Introduction
Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality: Regulatory and Industry Perspectives

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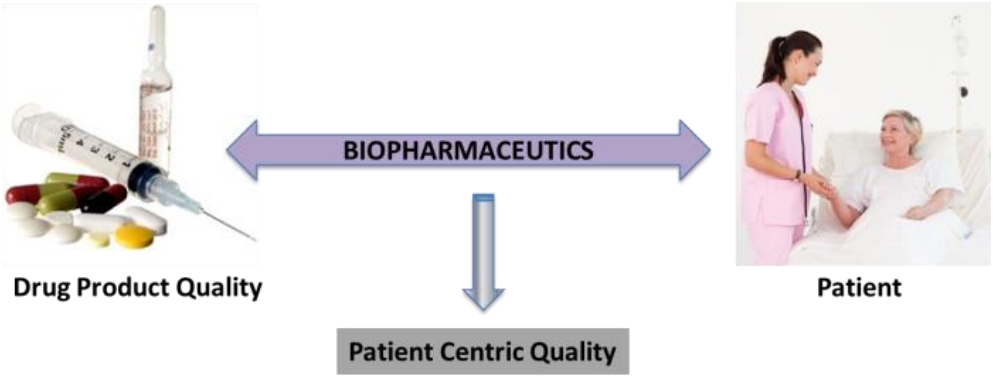
Disclaimer

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


Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

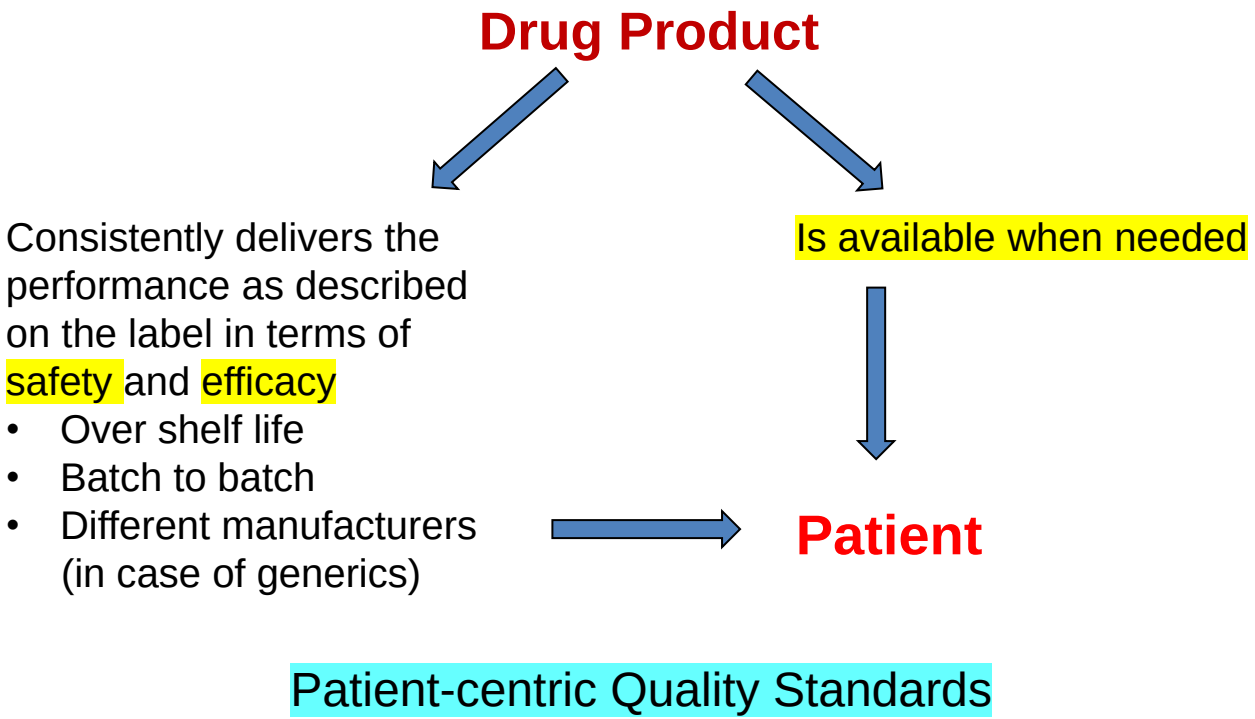
Biopharmaceutics

Biopharmaceutics is the study of the physicochemical properties of a drug, the dosage form, and the route of administration on bioavailability (rate and extent of absorption) which further determines the onset, duration, and intensity of drug action*



*Adapted from Shargel and Yu's Applied Biopharmaceutics and Pharmacokinetics

Patient Centric Quality



Patient-centric Quality Standards

Patient Centric Quality Standards

- Patient-centric quality standards can be defined as a set of criteria and acceptance ranges to which drug products should conform in order to deliver the therapeutic benefit (safety and efficacy) indicated in the label

- Patient-centric quality standards can increase flexibility within the pharmaceutical manufacturing sector while maintaining quality by establishing acceptance criteria based on clinical performance, instead of process capability or manufacturing process control

- Patient-centric quality standards avoid under- or over-discriminating specifications; both of which are contrary to patient needs and interests

Adapted from L. Yu's "Patient Centric Specifications for Small Molecules: An FDA Perspective" 2021 ISPE Patient-centric Specification Webinar

Patient Centric Quality Standards: Obstacles

- Link between in vitro and in vivo often missing or weak
  - QC dissolution often lacks biorelevance
  - Biorelevant dissolution may not be biopredictive
  - Animal study results often cannot predict human clinical performance
  - Clinical BA studies to evaluate every critical bioavailability attribute impractical and expensive

Physiologically-based Biopharmaceutics Models (PBBM)

- Subset of Physiologically-based Pharmacokinetic Models (PBPK) that is specific for Biopharmaceutics applications; >10 years regulatory history
- Mechanistic; integrates physicochemical properties of API and drug product, and dissolution as well as GI physiological parameters to predict in vivo exposures
- Can provide crucial link between in vitro and in vivo to establish patient-centric quality standards, if model building and validation are performed appropriately

Applications of PBBM

- Establishment of patient-centric quality standards
  - Dissolution method and acceptance criteria; dissolution safe space
  - Critical material attributes and process parameters that can affect bioavailability: Critical bioavailability attributes (CBAs)
    - E.g., particle size distribution, polymorphism, crystalline content, granule properties
- Supportive evidence for biowaivers (e.g., virtual bioequivalence trials)
  - SUPAC Level 3 changes (formulation, manufacturing process, site etc.)
  - Additional strength
- Model-based alternative BE approaches: Potentially in the future??

Prior Workshops on PBBM

- FDA/M-CERSI Workshop on Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development: May 15-17, 2017
  - Focused on dissolution and its utility in predicting in vivo performance, clarify dissolution terminologies, initial PBBM case study presentations from industry and regulators and approaches to set clinically relevant drug product specifications
- REdI (FDA)/M-CERSI Workshop on Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls: September 23-25, 2019
  - Focused on biopredictive dissolution methods; initial discussions on best practices in model development, verification and validation; case studies exemplifying PBBM applications

Draft FDA Guidance on PBBM

- The Use of Physiologically Based Pharmacokinetic Analyses – Biopharmaceutics Applications for Oral Drug product Development, Manufacturing Changes, and Controls: October 2020

  – Provides FDA's current thinking on the development and evaluation of PBPK models for Biopharmaceutics Applications (PBBM) as well as applications of these models to support product quality before and after product approval

Why Another PBBM Workshop? Objectives and Outcomes

- Science continues to advance; need to continue scientific discussion
  - E.g., Dissolution input models
- Knowledge and experience gained since the previous workshop need to be shared for scientific understanding
  - Key feature: Case study presentations by scientists from nine regulatory agencies
- Need to continue discussion on best practices related to model input (in vitro/in vivo), validation, and application (during product development and post-approval) due to,
  - Different expectations from industry and regulators
  - Potentially different expectations between regulators
- Explore new applications of PBBM: PBBMs in generics, MR products, virtual BE
- Explore areas of agreement; lay groundwork for future harmonization efforts
- Draft and submit three manuscripts for publication based on each workshop day theme

Workshop Themes

- Day 1: Best practices for in vitro data inputs into PBBM
  - Morning session: Regulator case study presentations
  - Afternoon session: Breakout sessions A-E
- Day 2: Best practices for in vivo data inputs, validation and applications steps for PBBM
  - Morning session: Regulator and industry case study presentations
  - Afternoon session: Breakout sessions F-I
- Day 3: Applications of PBBM; current state and new horizons
  - Morning session: Regulators' PBBM experience, PBBM in generics development, PBBM from clinical pharmacology perspective, PBBM for MR products
  - Afternoon session: Breakout sessions K-N

Regulatory Acceptance of PBBM: Overarching Issues

- Lack of PBBM strategy and planning in early drug product development; afterthought at late stage or post-approval
  - Inadequate model input and validation
- Data treatment to fit clinical outcomes
  - Lack of biological plausibility
    - E.g., Adjusting colon pH from basic to acidic
  - At what point does it cease to be a mechanistic model and become an empirical model?

Acknowledgments

- Workshop Organizing Committee
- OPQ, OCP, and OGD management
- Division of Biopharmaceutics colleagues (current and former)
- Special Thanks to
  - Dr. Paul Seo
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  - Dana Hammell
  - Gregory Rullo

Housekeeping and Logistics

- Light breakfast will be served each day, from 8am on Tue and Wed, and from 7:30am on Thurs.
- Restrooms are located outside this ballroom (Room 1400) and towards the left.
- PDFs of speakers' slides will be posted to a website within three (3) weeks of the workshop. Attendees will be emailed when such presentations are available.
- In-person attendees can approach a microphone to ask a question.
- Nametags indicate to which afternoon breakout session you have requested or assigned, each day. Breakout session assignments will also be listed near the respective rooms and at the registration table. Room numbers of each breakout session are listed in the agenda. There are both an elevator and stairs on the second floor, which are to the left when you exit this Ballroom-1400.
- Wi-Fi login information is included at the bottom of the agenda, along with QR code for accessing the bio document.

Keynote Speaker Introduction

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