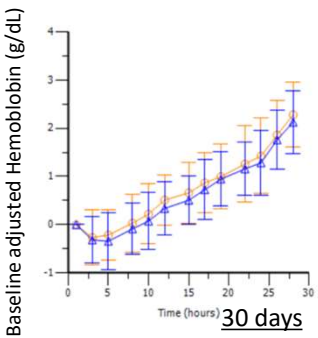
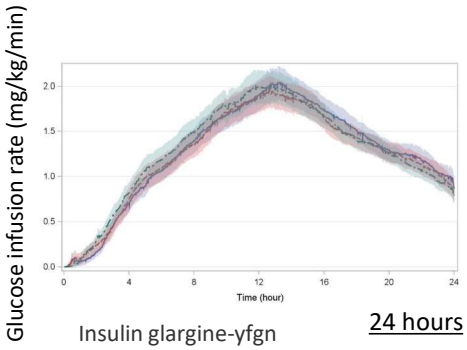
J.Li, et al. Advancing biosimilar development using Pharmacodynamic Biomarkers in Clinical Pharmacology Studies, CPT, doi:10.1002/cpt.1653



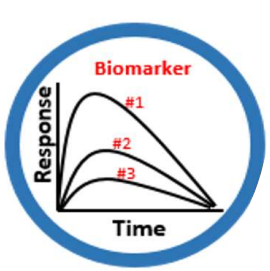
PD Biomarker Showing Time of Onset of Change And Its Return to Baseline Relative to Dosing



- Study a single dose, or multiple doses depending on the PD responses
- Compare estimated "area under the effect curve" (AUEC), maximum effect
  - Both are measured as the change from baseline

Filgrastim Pegfilgrastim	Filgrastim	Epoetin alfa		Insulin glargine
Absolute Neutrophil Count (ANC), single dose	CD34+ cell count (multiple dose)	Reticulocyte count (single dose)	Hemoglobin (multiple dose)	Glucose infusion rate in euglycemic clamp study
				
URL 5 days	URL 10 days	URL 20 days	30 days	Insulin glargine-yfgn 24 hours

PD Biomarker with Adequate Dynamic Range And Adequate Sensitivity to Detect Differences

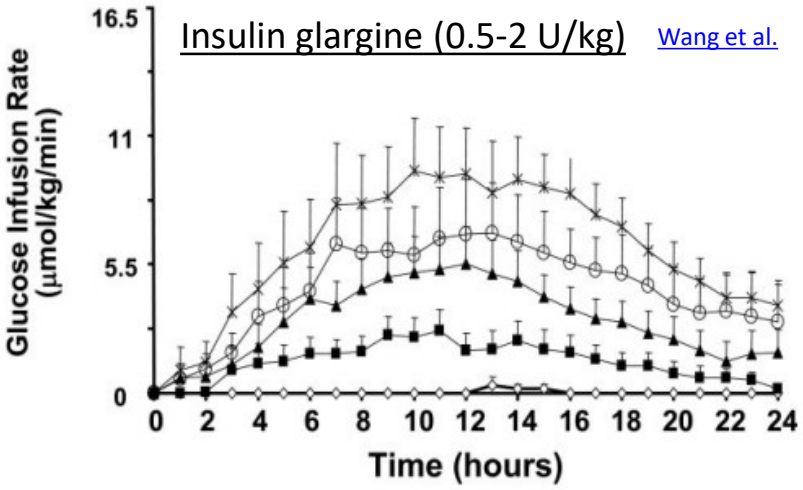


Ensure PD measure has a wide dynamic range over the range of drug concentrations observed in the study

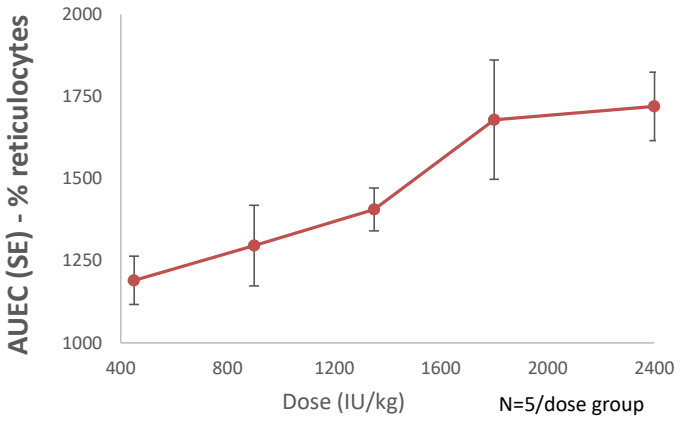
Identify a sensitive dose, on the steep part of the dose-response curve (i.e., before the plateau) from a range of studied doses

Data from a range of dose are generally needed to evaluate these two characteristics

Insulin glargine (0.5-2 U/kg) Wang et al.



Epoetin alfa Cheung et al.



Correlation Between PD Response And Clinical Outcome Is Beneficial, **But NOT required**

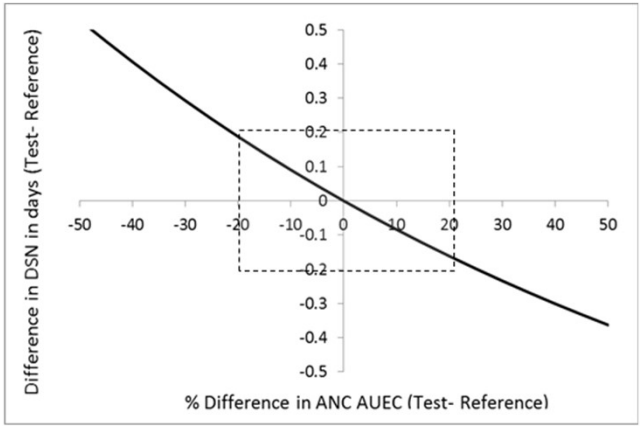
- Study data were from cancer patients received filgrastim after chemotherapy
- Study assessed absolute neutrophil count (ANC) daily
  → reduces time to neutrophil recovery &
  → reduces duration of severe neutropenia (DSN)
- Observed correlation of AUEC (ANC) & DSN
- 20% difference in AUEC (ANC) corresponds to DSN difference of $\leq$ 0.2 days
- Supports the sensitivity of ANC data for detecting clinically meaningful differences between products, if they exist

Quantitative Relationship Between AUEC of Absolute Neutrophil Count and Duration of Severe Neutropenia for G-CSF in Breast Cancer Patients

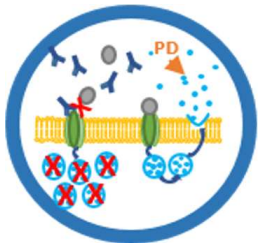
Liang Li, Lian Ma, Sarah J. Schrieber, Nam Atiqur Rahman, Albert Deisseroth, Ann T. Farrell, Yaning Wang, Vikram Sinha, Anshu Marathe

doi: 10.1002/cpt.991

Correlation of ΔDSN & ΔAUEC (ANC)



PD Biomarker Relevance to Drug's Mechanism of Action

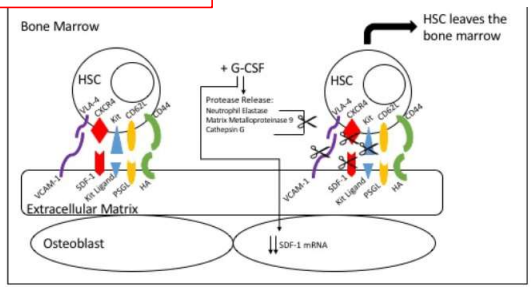


Measure PD response that effectively demonstrate the characteristics of the product's target effects

— Can be a single PD biomarker or a panel of biomarkers

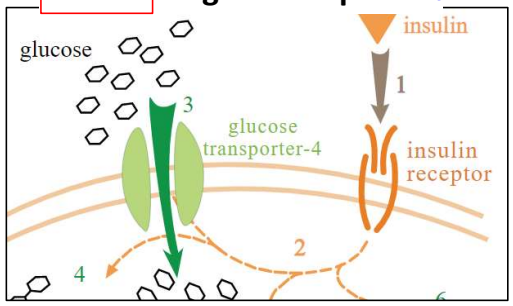
- Approved biosimilars used PD biomarkers tied to the efficacy endpoints
- More challenging for products with complex pharmacological effects and less well-characterized mechanism of action

Filgrastim **CD34+ ↑**



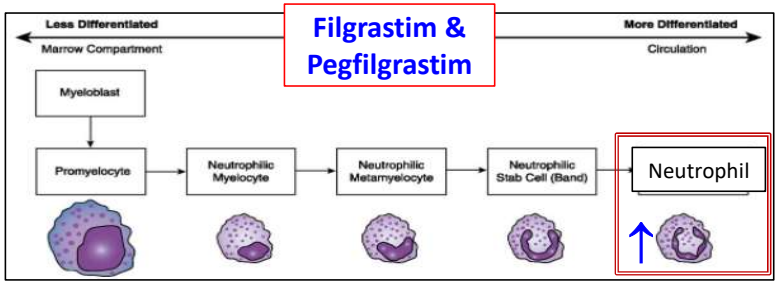
Mozobil | PPA - Quality Primary Cells Enhancing Your Research (pparesearch.com)

Insulin → glucose uptake ↑



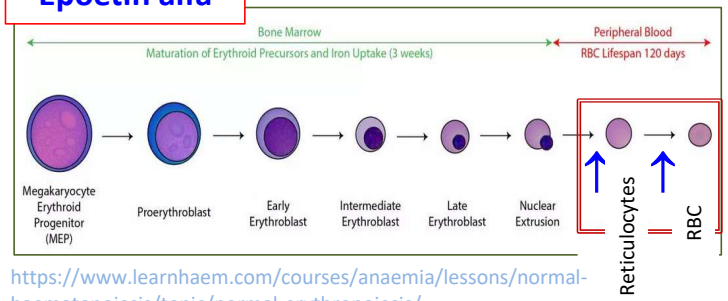
Insulin glucose metabolism ZP - Insulin - Wikipedia

Filgrastim & Pegfilgrastim



https://www.jimmunol.org/content/195/4/1341

Epoetin alfa



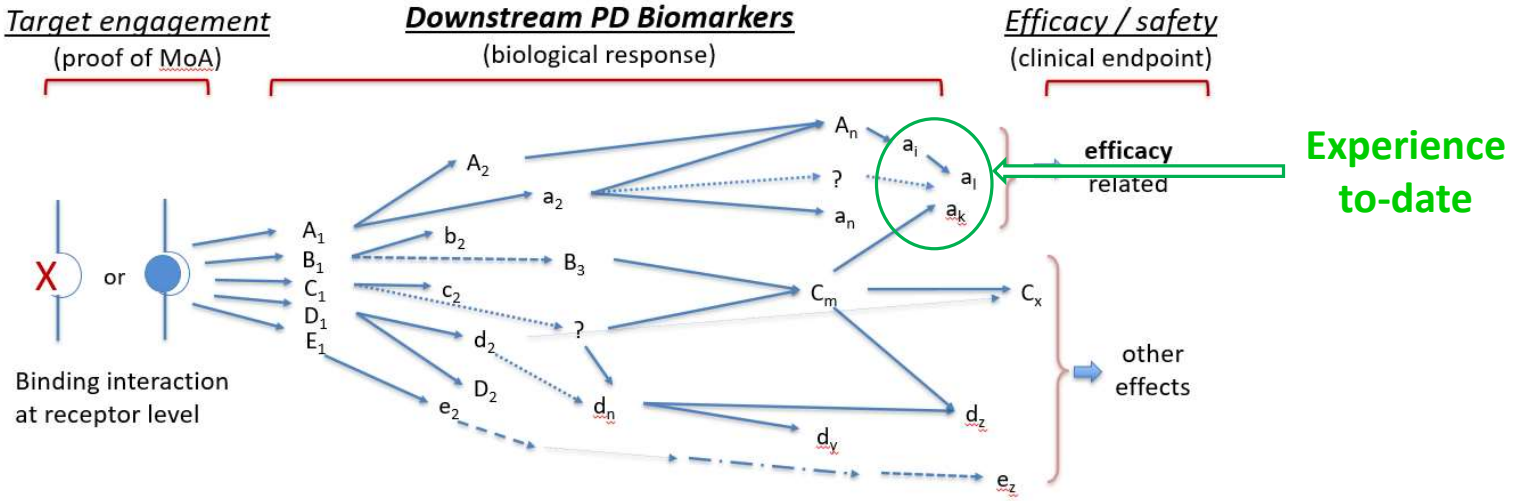
https://www.learnhaem.com/courses/anaemia/lessons/normal-haematopoiesis/topic/normal-erythropoiesis/

Seeking A Single or Multiple Relevant PD Biomarkers for Use

- Leverage literature knowledge to find potential PD biomarkers for biosimilar programs
- So far, approved biosimilars have used PD biomarkers that are tied to clinical efficacy
- PD biomarkers for biosimilar development are **not** required to reflect clinical efficacy

→ It presents an opportunity to explore PD biomarkers previously showed a dose-response relationship

A good understanding of MoA may reveal opportunities for multiple PD biomarkers



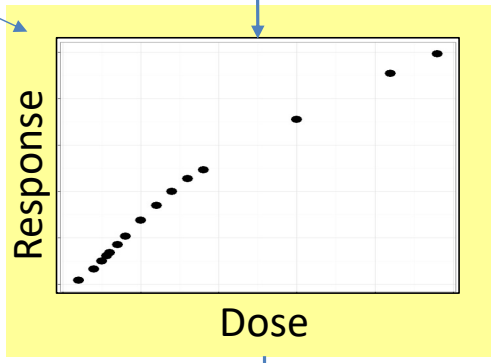
Pilot Studies May Be Necessary to Assess Suitability of PD Biomarker(s) and Inform Similarity Study Design

Literature data
(clinical / nonclinical)

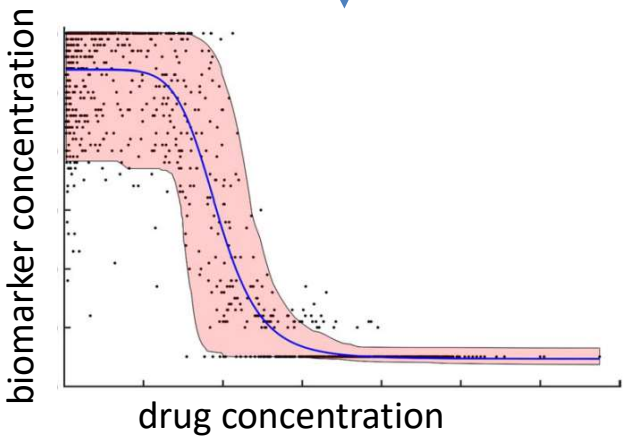
A pilot study

Temporal PK-PD profiles
(across a range of doses)

PK-PD
modeling



Design of
similarity study



Evaluate & refine the
assay for PD biomarker

Summary

- Clinical pharmacology principle: **similar PK (and PD) will provide similar efficacy and safety** (i.e., an exposure-response relationship exists)
- Use of PK + PD similarity data can remove the need for a comparative efficacy study for biosimilar approval, leading to a more efficient program
- FDA guidance recommends five characteristics for selecting PD biomarkers
  - a single appropriate PD biomarker or multiple relevant PD biomarkers
- PD biomarkers for biosimilar development are **not** required to reflect clinical efficacy or tie to efficacy endpoints
- There is an opportunity to explore PD biomarkers that showed dose-response relationship
- Pilot studies as well as modeling and simulation may be considered to provide justifications for PD biomarker selection, and facilitate study design

Acknowledgement

- Office of Clinical Pharmacology (OCP) Review Teams
- Members of Biologics Oversight Board, OCP
- PD Biomarkers Project Team
- PD Biomarkers Workshop Working Group
- Dr. Shiew Mei Huang
- Dr. Issam Zineh

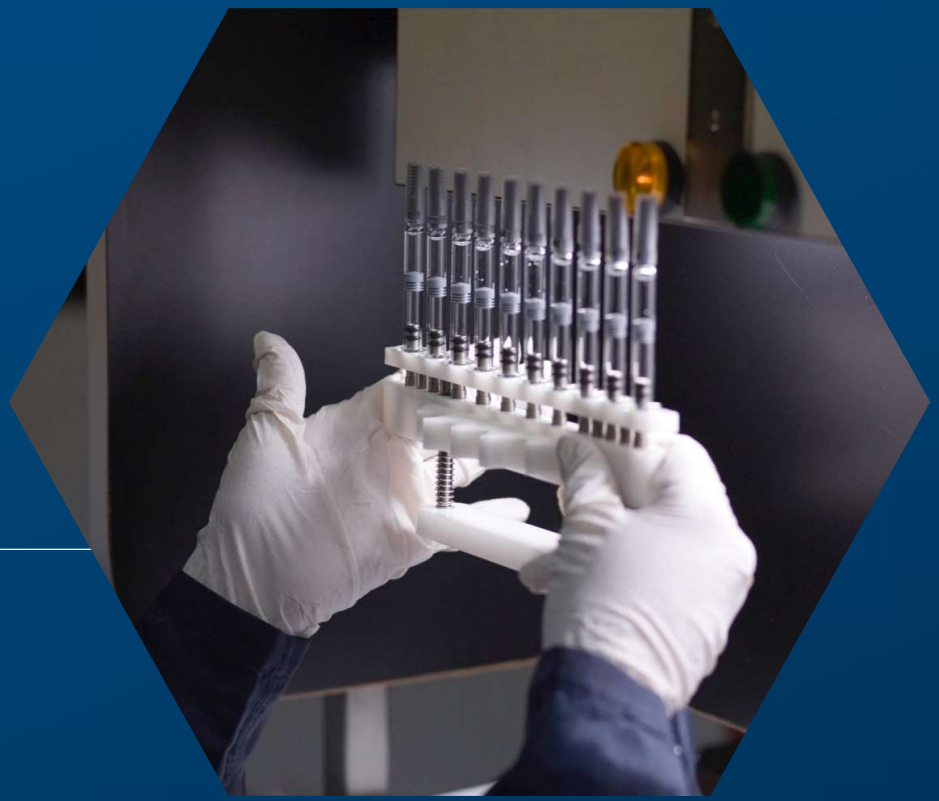
Leah Christl

Amgen Inc.

THE ROLE OF PHARMACODYNAMIC (PD) BIOMARKERS FOR BIOSIMILAR DEVELOPMENT AND APPROVAL – AN INDUSTRY PERSPECTIVE

LEAH CHRISTL, PhD
EXECUTIVE DIRECTOR, GLOBAL BIOSIMILARS REGULATORY AFFAIRS AND REGULATORY AND R&D POLICY
AMGEN

SEPTEMBER 20, 2021



Regulatory approval standards

The success of biosimilars depends on the development and maintenance of **scientifically sound and robust standards for approval and manufacturing**. For biosimilars, the totality of evidence to demonstrate biosimilarity, including comparative analytical and clinical studies, is necessary to support licensure.

AMGEN BIOSIMILARS

Analytical technologies

- New analytical technologies may provide additional informative data about structural and functional similarity
- Advanced *in vitro* and *in silico* technologies potentially can help target the clinical testing needed to support biosimilarity and resolve uncertainties seen in analytical testing
- Comparative clinical testing is still needed to demonstrate “no clinically meaningful differences”

ANALYTICAL TECHNOLOGIES

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As outlined in FDA guidance[1], in certain circumstances biosimilars may be approved based on PK and PD biomarker data without a comparative clinical study using efficacy endpoint(s).

"In certain circumstances, clinical PK and PD data that demonstrate similar exposure and response between a proposed biosimilar product and the reference product can be sufficient to completely assess whether there are clinically meaningful differences between products, notwithstanding the need for an adequate assessment of immunogenicity."

RIGOROUS REGULATORY FRAMEWORK

AMGEN BIOSIMILARS

[1]FDA. *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. Guidance for Industry*. Published December 2016.

PD biomarkers may improve biosimilar development efficiency and sensitivity

- Proposals for comparative clinical studies incorporating flexible study designs, such as studies in healthy subjects and the use of pharmacodynamic endpoints and arrays, should be considered when appropriate
- The FDA's goals include "the development and validation of pharmacodynamic biomarkers tailored to biosimilar development and *in silico* modeling and simulation to evaluate pharmacokinetic and pharmacodynamic response versus clinical response relationships using existing clinical data."[1]
- These approaches can reduce the size and increase the sensitivity of comparative clinical studies, allowing biosimilar development programs to be more efficient.

[1]FDA. *BIOSIMILARS ACTION PLAN: Balancing Innovation and Competition*. Published July 2018.

Scientific considerations whether a PD biomarker can adequately support a demonstration of no clinically meaningful differences

- PD biomarkers that reflect the MOA of the biological product have greater potential to be more sensitive endpoints for detecting clinically meaningful differences
  - ➢ If the MOA is unknown or not well understood a PD biomarker is less likely to be reasonably predictive of clinical outcome
- The sensitivity of the PD biomarker to differences between the proposed biosimilar product and the reference product
- The dynamic range of the PD biomarker over the exposure range to the biological product
- Various methodological considerations (e.g., assay validity)

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Considerations for the value of using PD biomarker(s)

- Identifying a novel biomarker or PD array to support a demonstration of biosimilarity may be more resource intensive than conducting a comparative clinical study with a traditional efficacy endpoint

- Lack of regulatory certainty/predictability for acceptance of a PD biomarker or array for a proposed biosimilar is risky compared to conducting a comparative clinical study with a traditional efficacy endpoint

The potential of pharmacodynamic biomarkers?

- Applying new and emerging technologies will enhance PD biomarker identification and inform the analytical strategies
- Additional scientific exploration outside and in advance of initiating a biosimilar development program
  - Establish what constitutes an appropriate PD biomarker
  - How to identify novel PD biomarkers for biosimilar development

➢ Regulatory transparency, clarity and predictability are critical to industry

➢ The success of biosimilars depends on the continued development and maintenance of scientifically sound and robust standards for approval

AMGEN BIOSIMILARS

THANK YOU FOR YOUR ATTENTION

AMGEN BIOSIMILARS

Abhijit Barve

Viatris Inc.

Learnings from Biosimilar Development over the Last Decade & Role of PD Biomarkers in Product Approvals

Abhijit Barve, M.D., Ph.D.

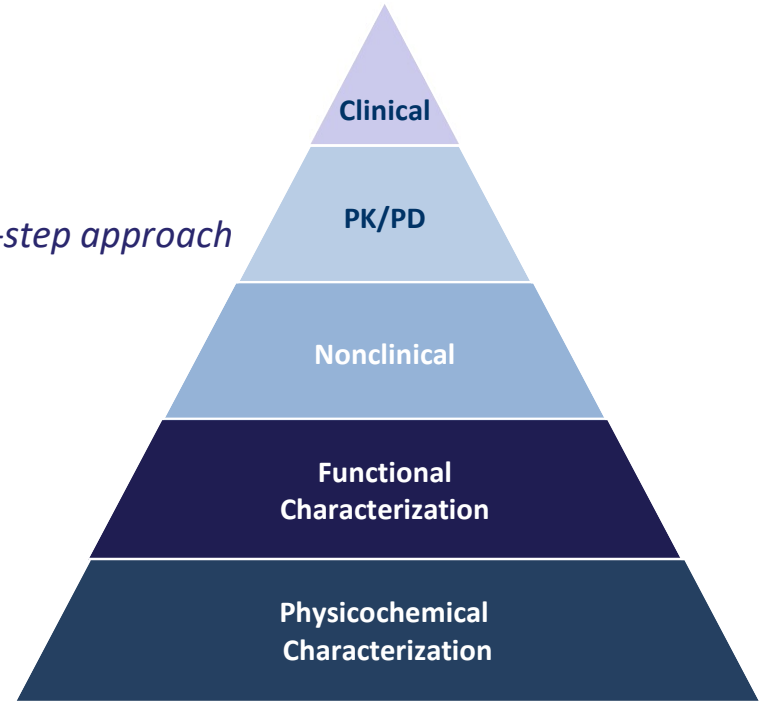
Chief Medical Officer, Viatris

Disclaimer

The views expressed in this presentation are presenters view and do not necessarily reflect that of Viatris

Conventional Biosimilar Development Paradigm

5-step approach

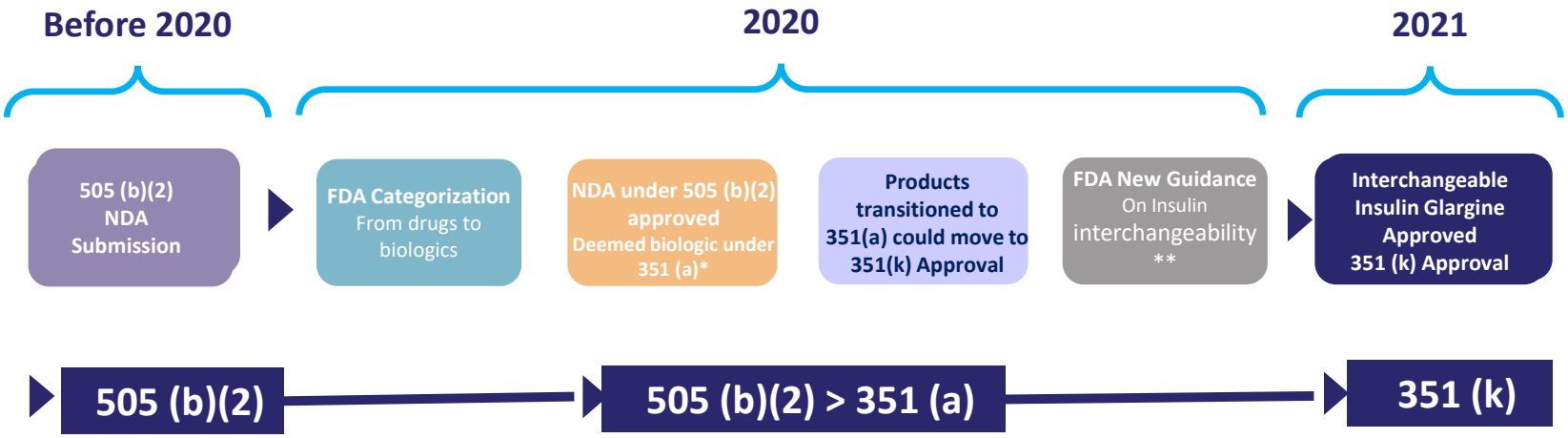


- Conventional Biosimilar development is a 5-step approach
- Overarching philosophy is to *eliminate residual uncertainty* at each step of the pyramid
- Sponsors have gained good understanding of efficacy study design incl. meta-analysis, equivalence margins, ratio vs differences & sample size
- In **some cases**, the use of comparative pharmacological studies (PK, PD) and a *clinical assessment of immunogenicity* may provide sufficient clinical data to confirm biosimilarity [1, 2]
- Conventional biosimilar paradigm is still relevant but needs to be adjusted to reflect learnings over last decade & scientific advances

1. *FDA biosimilar guideline 2015, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf*
2. *FDA clinical pharmacology guidance to support biosimilarity 2016, https://www.fda.gov/media/88622/download*

Evolution of Insulin Regulatory Pathway

A glance at the journey towards interchangeable Insulins



Prior to 2020

- Insulin biosimilars required a PK-PD study & comparative safety, efficacy studies to be approved under NDA

2020 and beyond

- Insulin approved under NDA were deemed to be a biologic
- Draft Guidance** on Immunogenicity for Insulin: if **high similarity** is demonstrated at analytical level, *then there is low residual uncertainty and clinical immunogenicity data are not required*

**On March 23, 2020, the approved new drug applications (NDAs) for insulin products were deemed to be licensed under section 351(a) of the PHS Act*

***FDA Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products Nov 2019: https://www.fda.gov/media/133014/download*

Evolution of Regulatory Expectations

- As the USFDA/EMA has gained more experience assessing biosimilars, it has also adopted a **more flexible approach to comparative efficacy studies** incl. cases where PK requirements were abbreviated (ophthalmic biologics) & integrated as part of efficacy/safety study
- In 2018, both the **EMA and USFDA approved pegfilgrastim biosimilars** without any confirmatory efficacy trials based on PK, biomarkers and immunogenicity **based on long experience and more extensive PK/PD** study compensating for Phase 3 requirement
- **Approval history of filgrastim and insulin biosimilars** shows the growing confidence of EU and US regulators to tailor clinical development programs without the need for comparative efficacy trials **where suitable biomarkers exist**
- However, the option for waiving comparative efficacy trials for many biosimilar candidates including most monoclonal antibodies (mAb) or fusion proteins is limited **because suitable biomarkers**, which would typically be required, are often **not available or meet the 5- point criteria**
- Furthermore, **assessment of immunogenicity** still requires safety/ efficacy study in patients for most biologics

Do classical comparative efficacy studies truly add value?

Outcome of retrospective review

Following CMC & Human PK data demonstrating comparability

In 95% of programs, the studies confirmed equivalence for efficacy & immunogenicity

In 36 of 38 biosimilar programs that required comparative efficacy trials, these trials just confirmed biosimilarity and would not have been necessary from a retrospective view

In 5% of programs, the efficacy studies revealed <u>higher immunogenicity</u>

In 2 (i.e., 5 %) of 38 biosimilar programs, the immunogenicity results triggered manufacturing process improvements to enable approval

Issues in both cases were caused by process impurities that should have been detected earlier

No issues with the molecule
Efficacy remained equivalent

Both issues could be prevented today based on progress on CQAs and advances in assay sensitivities

In <u>100%</u> of programs, the efficacy studies <u>confirmed comparable efficacy</u>

Comparable efficacy was always confirmed for all programs

Schiestl, M., Ranganna, G., Watson, K. et al. The Path Towards a Tailored Clinical Biosimilar Development. BioDrugs 34, 297–306 (2020). https://doi.org/10.1007/s40259-020-00422-1

Learnings from Biosimilar Development

- State-of-the-art analytical methods are sensitive to detect small differences in physicochemical profile, receptor binding and various bioactivities
- Strong understanding of critical quality attributes and their impact on PK, safety, efficacy and immunogenicity have ensured robust CMC comparability
- Clinical PK studies are highly sensitive to detect product differences
- Review of historical biosimilar studies indicate comparable efficacy was confirmed
- Couple of efficacy studies failed because of differences in immunogenicity driven by differences in impurities

- *Knowledge of CQA with physico-chemical & biological characterization are highly sensitive approaches*
- *Role and utility of large traditional efficacy comparability studies need to be evaluated against a given body of available CMC/analytical/ PK & PD biomarker data and residual uncertainty*

Frapaise, FX. The End of Phase 3 Clinical Trials in Biosimilars Development?. BioDrugs 32, 319–324 (2018). https://doi.org/10.1007/s40259-018-0287-0
Webster, C.J., Wong, A.C. & Woollett, G.R. An Efficient Development Paradigm for Biosimilars. BioDrugs 33, 603–611 (2019). https://doi.org/10.1007/s40259-019-00371-4
Schiestl, M., Ranganna, G., Watson, K. et al. The Path Towards a Tailored Clinical Biosimilar Development. BioDrugs 34, 297–306 (2020). https://doi.org/10.1007/s40259-020-00422-1

PD Biomarkers & Path Towards Biosimilar Approval

Biologic	Population	PK Assessment	PD Biomarkers Used	Immunogenicity
EPO/ Darbepoetin	NHV	C_{max} , $AUC_{0\text{-}t,}$ $AUC_{0\text{-}\infty}$	Reticulocyte count and hemoglobin level	Data needed in patients or NHV
Filgrastim/ Peg-filgrastim	NHV	C_{max} and $AUC_{0\text{-}t}$	E_{max} & $AUEC_{0\text{-}t}$ of absolute neutrophil count (ANC) & CD34+ count	Data needed in patients or NHV
Insulin Glargine	NHV, T1DM	$C_{insglar.max}$, $AUC_{insglar.0\text{-}24h}$	GIR_{max} , $AUC_{GIR.0\text{-}24h}$	Not needed if high similarity demonstrated
Insulin Aspart	NHV, T1DM	$C_{insasp.max}$, $AUC_{insasp.0\text{-}12h}$	GIR_{max} , $AUC_{GIR.0\text{-}12h}$	Not needed if high similarity demonstrated
Recombinant Human Insulin	NHV, T1DM	$C_{ins.max}$, $AUC_{ins.0\text{-}t}$	GIR_{max} , $AUC_{GIR.0\text{-}t}$	Not needed if high similarity demonstrated

*Each PD Biomarker satisfied the 5 criteria outlined by FDA namely the **time of onset** of change, **dynamic range** over exposure, the **sensitivity** of PD biomarker, relevance to the **mechanism of action** of the drug and the **analytical validity** of the PD biomarker assay*

FDA 2016. Guidance for industry. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

Are Alternate Pathways Possible for Products Without Biomarkers?

- Classical sample size calculations based on traditional meta-analysis are becoming increasingly difficult for newer biologic molecules (Wave 3) molecules
  - Data from multiple studies to assess true biologic response is become increasingly difficult
  - Combination of multiple biologics leading to smaller effect sizes impacting sample size calculations
  - Many biologics moving from once a month to once in 3-6 months, making studies incredibly complicated especially for immunogenicity assessment
- Do biomarkers/ prognostic efficacy indicators have to satisfy all 5 criteria outlined in guidance?
- Can we look at innovative approaches where biomarkers may not satisfy all 5 criteria?
- Combining orthogonal biological characterization techniques e.g. dose dependent binding in vitro supplemented with PK & or prognostic/ mechanistic assessments likely to be more sensitive than large efficacy equivalence studies, even in absence of traditional biomarkers
- Smaller clinical studies may still be needed for safety & immunogenicity & supporting efficacy

- *For newer biologics, traditional meta-analysis and sample size calculation may not be feasible or efficient*
- *Novel orthogonal approaches combining in-vitro with ex-vivo assessment should be seriously considered*

Summary and Conclusion

- Biosimilar regulation as initially developed was cautiously set-up based on the analytical procedures and manufacturing processes used at that time, as well as on clinical and regulatory experiences for biological medicines
- Robust understanding of CQA's impact, along with physico-chemical, biological characterization & clinical PK appear to be most sensitive tools to detect difference between the biosimilar and reference product
- Technological advances in analytics and adequate process controls can ensure comparable immunogenicity
- Qualified PD markers have definitely streamlined development for handful of simpler biologics and has accelerated development of biosimilars
- Biggest hurdle remains for biologics where no suitable biomarker is available. Novel orthogonal approaches like in-vitro PD assays along with ex-vivo assessments could offer a bridge towards efficient biosimilar development

Session 1: Panelists

- **Abhijit Barve,** Viatris Inc.
- **Leah Christl,** Amgen Inc.
- **Yow-Ming Wang,** U.S. Food & Drug Administration
- **Elena Wolff-Holz**, European Medicines Agency
- **Sarah Yim,** U.S. Food & Drug Administration
- **Issam Zineh,** U.S. Food & Drug Administration

Session 2: Leveraging Pharmacology to Advance PD Biomarkers for Biosimilar Development

12:50 pm – 2:20 pm

David Strauss

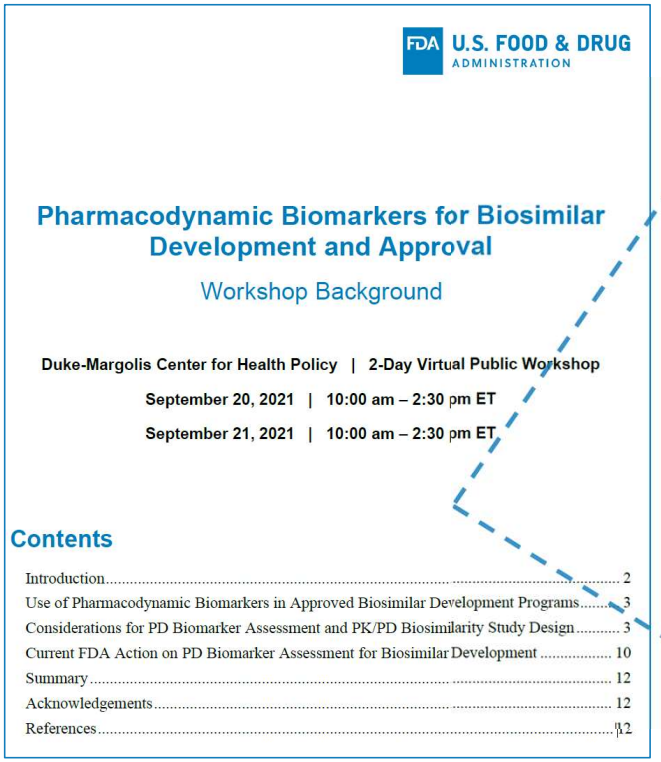
U.S. Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Developing an Evidentiary Framework to Advance the Use of PD Biomarkers for Biosimilars

David Strauss, MD, PhD
Division Director
Division of Applied Regulatory Science
Office of Clinical Pharmacology/OTS/CDER

Outline



U.S. FOOD & DRUG ADMINISTRATION

Pharmacodynamic Biomarkers for Biosimilar Development and Approval

Workshop Background

Duke-Margolis Center for Health Policy | 2-Day Virtual Public Workshop

September 20, 2021 | 10:00 am – 2:30 pm ET

September 21, 2021 | 10:00 am – 2:30 pm ET

Contents

- **Use of PD biomarkers in approved biosimilar development programs**
- **Considerations for PD biomarker assessment and PK/PD similarity study design**
- **FDA action to fill information gaps and inform on best practices for PD biomarkers to support biosimilar development**

This presentation reflects the views of the presenter and should not be construed to represent FDA's view or policies

Key Points

- PD biomarkers for biosimilars do not need to be surrogate endpoints for clinical efficacy outcomes
- Characterization of PD biomarkers according to the 5 key characteristics is critical to assess their suitability
- A single clinical pharmacology study can assess both PK and PD similarity if designed appropriately
- **Utilization of PD biomarkers can eliminate the need for comparative clinical efficacy studies, streamlining biosimilar development**

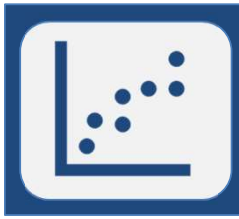
Use of PD Biomarkers in Biosimilar Development

- Biosimilars may be approved based on PK and PD biomarker data **without a comparative clinical efficacy study**

- Evaluation of PK and PD similarity can have an additional advantage of being **more sensitive** than clinical efficacy endpoints in detecting differences should differences exist

Considerations for PD Biomarker Assessment

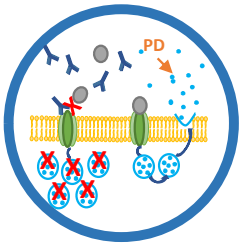
Criteria for PD biomarkers intended to support a demonstration of biosimilarity are **inherently different from criteria for surrogate biomarkers** used to support new drug approvals



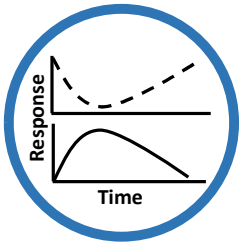
As the purpose is to confirm similarity instead of independently establishing safety and effectiveness, **a correlation between the PD biomarker and clinical outcomes is not a requirement**

Biosimilar development programs use PD biomarker similarity studies to **address residual uncertainties** about biosimilarity

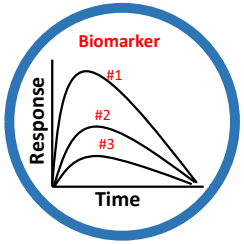
Five Essential Characteristics of a PD Biomarker for Biosimilars



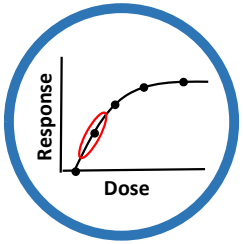
Relevance to the **mechanism of action** of the drug



Time of onset of change relative to dosing and return to baseline with discontinuation of dosing



Dynamic range over the drug's exposure range



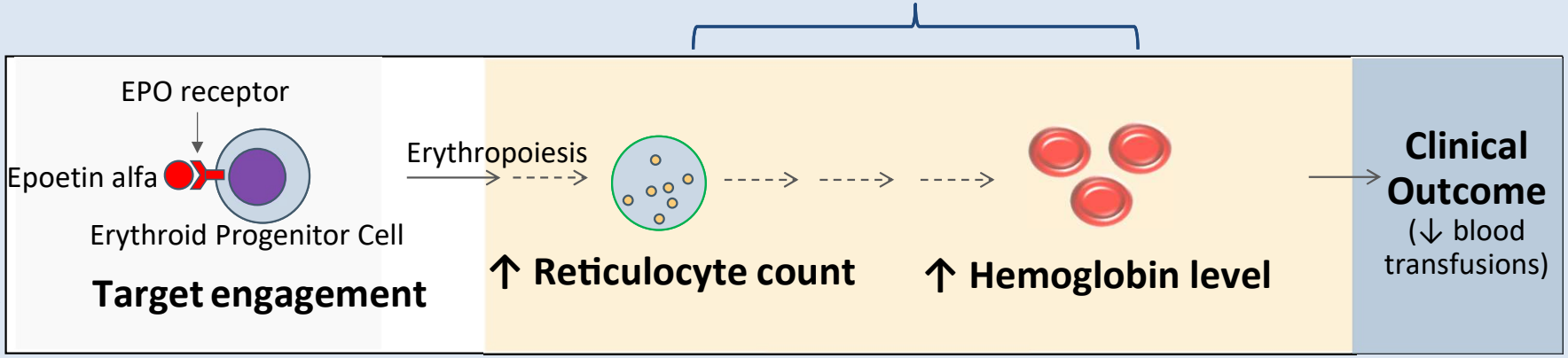
Sensitivity to differences between the proposed biosimilar and reference product

Analytical validity of the assay

Relevance of the PD Biomarker to the Drug's Mechanism of Action

Example drug and PD biomarkers

Both reticulocyte count and hemoglobin level are PD biomarkers that are relevant to the MOA of the drug and are candidate biomarkers for a PD biosimilarity study



While target engagement is the critical first step, it has generally not been considered an adequate PD biomarker (by itself) that would obviate the need for a comparative clinical efficacy study

Drugs with Complex Pharmacology

Some drugs have complex pharmacology with many measurable PD biomarkers

Difficult to pinpoint any one PD biomarker as being definitive within mechanism of action pathway

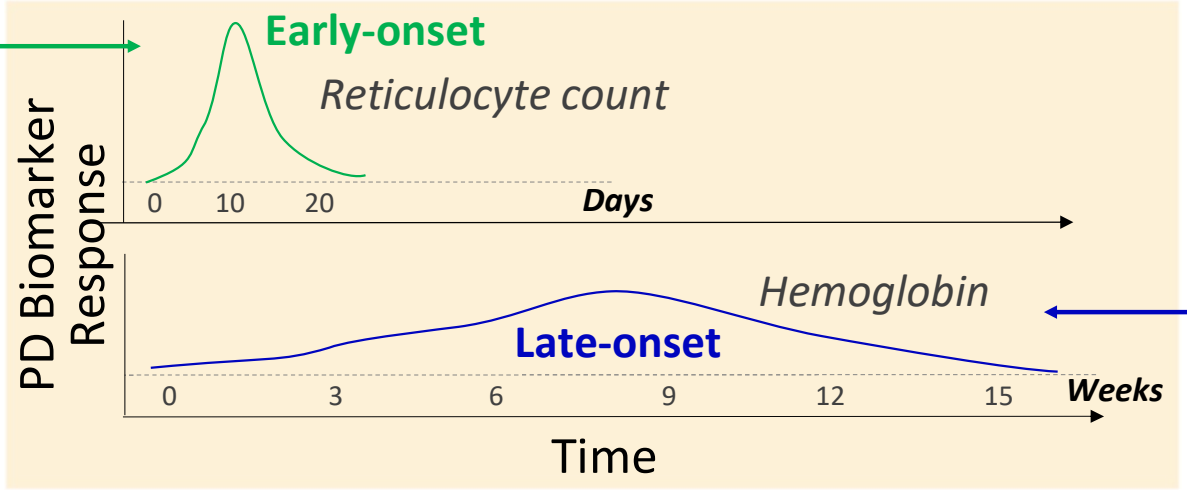
Does not rule out a PD biomarkers-focused approach to establish biosimilarity

The need for a comparative clinical efficacy study will depend on the totality of evidence

PD Biomarker(s) Temporal Profile

Important to understand the temporal profile of candidate PD biomarkers

Early-onset PD biomarkers may allow for
- ↓ study duration
- ↑ sensitivity



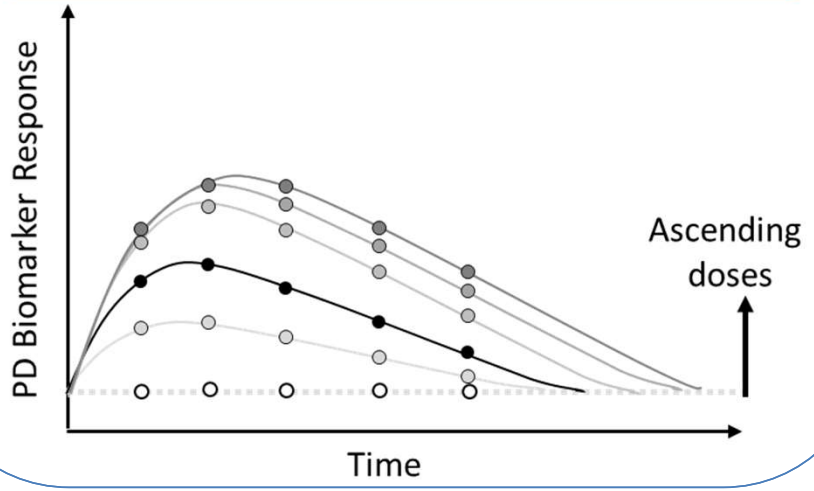
Late-onset PD biomarkers may require longer study periods

- **Approved epoetin alfa biosimilar included data for early & late onset biomarkers**
  - 20-day reticulocyte count study
  - 30-day hemoglobin study
- **However, biosimilars can be approved based on data from a single biomarker**
  - For example, absolute neutrophil count for pegfilgrastim biosimilars

Dynamic Range of the PD Biomarker

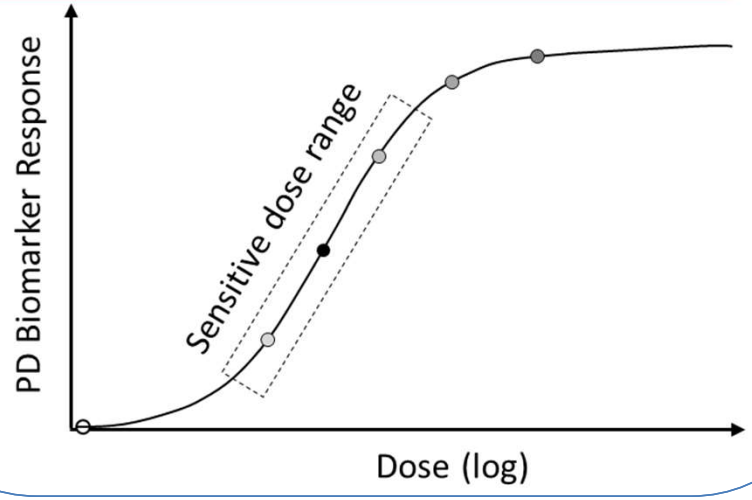
PD biomarkers that achieve a large dynamic range over the drug concentrations achieved in the PK similarity study are recommended

Temporal and Dose-Response Data



Modeling of dose-response data can be used to identify the sensitive dose range (i.e., not on the plateau of the dose-response curve)

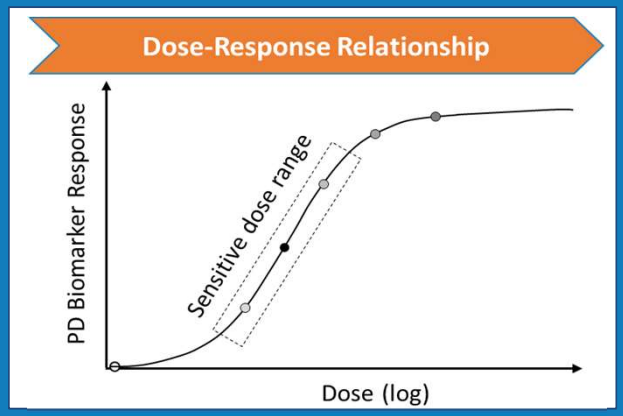
Dose-Response Relationship



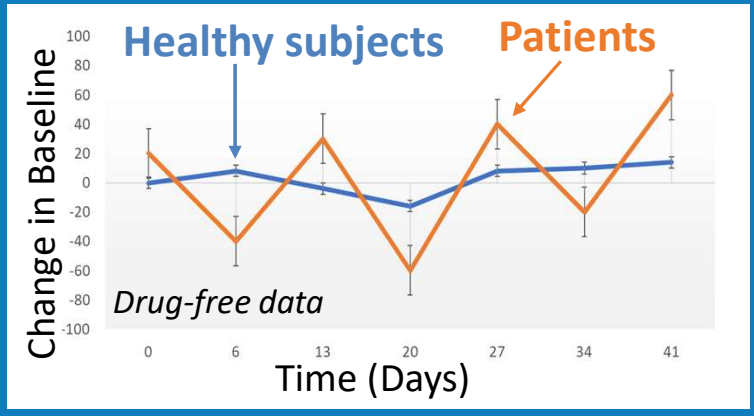
Sensitivity of the PD Biomarker

Sensitivity of the PD biomarker to detect differences between products depends on multiple factors:

Dose – sensitive part of dose-response curve



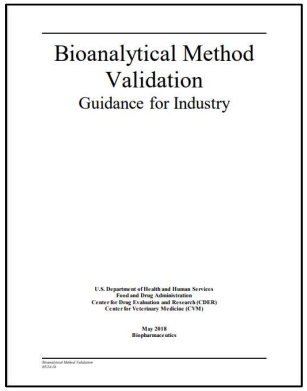
Study population – minimize inter- and intra-subject variability

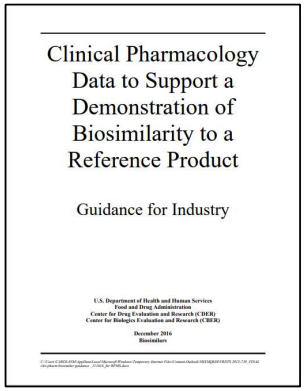


Selection of least variable population in which the PD response can be measured will ↑ sensitivity and can ↓ sample size required for a PD biosimilarity study

Analytical Validity of the Assay

Important to demonstrate bioanalytical validity of PD biomarker assays


Bioanalytical Method Validation
Guidance for Industry


Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

Guidance for Industry

Outlined in FDA's Bioanalytical Method Validation Guidance and summarized in FDA's biosimilarity clinical pharmacology guidance

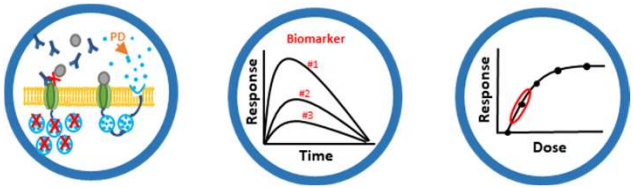
A fit-for-purpose approach may be applied when demonstrating the bioanalytical validity

- Assays used in pilot studies may not require full validation
- Assays to support regulatory decision-making require full validation

FDA Action to Fill Information Gaps

Under FDA's Biosimilars Action Plan, FDA is conducting targeted/applied research to fill information gaps, inform best practices and evaluate new methodologies

Characterize known PD biomarkers

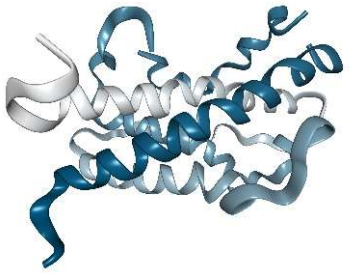


- 2 studies with 2 originator biologics each
  - PD biomarkers closely tied to the drug's mechanism of action
- 1 study with 2 originator biologics
  - PD biomarkers for drugs with complex pharmacology

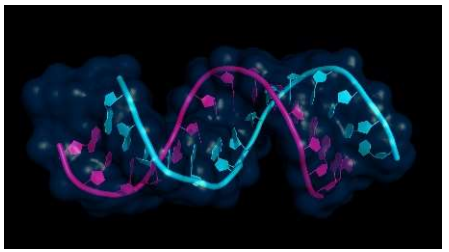
Details to be presented by Jeffry Florian (FDA)

Explore the use of new technologies to identify PD biomarkers or assess multiple biomarkers simultaneously

Proteomics



Small-RNA transcriptomics



Details to be presented by Paula Hyland (FDA) – Session 4

FDA Clinical Studies Outcome Measures

Primary Outcome Measures

Standard PD metrics (area under the effect curve and maximal change) for a primary pre-specified PD biomarker at multiple doses (3 or 4) for each drug

Secondary Outcome Measures

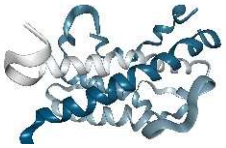
1. Standard PD metrics for a secondary pre-specified PD biomarker (2 of 3 studies)
2. PK characteristics at multiple doses for each drug
3. PK/PD model parameters after combining data from multiple doses

Exploratory Outcome Measures

1. Plasma proteomics (differential expression of proteins)
2. Plasma small RNA transcriptomics (differential expression of microRNAs)

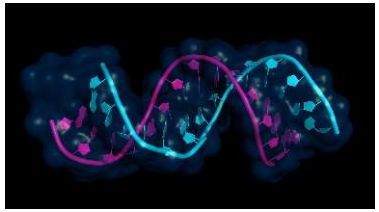
FDA Clinical Studies: Novel Approaches to Identify Biomarkers

Proteomics



Simultaneous assessment of ~7,000 proteins

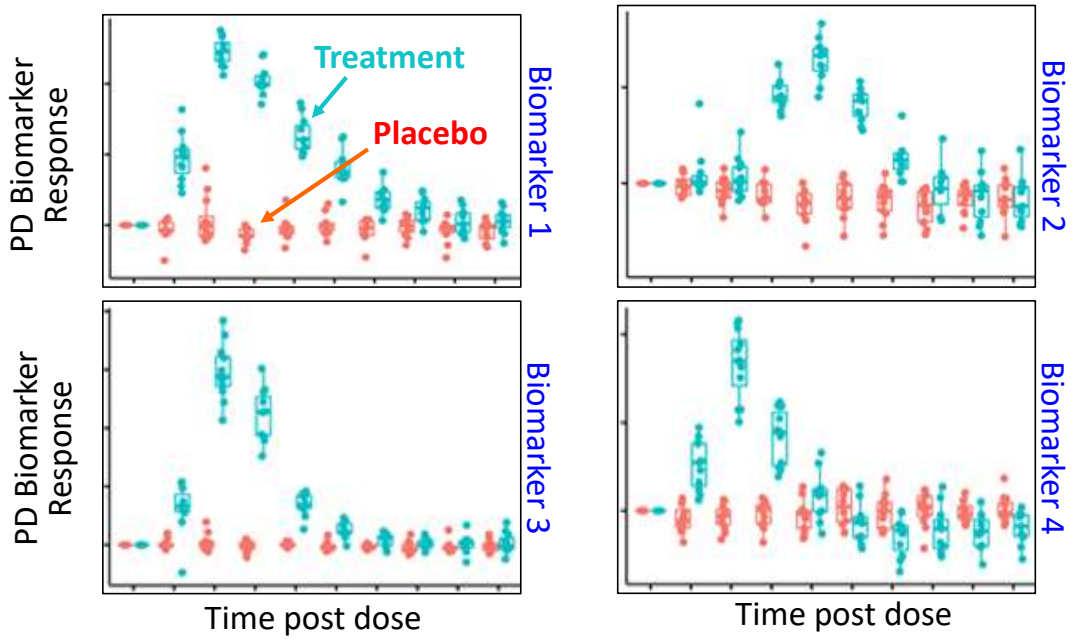
Micro-RNA



MicroRNA sequencing

Real data from FDA study

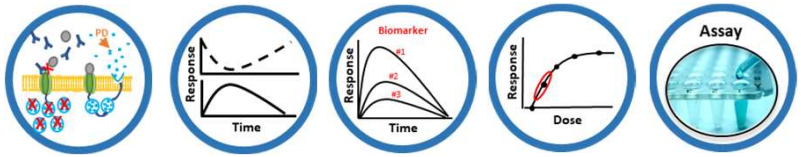
4 example plasma proteins with significant changes



Details to be presented by Paula Hyland (FDA) – Session 4

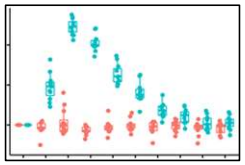
Summary: Developing an Evidentiary Framework

Evidentiary considerations



Targeted/applied research to:

- Fill information gaps
- Inform best practices
- Evaluate new methodologies



Pharmacodynamic Biomarkers for Biosimilar Development and Approval

Virtual Public Workshop

September 20, 2021 | 10:00 am – 2:30 pm ET
September 21, 2021 | 10:00 am – 2:30 pm ET

Multi-stakeholder global discussion

Goal

Increase utilization and acceptance of PD biomarkers to streamline biosimilar development

Key Points

- PD biomarkers for biosimilars do not need to be surrogate endpoints for clinical efficacy outcomes
- Characterization of PD biomarkers according to the 5 key characteristics is critical to assess their suitability
- A single clinical pharmacology study can assess both PK and PD similarity if designed appropriately
- **Utilization of PD biomarkers can eliminate the need for comparative clinical efficacy studies, streamlining biosimilar development**


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Jeffry Florian

U.S. Food and Drug Administration

FDA-Sponsored Clinical Studies to Address Information Gaps and Inform Best Practices for Study Design and PD Biomarker Analysis

Jeffry Florian, PhD

Division of Applied Regulatory Science

Office of Clinical Pharmacology/OTS/CDER

The opinions expressed in this presentation are the presenter's and do not necessarily reflect the official views of the United States Food and Drug Administration (FDA)

Outline

- Overview
- Studies-at-a-Glance
- PCSK9 Antagonists Study Characteristics and Results
- Interferon β-1a Study Characteristics and Results
- Summary

Overview of Pilot PK/PD Clinical Studies

Challenge: Limited experience with pilot PK/PD clinical study designs and information gaps with respect to potential PD biomarkers

Therapeutic Class	Type of Biomarker(s)
PCSK9 Antagonist	Tied to the mechanism of action and used as a surrogate endpoint
IL-5 Antagonist	Tied to the mechanism of action but not used as a surrogate endpoint
Interferon β-1a	PD biomarker where activity initiates a complex signaling system Difficult to determine the precise mechanism of action

Approach: Conduct pilot clinical studies to fill information gaps, inform best practices, and demonstrate methods, standards and approaches for biomarker selection and characterization

Abbreviations: PCSK9: Proprotein convertase subtilisin/kexin type 9 serine protease; IL-5: Interleukin-5

Pilot Study Design Considerations

Guidance* outlines multiple expectations for study designs:

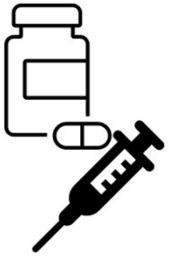
DESIGN

- Single-dose, randomized, crossover study preferred
- Parallel design may be needed depending on factors such as long half-life / immunogenicity

POPULATION

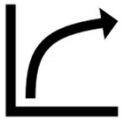
- Informative and sensitive for detecting & evaluating differences
- Can be conducted in healthy subjects if safe and feasible

DOSE AND ROUTE OF ADMINISTRATION



- A range of doses on the steep part of the exposure-response curve. Approved dose can be included
- Same route of administration as reference product (or sensitive route if multiple routes approved)

PD MEASURES



- Sampling (or study) design depends on PD biomarker characteristics
- Compare area under the effect curve (AUEC) and maximum effect
- A composite of multiple PD biomarkers may be appropriate

**As described in Guidance for Industry "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product."*

Design of Pilot PD Clinical Studies

- All three clinical studies are single-dose, parallel, and double-blinded studies
- Each study had intensive sampling for PK, PD, and exploratory proteomics analyses

	PCSK9 Antagonists	IL-5 Antagonists	Interferon β-1a
Drugs	Alirocumab and Evolocumab	Mepolizumab and Reslizumab	Interferon and Peginterferon β-1a
Population	Healthy subjects (n=72)	Healthy subjects (n=72)	Healthy subjects (n=84)
Doses	4 dose levels per product + placebo (Doses include approved dose)	4 dose levels per product + placebo (Doses lower than approved dose)	3 dose levels per product + placebo (Doses include approved dose)
PD Biomarkers	**LDL-C**, Apolipoprotein B (ApoB), PCSK9	**Eosinophils (blood)**	**Neopterin**, myxovirus resistance protein 1 (MxA)*
PD Endpoints	Baseline-subtracted AUEC and E_{min}		Baseline-subtracted AUEC and E_{max}

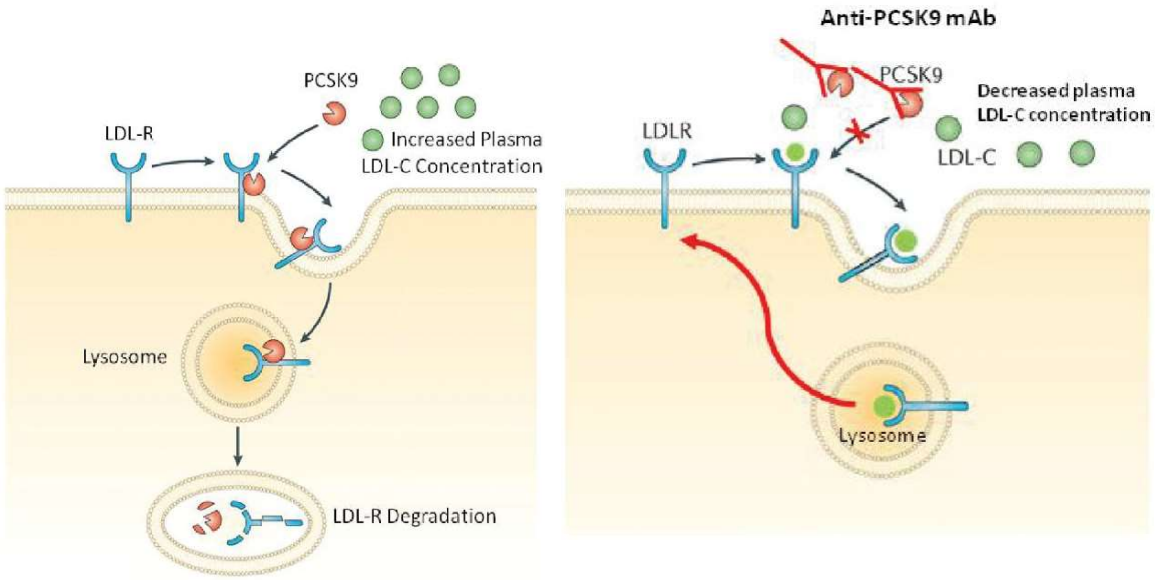
Study characteristics and results will be presented for **PCSK9 antagonists** and **interferon β-1a**

*PD biomarkers recommended by EMA https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-interferon-beta_en.pdf

PCSK9 Antagonists: Evolocumab and Alirocumab

PD Biomarker Characteristic: Mechanism of Action

- Drugs bind to free PCSK9, preventing it from binding to LDL-C receptors (LDL-R) and promoting degradation
- This increases the number of LDL-R available to clear LDL from the blood

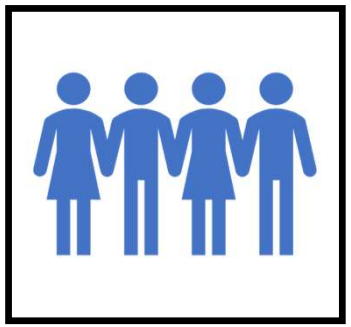


Abbreviations: LDL-C: Low-density lipoprotein cholesterol; LDL-R: Low-density lipoprotein receptor

Reference: Zhang et al., 2018 (Bayl Univ Med Cent)

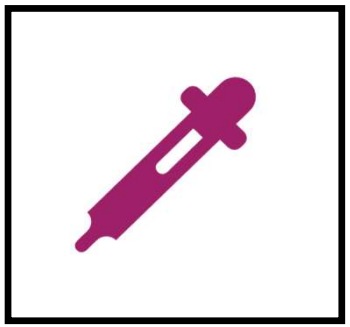
PCSK9 Antagonists: Evolocumab and Alirocumab

PD Biomarker Characteristics: Rationale for Doses



Population
LDL-C changes can be observed in healthy volunteers

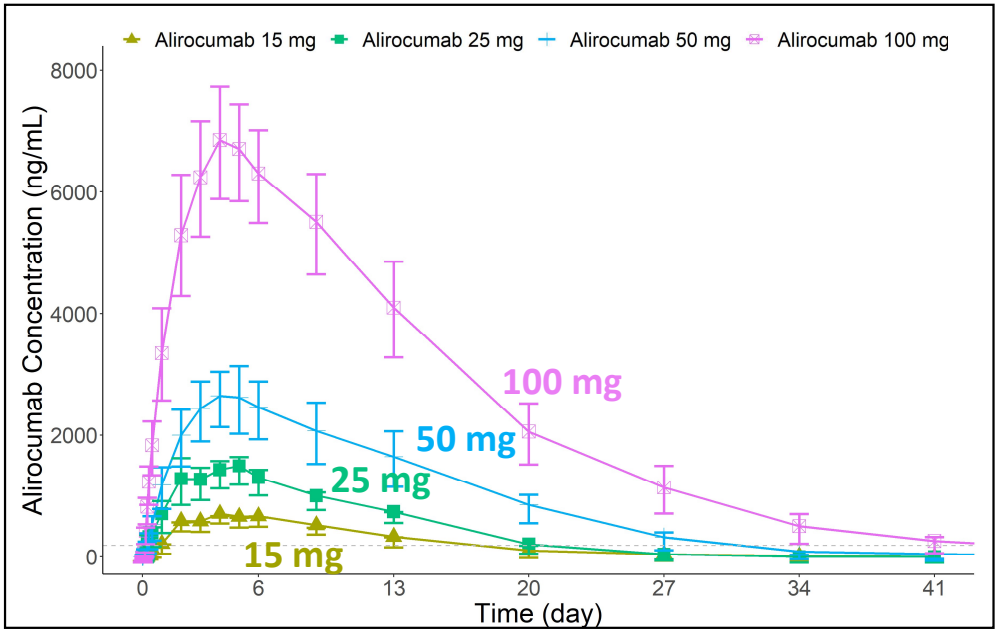
Biomarker
Primary biomarker was LDL-C. Secondary biomarkers were ApoB and PCSK9



Dosing
Range of doses selected up to the lowest approved dose

Remaining questions
Variability at different doses & how to analyze the PD measure

Alirocumab and Evolocumab Pharmacokinetics



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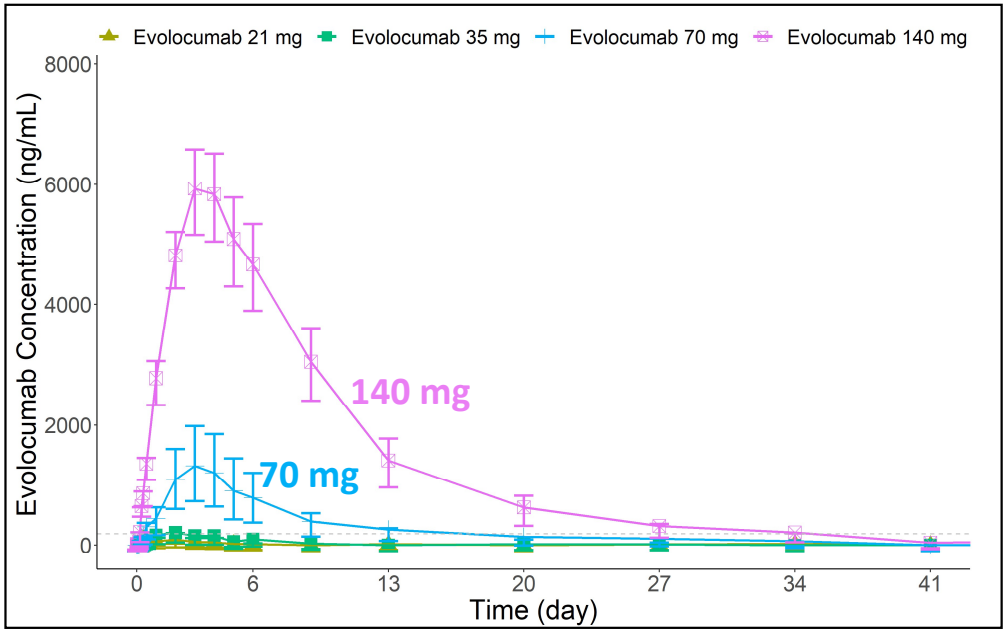
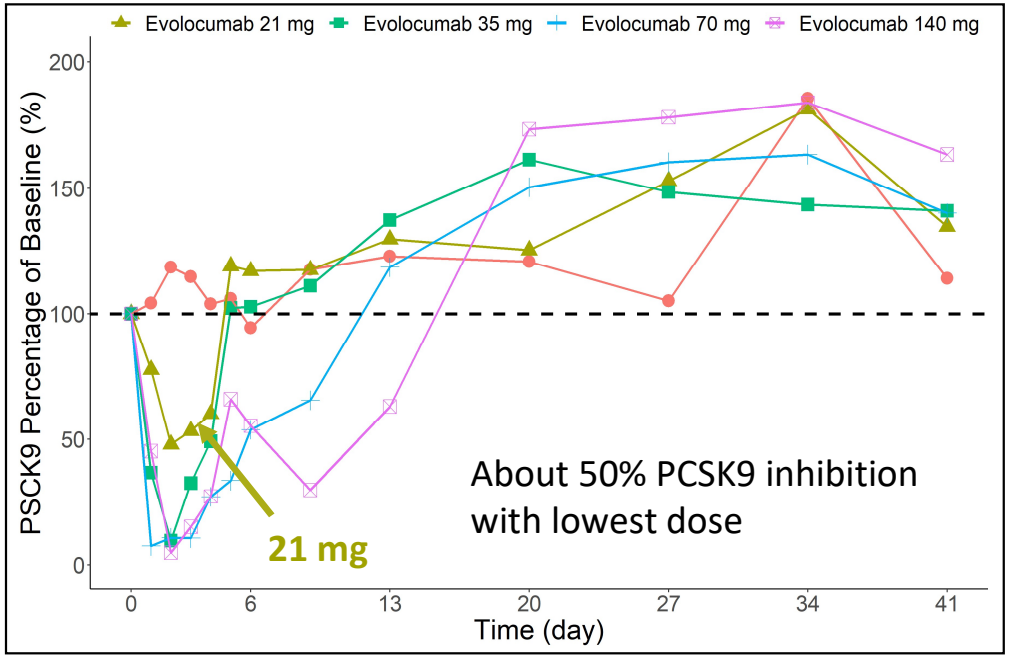
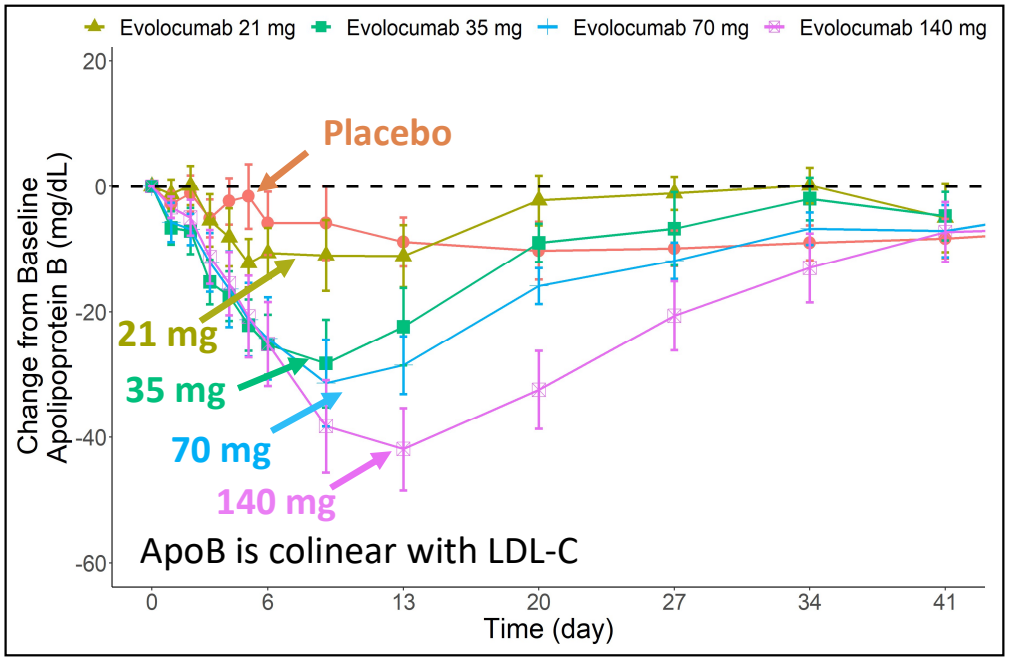


Most 21 and 35 mg plasma samples were below limit of quantification

Evolocumab: Free PCSK9 and ApoB





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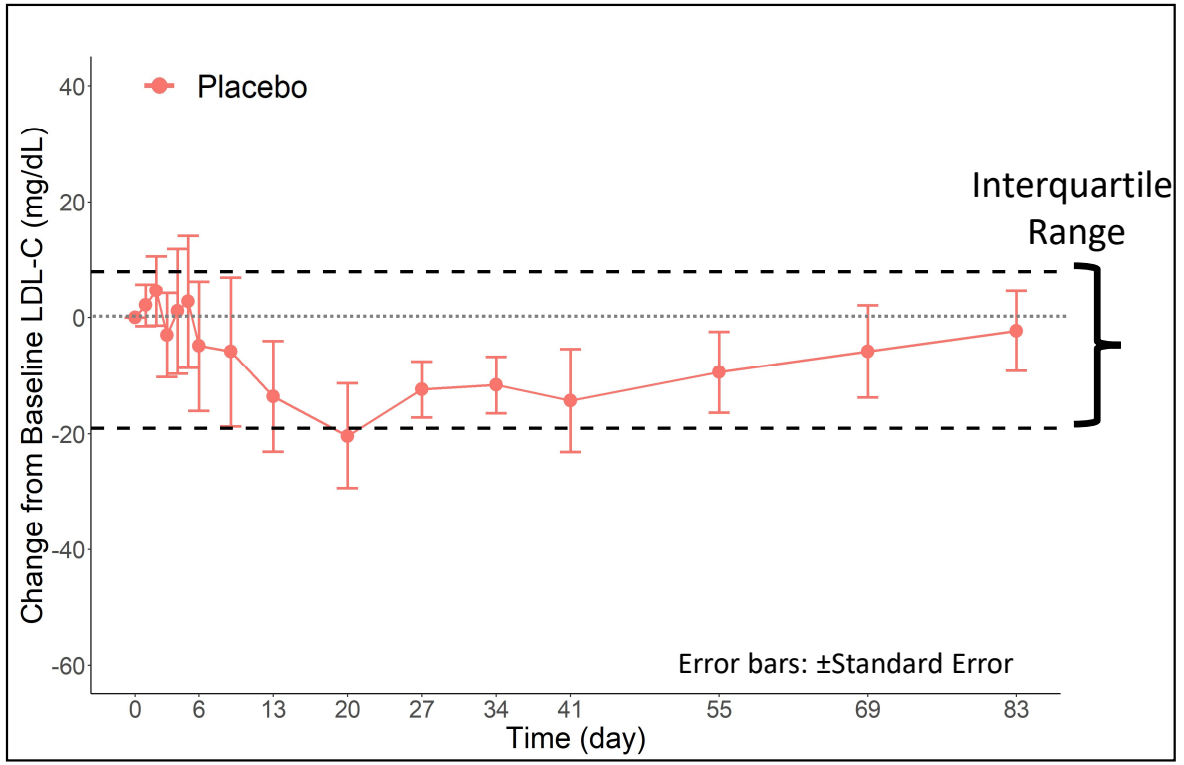
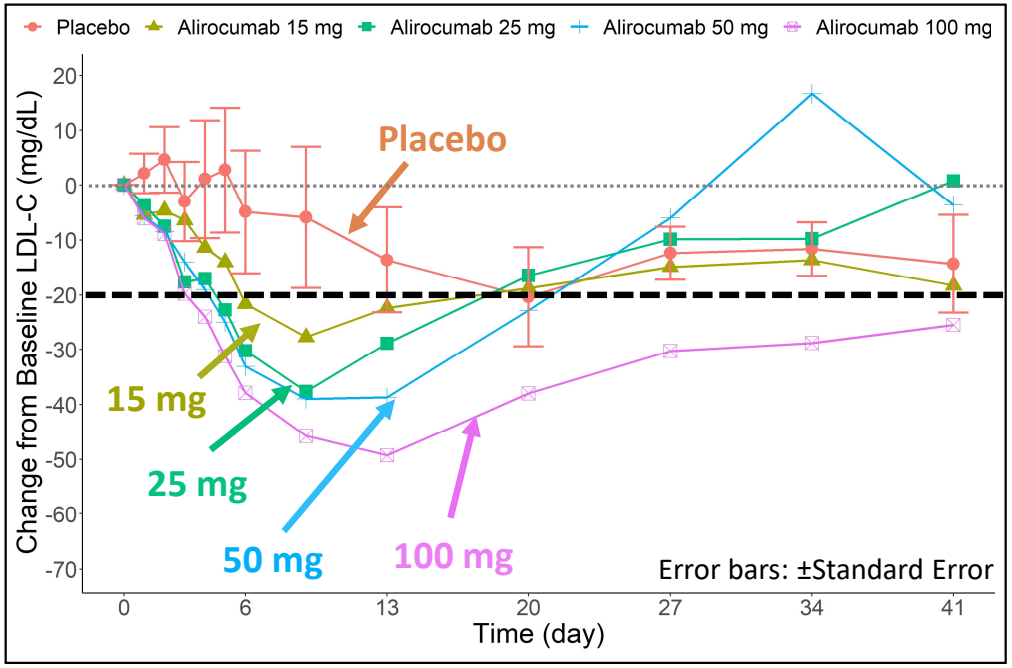
LDL-C Placebo Variability

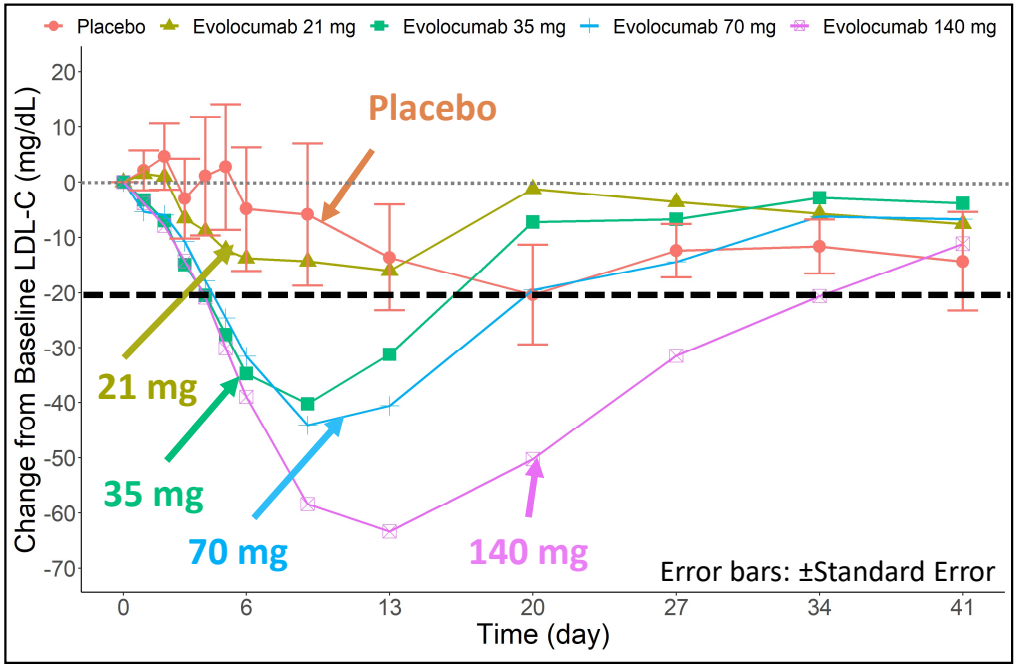
- High inter-subject variability in placebo
- Baseline noise can overwhelm the effect of low doses
- Averaging multiple baseline measurements can mitigate some variability



Dose-Dependent Changes in LDL-C



Alirocumab



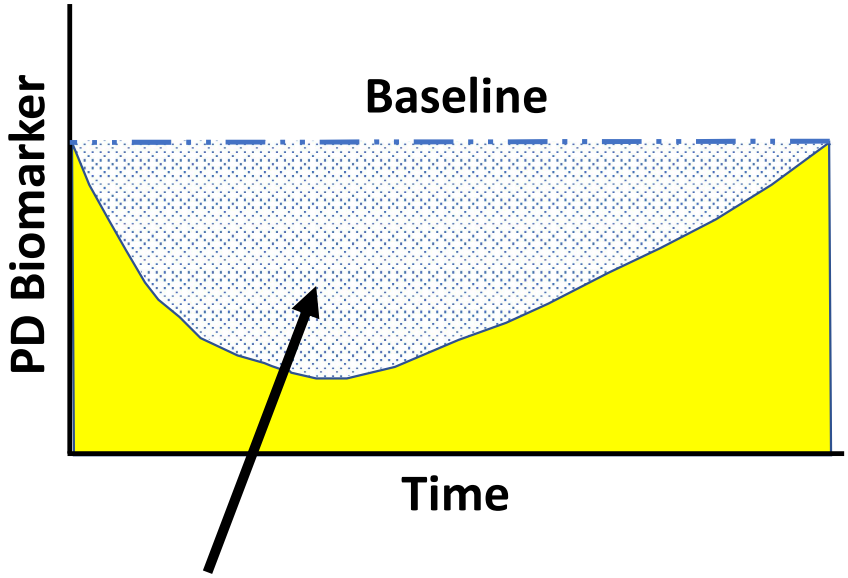
Evolocumab

Implications of Different Derived PD Measures

- For inhibition, a baseline adjusted measure may be needed
  - Yellow area does not reflect drug effect
  - Baseline LDL-C is 110-140 mg/dL so similar results for change from baseline or percentage change from baseline

Higher Variability

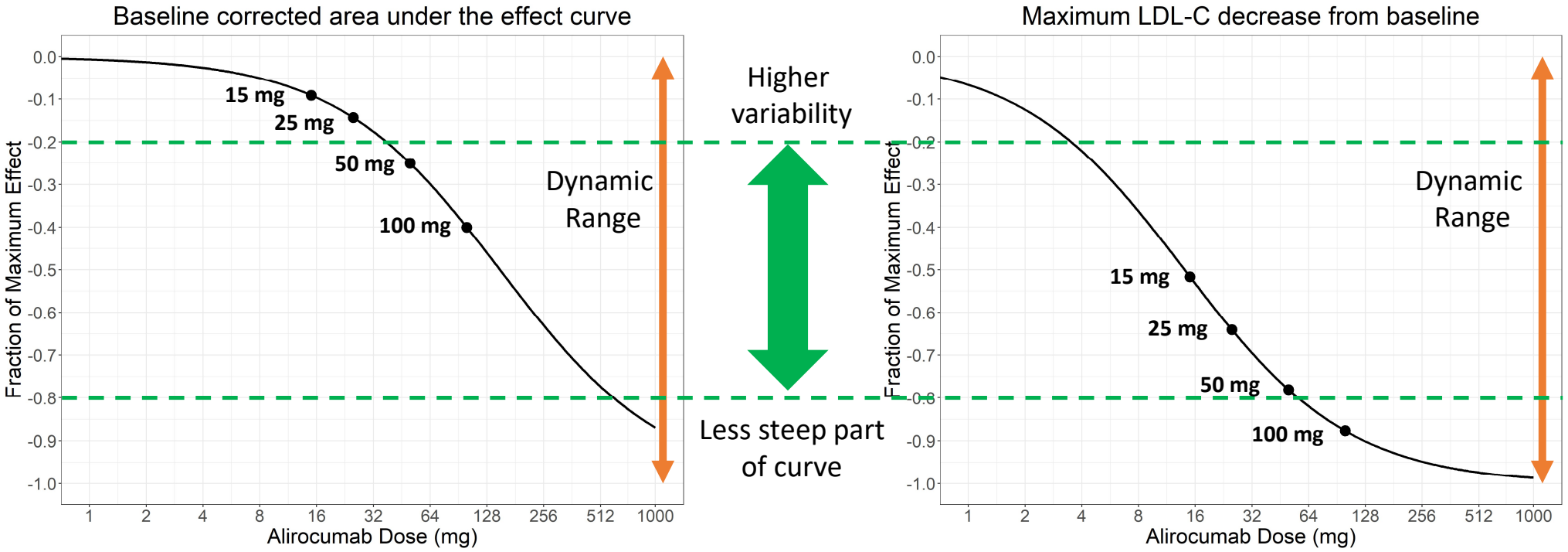
Treatment	Area under the effect curve (day*mg/dL)
	Mean
Evolocumab 21mg (n=7)	-477
Evolocumab 35mg (n=8)	-821
Evolocumab 70mg (n=8)	-981
Evolocumab 140mg (n=8)	-1932



Area under the effect curve

PCSK9

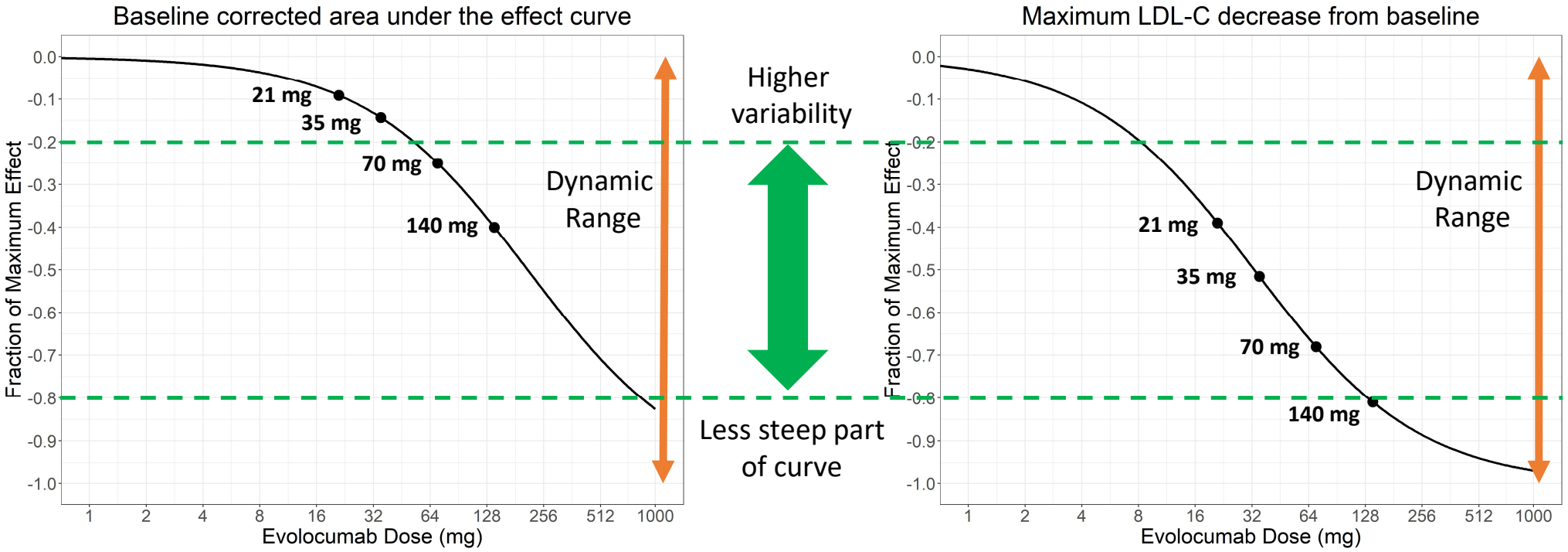
Alirocumab: Dynamic Range and Sensitivity



Sponsor's data supports saturation at higher doses

PCSK9

Evolocumab: Dynamic Range and Sensitivity



Sponsor's data supports saturation at higher doses

PCSK9

Key Takeaway Points: PCSK9 Study

- Results align with published findings from single-ascending dose healthy volunteer studies
- LDL-C baseline corrected area under the effect curve increases up to the therapeutic dose
  - Response at the therapeutic dose is on the steep part of the exposure-response curve and supports use in PD similarity studies
- Important to have doses that can be distinguished from baseline noise
- Include design elements to reduce variability (multiple baseline measurements, length of data collection, sufficient sample size)

Interferon

Interferon products

PD Biomarker Characteristic: Mechanism of Action and Dynamic Range

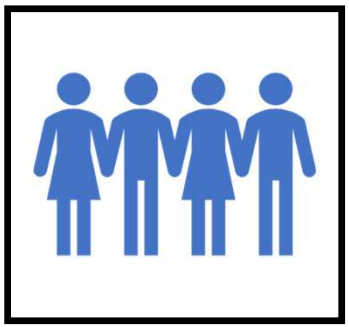
- Five interferon-β1 products approved for treatment of patients with relapsing forms of multiple sclerosis
- Mechanism of action of drugs for the disease process is not well-understood but hypothesized to be related to anti-inflammatory properties and ability to limit leukocyte migration across the blood brain barrier
- Literature describes multiple biomarkers altered by interferon β1 product administration
  - Neopterin, myxovirus resistance protein 1 (MxA), β_2-macroglobulin have demonstrated significant differences between interferon-β1 and placebo treatment groups
- Limited dose-ranging information available in the literature but the above PD biomarkers have the least incomplete information available

Abbreviations: IFN, interferon; pegIFN, pegylated interferon

Interferon

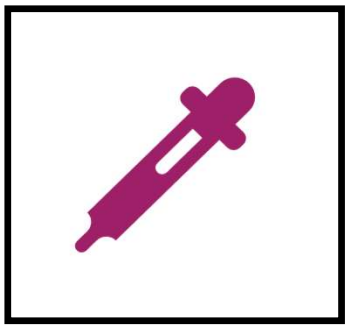
Interferon products

PD Biomarker Characteristics: Rationale for Doses

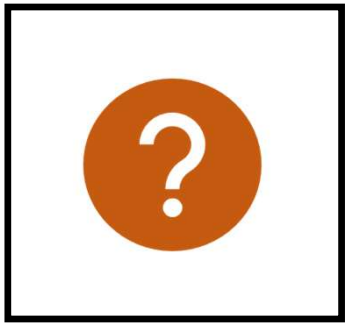


Population
Changes in neopterin can be observed in healthy volunteers

Biomarker
Primary biomarker was neopterin. Secondary biomarker was MxA (potentially independent information from neopterin)

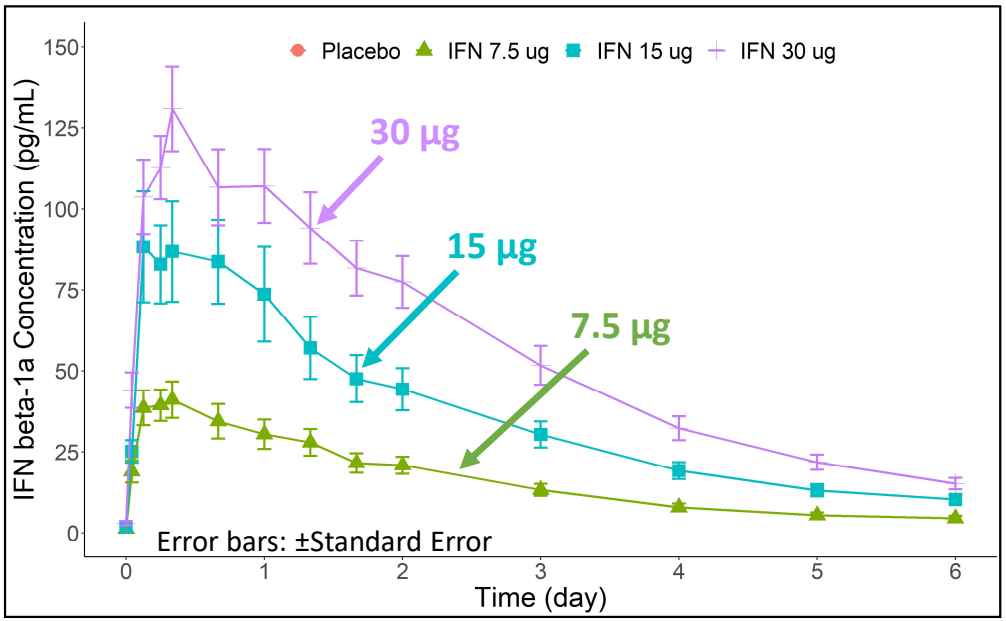


Dosing
Doses up to therapeutic selected. Response may saturate but return to baseline is within 1-2 weeks

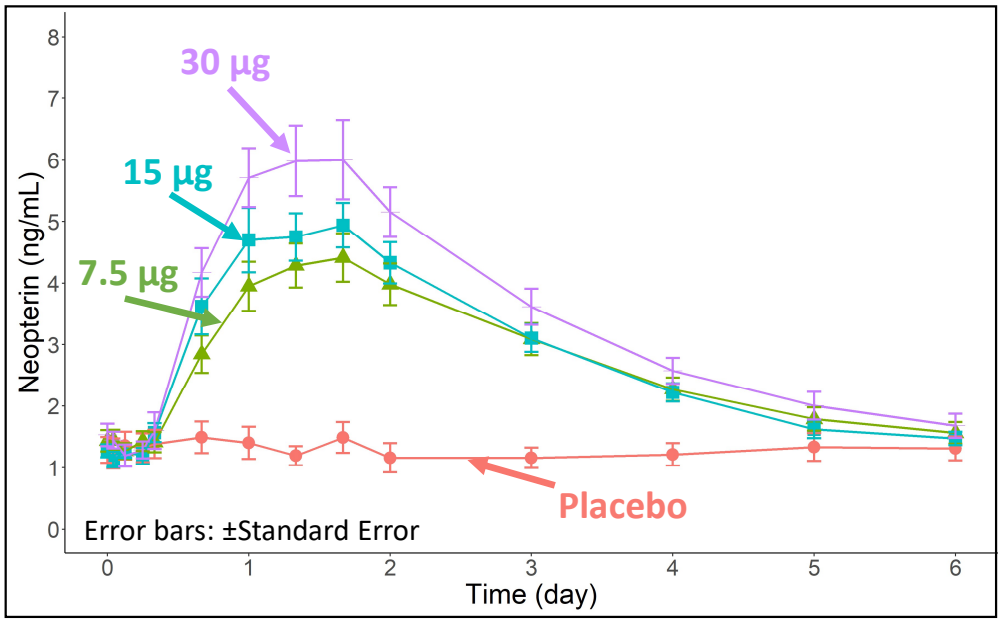


Remaining questions
Limited dose-ranging data to determine if there is dynamic range across 4-fold dosing

Interferon (IFN) β1-a: PK and Neopterin PD

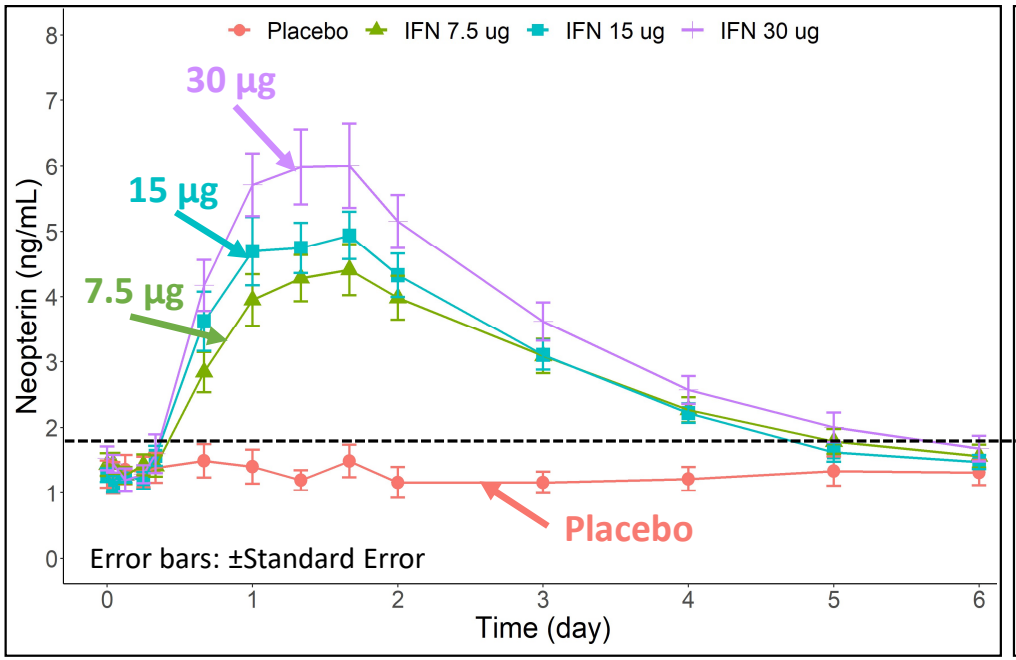


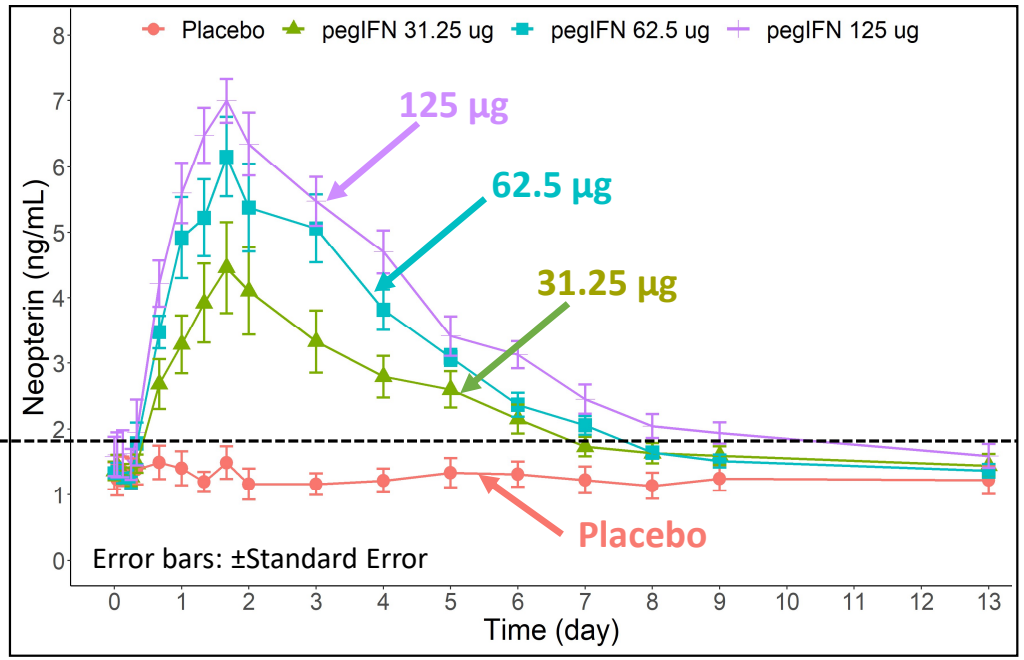
Pharmacokinetics



Pharmacodynamics

Neopterin PD: IFN and peginterferon (pegIFN) β1-a



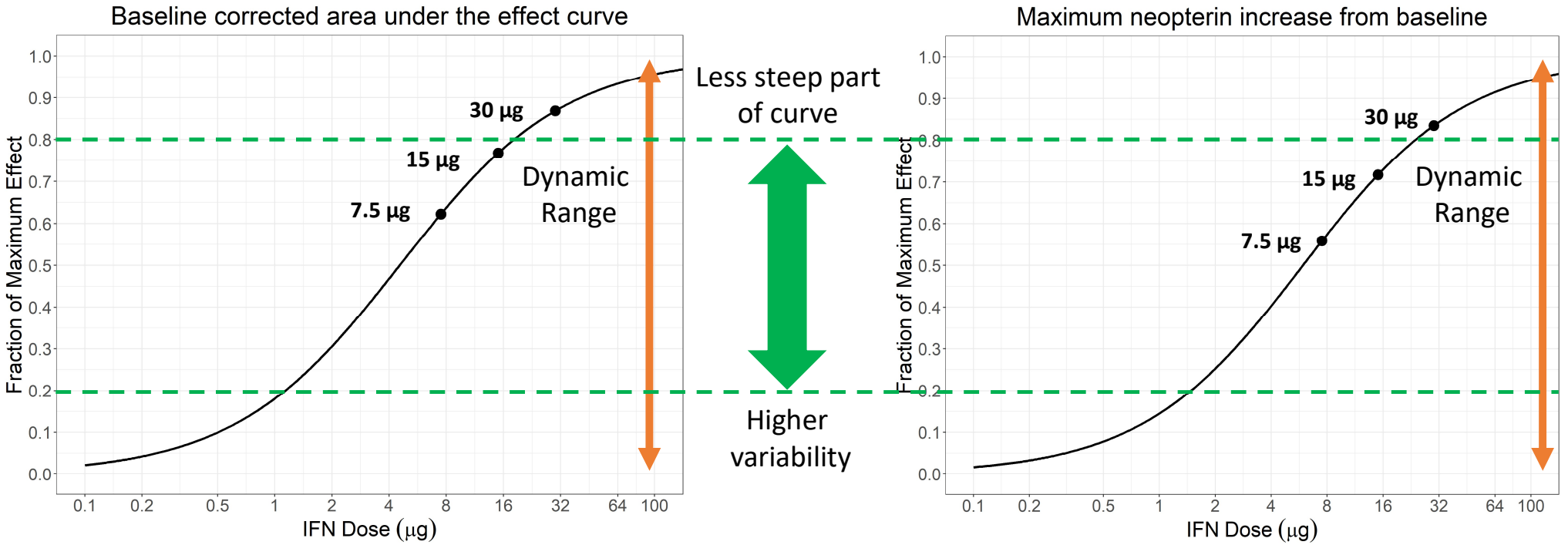


IFN **pegIFN β1-a**

Clear separation between neopterin time course for all doses with both products compared to placebo

Interferon

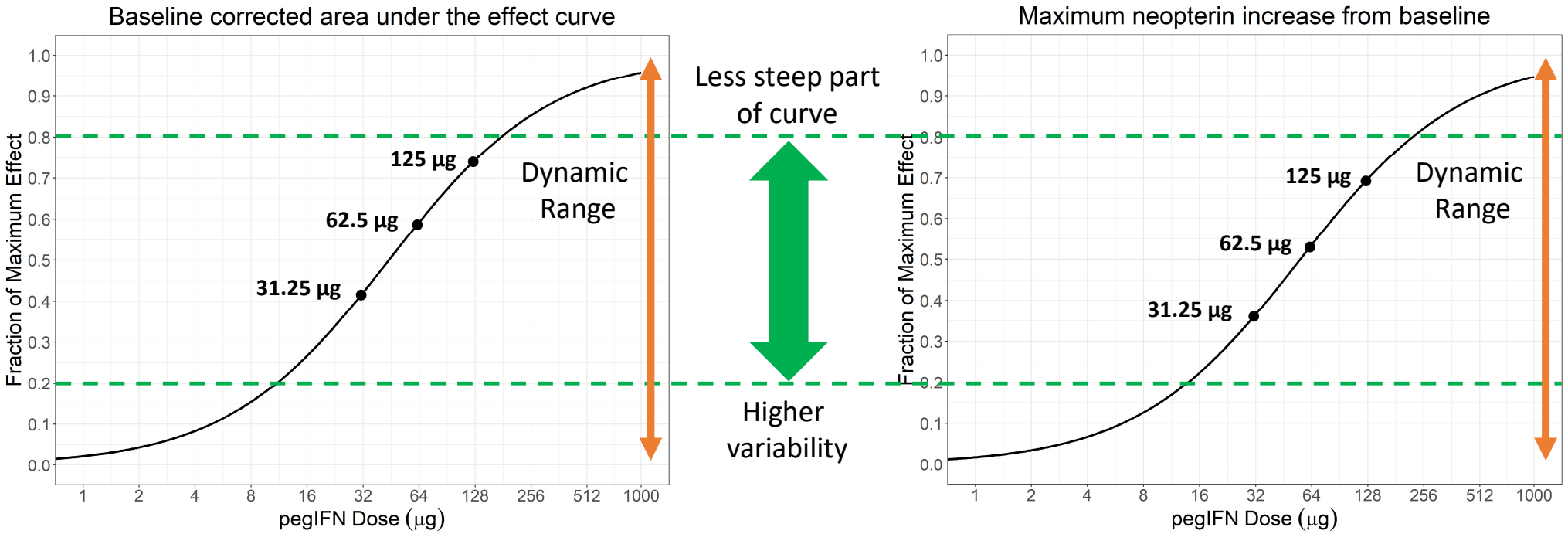
IFN β1-a: Dynamic Range and Sensitivity



Similar dose-response relationships between area under the effect curve and maximum neopterin change from baseline

Interferon

pegIFN β1-a: Dynamic Range and Sensitivity



Similar dose-response relationships between area under the effect curve and maximum neopterin change from baseline

Interferon

Key Takeaway Points: Interferon products

- Neopterin PD data (for IFN β-1a and pegIFN β-1a) exhibited clear, measurable response across all 3 doses
  - Contributes to understanding of dose-response
  - Can facilitate dose selection (and study design) for PD similarity studies
- All drug arms demonstrate clear separation from baseline and from placebo
- Neopterin PD response saturates at higher doses for both drugs

Summary: Filling Information Gaps

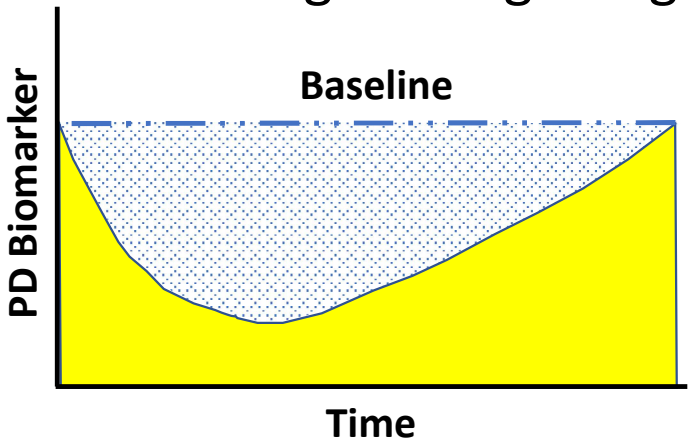
- FDA conducted three pilot PK/PD biomarker clinical pharmacology studies, each with two marketed originator biologics with the same mechanism of action

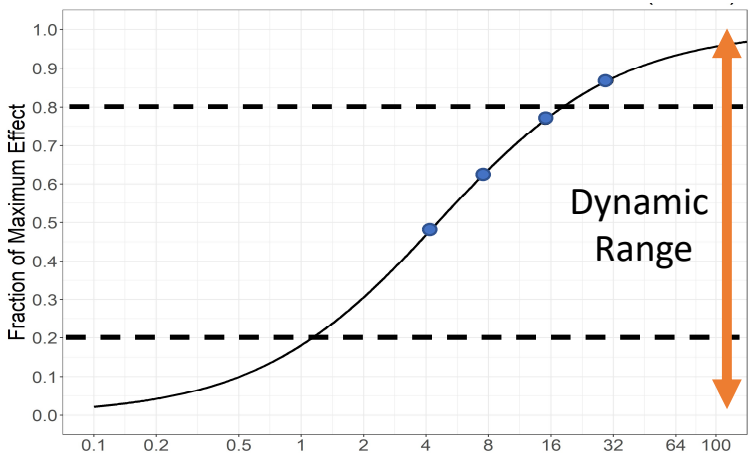
Therapeutic Class	Type of Biomarker(s)
PCSK9 Antagonist	Tied to the mechanism of action and used as a surrogate endpoint
IL-5 Antagonist	Tied to the mechanism of action but not used as a surrogate endpoint
Interferon β-1a	PD biomarker where activity initiates a complex signaling system Difficult to determine the precise mechanism of action

- These studies have confirmed existing information or addressed information gaps regarding potential PD biomarkers for each of these products

Summary: Informing Best Practices

- Results highlight the importance of how pilot study data may be analyzed and role of modeling in integrating available information





- The intent is to share all study results and data so that it can be available for biosimilar developers interested in these biologics

Summary: Evaluating New Methodologies

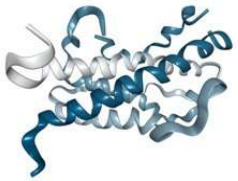
- PD biomarkers for biosimilar development are **not** required to reflect clinical efficacy

FDA pilot studies considered PD biomarkers beyond surrogate endpoints

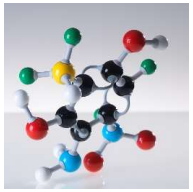
Ongoing efforts evaluating novel methods for PD biomarker identification (Session 4)

Genomics

Transcriptomics



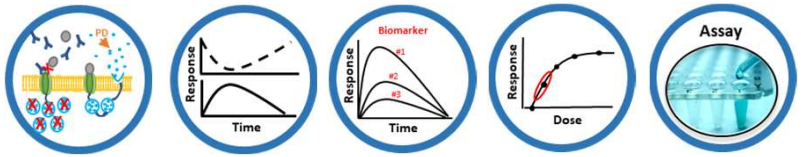
Proteomics



Metabolomics

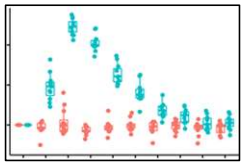
Summary: Developing an Evidentiary Framework

Evidentiary considerations



Targeted/applied research to:

- Fill information gaps
- Inform best practices
- Evaluate new methodologies



Pharmacodynamic Biomarkers for Biosimilar Development and Approval

Virtual Public Workshop

September 20, 2021 | 10:00 am – 2:30 pm ET
September 21, 2021 | 10:00 am – 2:30 pm ET

Multi-stakeholder global discussion

Goal

Increase utilization and acceptance of PD biomarkers to streamline biosimilar development

www.fda.gov

Acknowledgements

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Aanchal Shah
Daniel Mayne
Chase Tarnstrom
Annabel Hart
*and many others

Clinical Site Staff and all Study Participants

Session 2: Panel and Moderated Discussion

Lead Reactants

- **Martin Schiestl,** Sandoz Inc.
- **Gillian Woollett,** Avalere Health

Additional Panelists

- **Jeffry Florian,** U.S. Food & Drug Administration
- **Ping Ji,** U.S. Food & Drug Administration
- **Stacey Ricci,** U.S. Food & Drug Administration
- **David Strauss**, U.S. Food & Drug Administration

Concluding Remarks | Day 1

Mark McClellan, Duke-Margolis Center for Health Policy

Pharmacodynamic Biomarkers for Biosimilar Development and Approval

September 20, 2021 | 10:00 am – 2:30 pm ET

September 21, 2021 | 10:00 am – 2:30 pm ET

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome and Opening Remarks | Day 2

Mark McClellan

Duke-Margolis Center for Health Policy

Agenda

Session 1

Biosimilar Development Paradigms—Current and Future Perspectives

Session 2

Leveraging Pharmacology to Advance PD Biomarkers for Biosimilar Development

Session 3

Emerging Experiences and Approaches Using PD Biomarkers in Biosimilar Development

Session 4

Extending PD Biomarker Opportunities Across Therapeutic Areas & Advancing PD Biomarker Use in Future Biosimilar Development

Session 5

Regulatory Perspectives and Efforts to Advance PD Biomarkers for Biosimilars

Statement of Independence

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- Identity and other information about present or potential customers, healthcare providers or payers, including costs, prices, profitability, marketing plans, and product development plans
- Research & development plans
- Other confidential or proprietary activities, strategies, processes or procedures
- Refusals to deal with any company or supplier
- Strategies or plans to award business or remove business from a specific company, to participate or not participate in any particular business opportunity or type of business opportunity
- Status of negotiations with present or potential customers, suppliers, payers or healthcare providers
- Any other confidential business information that could be used to reduce competition

Virtual Meeting Reminders

- Attendees are encouraged to contribute through the meeting with questions in the Zoom Q&A function.
- Panelists should go on video during the panel discussion
- Presenters should provide a verbal indicator when they'd like to advance the slides

Session 3: Emerging Experiences and Approaches Using PD Biomarkers in Biosimilar Development

10:10 am – 11:15 am

Salaheldin Hamed

U.S. Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

PD Biomarkers: Contribution to Biosimilars Approvals

Salaheldin S. Hamed, Ph.D.
Division of Cancer Pharmacology 1 & 2
OCP/CDER

salaheldin.hamed@fda.hhs.gov

Disclaimer

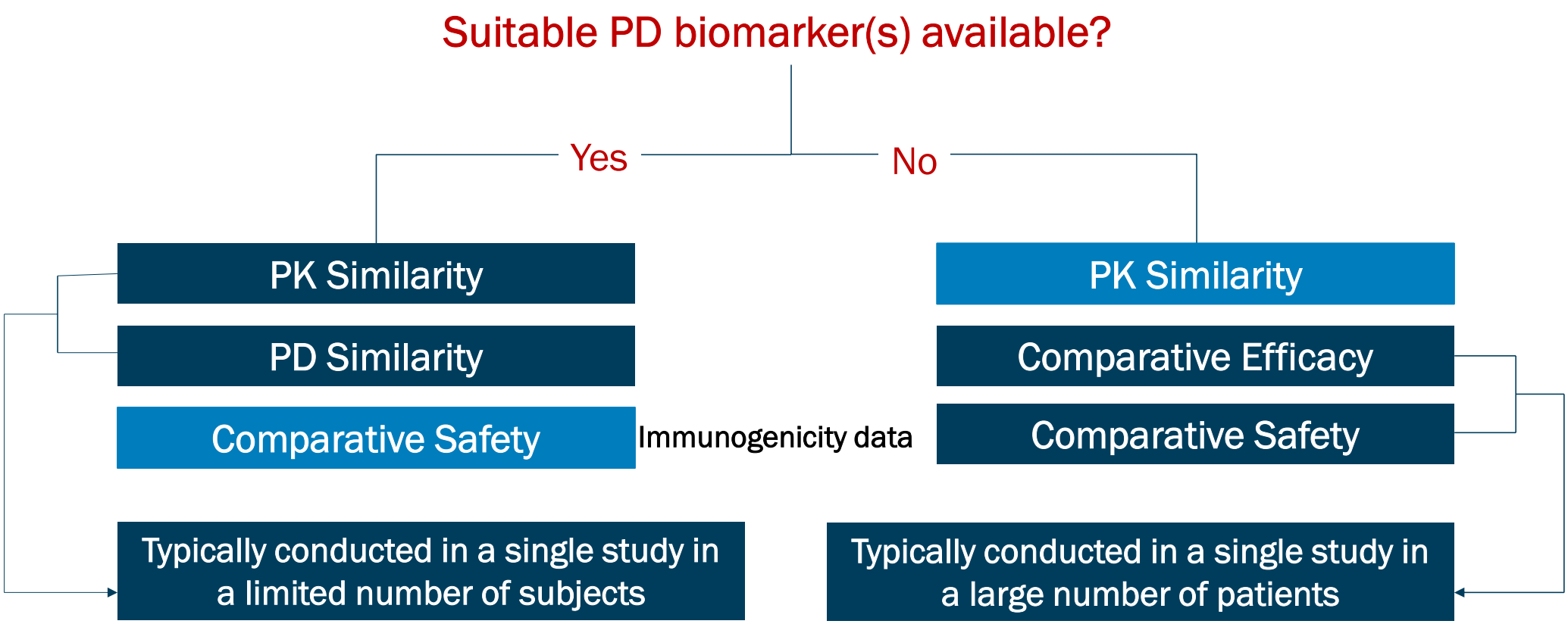
- Opinions presented are those of the speaker and are not to be misconstrued as FDA's recommendations or current thinking

- Information included in this presentation is publicly available

Outline

- Introduction
  - PD-based approvals of biosimilars
  - PD marker characteristics
- Case examples
  - Filgrastim/pegfilgrastim
  - Epoetin
- Conclusions

Biosimilar Approvals*

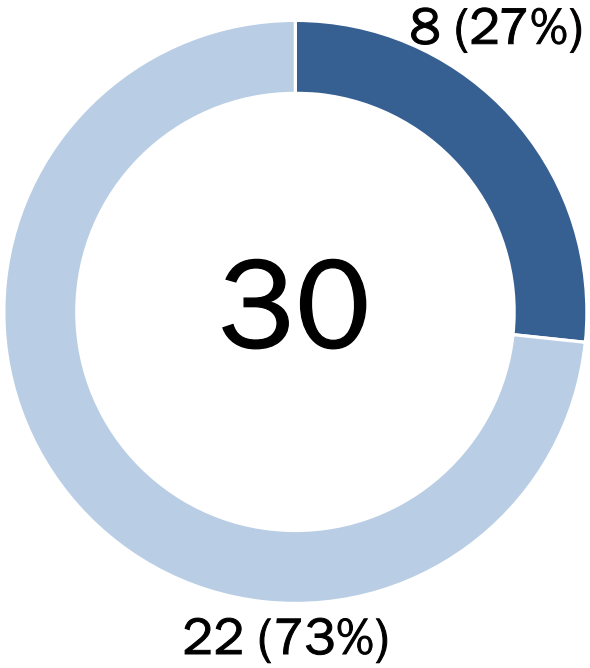


*courtesy of TBP/OCP

Approved Biosimilars

Clinical Study

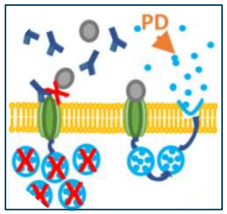
- Adalimumab (6)
- Bevacizumab (2)
- Etanercept (2)
- Infliximab (4)
- Rituximab (3)
- Trastuzumab (5)

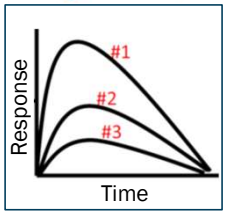


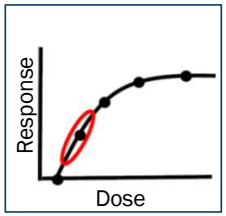
PD Biomarker

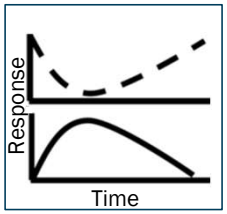
- Filgrastim (2)
- Pegfilgrastim (4)
- Epoetin (1)
- Insulin (1)

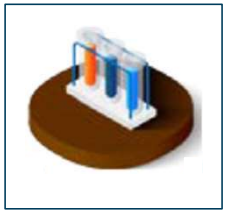
Characteristics of a Biomarker











Relevant to mechanism of action of the product

Capable to detecting differences between products (sensitive)

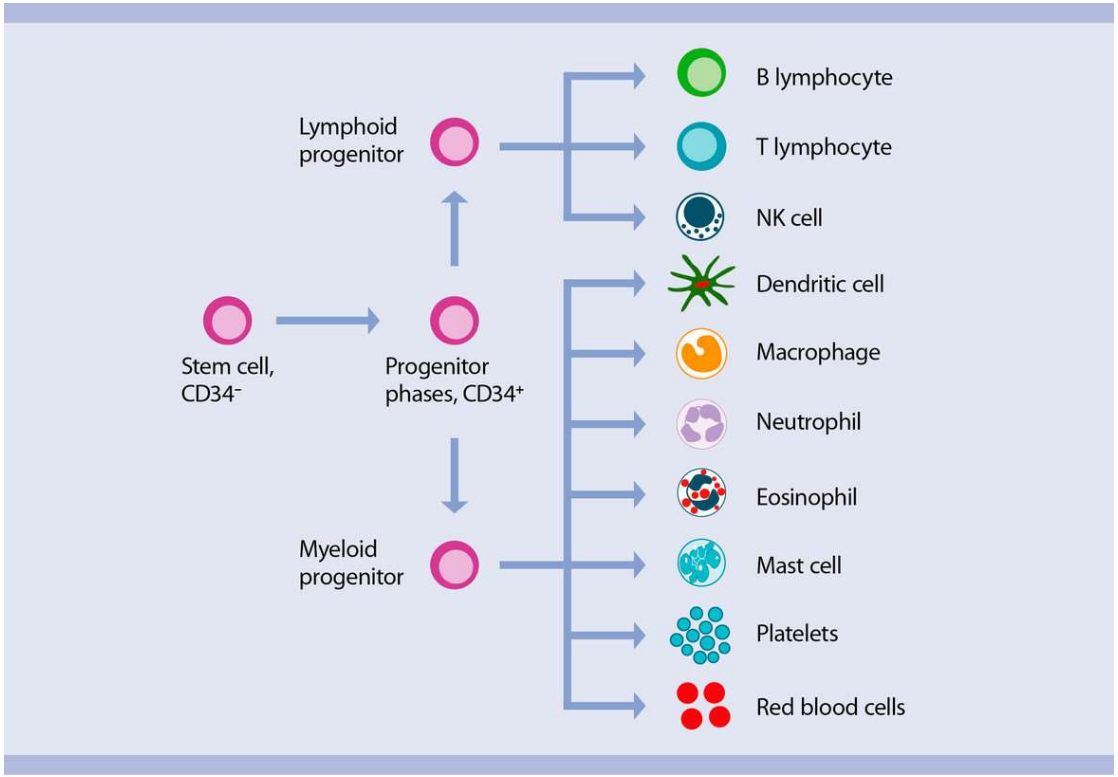
Well-characterized time course (max change and return to baseline)

Validated assays to measure the PD Marker

Clinical Pharmacology & Therapeutics, Volume: 107, Issue: 1, Pages: 40-42, First published: 31 October 2019, DOI: (10.1002/cpt.1653)

Filgrastim and Pegfilgrastim

- Treatment of neutropenia
  - Duration of severe neutropenia
- Increase in ANC
- Mobilization of hematopoietic progenitor cells (CD34+)

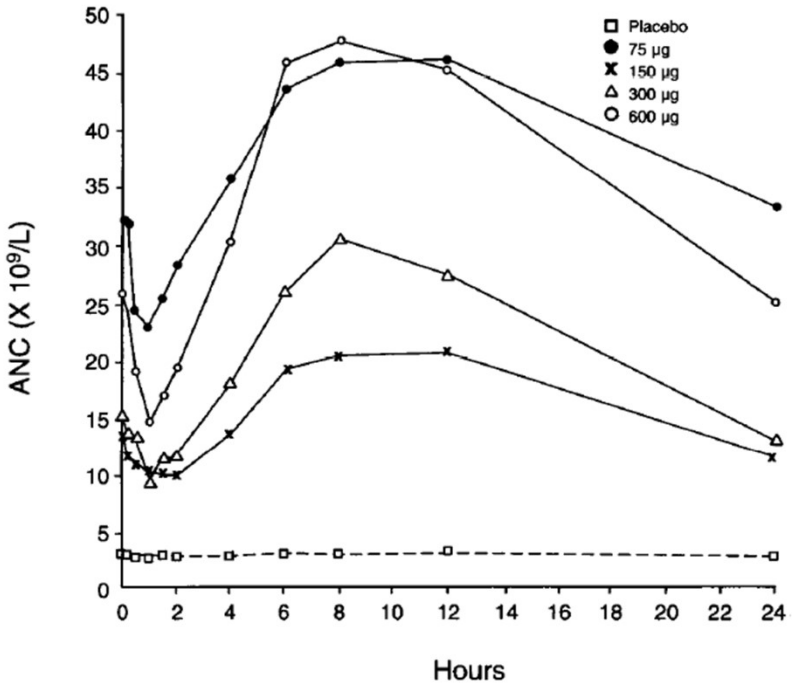


https://www.miltenyibiotec.com/NL-en

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125553Orig1s000ClinPharmR.pdf

ANC as a PD Biomarker

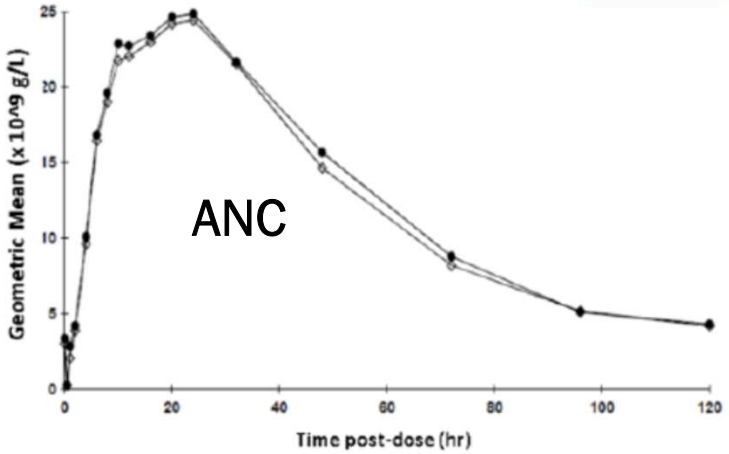
- ✓ Relevant to mechanism of action
- ✓ Dose-dependent increase in maximum ANC counts and AUEC
- ✓ Has wide dynamic range
- ✓ Time course of action is well-characterized

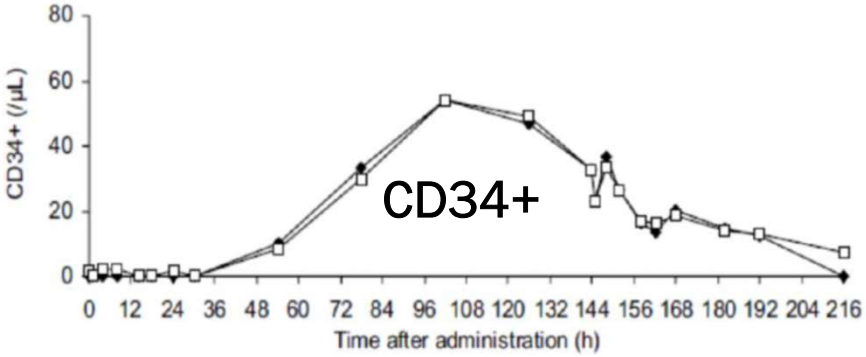


Borleffs et al, Clinical Therapeutics, Vol. 20, No. 4, 1998

PD Similarity Criteria

- PD parameters met acceptability criteria
  - ANC_{max} and $AUEC_{ANC}$
  - $CD34+_{max}$ and $AUEC_{CD34+}$
  - GMR and 90% CI within 80%-125%

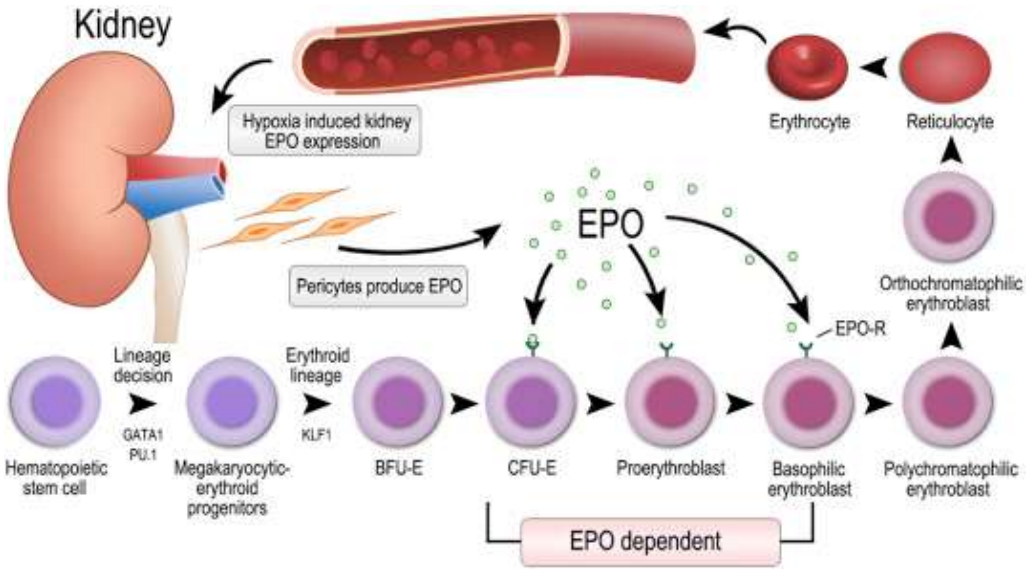




https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125553Orig1s000ClinPharmR.pdf

Epoetin

- Treatment of anemia
- Stimulates erythropoiesis
- Release of reticulocytes
- Mature RBCs formation
- Increase in hemoglobin levels

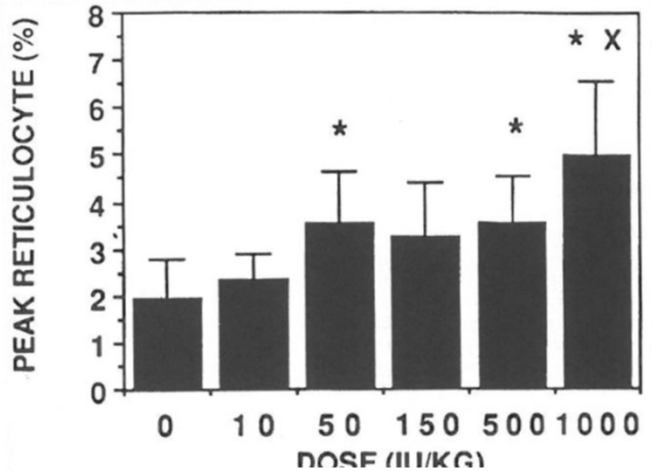


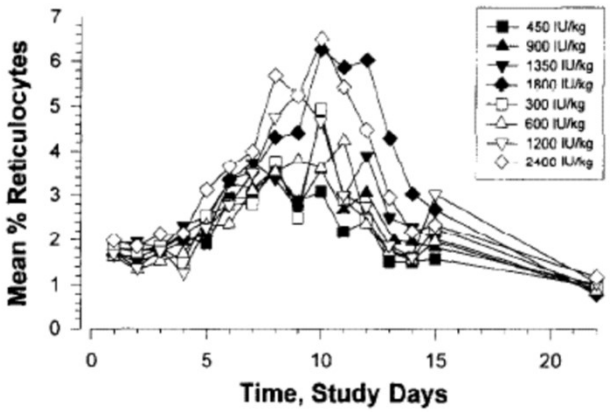
https://www.sciencedirect.com/science/article/pii/S0929664618300639

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/125545Orig1s000ClinPharmR.pdf

Reticulocytes as a PD Marker

- ✓ Relevant to mechanism of action
- ✓ Dose-dependent increase in reticulocytes
- ✓ Wide dynamic range
- ✓ Time course is well-characterized
- ✓ Similar trends for hemoglobin

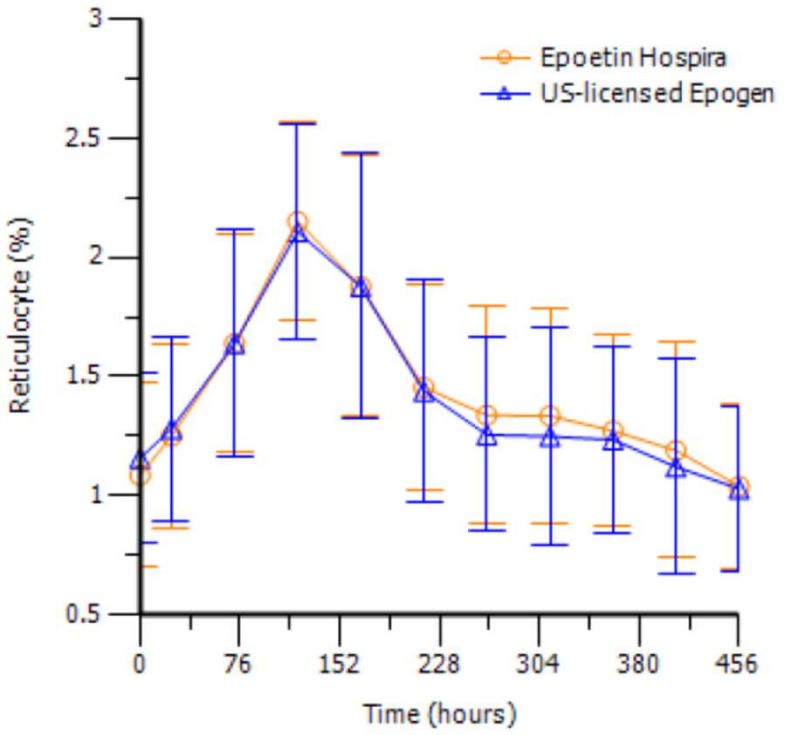




Cheung et al, Clinical Pharmacology & Therapeutics, Vol. 64, No. 4, 1998

PD Similarity Criteria

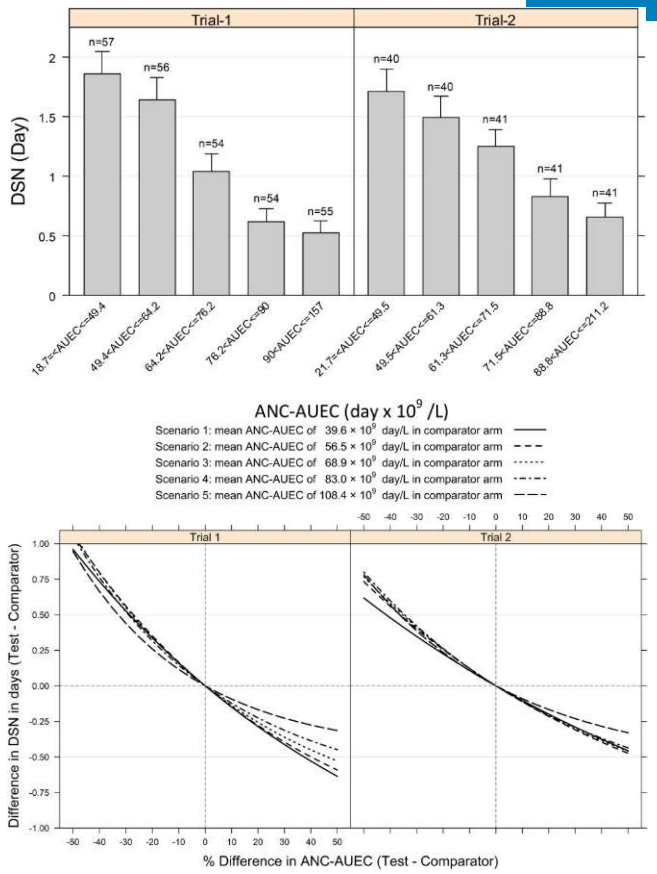
- PD parameters met acceptability criteria
  - Ret_{max} and $AUEC_{ret}$
  - $AUEC_{Hgb}$
  - GMR and 90% CI within 80%-125%



https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/125545Orig1s000ClinPharmR.pdf

PD Marker vs. Endpoint

- Relationship between AUEC and DSN
- Large changes in AUEC (up to ±40%) result small changes in DSN (less than 1 day)
- PD marker is more sensitive than the clinical endpoint



Li et al., CPT, (2018) 104 (4): 742-748

Conclusions

- The biomarker-based approvals meet the criteria
  - Relevance to mechanism of action
  - Sensitivity based on dynamic range and dose-response relationships
  - Well-characterized time of onset and return to baseline
  - Validated Assays
- Pharmacodynamic biomarkers provide higher sensitivity
  - Smaller sample size and shortened study duration
- Pharmacodynamic biomarkers for the approved products are closely related to the clinical endpoints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Andrej Skerjanec

Sandoz Inc.

Clinical pharmacology feasibility assessment of PD biomarkers for immuno-oncology biosimilars

Andrej Skerjanec, PhD

Head Clinical Pharmacology Biosimilars, Sandoz AG, Switzerland

SANDOZ A Novartis Division

Objectives

- PD biomarkers in immuno-oncology (IO)
- Case study: feasibility assessment of IL-18
- Summary and conclusions

Stringent selection criteria limit availability of immuno-oncology biomarkers for clinical similarity assessment

- EXCELRA's GOBIOM database identified 95 biomarkers across a broad range of IO therapeutics (PD-1, PD-L1)
- Mapping criteria, aligned with FDAs position paper (Li et al, 2019) were applied for further shortlisting of PD biomarkers (dose-response/dynamic range, onset and time course, variability)
- Based on mapping criteria, IL-18 was identified as potential biomarker for clinical assessment of biosimilarity

Case study with atezolizumab (Netterberg et al 2019)
Feasibility assessment of IL-18

- Originator study (N=88, r/rNSCLC) explored >90 plasma markers for response assessment (4 doses: i.v. infusion Q3W 10, 15 and 20 mg/kg and 1200 mg flat dose)
- **IL-18** remained as potential PD marker that was incorporated into PK/PD model, linking drug kinetics, IL-18 systemic time course and tumor shrinkage (Netterberg et al 2019)

- **Sensitivity analysis conducted by Sandoz**
  - Characterization of dose-response relationship and dynamic range of IL-18 responses using originator's PKPD model
  - Changes in IL-18 response as a function of variation in systemic drug exposure, using drug clearance as a surrogate measure of variation in drug characteristics
- **Investigated PD metrics**
  - Baseline corrected total area under the effect curve AUEC (derived by Sandoz)
  - Relative change from baseline (RCFB) at day 21 was a predictor of tumor shrinkage (Netterberg et al 2019)

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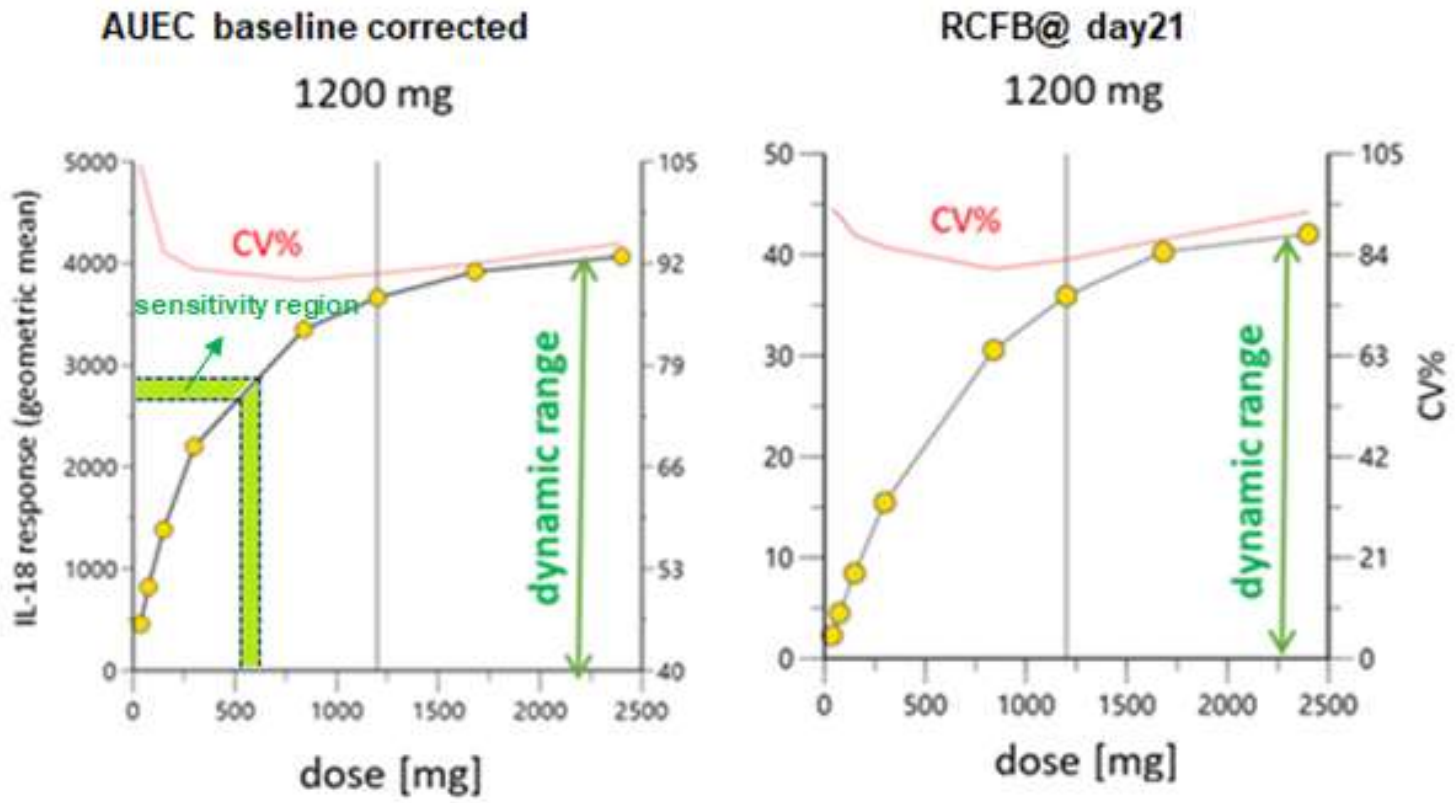
IL-18 Response Characteristics

Moderate Sensitivity, Low Dynamic Range, High Variability*



*Atezolizumab Q3W; simulations and illustrations performed by Sandoz using PK/PD model from Netterberg et al. 2019

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Moderate Sensitivity and High Variability of IL-18

1200 mg Q3W*

PD metric (% change)	CL (% change) +20%	-20%	Variability of PD metric [CV%]
AUEC baseline corrected	-2.9	2.4	86.0
RCFB %	-5.1	4.3	78.5

* 1200 mg is an approved dose
CL=systemic drug clearance, surrogate for PK

500 mg Q3W*

PD metric (% change)	CL (% change) +20%	-20%	Variability of PD metric [CV%]
AUEC baseline corrected	-5.1	4.4	85.3
RCFB %	-7.0	6.2	79.3

* 500 mg not clinically tested-for illustrative purposes only

- Longitudinal endpoints
  - Baseline corrected AUEC: minimal sensitivity to detect differences in PD and high variability of PD response
- Single endpoint
  - RCFB @ day 21: moderate sensitivity towards changes in drug clearance, high variability (≈900 pts required for a 3-way PD based comparability study)

Summary & Conclusions

- Efficacy and biomarker endpoints have limited utility for clinical similarity assessment due to low sensitivity as clinically approved doses are optimized towards maximum response
- Sensitivity is a function of dynamic range of drug responses (efficacy or biomarker) and response range is generally too narrow to meet the sensitivity criteria required for addressing structural variation at the molecular level and associated residual uncertainty
- Dynamic response range across broad range of therapeutics (not limited to IOs) is typically narrow due to physiological limits that are part of body's intrinsic control mechanisms for the homeostasis
- Pharmacokinetics remains the most sensitive clinical endpoint and could be readily used as a primary endpoint in the field of immuno-oncology biosimilars, together with safety and immunogenicity assessments due to strict adherence to approved posology
- Comparative efficacy study could be readily waived by the combination of in-vitro bioassays and pharmacokinetics

Acknowledgement

Roland Baumgartner, PhD, for setting-up the pharmacometrics platform and conducting the modeling and simulations work

Oliver von Richter, PhD, for leading the GOBIOM PD biomarker search

Wojciech Krzyzanski

State University of New York at Buffalo

Impact of Tolerance Effect on AUEC for Hematological Biomarkers

Wojciech Krzyzanski, PhD

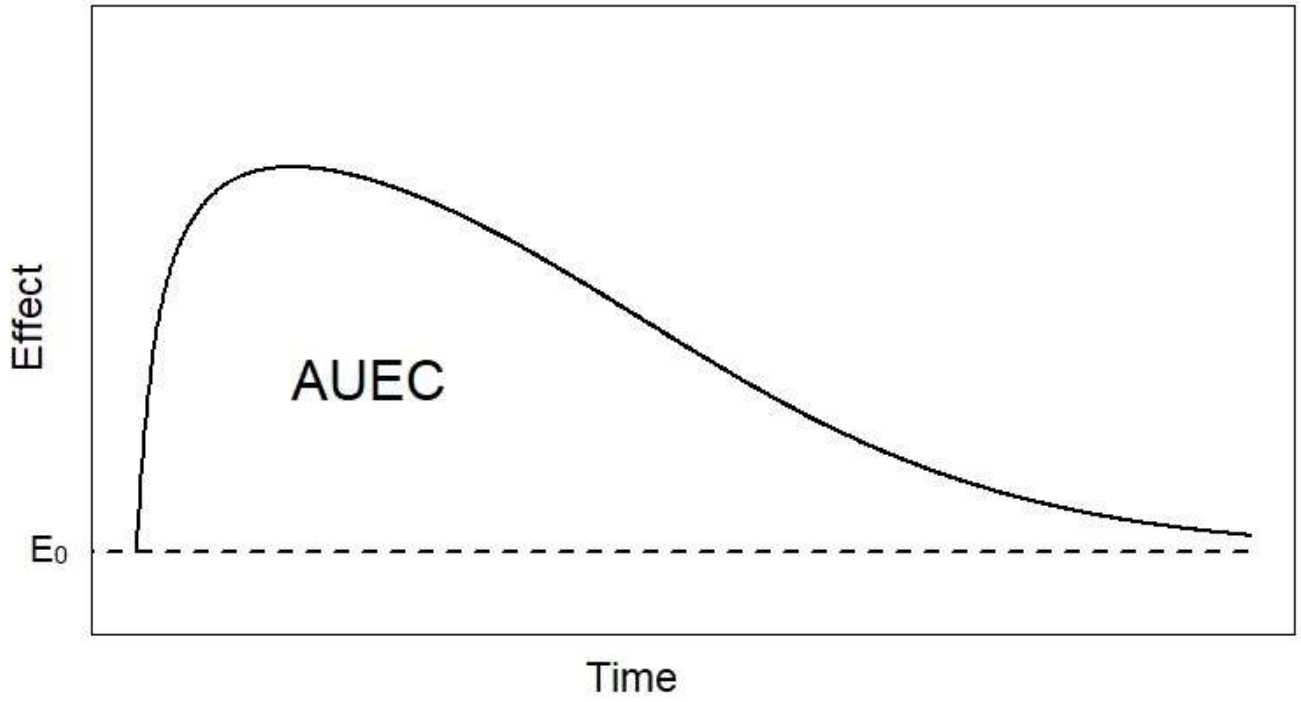
Pharmacodynamic Biomarkers for Biosimilar Development and Approval
FDA Virtual Public Workshop
September 21 2021

University at Buffalo

Outline

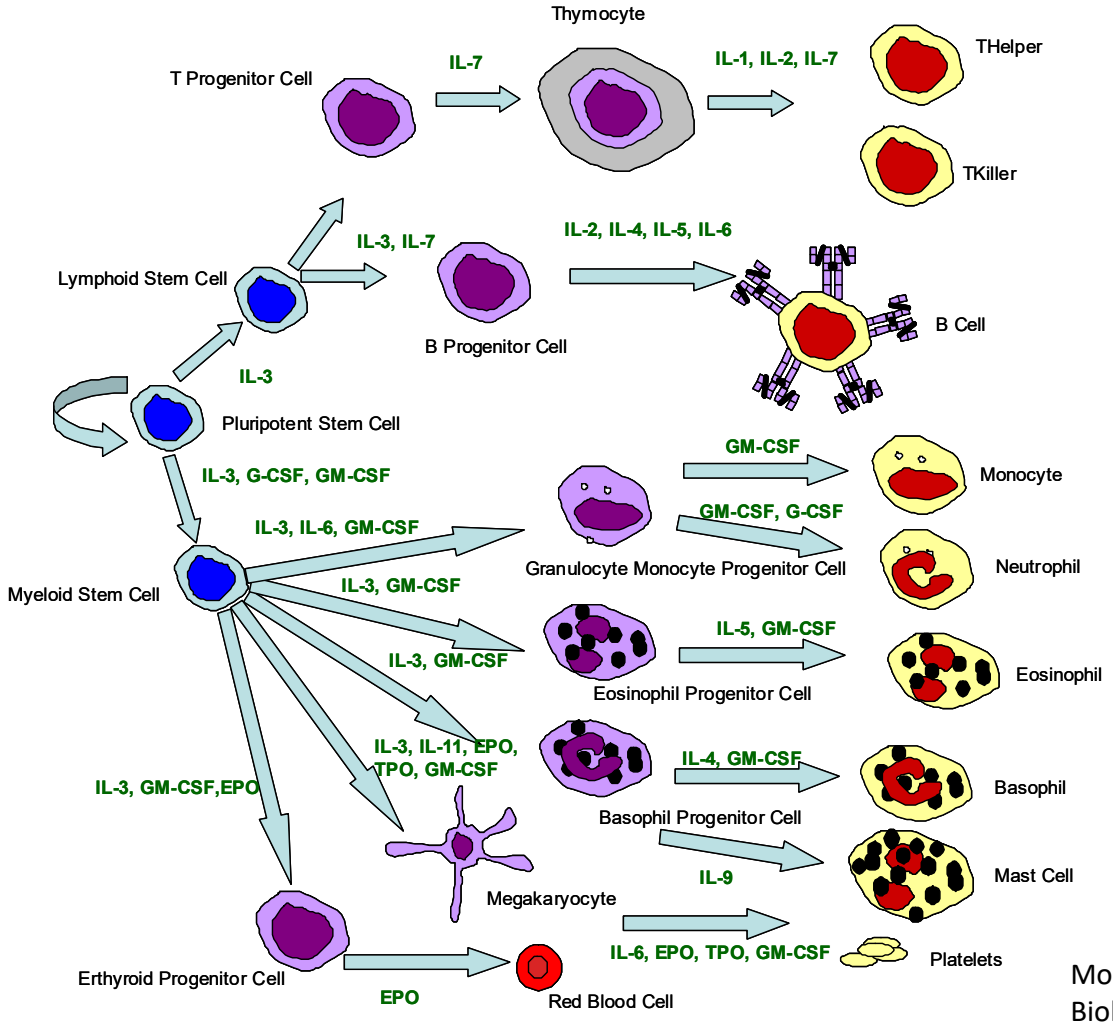
- Area under the effect curve as a measure of net PD response
- Cellular PD markers for biologics affecting hematopoietic systems
- Tolerance phenomena in hematological responses:
  - depletion of precursor cell pools in the bone marrow
  - negative feedback
- AUEC calculation for PD responses with tolerance

Area Under Effect Curve



AUEC is a measure of the net drug effect. It is calculated as the **A**rea **b**etween **E**ffect vs time **C**urve and the baseline E_0.

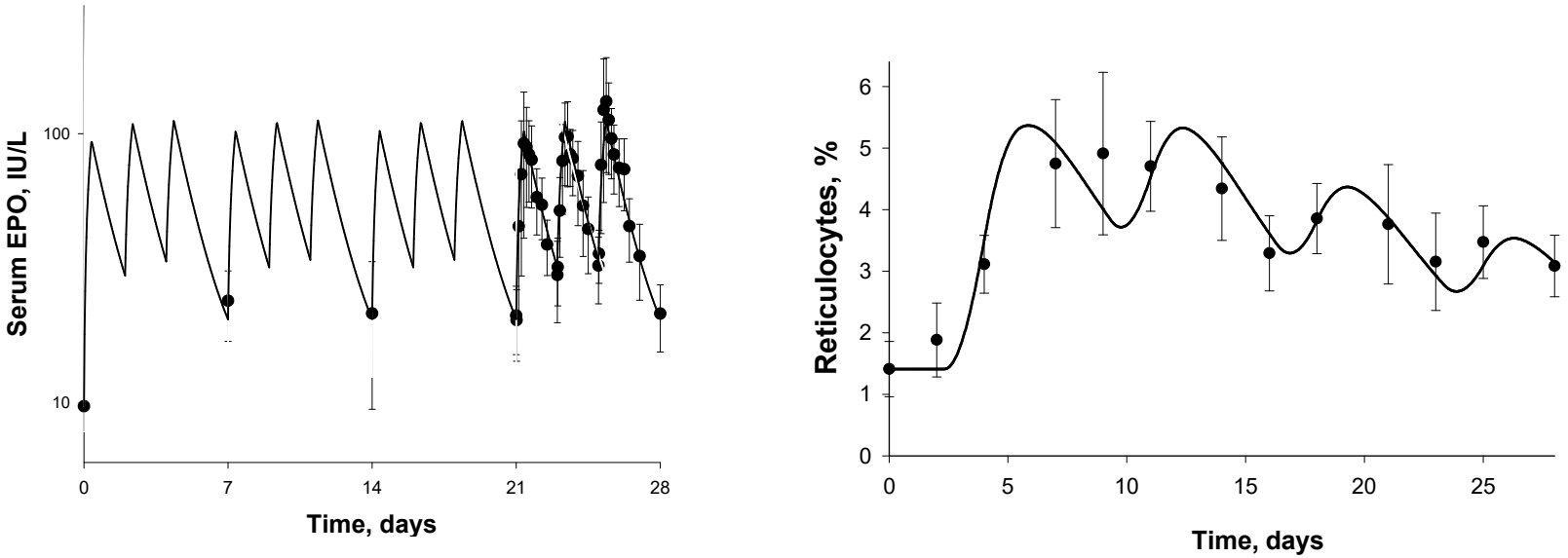
Cellular PD Markers for Biologics Affecting Hematopoietic Systems



- Red blood cells:
  - RBC count
  - Reticulocytes,
- White blood cells
- Neutrophils
- Platelets
- Basophils
- Eosinophils
- T Helper cells
- T Cytotoxic cells

Mould DR. (2005) Chapter: "Using Pharmacometrics in the Development of Biological Therapeutic Biological Agents".

Tolerance

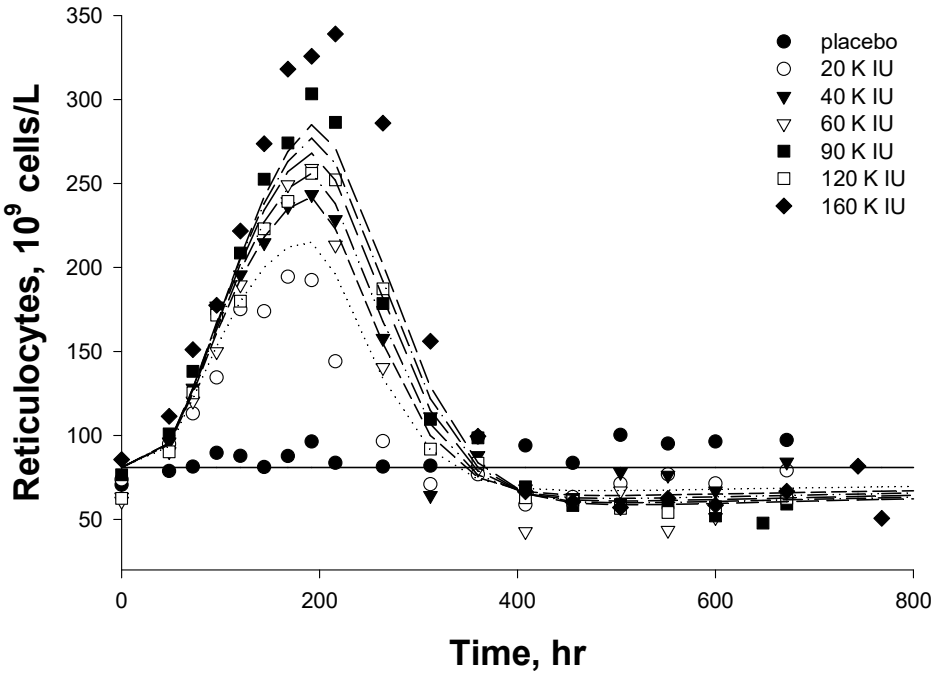


Reticulocyte counts (right panel) following chronic subcutaneous doses 150 IU/kg t.i.w. of EPO (left panel).

Tolerance manifests itself when the drug effect diminishes despite of a constant exposure

Data from Cheung et al, Eur. J. Clin. Pharmacol. 57: 411 (2001)

rHuEPO PD: Reticulocytes

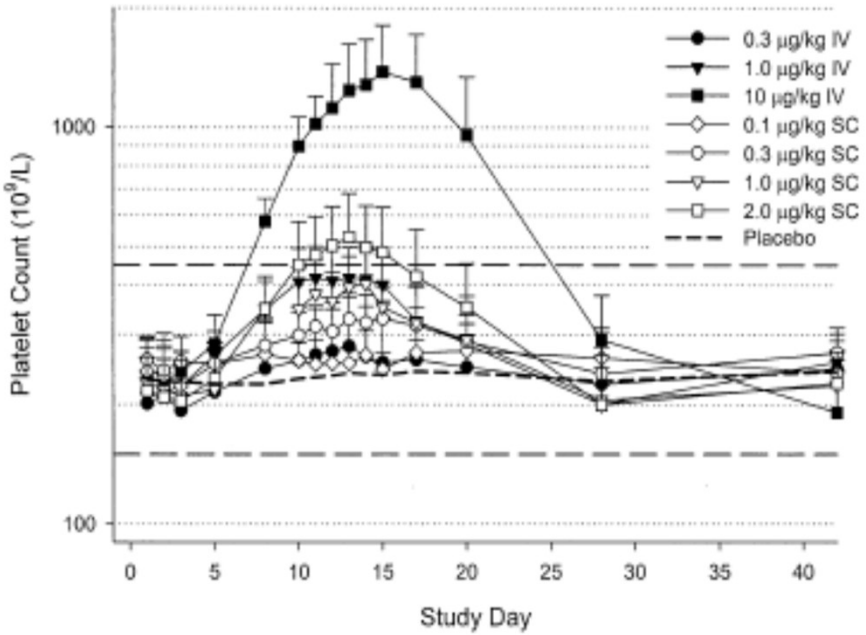


A prolonged rebound in reticulocyte counts for all doses starts about 400 h

SC dose of rHuEPO was administered to healthy male subject (n=8 per group). Reticulocytes were measured up to day 43.

Krzyzanski and Perez-Ruixo, Pharm. Res. 24:758 (2007).

Romiplostim Effect on Platelets



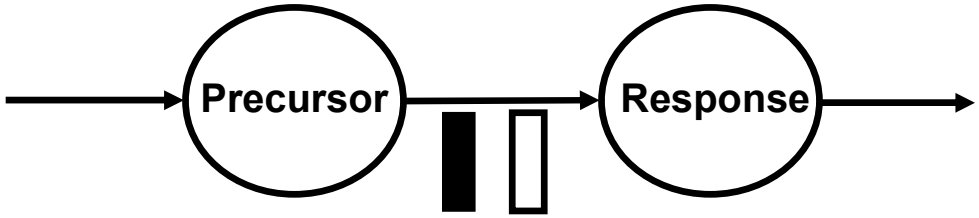
A rebound in platelet response is observed for higher IV and SC doses

48 healthy subjects received a single IV or SC injection of romiplostim. The dose ranges were 0.3 to 10.0 ug/kg (IV) and 0.1 to 2.0 ug/kg (SC). The pharmacodynamic response was measured as the elevation in platelet counts.

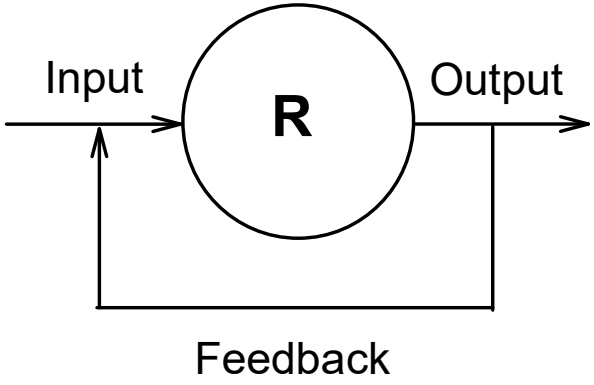
Wang et al., Clin Pharmacol Ther 76:628-38 (2004)

Mechanisms of Tolerance in Cellular Responses

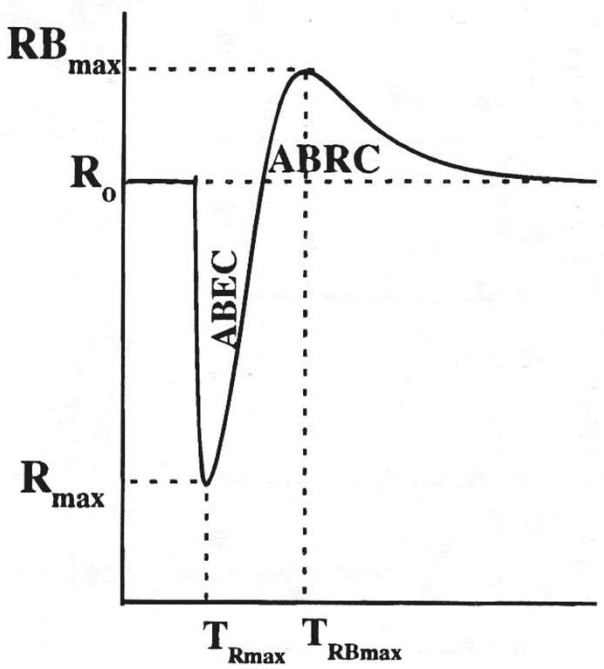
- **Precursor blockage/depletion**: Drug blocks or accelerates transition of cells from the precursor pool to the response pool

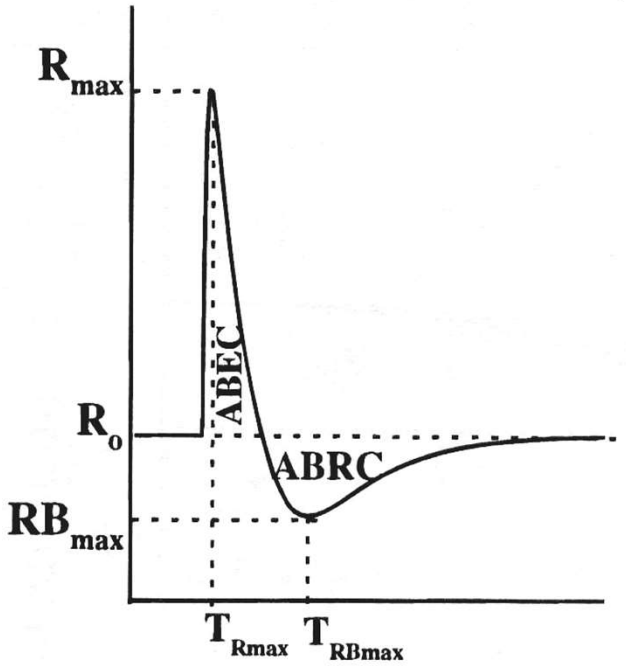


- **Negative feedback**: Increase/decrease in cellular output reversely affects the cellular input (e.g. via cytokine signaling)



Metrics of Net Effect for Responses with Rebound





ABEC = Area Between the Baseline and Effect Curve

ABRC = Area Between the Baseline and Rebound Curve

Net effect is characterized by both ABEC and ABRC

Sharma et al., J Pharm Sci 87: 1577 (1998)

Conclusions

- Hematological cell responses to biologics such as hematopoietic growth factors and monoclonal antibodies might exhibit a tolerance
- Tolerance following a single dose results in a rebound. Tolerance following multiple doses results in a slower onset of the response and a slope on the steady state response
- To proper quantify a response with rebound the baseline must be determined with at least two time points prior to the first dose. The response (rebound) curve must return to the baseline
- The net effect of a response with rebound should be characterized with both ABEC and ABRC

Session 3: Panelists

- **Patrick Archdeacon,** U.S. Food & Drug Administration
- **Salaheldin Hamed,** U.S. Food & Drug Administration
- **Wojciech Krzyzanski,** State University of New York at Buffalo
- **Andrej Skerjanec,** Sandoz Inc.
- **Hong Zhao**, U.S. Food & Drug Administration

Session 4: Extending PD Biomarker Opportunities Across Therapeutic Areas and Advancing PD Biomarker Use in Future Biosimilar Development

11:15 am – 12:20 pm

Qin Sun

U.S. Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Use of Multiple Biomarkers in Assessing Pharmacodynamic (PD) Similarity

Qin Sun, PhD

Therapeutic Biologics Program (TBP) Biologics Lead
FDA/CDER/OTS/OCP/IO

Duke-Margolis & FDA workshop
9/20/2021 - 9/21/2021

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.

- 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.

Outline

Key question: When should multiple PD biomarkers be used?

- **Guidance recommendation**
- **Case study 1: filgrastim biosimilar** (approved)
- **Case study 2: epoetin alpha biosimilar** (approved)
- **Case study 3: a biosimilar to product X** (under development)
- **Conclusion**

Guidance recommendation

- **FDA guidance:** *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (December 2016)
  https://www.fda.gov/media/88622/download

Biosimilar approval can rely on **pharmacokinetic/pharmacodynamic (PK/PD) approach** if suitable PD biomarker(s) are available

comparative clinical study (CCS) for efficacy and safety in patients: long duration, large sample size, confounding factors

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

Using **broader** panels of PD biomarkers that capture multiple pharmacological effects of the product can be of **additional value**.

Multiple PD biomarkers for filgrastim biosimilar

- **Reference product information:**

  Product: Neupogen® (filgrastim)

  a human granulocyte colony-stimulating factor (G-CSF), 18.8 KDa

  Indications:

  1) Treatment of neutropenia related diseases (e.g., febrile neutropenia in cancer patients)

     relevant PD biomarker: absolute neutrophil count (ANC), reflects mechanism of action (MOA) and correlates with clinical endpoint (duration of severe neutropenia)

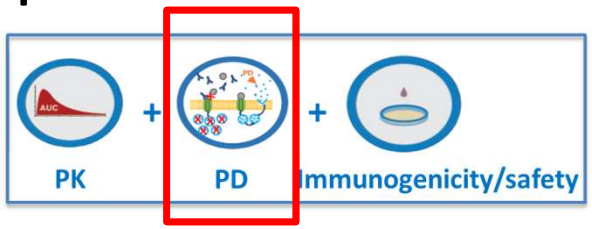
  2) Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis

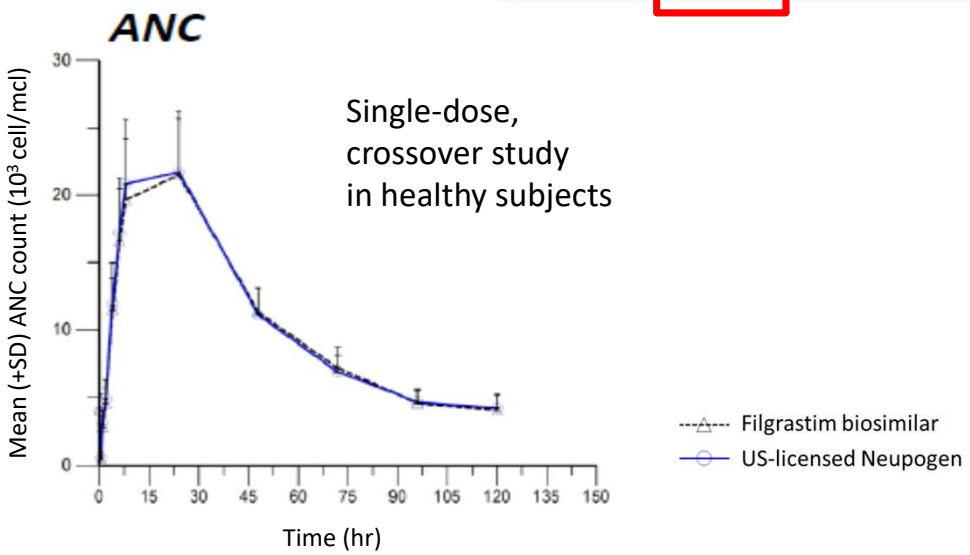
     relevant PD biomarker: CD34+ cell count, reflects MOA and correlates with clinical endpoint (required days for platelet transfusion)

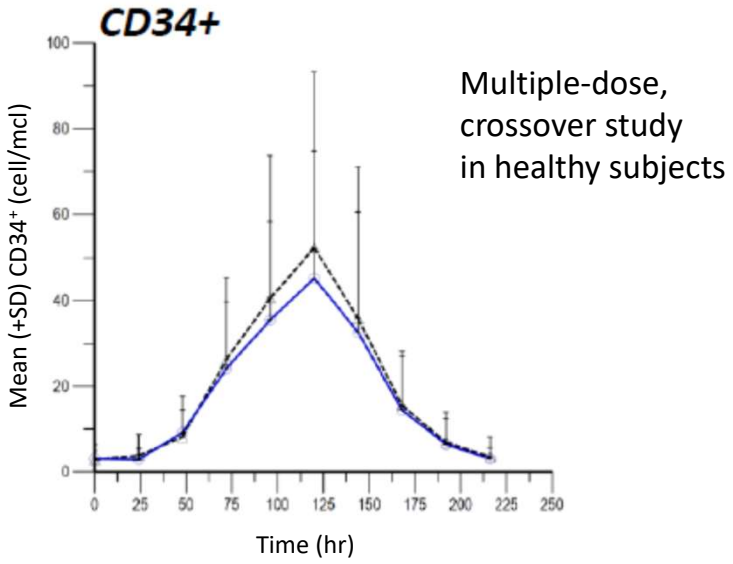
Different PD biomarkers for different indications;
Using both PD biomarkers to support approval of both indications

Multiple PD biomarkers for filgrastim biosimilar

- **Filgrastim biosimilar example:**







Note: For additional information, please refer to FDA BLA 761080 review summary.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761080Orig1s000ClinPharmR.pdf

Multiple PD biomarkers for epoetin alpha biosimilar

- **Reference product information:**

  Product: Epogen® (epoetin alfa)

  an erythropoiesis-stimulating agent to increase red blood cell (RBC) count, 30.4 KDa

  Indications:

  1) Anemia (due to chronic kidney disease, zidovudine in patients with HIV-infection, concomitant myelosuppressive chemotherapy)

  2) Reduction of allogeneic RBC transfusion in patients undergoing elective, noncardiac, nonvascular surgery

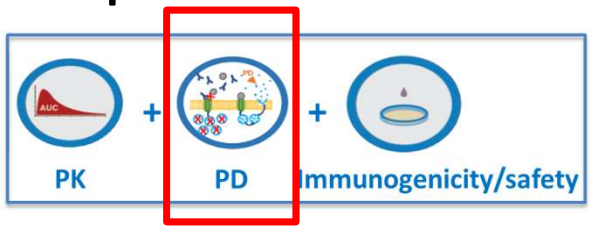
     relevant PD biomarker: reticulocyte count, reflects MOA and correlates with clinical endpoint

     hemoglobin, clinically relevant endpoint

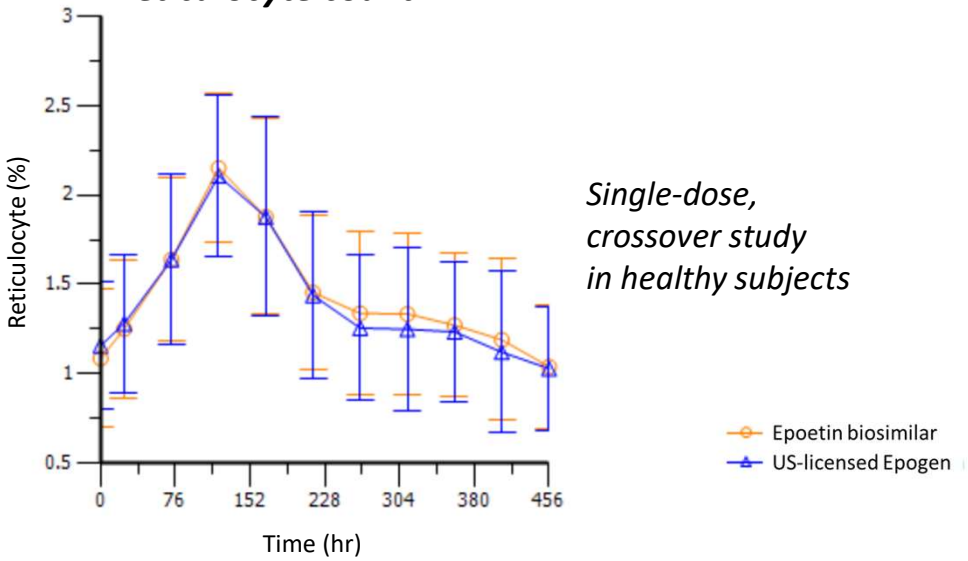
Hemoglobin increase is smaller in healthy subjects than in patients;
Adding a second biomarker with wider dynamic range can increase sensitivity.

Multiple PD biomarkers for epoetin alpha biosimilar

- **Epoetin alpha biosimilar example:**

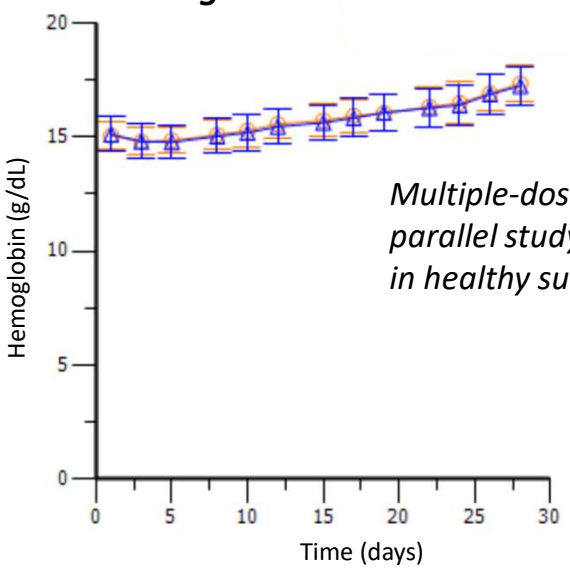


Reticulocyte count



Single-dose, crossover study in healthy subjects

Hemoglobin



Multiple-dose, parallel study in healthy subjects

Note: For additional information, please refer to FDA BLA 125545 review summary.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/125545Orig1s000ClinPharmR.pdf

Multiple PD biomarkers for a biosimilar to product X

- **Reference product information:**

  Product: X, humanized mAb, ~ 150 KDa

- **PD biomarker strategy:**

  - PD biomarker(s) demonstrating correlation with clinical endpoints are not available
  - Clinical endpoints require long treatment duration (up to 2 years) and large sample size
  - A composite of potential PD biomarkers in healthy subjects to facilitate biosimilar development:

    Pilot study: 1) evaluate dose-response relationship 2) select suitable biomarkers 3) select a sensitive dose

    PD biomarkers for PD similarity study:

    1) receptor occupancy (RO) – upstream target engagement

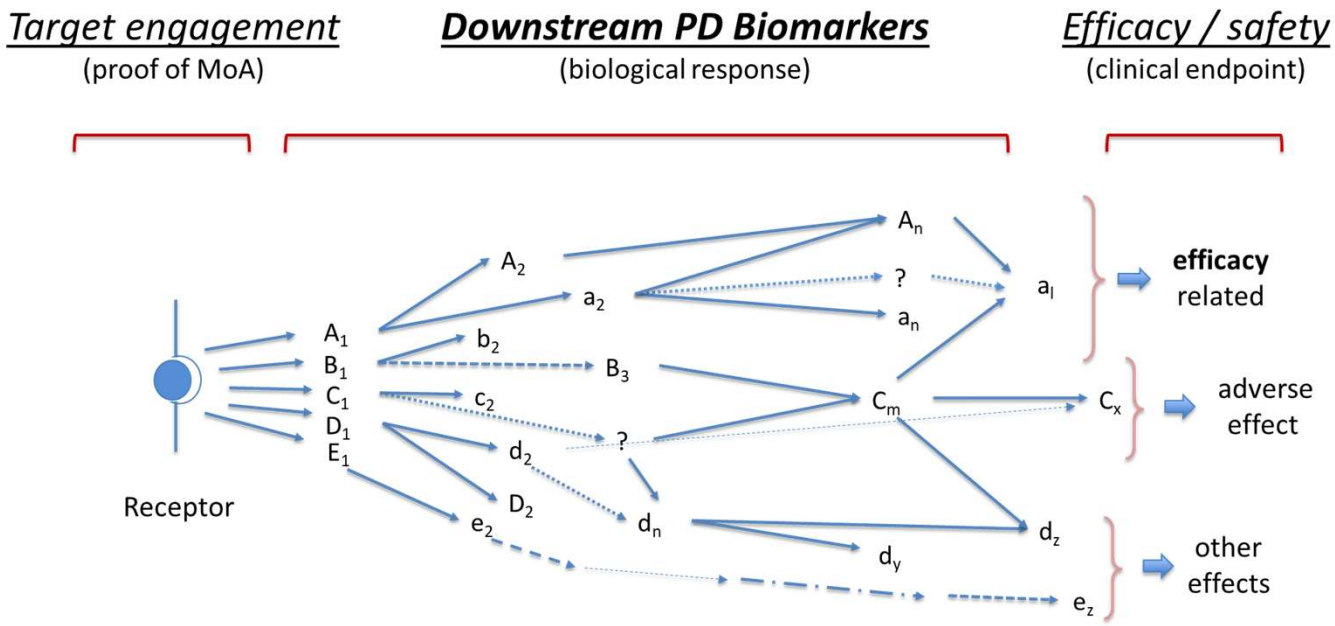
    2) series of PD signals for each MOA – downstream PD responses for each indication

Evaluating a composite of upstream and downstream PD biomarkers can help reduce residual uncertainty and accelerate biosimilar development

Conclusion

Application scenario and value of multiple PD biomarkers:

- address different MOAs for different indications;
- increase sensitivity;
- increase confidence in demonstrating biosimilarity based on totality of evidence by using a composite of upstream and downstream PD biomarkers



Resources

- **FDA guidance:**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents
  (search "biosimilars")

- **FDA biosimilar website:**
  https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

- **FDA approved biologics and biosimilars** (labeling and review summary):
  https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

- **FDA purple book**:
  https://purplebooksearch.fda.gov/downloads

Acknowledgements

- Workshop organization committee
- OCP management (Dr. Shiew-Mei Huang and Dr. Issam Zineh)
- Dr. Yow-Ming Wang and Therapeutic Biologics Program team
- Biosimilar guidance and PD biomarker working groups
- Biosimilar reviewers
- **Everyone who contributes to biosimilar development and approval**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Paula Hyland

U.S. Food and Drug Administration

Use of Novel Approaches in Identifying PD Biomarkers for Biosimilar Development

Paula Hyland, DPhil, MPH
Division of Applied Regulatory Science (DARS)
Office of Clinical Pharmacology/OTS/CDER

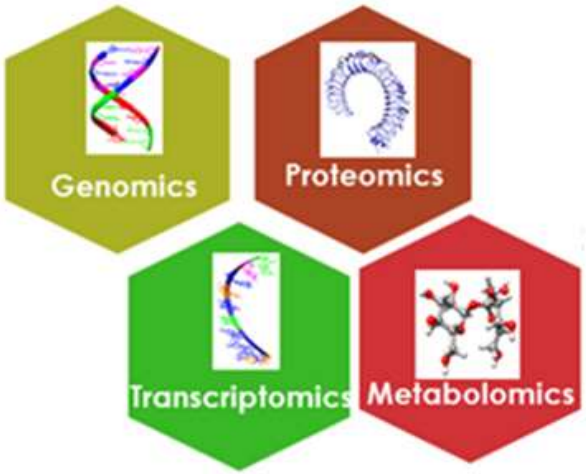
Outline

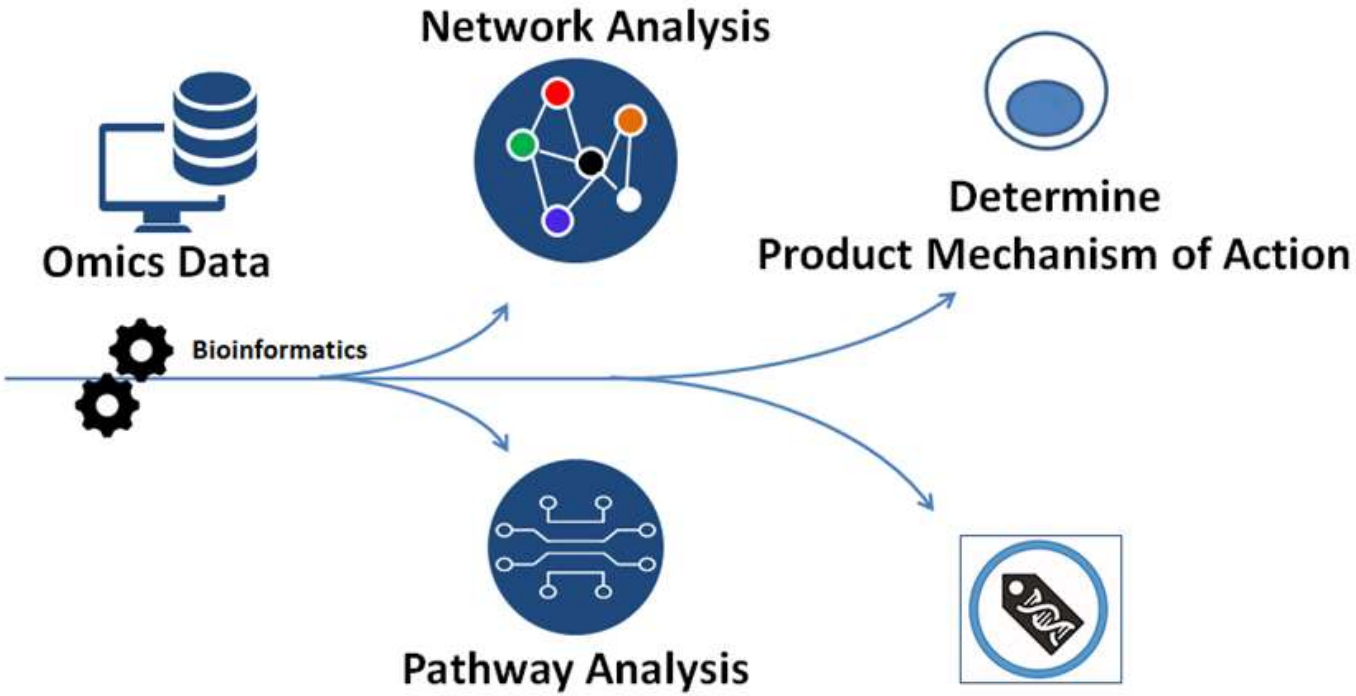
- Status of PD biomarkers for biologics and previous use of omics technologies
- Considerations for omics-based applications for the discovery of PD biomarkers for biosimilars
- Applied research to fill information gaps on the utility of omics technologies for identification of PD biomarkers for biosimilars
- Summary and conclusions

Status of PD Biomarkers and Use of Omics Technologies

- Since 2015, 322 biologics have been approved including 30 multiple biosimilars for 10 originator products
- However, only 8/30 approved biosimilar products for 4 originator products included PD similarity data
- For many originators well characterized PD biomarkers do not exist
- Some sponsors for originator products have carried out early phase exploration using omics technologies to fill knowledge gaps
- Further exploration of the utility of progressively maturating omics technologies and the analytical framework needed to identify relevant PD biomarkers is needed

Applications of Omics-Based Approaches to PD Biomarkers for Biosimilars

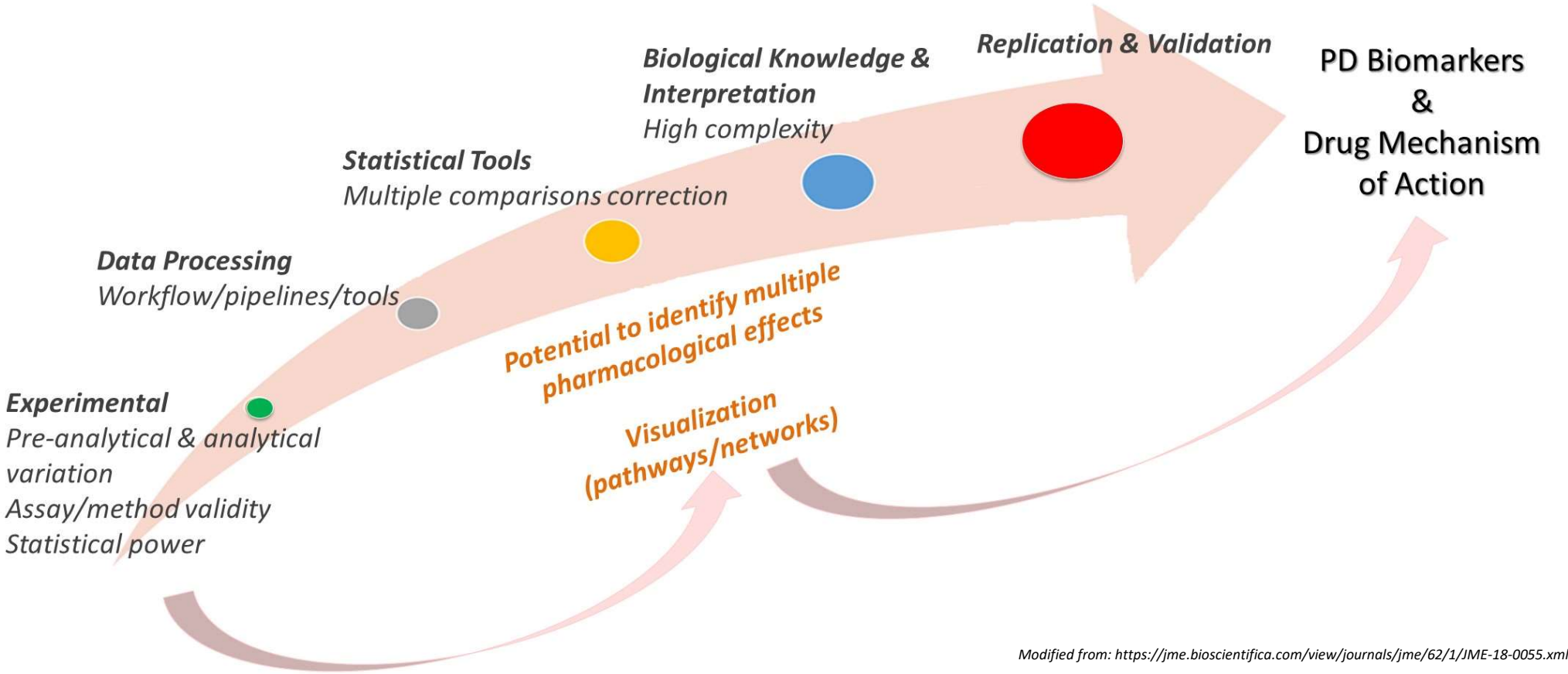




Omics technologies can capture multiple collective pharmacological effects

(Modified from: https://pubs.acs.org/doi/abs/10.1021/acsinfecdis.9b00080)

Considerations for Omics-Based Detection of PD Biomarkers for Biosimilars

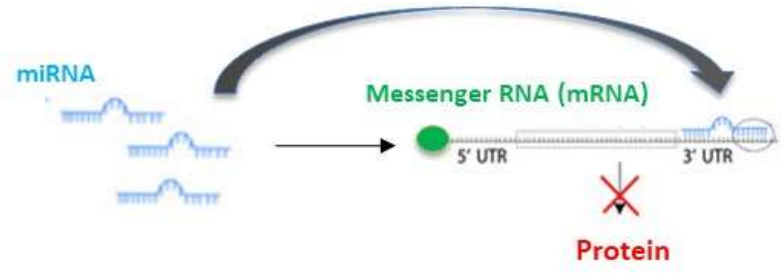


Modified from: https://jme.bioscientifica.com/view/journals/jme/62/1/JME-18-0055.xml

Example Omics Platforms for Detection of PD Biomarkers for Biosimilars in Plasma

Small RNA Transcriptomics

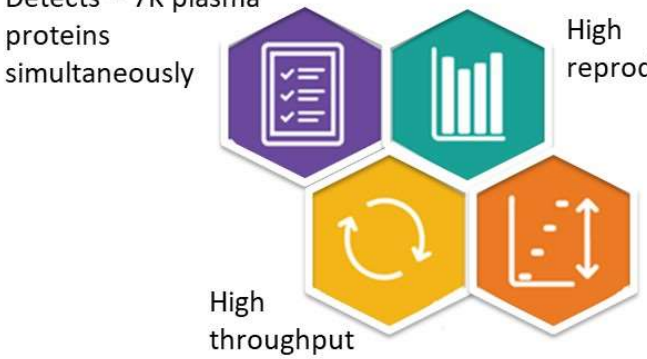
Cell-free microRNAs play important roles in cell communication and regulating gene expression and protein production



In-house Small RNA sequencing method

Proteomics

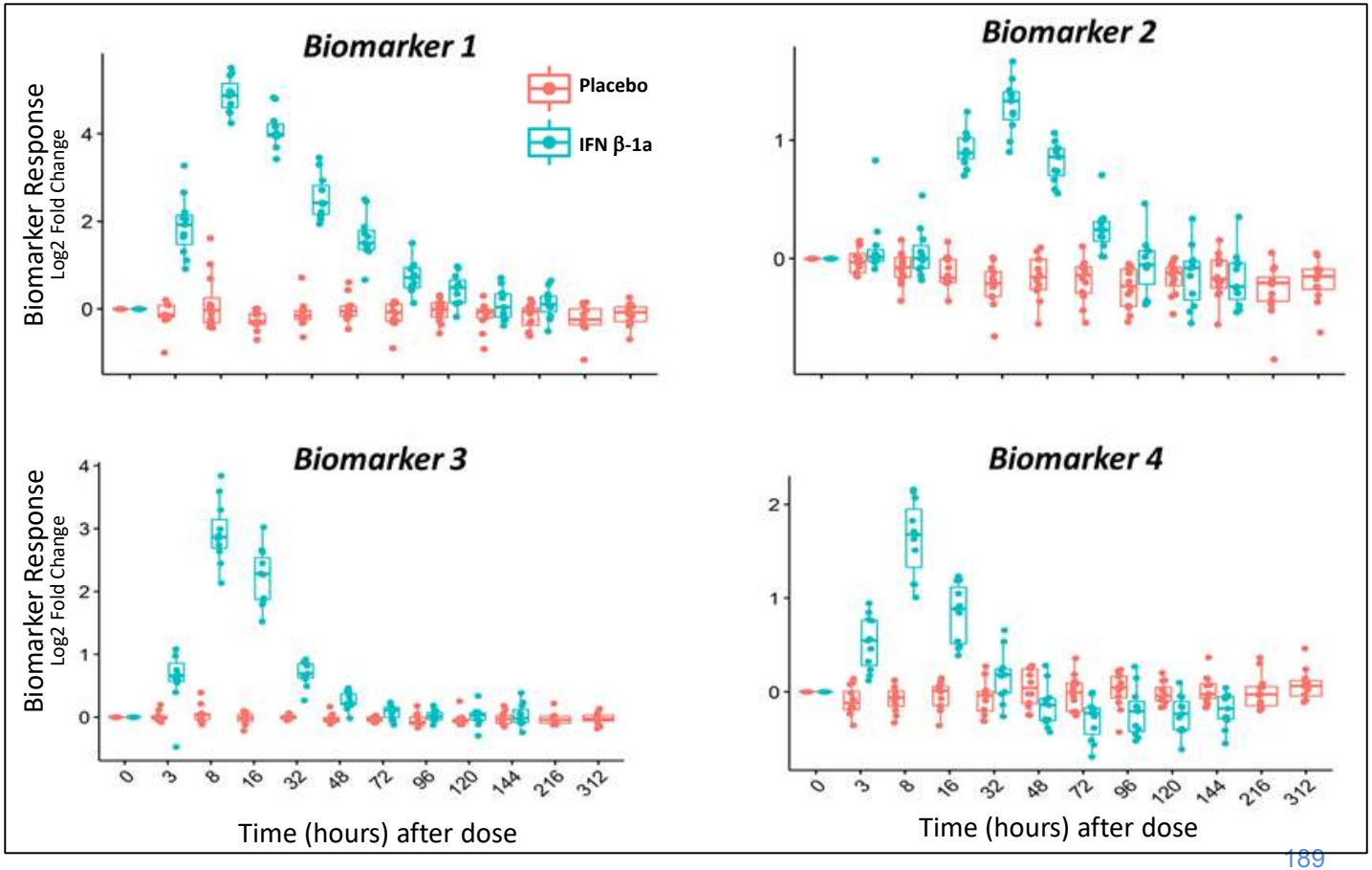
Proteins reflect real-time biology and respond to changes in health status, diet, age, environment, and drug treatment etc.



Adapted from: SomaLogic

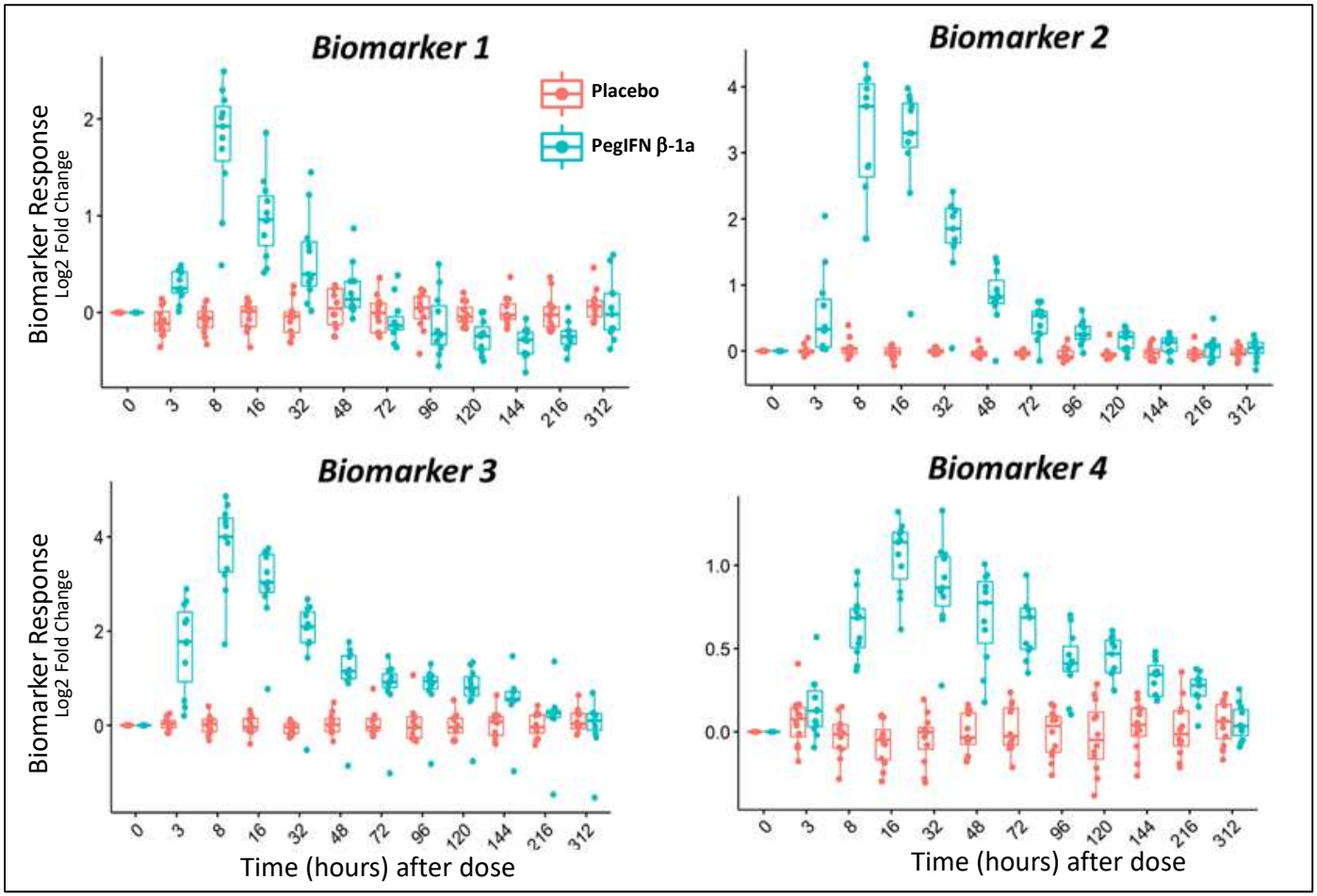
Identifying Candidate Interferon Beta-1a PD Biomarkers Using Plasma Proteomics

- Response curves for **4 candidate protein** affected by IFN β-1a treatment (30 µg) over time compared to placebo



Identifying Candidate Peginterferon Beta-1a PD Biomarkers Using Plasma Proteomics

- Response curves for **4 candidate proteins** affected by PegIFN β-1a treatment (125 µg) over time compared to placebo



Summary & Conclusions

- Omics technologies can capture multiple collective pharmacological effects
- Potential to identify novel PD biomarkers and fill knowledge gaps about drug mechanism of action
- A sensitive, dynamic, highly reproducible method and a well-designed discovery framework is required to achieve high sensitivity and low variability in identifying PD biomarkers using omics
- Many candidate PD biomarkers for potential use in PD biosimilarity studies were identified using a proteomics-based platform
- Future studies should evaluate other omics technologies for the identification and validation of potential PD biomarkers

Acknowledgements

- Workshop organization committee
- OCP management
- Dr. David Strauss, the DARS omics and GMBL teams
- Biosimilar guidance and PD biomarker working groups
- Biosimilar reviewers
- **Everyone who contributes to biosimilar development and approval**

Thank you!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R. Donald Harvey III

Emory University

Clinician Concerns with PD-Based Data in Oncology Biosimilar Approvals

R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA
Professor, Depts. of Hematology/Medical Oncology and Pharmacology
Medical Director, Clinical Trials Office
Director, Phase I Clinical Trials Section

Oncology Clinicians and Biosimilars

- Perspectives depend on place in therapy, time and familiarity with the field
- Patient scenarios
  - Supportive care (e.g., filgrastim)
  - Metastatic disease
  - Curative intent
- Comfort will likely increase with time-based experience, safety, and efficacy data
- Truisms:
  - Safety and efficacy matter the most
  - Clinicians generally consider them equal to generics

Academic oncology clinicians' understanding of biosimilars and information needed before prescribing

John W. Cook, Megan K. McGrath, Margie D. Dixon, Jeffrey M. Switchenko, R. Donald Harvey# and Rebecca D. Pentz#

- 12 question survey of 77 oncology clinicians
  - MD – 52, pharmacist – 16, APP – 7
- Three domains: clinician understanding, prescription preferences, and patient involvement
- Follow-up interviews on cost, safety and efficacy, patient preference, and disease stage

Ther Adv Med Oncol 2019;11:1-12. PMID:30671144

Academic oncology clinicians' understanding of biosimilars and information needed before prescribing

John W. Cook, Megan K. McGrath, Margie D. Dixon, Jeffrey M. Switchenko, R. Donald Harvey# and Rebecca D. Pentz#

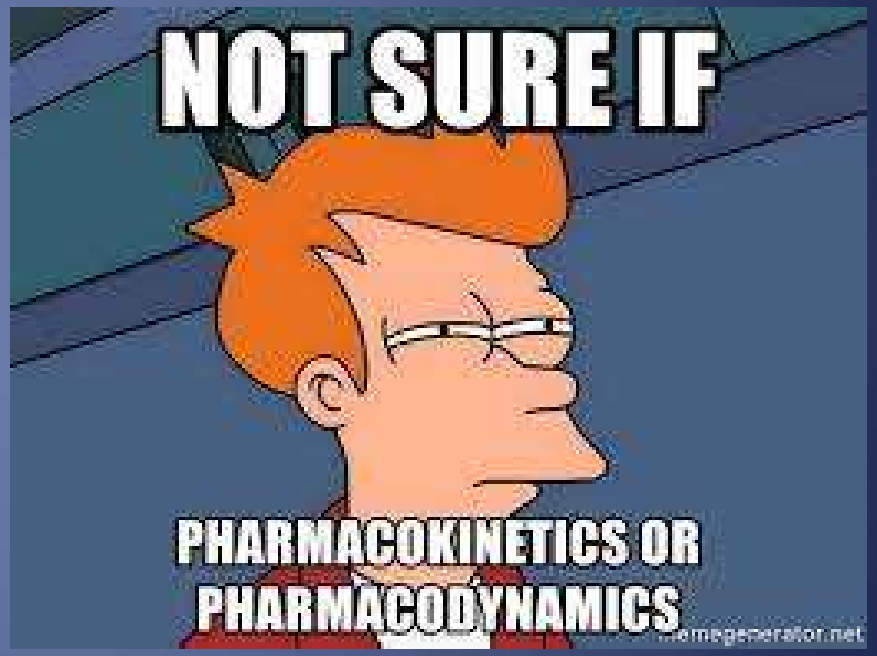
- Findings
  - Poor understanding of regulatory process
  - Biosimilar = generic? Yes = 40%
- Factors important for prescribing (out of 5)
  - Safety, efficacy 4.51
  - Cost 4.34
- Shared decision-making with patients
  - Split: 50.7% important or extremely important, 39% not at all important
- Adjuvant use – undecided/never/not confident 48%, somewhat confident 40%
- Metastatic – somewhat/very confident 51%, undecided 30%

closely by cost differences (4.34 out of 5). PK similarities, colleague and expert opinion, and chemical/physical characteristics were all considered less important than safety and efficacy ($p < 0.001$). As one participant stated, 'I think

Ther Adv Med Oncol 2019;11:1-12. PMID:30671144

Oncology Clinicians and Pharmacodynamics

- Tend to have a very elementary understanding
  - "What the drug does to the body"
- But…can be taught through familiar examples
  - Safety: neutrophil counts
  - Surrogate efficacy: myeloma paraprotein changes
  - Direct efficacy: radiographic reductions in tumor volume
  - Research: phosphorylated protein changes, PBMCs



Challenges in PD Data Acceptance by Clinicians

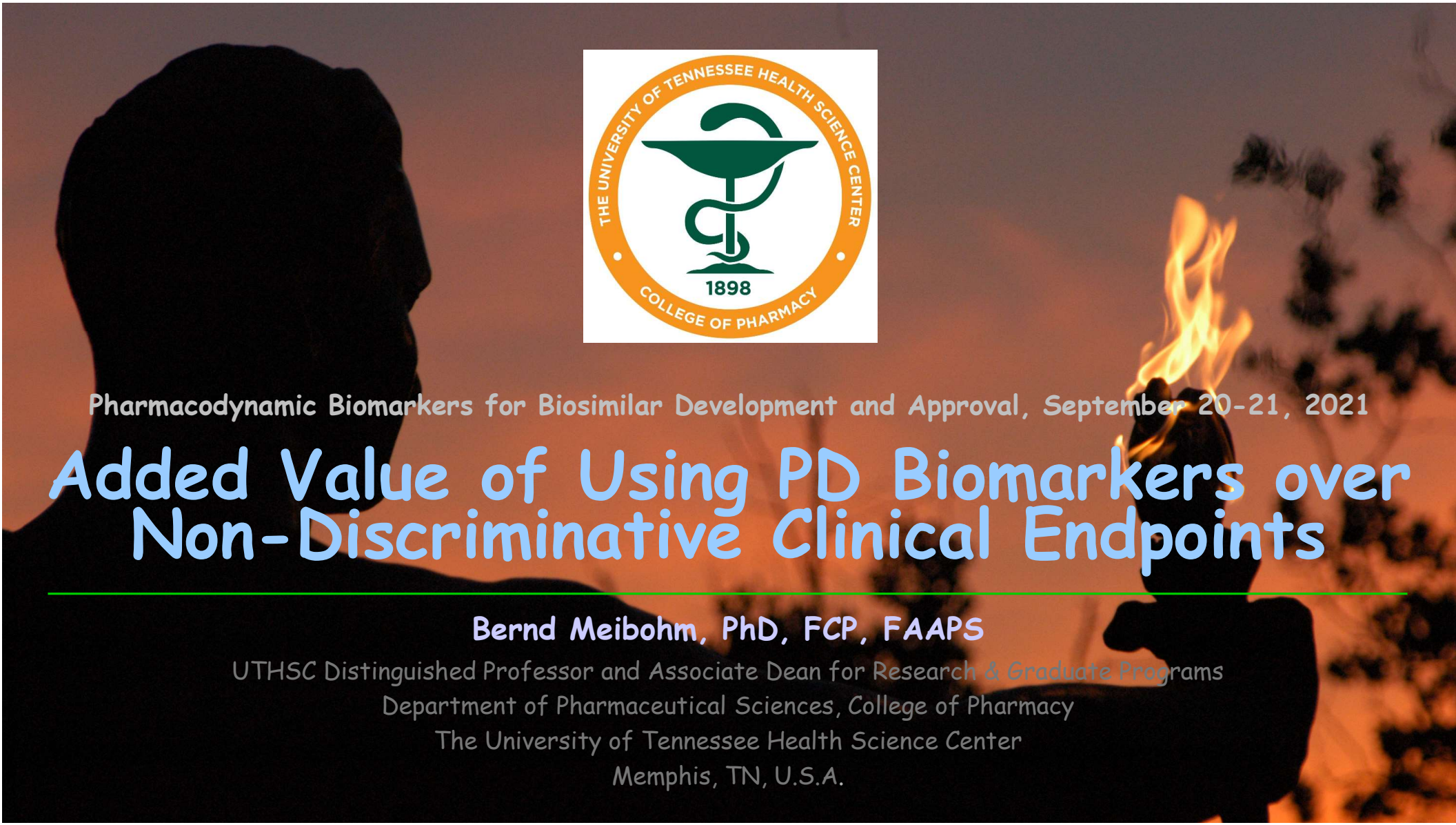
- PD data is not routinely used in daily practice
- “No clinically meaningful difference” is safety and efficacy, not PD data
- Reference agents not developed (beyond phase I trials) and/or marketed with PD outcomes prominently featured
- Many PD markers do not directly relate to efficacy, and/or have not been evaluated in late phase trials

Further Considerations

- PD has been around as a concept for oncology clinicians for decades with little uptake or expansion
- An evolution of the definition of “clinically meaningful” (or alternative wording) may aid in increasing clinician acceptance of PD data in the oncology biosimilar space
- More PD data may not be necessary (or adequate) for clinician acceptance of biosimilar products in oncology

Bernd Meibohm

University of Tennessee



Pharmacodynamic Biomarkers for Biosimilar Development and Approval, September 20-21, 2021

Added Value of Using PD Biomarkers over Non-Discriminative Clinical Endpoints

Bernd Meibohm, PhD, FCP, FAAPS

UTHSC Distinguished Professor and Associate Dean for Research & Graduate Programs

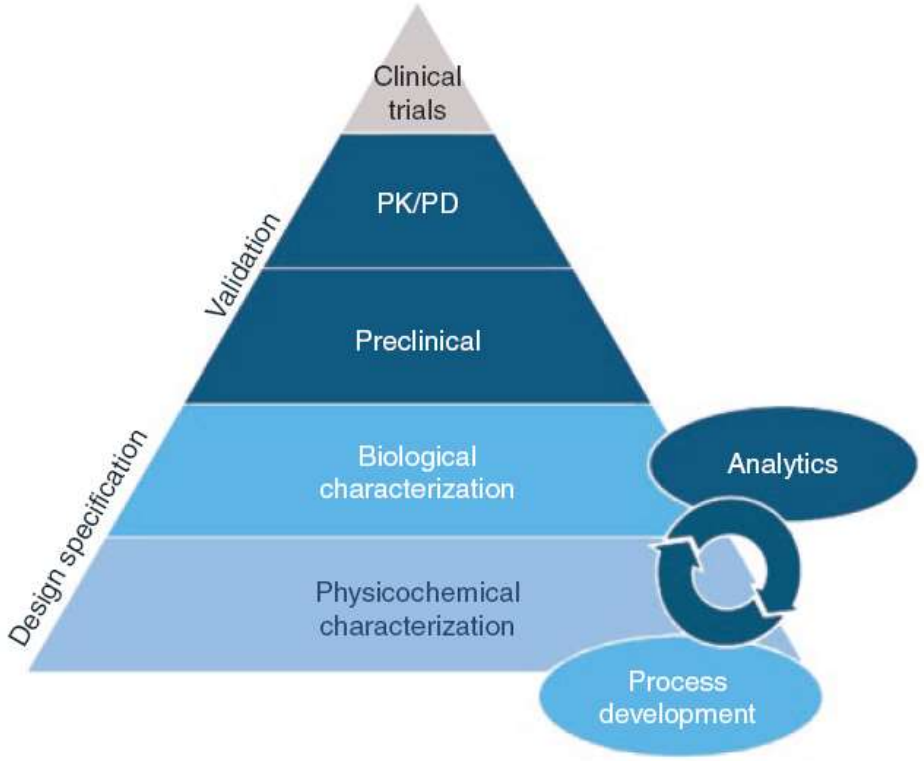
Department of Pharmaceutical Sciences, College of Pharmacy

The University of Tennessee Health Science Center

Memphis, TN, U.S.A.

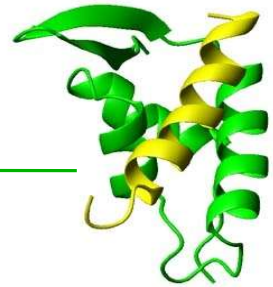
Biosimilar Regulatory Approval Requirements

Is the tip of the iceberg needed?



McCamish and Woollett, Clin Pharmacol Ther 2012, 91, 405-17

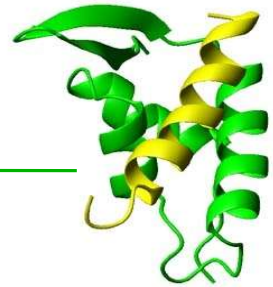
Limitations of Clinical Endpoints



Limitations in Biosimilarity Assessments

- Endpoints in pivotal phase 3 clinical trials in drug development for novel biologics are 'designed' and intended to show efficacy in treating a condition
  - ✓ Whether outcome measures are useful in discriminating between different degrees of efficacy is at best a secondary consideration
- Clinical efficacy studies in biosimilarity assessments are intended to establish similarity in efficacy (and safety) between a reference product and a biosimilar
  - ✓ The objective is not to establish efficacy, but to detect potential differences in the degree of efficacy: different requirement for outcome measures
- Especially aggregate clinical endpoint measures seem to have oftentimes little discriminative power
  - ✓ 'Noisy' measures, oftentimes with subjective elements
  - ✓ Examples: Composite outcome measures

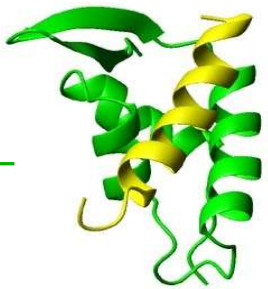
Limitations of Clinical Endpoints



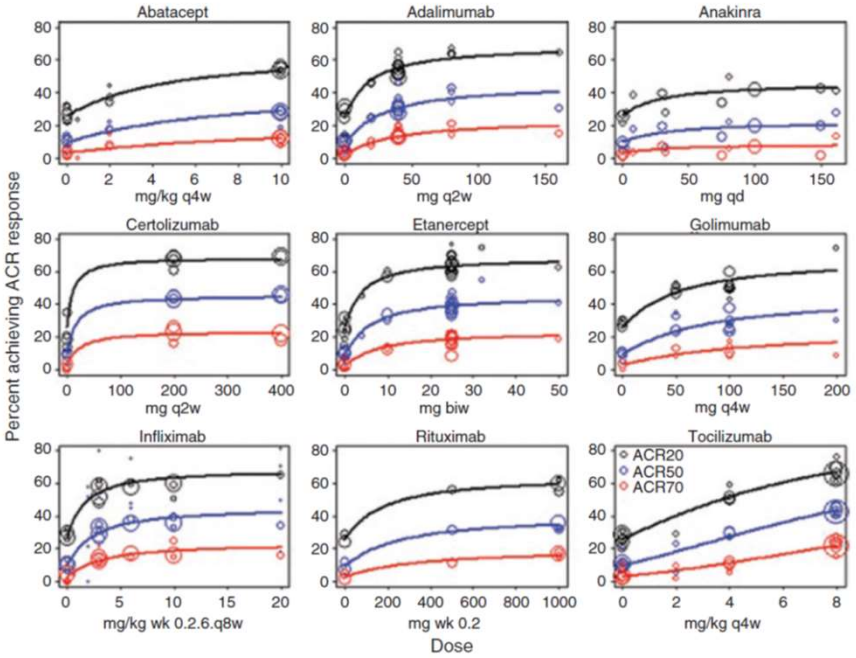
Composite Outcome Measures

- Examples: PASI, ACR20/50/70, DAS28, CDAI, SCCAI etc.
- Details on ACR20
  - ✓ ACR20 is a composite measure defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure [most often Health Assessment Questionnaire (HAQ)], visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (CRP).
  - ✓ ACR50 and ACR70 are the same instruments with improvement levels defined as 50% and 70% respectively versus 20% for ACR20

Non-Discriminative Clinical Endpoints



ACR20 for DMARDs

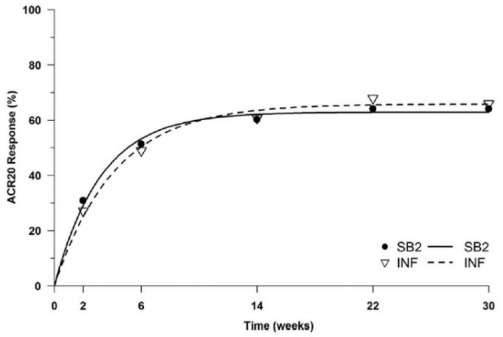


Estimated vs. observed dose-response

- ✓ For ACR 20, 50, and 70 in RA patients based on a model based meta-analysis

Mandema et al., Clin Pharmacol Ther 2011, 90, 828-35

Used in biosimilarity assessments

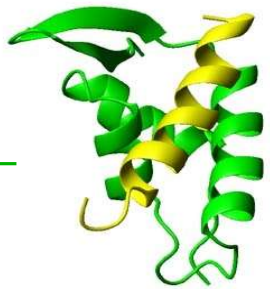


ACR20 response over time

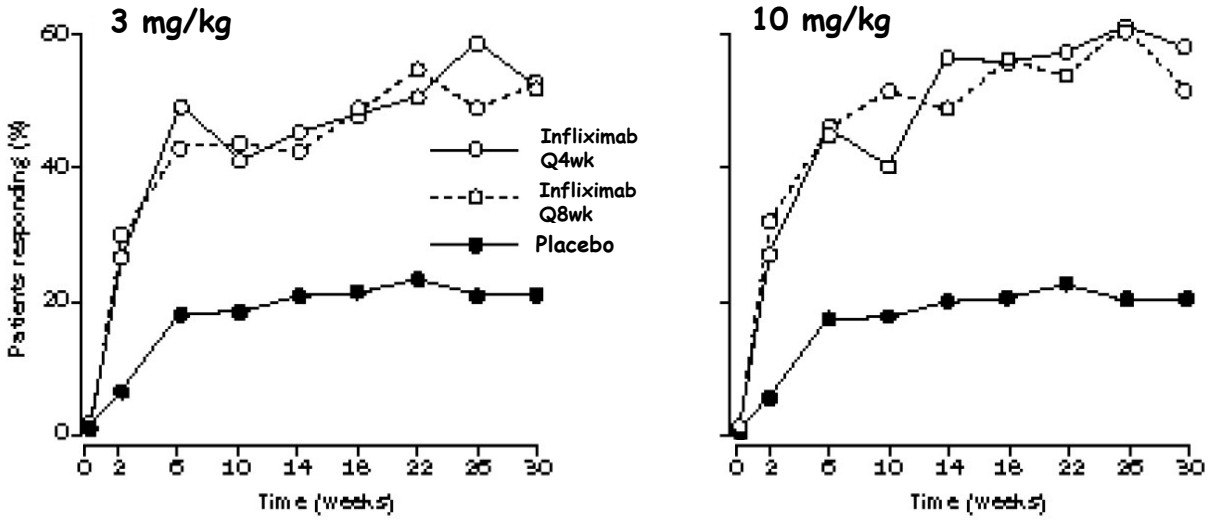
- ✓ Infliximab or SB2 biosimilar (3 mg/kg) in 584 subjects with RA with MTX therapy.

Choe et al., Ann Rheum Dis 2017, 76, 58-64

Non-Discriminative Clinical Endpoints



ACR20 for Infliximab

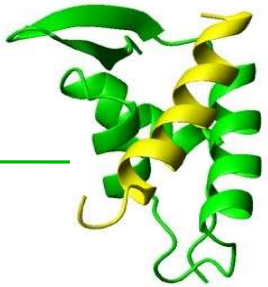


Infliximab or placebo in 428 RA patients on stable MTX

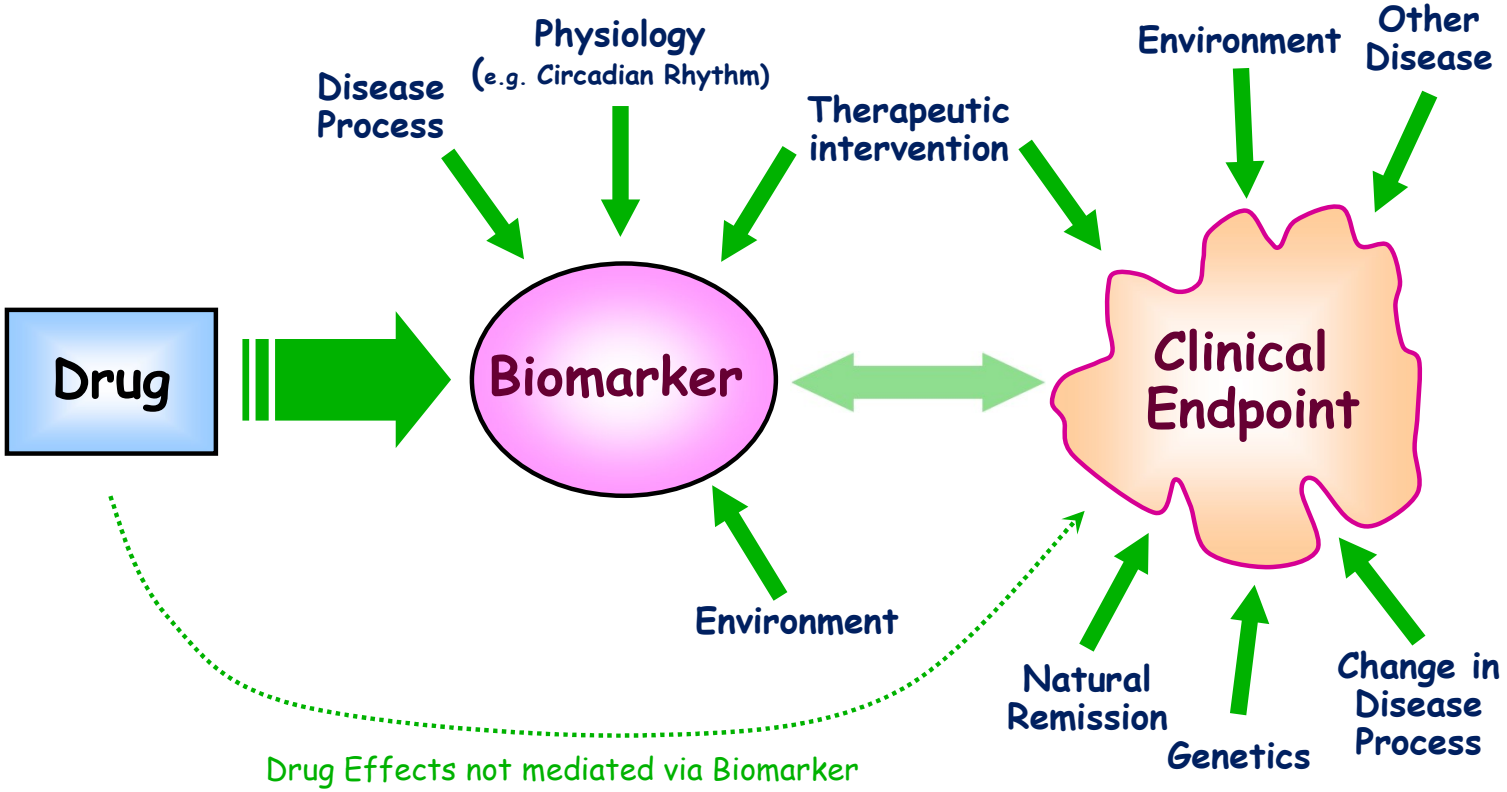
- ✓ 5 groups: Placebo, 3 mg/kg Q8wk, 3 mg/kg Q4wk, 10 mg/kg Q8wk, 10 mg/kg Q4wk after wk 0, 2, 6 induction
- ✓ Increased dose or dosing frequency above 3 mg/kg Q8wk did not increase ACR20 response rates
- ✓ Approved dosing regimen: 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks
  (Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks)

Maini et al., Lancet 1999, 354, 1932-9

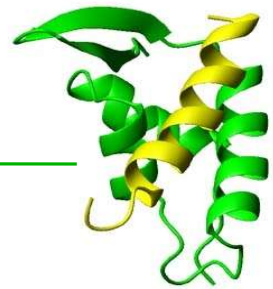
Biomarkers vs. Clinical Endpoints



Intermediate Measure of Drug Response



Biomarkers vs. Clinical Endpoints

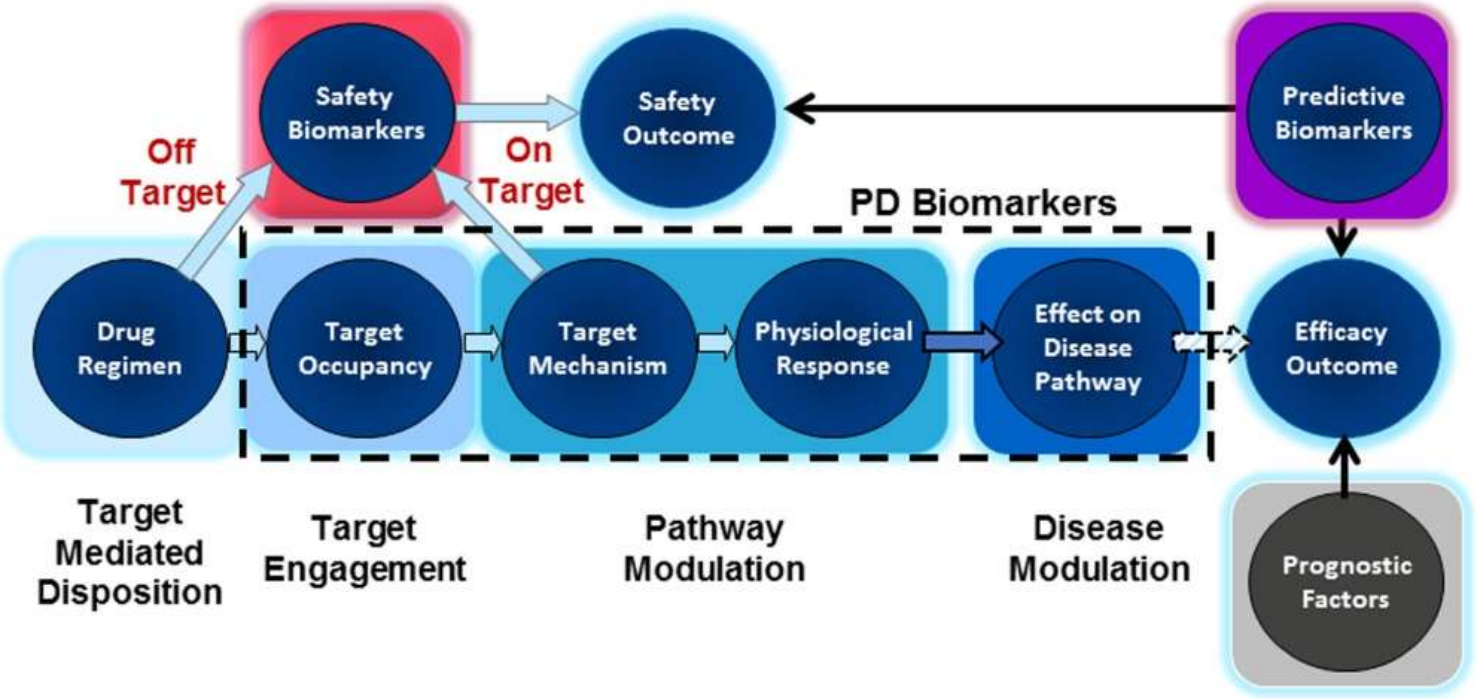


Reasons for Preferential Use

- Clinical endpoints
  - ✓ Pro
    - Historically accepted in the therapeutic area as efficacy endpoint for innovator drugs
    - No need to justify use of established outcome measure
  - ✓ Con
    - Low discriminative power to differentiate outcomes between biosimilar and innovator
- Biomarkers
  - ✓ Pro
    - More causally related to drug effect than variations in clinical endpoints
    - More precisely measured with validated assays compared to clinical outcomes
    - Larger dynamic range than clinical endpoints
    - Potentially reduced sample size requirements
  - ✓ Con
    - Need to justify its use as it is not an established outcome measure in the therapeutic area

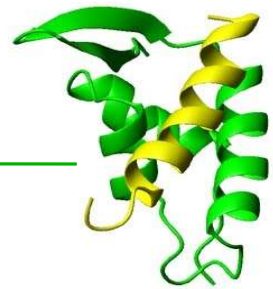
Biomarkers vs. Clinical Endpoints

Cascade of Intermediary Biomarkers for Therapeutic Proteins



Vicini & Roskos, Clin Pharmacol Ther 2017, 102, 27-9

Biomarkers in Biosimilarity Studies



Opportunities for more meaningful studies

- Biomarkers may provide more discriminative power for biosimilarity assessments than clinical outcomes
- Whether to monitor one ore several biomarkers should depend on the proximity to the mechanism of action and disease modulation
  - ✓ For disease modulation biomarkers only one monitored PD measure may be sufficient
  - ✓ For target engagement and pathway modulation biomarkers, more than one PD measure may be needed to establish confidence in PD biosimilarity
- PD biomarkers that are more discriminative and more precisely quantifiable than clinical endpoints may provide a better opportunity to identify potentially existing differences between biosimilar and innovator compounds
  - ✓ That does not mean that any difference is clinically relevant. Further interpretation needs to address this question.

Session 4: Panelists

- **R. Donald Harvey III,** Emory University
- **Paula Hyland,** U.S. Food & Drug Administration
- **Bernd Meibohm,** University of Tennessee
- **Sarah Schrieber,** U.S. Food & Drug Administration
- **Qin Sun,** U.S. Food & Drug Administration

Session 5: Regulatory Perspectives and Efforts to Advance PD Biomarkers for Biosimilars

1:10 pm – 2:25 pm

Peter Stein

U.S. Food and Drug Administration

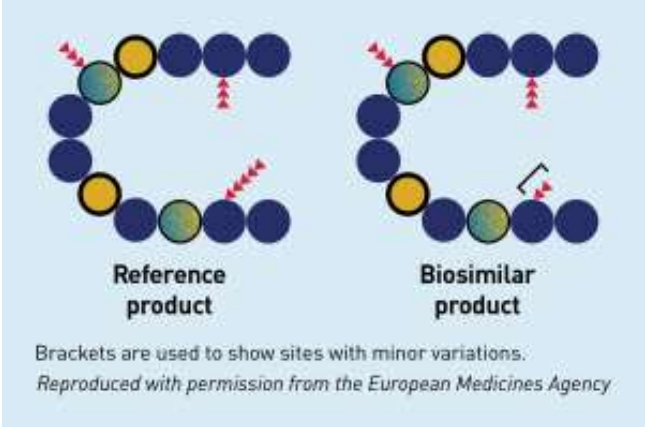
The Role of Pharmacodynamic Biomarkers in The Assessment of Biosimilar Drugs: Some Regulatory Considerations

Peter Stein, M.D.
Director, Office of New Drugs
Center for Drug Evaluation and Research (CDER)
FDA

"Biosimilar" or "Biosimilarity"

Definition:

- 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 safety, purity, and potency



Goal: to establish biosimilarity between proposed product and reference product, not to establish safety & effectiveness

- Mechanism(s) of action, route of administration, dosage form, strength, condition(s) of use
- Based upon data from analytical studies, and, *as appropriate,* from animal studies, clinical PK/PD, and comparative clinical efficacy studies

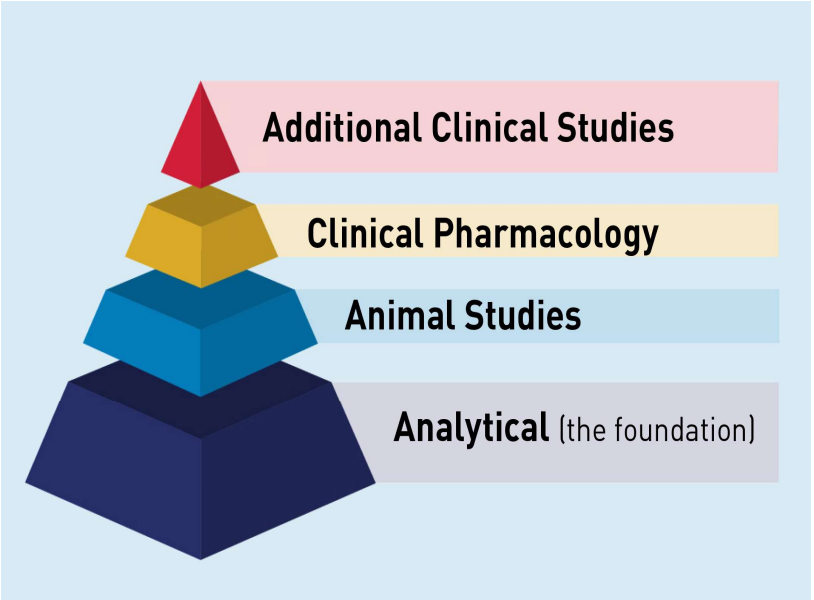
Use: in patients who have previously been treated with the reference product (treatment-experienced), as well as in patients who have not previously received the reference product (treatment-naïve)

Can most biologics be copied exactly? No

- Most biologics are mixtures of variants, with post-translational modifications related to differences in cell source and downstream processes, formulations, etc.
- Current advanced analytic assays allow detailed assessment of biosimilar candidates relative to the reference listed drug – often with orthogonal approaches
  - Structural analyses
  - In vitro functional analyses
- Evolving understanding of differences (e.g., a particular glycosylation pattern, charge differences, proportion of a particular variant, etc.) and related functional consequences
- Across specific drugs, there is a varying understanding of how the structural differences and correlative in vitro functional differences relate to the drug's mechanism(s) of action, and ultimately, to efficacy and safety
  - Complexity of the molecule (e.g., small proteins such as insulin, monoclonal antibody, highly complex proteins)
  - Clarity of understanding of all mechanisms of action – and structural correlates with MOA: what differences may alter the MOA, what differences would not?
  - How reliably *in vitro* functional assays detect relevant differences in MOA(s) of drug and predict effectiveness
- The better we can characterize a biosimilar candidate's structure, and can interpret in vitro functional assay results, the less may be the residual uncertainty

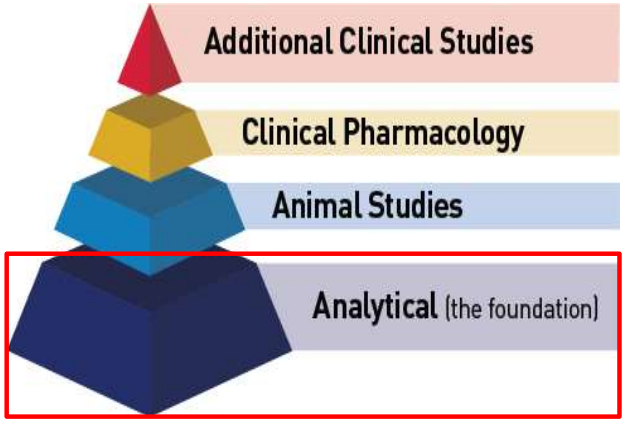
Demonstrating biosimilarity

- Stepwise approach to generate data in support of a demonstration of biosimilarity
  - Foundation: comparative analytical data
  - Evaluation of residual uncertainty at each step of data generation
  - Nature and scope of clinical studies depends on the extent of residual uncertainty after analytical assessment and, where relevant, animal studies.
- *Totality-of-the-evidence* approach to evaluating biosimilarity

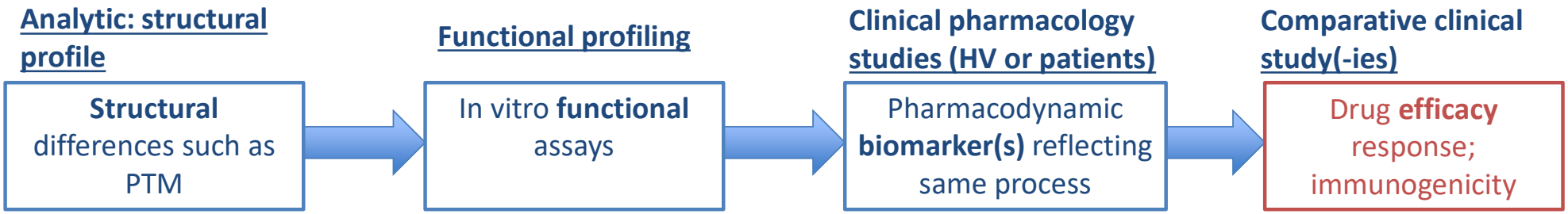


Comparative analytical assessment

- Comparative assessment of multiple physicochemical and biological attributes
- Assays must be fit for purpose – able to detect differences if they exist
- Analyze multiple lots of the reference product and proposed biosimilar for each attribute:
  - Primary amino acid sequence
  - Biological activity - evaluation of attributes that affect the known mechanism(s) of action
  - Post-translational modifications (glycosylation, phosphorylation, etc.)
  - Protein folding (higher order structure)
  - Heterogeneity (charge, size, aggregates, etc.)
  - Thermal and temporal stability
  - Impurities
- Comparative assessment of a **wide range** of physicochemical and biological attributes



The "positioning" of PD biomarkers in evaluation of biosimilarity



- Structural differences nearly always detected
- Based upon understanding of specific change / extent of difference -- may or may not suggest potential clinical meaningfulness
- Residual uncertainty – potential for clinical relevance - addressed by subsequent evaluation

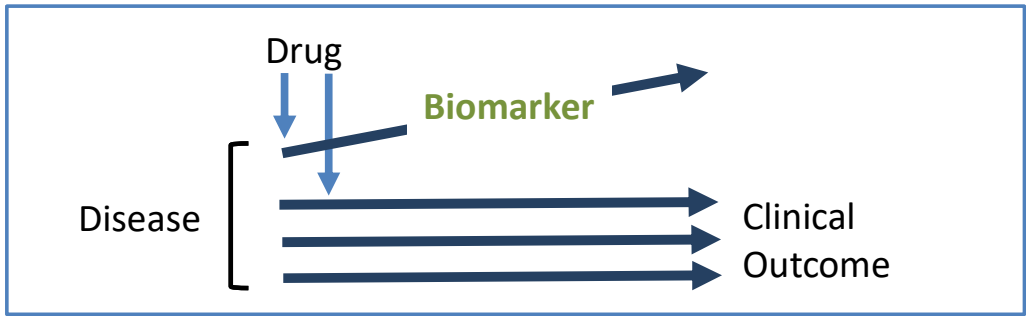
- Extent of structure-function understanding – how well *in vitro* functional assays reflect downstream drug response / efficacy
- Understanding of all mechanisms contributing to response – and "coverage" of in vitro functional assays for these MOAs.

- Availability of biomarkers that reflect MOAs
- Extent of support for PD BM in prediction of drug efficacy
- Whether all mechanistic pathways contributing to drug response adequately reflected in PD marker(s) used
- Overlap of exposure-response or dose-response of biosimilar and reference drug similar, including on **steep part** of the relationship?

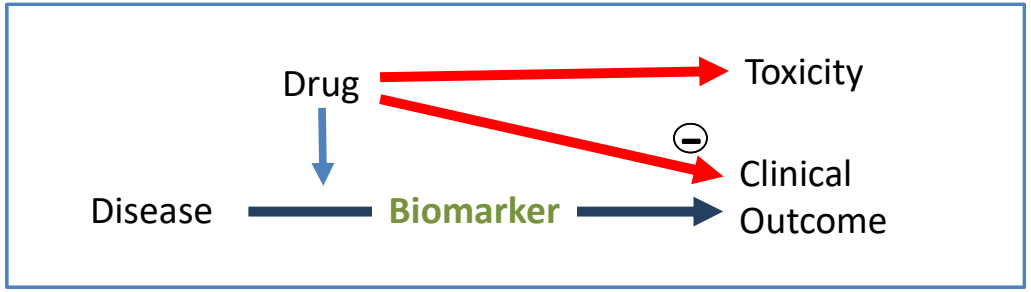
The limitations of biomarkers: complex relationships between *disease – biomarker – and clinical outcome*

- Biomarker on **causal pathway** modulated by drug
- Biomarkers may reflect changes induced by **outcome** of disease

- Biomarker ***not* on pathway** of drug MOA (so BM may only **indirectly** correlate with outcome)
- **Multiple disease MOAs** may lead to clinical outcome – and drug may impact only one



- Drug may induce **adverse effects on desired clinical outcome** through a pathway *not reflected* by BM
- May lead to other toxicities = BM does not adequately predict benefit / risk balance

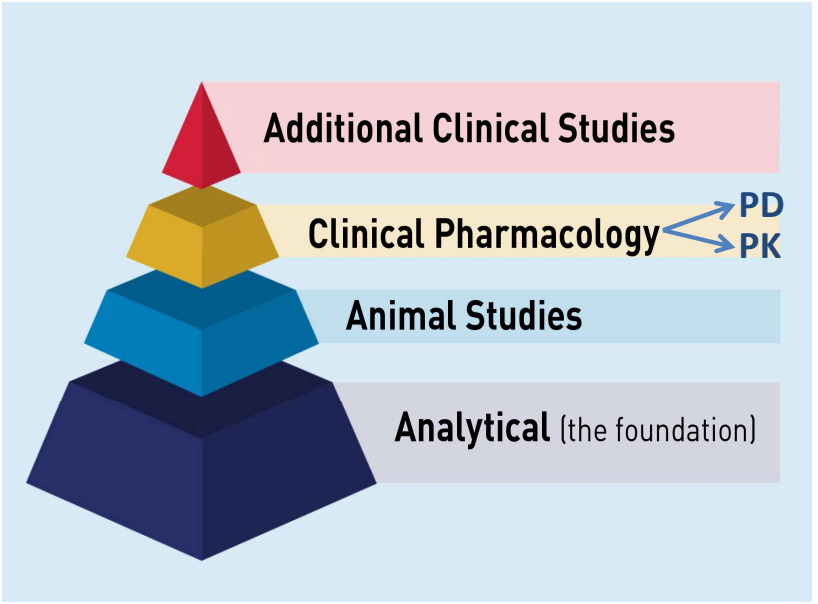


Often inability to separate prognostic biomarker from response biomarker

After Fleming Statistics in Medicine 2012

The role of PD biomarkers: evaluating residual uncertainty

- Intent of development programs for biosimilars (351(k)) to show biosimilarity – not establishing efficacy and safety (351(a))
- Starting with analytic structural assessment – the central component of biosimilarity evaluation
- Each "step" evaluated to determine extent of residual uncertainty – which then is to be addressed in subsequent steps
  - From analytic structural assessment→ to in vitro functional assessment→ to clinical PK→ to clinical PD → to clinical trials
  - Need to consider extent of residual uncertainty, specific issue resulting in uncertainty, and capabilities of subsequent step (e.g., clinical PD, comparative clinical study) to address uncertainty
- With increasing quality (and quantity with orthogonal approaches) of analytic assessment + PK may be sufficient



The role of PD biomarkers: evaluating residual uncertainty

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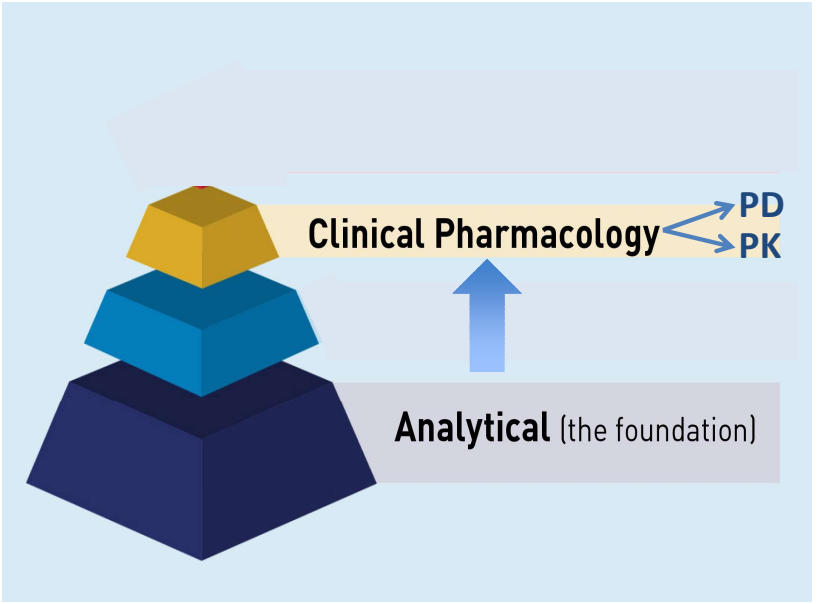


Biomarker selection: characteristics

- Time of onset and offset of biomarker response to drug
- Range of biomarker response relative to drug exposure
- Sensitivity to differences in reference drug activity – precision/variability in biomarker level
  - Wide range of PD biomarkers – generally greater variability vs drug concentration; assay variability may limit use to support biosimilarity
- Relevance of the biomarker to the drug MOA or MOAs
- Analytic validity of the biomarker assay

Interpreting biomarker response information

Uses/Value of pharmacodynamic biomarkers

- PD endpoints generally less variable than clinical endpoints – and may be obtained from HV studies
  - May be more sensitive to differences – use of the ascending part of the exposure-response relationship
  - May not be practical or ethical to use lower doses in comparative clinical study settings
- If MOA is well understood and biomarker is directly on the pathway from drug exposure to efficacy response, use of PD endpoint may support conclusion of biosimilarity
  - E.g., Insulin concentration – glucose uptake using insulin clamp
- Even without biomarker reflecting known primary drug pharmacology, pattern of multiple biomarkers reflecting different drug MOAs may provide reassurance that drug response is comparable, and supporting conclusion of structural and functional similarity

Interpreting biomarker response information

Limitations

- Potential for several distinct mechanisms to contribute to drug effectiveness
  - E.g., monoclonal antibody blocking a target receptor, + ADCC and + other F_c-related functions
  - All relevant mechanistic pathways may not be known – so relevant structural sites, functional assays may not be established
- PD endpoint assays may be variable, may be marked floor or ceiling effects such that "dynamic range" not sufficient
- Efficacy dose-response or efficacy exposure-response and biomarker exposure-response may not correspond – suggesting additional MOAs not "captured" by PD endpoint

Comparative clinical studies: uses and limitations

- With residual uncertainty, comparative clinical study may be needed
- Population, endpoint, sample size and study duration should be **adequately sensitive to detect differences**, should they exist
- Typically, an equivalence design would be used, but other designs may be justified
- *However*,
  - Variability of endpoint / practical issues in study sample size may limit bioequivalence margin, and assessment of "similarity"
  - The challenge is that the residual uncertainty may suggest a potentially meaningful but small clinical difference, and the study powering may be insufficient to detect small differences
  - So, using sensitive, relevant PD biomarkers, if possible, a better approach
- Assessment of immunogenicity is expected
- Results may be reassuring to physicians considering use of biosimilar product

Case in point: guidance on insulin biosimilar and interchangeable development

- Prior status: development of insulin biosimilar and interchangeable drugs included comparative clinical study – supporting assessment of immunogenicity
- Issue underwent detailed scientific assessment
  - Insulin is very well characterized, structurally uncomplicated, so analytic characterization may leave little residual uncertainty
  - Limited relevance of immunogenicity with insulin products
- Recommendations in guidance (Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products, Draft 2019)
  - In general, a comparative clinical study to assess immunogenicity not necessary (unless greater residual uncertainty based upon bioanalytic comparison)
  - Package to include detailed analytic comparison + comparative clinical PK/PD study
  - No additional studies necessary for IC, if very low residual uncertainty
- Illustrates potential to simplify the development program for a biosimilar and interchangeable product class

Thank You

Jian Wang

Health Canada

Health Canada Santé Canada

Canada

Canadian Perspectives on Using Pharmacodynamic Markers for Biosimilar Development and Approval

Jian Wang, MD, PhD
Division Manager, Clinical Evaluation Division – Radiopharmaceuticals and Haematology
Biologic and Radiopharmaceutical Drugs Directorate
Health Canada

Duke-Margolis/FDA PD Biomarkers Public Workshop

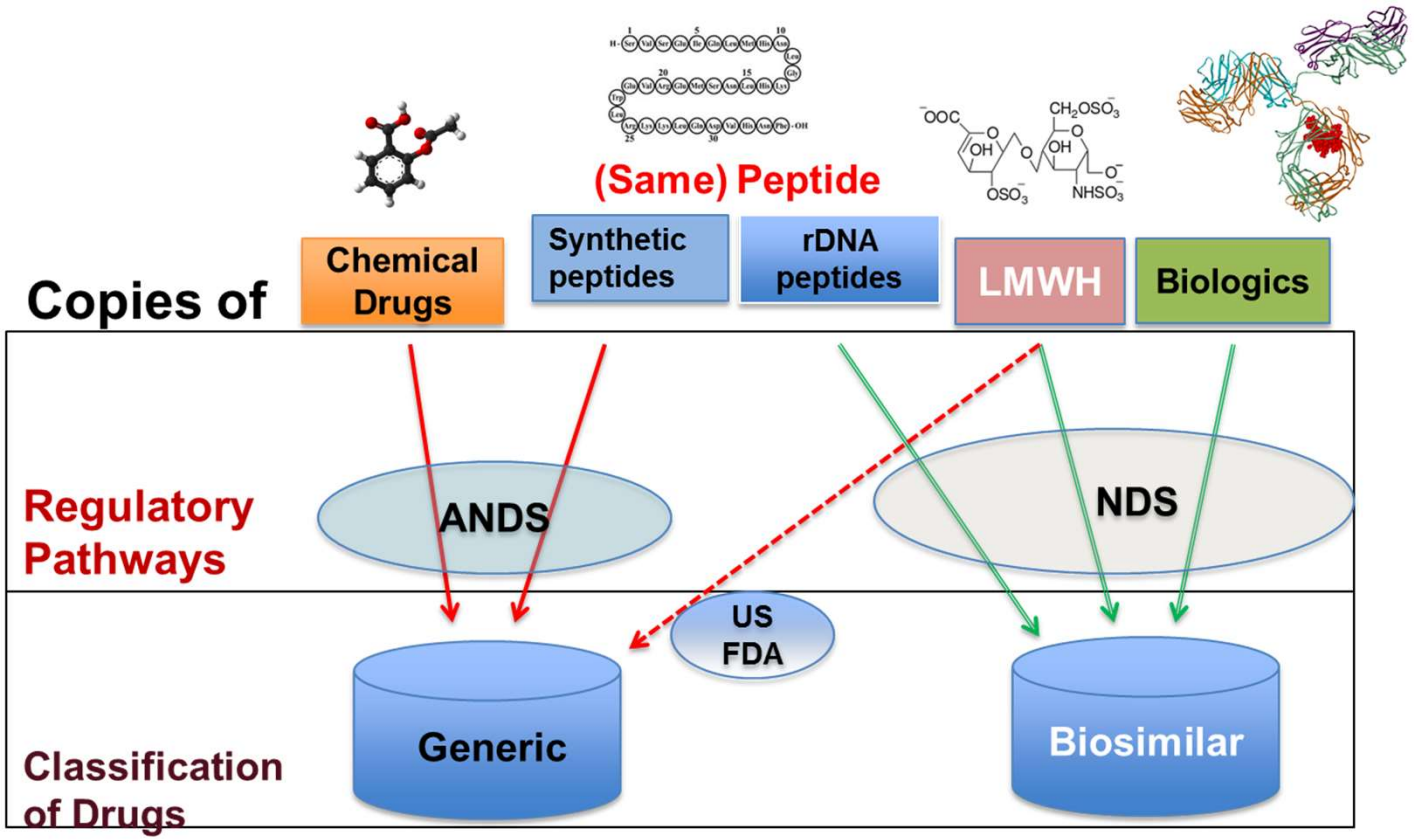
Sep 20 – 21, 2021

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Highlights

- General comparison between pharmaceuticals/generics and biologics/biosimilars
- PD endpoint in biosimilar studies
- Current Health Canada guidance, and agency's support for a flexible approach such as use of PD biomarkers
- Challenges in using novel PD biomarkers

Regulatory Pathways for Biosimilars in Canada



More Data Required for Biosimilars than Generics

	Biosimilars	Generics
Regulatory Pathway	New Drug or biosimilar pathway	Generic
Drug Substance	Identical amino-acid sequence to reference	Identical to reference (Pharmaceutical equivalence)
Comparative Dissolution Profiles	**Not required (injectable)**	**Required at 3 pH levels**
Structure characterization	**Comparable to reference**	
Function characterization	**Comparable to reference**	
Non-Clinical Study	**Reduced and comparable to reference**	
PK Profile	**Comparable PK profile to reference**	**PK equivalence to reference**
PD Profile	**Comparable PD profile to reference**	**Not required**
Efficacy	**No clinically meaningful differences**	
Safety/Immunogenicity	**No clinically meaningful differences**	
Indication	**May receive all indications of reference (switchable)**	**Receive all indications of reference (interchangeable)**

Canadian Guidance: Information and Submission Requirements for Biosimilar Biologic Drugs (2016)

Pharmacodynamic (PD) studies

- PD studies should be comparative in nature.
- Parameters investigated in PD studies should be clinically relevant.
- Use of a particular PD marker should be scientifically justified.
- PD markers should be relevant to the mechanism of action of the drug but may not need to be established surrogates for efficacy.
- In general, the principles regarding study design, conduct, analysis and interpretation that are relevant to equivalence trials with a clinical outcome as the primary endpoint are applicable to equivalence trials with a PD marker as the primary outcome.
- PD studies should be combined with PK studies, in which case the PK/PD relationship should be characterized.

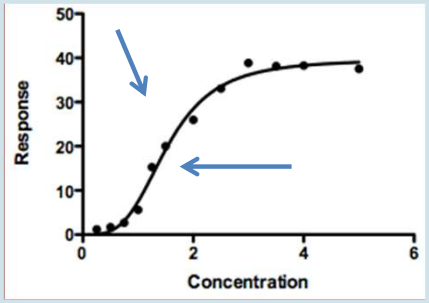
Canadian Guidance: Information and Submission Requirements for Biosimilar Biologic Drugs (2016)

Clinical efficacy trial(s)

- In most cases, a comparative clinical trial(s) is important to rule out clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic drug.
- A clinical efficacy trial may not always be necessary, e.g. where there is a clinically relevant PD endpoint. In such cases, a scientific justification is needed and safety as well as comparative immunogenicity data are still required.

Comparative PD Studies

- **Comparative PD data are desirable (if available) and can help to reduce residual uncertainty**

Clinical sensitivity	Assay sensitivity	Dosing sensitivity
PD (surrogate) marker should be clinically relevant e.g., absolute neutrophil count for a biosimilar G-CSF and be clinically validated The PD (bio) marker should be relevant to the mechanism of action	PD marker should be sensitive to PK changes Dose in the steep part of the dose-response curve should be considered 	A therapeutic dose for patients may induce a ceiling effect in healthy volunteers, thus masking potential differences • A lower dose may be required

PD Endpoint: Used or Proposed for PK/PD Study

Biologics	PD Endpoints
Filgrastim (G-CSF)	Absolute neutrophil count (ANC)
Insulin	Glucose infusion rate (Euglycaemic clamp test)
Epoetin	Hemoglobin levels
LMWH	anti-Fxa and anti-FIIa activity, and their ratio
Denosumab	C-terminal telopeptide of type I collagen (CTX)
Teriparatide	Serum calcium concentrations
alpha interferons	Early viral load reduction

PD Endpoint: Used and Proposed in Efficacy Study

Biologics	PD Endpoints
Trastuzumab	Pathological complete response (pCR)
Denosumab	Bone mineral density (BMD)
Rituximab	B-cell depletion and recovery in serum
Teriparatide	Bone mineral density (BMD)
Follicle stimulating hormone (r-hFSH)	Number of oocytes retrieved

- PD biomarkers are investigated as part of the comparative efficacy trial.
- A PD biomarker can be used to examine the link between drug regimen, target effect, and biological response.

PK/PD Endpoint Parameters: Not Harmonized

PK Endpoint

- Health Canada considers that the 90% CI of the geometric mean ratio of AUCt and the 90% ratio of Cmax of the test to the reference should be within 80.0% to 125.0%.

PD Endpoint

- Health Canada considers that the 95% CI, for mean ratio (test to reference) should be within the predefined acceptance limits of 80–125% or 95% CI is within the predefined equivalence margins.

PD Markers in Biosimilar Development Programs

- Progress in analytical science and accumulated experience with biosimilars continue to reshape regulatory requirements, generally leading to a reduced requirement for clinical trials. This trend is expected to continue.
- Biosimilar development programs have used PD endpoints to address residual uncertainties and/or detect clinically meaningful differences between a proposed biosimilar and the reference product.
- Current PD endpoints for products like filgrastim and insulin relate well to clinical outcomes (considered as PD surrogate), but for other products, PD end points—such as C-terminal telopeptide of type I collagen (CTX) with Denosumab—are less refined.
- As the purpose is to confirm similarity instead of establishing patient benefit, a correlation between the PD endpoints and clinical outcomes, while beneficial, is not a requirement.

PD Markers in Biosimilar Development Programs (con't)

- While PD biomarkers have not been prominently used across biosimilar approvals to date, there is opportunity to utilize such information alongside or in place of comparative clinical studies with efficacy end point(s) moving forward.
- New PD biomarkers need to be identified and explored so that biomarker data can be used in clinical pharmacology studies.
- To extend PD biomarkers beyond surrogate end points, it will be important to invest in evaluating and synthesizing available information from the literature, conduct pilot studies, complete model-based assessments, and investigate novel or emerging technologies.
- There are still challenges in using novel PD biomarkers, such as lack of or sparse historical data, assay sensitivity, setting the equivalence margin, and establishing adequate data requirements among others.

Potential Benefits of Using Biosimilars

Biosimilars offer stakeholders, including physicians, patients and payers - more choices when it comes to treatment options.

Thank you

Merci

Jian.wang@hc-sc.gc.ca

Elena Wolff-Holz

European Medicines Agency

Federal Institute for Vaccines
and Biomedicines

Paul-Ehrlich-Institut

www.pei.de

EMA: Current thinking on role of Pharmacodynamic Biomarkers for Biosimilar Development and Approval

Dr. Elena Wolff-Holz

The views presented here are my own and do not necessarily reflect the views of the Paul-Ehrlich-Institut or the European Medicines Agency.

The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

Current thinking on role of Pharmacodynamic Biomarkers

- Status Quo in Europe
- What have we learned from experience gained so far?
- Weighing the evidence

Optimization of **Biosimilar regulatory framework and registration process is a strategic priority in the EU regulatory agency agenda**

European Medicines Agencies network strategy to 2025; Annex 1:

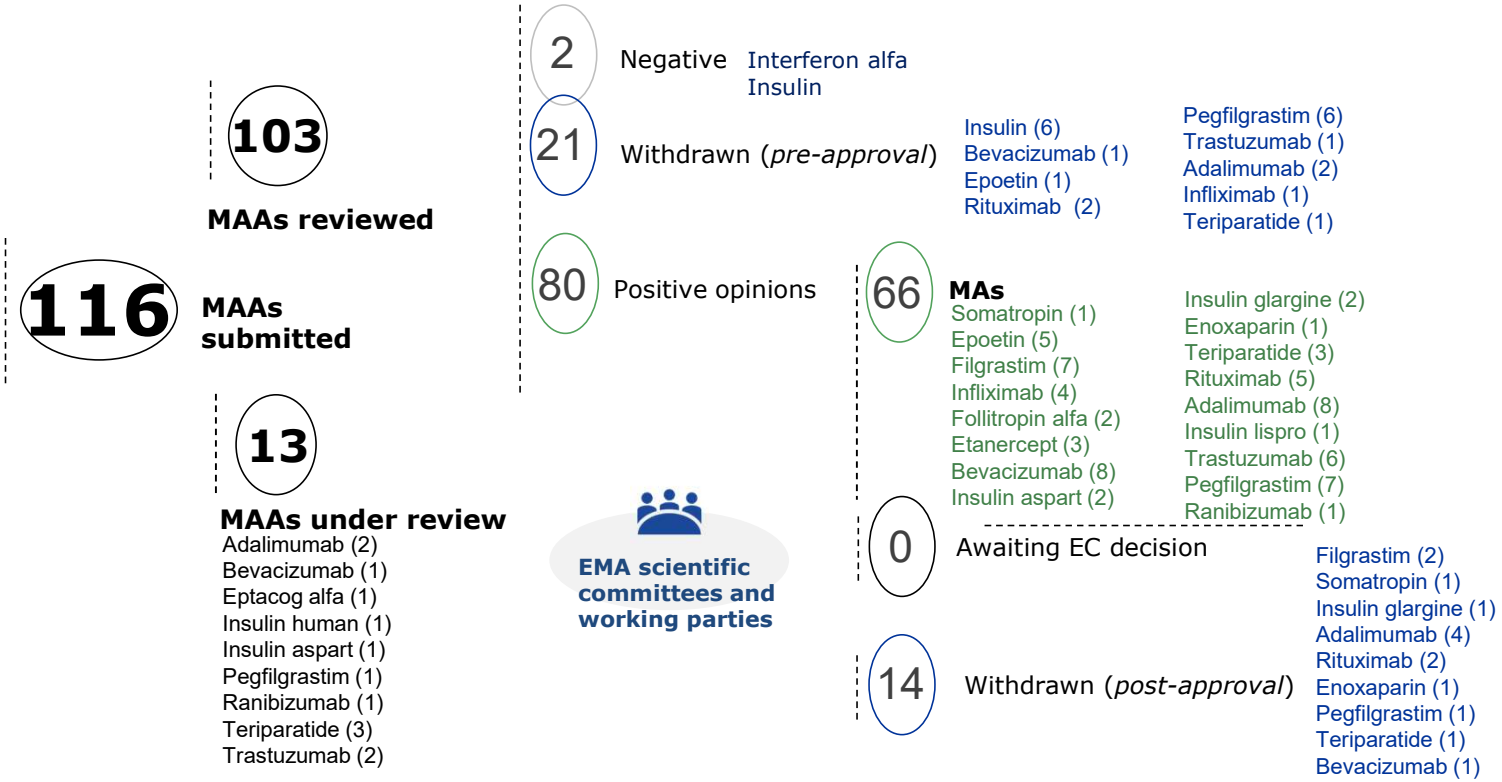
- Strengthen the availability of medicines to protect the health of European citizens (page 32/46)

EMA Regulatory Science 2025

- Section 3.3, page 30: The public health aim is to ensure that patients receive timely access to affordable medicines that meet their medical needs, and that all players involved in healthcare have the information they need to guide correct prescription and use.

- Section 3.3.7, Page 38: The EU is the world leader in biosimilar regulation and approval and shares this expertise cooperatively with regulators in other parts of the world. EMA is recommending that this knowledge base should continue to be developed, to ensure that quality, safe and effective biological medicines are available to EU citizens.

Biosimilars in Europe (16 September 2021)*



* Information on the EMA website

EMEA/CHMP/BMWP/42832/2005 Rev. 1

Current General Guideline: Clinical Issues

- PK + PD studies may replace efficacy study(ies), if for PD marker

  - Comparable dose-response or concentration-response relationship has been demonstrated (single and/or multiple dose studies)
  - A particular PD marker/biomarker is an accepted/validated surrogate marker or a combination of markers can be selected based on sound pharmacological principles, including dose/concentration sensitivity
  - Predefined equivalence margins are mandatory

Product-specific biosimilar guideline	Acceptance of a surrogate PD endpoint
R-IFN-a (interferon alfa) EMEA/CHMP/BMWP/102046/2006	**Pharmacodynamic fingerprint approach:** biological markers, e.g. expression of serum proteins as sensitive parameters even if mechanism of action unknown
R-IFN-b (interferon beta) CHMP/BMWP/652000/2010	Magnetic Resonance Imaging (MRI)
R-EPO (erythropoietins) EMEA/CHMP/BMWP/301636/08	Reticulocyte count and hemoglobin level
R–GCSF (granulocyte CSF) EMEA/CHMP/BMWP/31329/2005	Absolute neutrophil count for filgrastim products and pegfilgrastim products; CD34+ cells for filgrastim products in healthy volunteers
R-human insulin EMEA/CHMP/BMWP/32775/2005	Euglycemic clamp study: Glucose infusion rate for insulin glargine products
R-somatropin EMEA/CHMP/BMWP/94528/2005 Rev. 1	Insulin like growth factor IGF-1 (preferred), IGFBP-3. Current text: Due to the lack of a clear relationship between serum IGF-1 levels and growth response, IGF-1 is not a suitable surrogate marker for efficacy → Efficacy trial with change in height velocity as clinical outcome measure recommended

Currently discussed PD markers for monoclonal antibodies

	Substance	Model Indication	PD marker
1	Trastuzumab	Neoadjuvant breast cancer	pCR at surgery
2	Denosumab	Postmenopausal osteoporosis women	greater clinical relevance: lumbar spine BMD at 12 months
			Clear dose/response + larger dynamic range: bone resorption: serum C-terminal telopeptide of type I collagen, sCTX bone formation: serum procollagen type I N propeptide, sPINP), bone specific alkaline phosphatase (BSAP)
3	Eculizumab	Paroxysmal nocturnal haemoglobinuria (PNH).	proportion of serum lactate dehydrogenase Levels LDH (U/L) level at Week 12 < 1.5 × upper limit of normal (ULN)
4	Pertuzumab	Neoadjuvant breast cancer	pCR at surgery
5	Natalizumab	Mulitiple Sclerosis	MRI: patients without new gadolinium enhancing T1- lesions α4-integrin receptor saturation (?)

Differences or omissions in comparability exercise not precluding conclusion on biosimilarity

Table 2 Summary of differences or omissions in comparability exercise not precluding conclusion on biosimilarity

Reference	Quality	Functional	PK	PD	Clinical (E/S)	Immunogenicity	Regulatory outcome in EU
Remsima (infliximab)	Decreased % of afucosylated species	Decreased ADCC activity	✓	Supportive	✓	✓	Approved
Cyltezo (adalimumab)	✓	✓	Initial PK study failed	Supportive	✓	✓	Approved
Hyrimoz (adalimumab)	✓	✓	Initial PK study failed	Supportive	✓	✓	Approved
Terrosa (teriparatide)	✓	✓	90% CI of primary endpoints not covering unity	✓ (PD analysis included in PK study)	NA	NA	Approved
Efgratin (pegfilgrastim)	✓	✓	PK study failed	✓	✓	✓	Withdrawn
Ziextenzo (pegfilgrastim)	✓	✓	Initial PK study failed	✓ (PD analysis included in PK study)	✓	✓	Approved
Grastofil (filgrastim)	✓	✓	90% CI of some endpoints not covering unity	✓	NA	NA	Approved
Semglee (insulin glargine)	✓	✓	✓	Formally failed PD (AUCGIR 0–30 h and GIR max) due to several patients with very low PD response	✓	✓	Approved
Ontruzant (trastuzumab)	✓	✓	✓	NA	Failure to meet upper equivalence limit for 1st EP of clinical S/E trial	✓	Approved
Kanjinti (trastuzumab)	✓	✓	✓	NA	Failure to meet upper equivalence limit for 1st EP of clinical S/E trial	✓	Approved
Rixathon (rituximab)	✓	✓	✓	Supportive	Pivotal trial: 1st EP: ORR was met, uncertainty regarding 2nd EPs PFS, OS	✓	Approved
Truxima (rituximab)	✓	✓	✓	Supportive	Pivotal trial: 1st EP: ACR20 was met, uncertainty regarding 2nd EPs PFS, OS	✓	Approved
Flixabi (infliximab)	✓	✓	✓	Supportive	✓	Slightly increased ADA	Approved
Benepali (etanercept)	✓	✓	✓	✓	✓	Reduced immunogenicity	Approved

→ **Clinical efficacy data cannot overrule a failed PK trial**

→ **Formally failed PD study …due to several patients with very low PD response may be acceptable**

→ **A formally failed clinical trial may be acceptable depending on the totality of evidence**

Wolff-Holz, E. et al; BioDrugs 2019 https://doi.org/10.1007/s40259-019-00377-y

Weighing the evidence: PK versus PD versus Efficacy trial

e.g. Biosimilar Insulin; EMEA/CHMP/BMWP/32775/2005_Rev. 1

Class of drug	PK	PD	Efficacy	Safety/ Immunogenicity
Insulin	YES	Euglycaemic hyperinsulinaemic clamp technique: glucose-infusion rate (GIR) GIR-AUC(0-t) and GIRmax For primary PD parameters, the 95% confidence intervals of the ratio test/reference should be contained within the pre-defined equivalence margins. Possibility of considering PD endpoints as secondary (thus allowing descriptive analyses)	There is no anticipated need for specific efficacy studies since endpoints used in such studies, usually HbA1c, are not considered sensitive enough to detect potentially clinically relevant differences between two insulins.	In certain cases, a pre-licensing safety study including immunogenicity assessment may be waived.**

**

When biosimilarity between the biosimilar and the reference insulin can be convincingly concluded from the physicochemical and functional characterisation and comparison using sensitive, orthogonal and state-of-the-art analytical methods, and from the comparison of the pharmacokinetic and pharmacodynamic profiles. These data would already provide sufficient reassurance that adverse drug reactions which are related to exaggerated pharmacological effects (e.g. hypoglycaemia) can be expected at similar frequencies. Secondly, the impurity profile and the nature of excipients of the biosimilar do not give rise to concerns. Appropriate scientific justification for waiving a safety/immunogenicity study should always be provided.

Weighing the evidence: PK versus PD versus Efficacy trial

Comparability exercise without PK possible?	Yes !
	intra-ocular administration of aflibercept
	intra-ocular administration of ranibizumab
PK „without“ PD possible in principle?	Yes !
	Insuline glargine, Semglee, 2018
Efficacy trial still necessary	For Mabs: 18 of 23 substances no defined or agreed marker(s) yet
PD without PK possible?	Yes !
	LMWH: PK not measurable PD: at least Factor Xa and Factor IIa
	Romiplostim: unacceptable PK variability PD: thrombocyte count

Weighing the evidence

Tailored Scientific Advice (Adopted by CHMP (February 2021)

Convincing Quality package + **PK or PD or PK/PD**

+/- additional efficacy data

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- Ana Hidalgo-Simon, European Medicines Agency
- Antonella Baron, European Medicine Agency

Session 5: Panelists

- **Abhijit Barve,** Viatris Inc.
- **Janet Franklin,** Amgen Inc.
- **Shiew-Mei Huang,** U.S. Food & Drug Administration
- **Shinichi Okudaira,** Pharmaceuticals and Medical Devices Agency
- **Peter Stein,** U.S. Food & Drug Administration
- **Jian Wang**, Health Canada

Concluding Remarks

Mark McClellan, Duke-Margolis Center for Health Policy

David Strauss, U.S. Food and Drug Administration

Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at
dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

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