Pharmacodynamic (PD) Biomarkers for Biosimilar Development & Approval

BsUFA Research Activities

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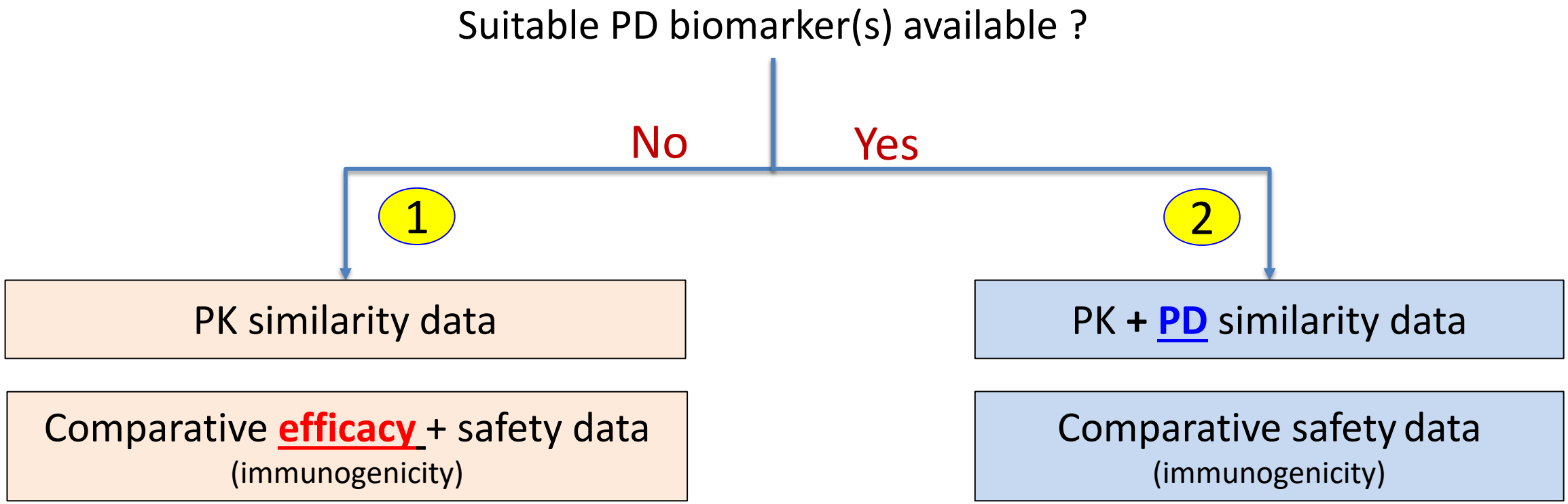
OTS/CDER/FDA

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.

Biosimilar approvals can rely on PD biomarker data



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

The use of PD biomarkers can enable more efficient, streamlined biosimilar programs

- Comparative efficacy studies (CES) are more costly (larger study with longer duration)
- PD similarity studies have smaller numbers of subjects, shorter durations, lower cost, and often can be conducted in healthy subjects
- PD endpoints are more sensitive than clinical efficacy endpoint for detecting clinically meaningful differences

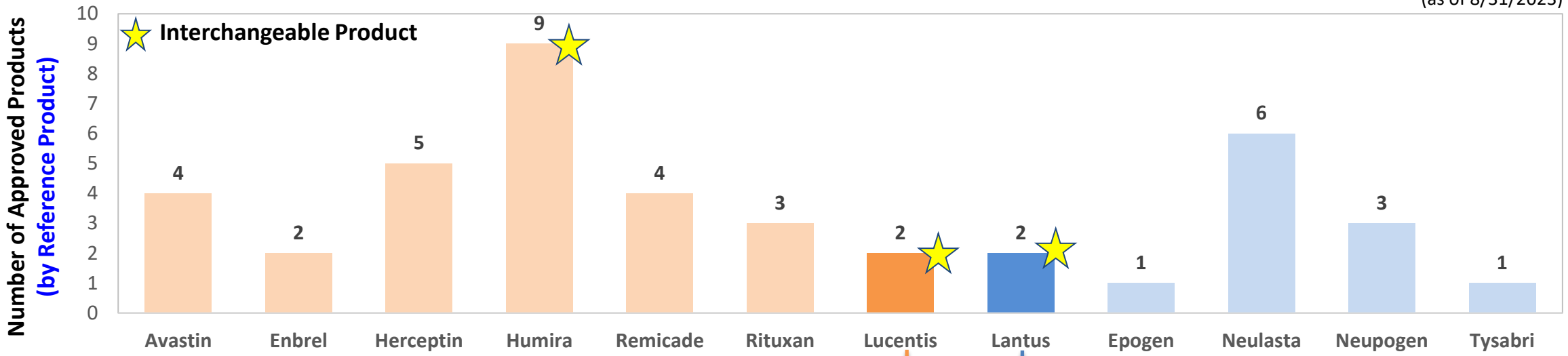
Products approved by Oct. 2019 (Moore et al.)	No. of Trials	No. of Biosimilars	Median (Inter-Quartile Range)		
			No. of subjects	Treatment duration (wk)	Estimated cost[a]
Overall	29	23	504 (258-612)	52 (28-68)	20.8 (13.8-35.3)
2 **PK-PD similarity study**	**5**	**2**	**122 (60-256)**	**15 (14-15)**	**1.9 (1.6-1.9)**
1 **CES**	**24**	**21**	**538 (372-644)**	**55 (46-78)**	**27.6 (18.0-36.7)**

[a] *In millions of US dollars*

Source: Moore T.J. et. al, Assessment of Availability, Clinical Testing, and US Food and Drug Administration Review of Biosimilar Biologic Products, JAMA Intern Med., 2021, 181, 1.

PD biomarker data supported demonstration of biosimilarity for 13 of 42 FDA-approved biosimilar products

(as of 8/31/2023)



N=29

1

PK similarity data ✗

Comparative **efficacy** + safety data ✓
(immunogenicity)

N= 13

2

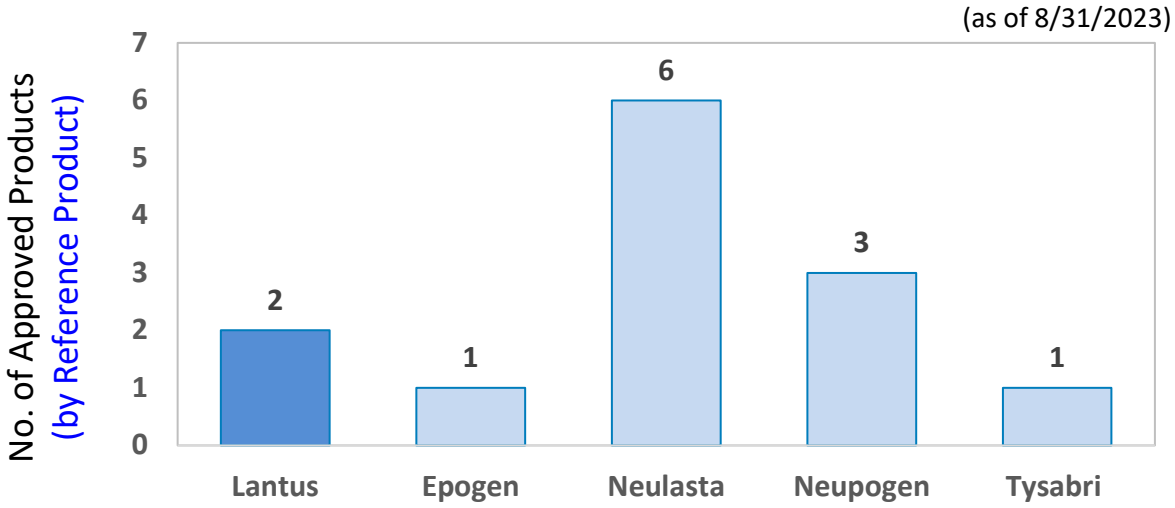
PK + **PD** similarity data ✓

Comparative safety data ✗
(immunogenicity)

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

See the FDA's Purple Book for lists of licensed biological products, with reference product exclusivity and biosimilarity or interchangeability evaluations
https://go.usa.gov/xz6Ud

Support biosimilar approval using ≥1 PD biomarker(s)



Five characteristics of PD biomarkers (FDA guidance)

1. Relevance to mechanism of action (MoA)
2. Sensitivity to differences between products
3. Dynamic range
4. Time of onset & return to baseline (temporal profile)
5. Analytical validity of the biomarker assay

Glucose infusion rate (SD)

Reticulocyte count (SD)

Hemoglobin level (MD)

Neutrophil counts (SD)

CD34+ cell count (MD)

CD19+ cell counts (SD)

CD34+ cell count (SD)

MAdCAM-1 level (SD)

VCAM-1 level (SD)

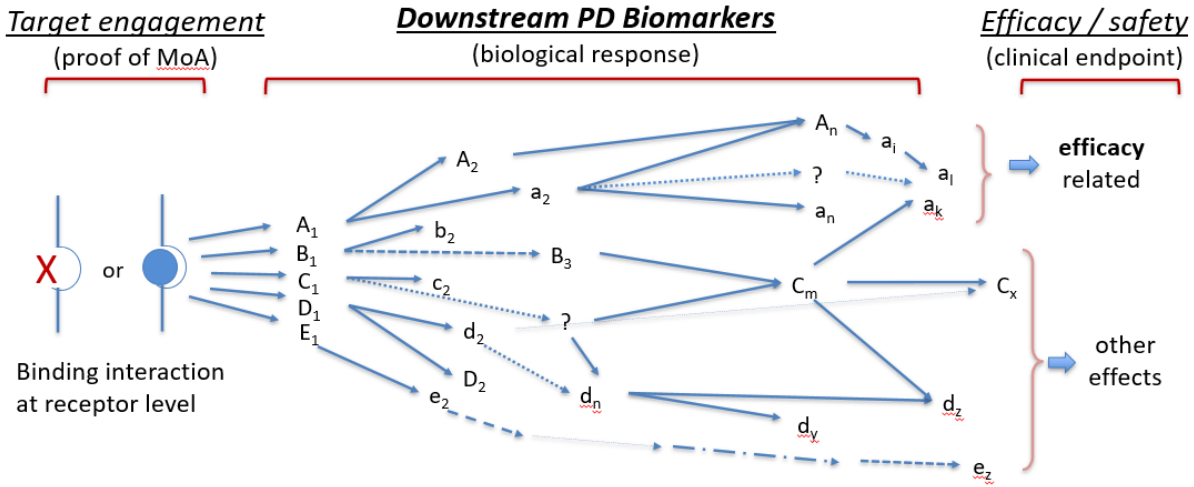
Receptor occupancy (SD)

SD: single dose study; MD: multiple dose study

To seek PD biomarker (one or multiple) for biosimilar programs

- One can leverage literature knowledge to find potential PD biomarkers
- A good understanding of MoA may reveal opportunities for multiple PD biomarkers
- Suitable PD biomarkers are **not** required to reflect clinical efficacy

➢ PD similarity results provide confidence on similarity in pharmacological response (at a lower cost vs. comparative efficacy studies); an important option for some products

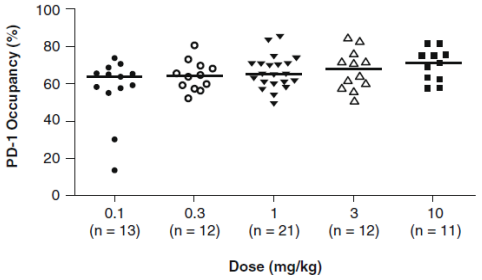


Abbreviation – MoA: mechanism of action

Suitability of target engagement (TE) biomarkers ?

An example of OCP research projects

- Objective: to evaluate the congruence of two doses: (1) *the **projected efficacious dose** using TE biomarker response* data, (2) *the **approved dose** in the product labeling*
- Dataset: 25 out of 223 products (11%) had TE biomarker response data to inform dose selection for pivotal studies (source of primary evidence to support drugs' effectiveness)
- 5 of them are immune-checkpoint inhibitors: TE biomarker = receptor occupancy (RO)
- Findings from these 5 immune-checkpoint inhibitors
  - The incongruence in two doses was up to 33-fold
  - The TE projected efficacious dose < the approved dose
  - Agrawal et al. reported: RO saturation in blood occurs at low nivolumab doses & with limited dose-response (2016, PMID: 27879974)



TE biomarker responses observed in blood may not represent those in target tissues

OCP conducted clinical studies to inform best practices on designing pilot clinical studies and analyzing PD data

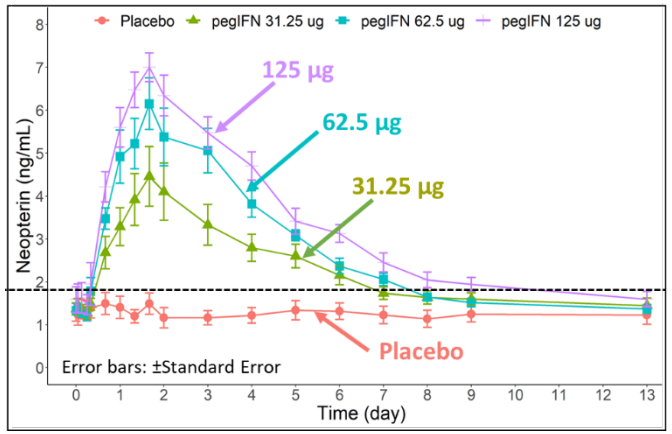
- Study drugs: (1) alirocumab/evolocumab, (2) mepolizumab/reslizumab, (3) interferon/peginterferon β-1a
- PD biomarkers: showing different degrees of association with efficacy endpoints
- PD endpoints: area under the effect curve (AUEC), maximum observed effect
- Study groups: placebo, single dose of drug@3-4 levels, n=8-12 healthy subjects /group

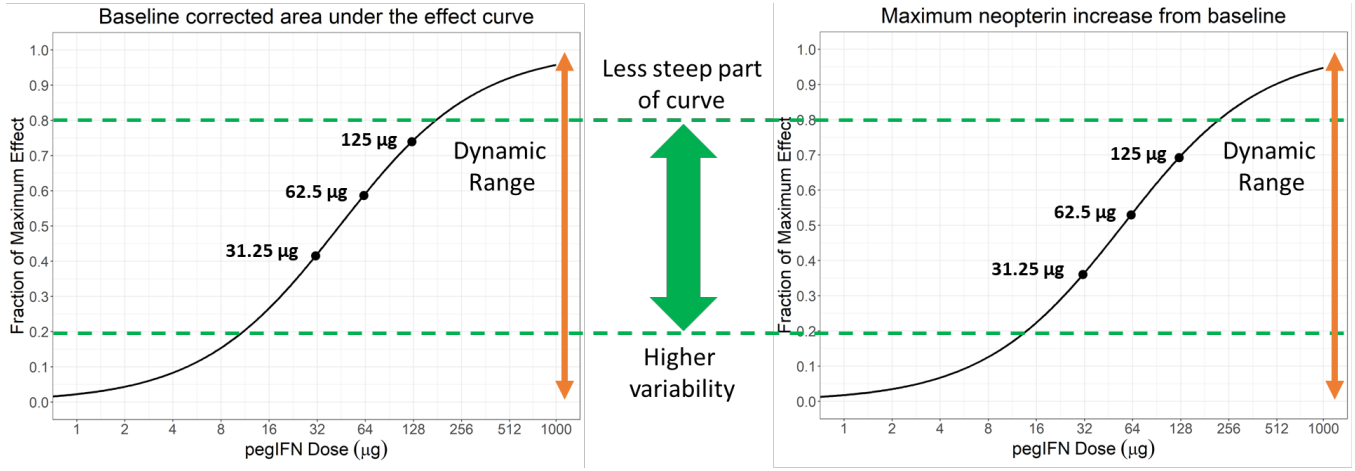
	Therapeutic Class	Mechanism of action (MoA)	Type of Biomarker(s) ~ vs. Efficacy endpoint(s) ~	Example PD biomarkers
1	PCSK9 Antagonist	Well-understood	PD biomarker = surrogate endpoint	LDL-C, ApoB
2	IL-5 Antagonist	Relatively well-understood	PD biomarker ≠ a surrogate endpoint	Eosinophil
3	Interferon β-1a	Complex, difficult to determine precise MoA	PD biomarker shows drug activity, initiates a complex signaling system	Neopterin, MxA

Abbreviations: PCSK9: Proprotein convertase subtilisin/kexin type 9 serine protease; IL-5: Interleukin-5; LDL-C: low density lipoprotein cholesterol; ApoB: Apolipoprotein B; MxA: myxovirus resistance protein 1

Best practices informed by the pilot clinical studies (1)

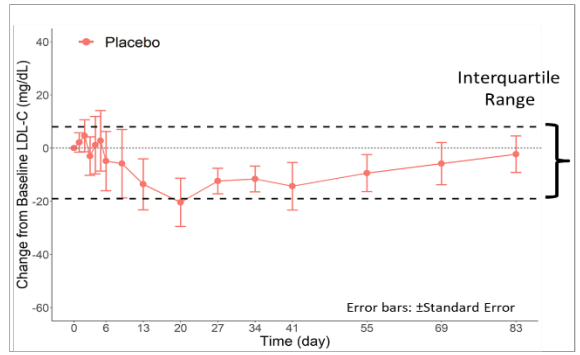
- Evaluate a range of doses & assess dose-response relationship with modeling and simulation tools
- Consider the variability of PD biomarkers at baseline and without any treatment
- Select a dose with a robust PD response above the biological variabilities and not at the plateau of the dose-response curve for the PD similarity study

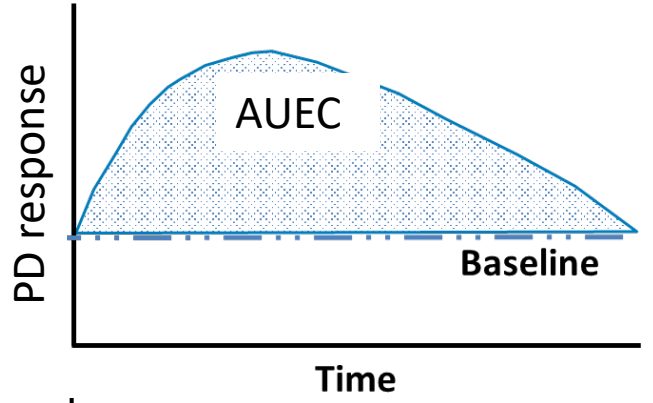


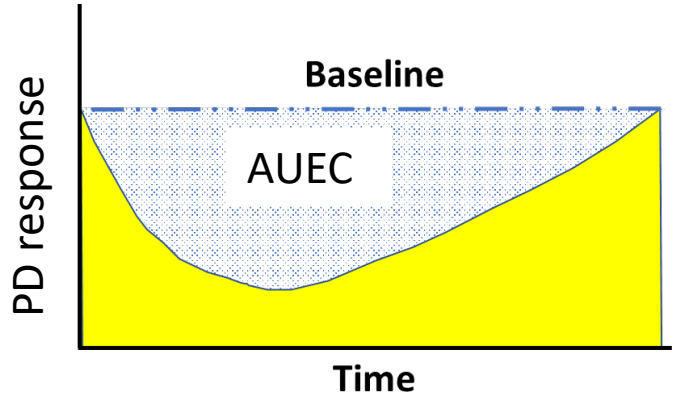


Best practices informed by the pilot clinical studies (2)

- Baseline adjustment may be needed to assess the magnitude of PD responses as PD biomarkers have endogenous level even without any treatment
- Collecting multiple baseline measurements is important to derive a baseline level to calculate the baseline-adjust PD responses - addressing the variability at baseline
- PD response profiles over time support two PD endpoints: area under the effect curve (AUEC), maximum effect
- The AUEC of PD response calculated based on the change from the baseline (the blue shaded area) is appropriate
- More information can be found in our 2023 publications in Clinical Pharmacology and Therapeutics:
  PMID: 36282186, 36184697, 36324229







Summary

- PD similarity data can be used in lieu of comparative efficacy data for biosimilar approvals to increase the efficiency of biosimilar development
- PD similarity results provide confidence on similarity in pharmacological response without a clinical comparative efficacy study
- Literature contains rich information about PD biomarkers to be explored for use to support biosimilar development and approval
- Thoughtful evaluations of suitability of PD biomarkers are necessary
  - Refer to FDA guidance entitled *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (2016)
- FDA's research activities aim to facilitate a more streamlined clinical program for biosimilar development with increasing use of PD biomarker data to support biosimilar approvals

Resources on FDA's efforts on advancing biosimilar development – from workshops to a themed issue of CPT journal (Jan. 2023)

Biosimilars Workshops

Innovations in Biosimilars

16 articles published

Clinical Pharmacology & Therapeutics Themed Issue (January 2023)

Canada

India

Biosimilar developers

Europe

Pharmaco-economics

Japan

US

US

- Included global stakeholder viewpoints
  - industry (biosimilar developers),
  - regulatory agencies,
  - academia,
  - practicing physicians
  - pharmaco-economics community
- Available podcasts on
  - ClinPharmPod (CPT's channel)
  - SBIA (CDER Small Business and Industry Assistance Chronicles)
    - https://ascptpod.com/podcast/building-on-biosimilars/
    - https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/role-pharmacodynamic-biomarkers-biosimilar-drug-development