Challenges of Developing Biopredictive in vitro Characterization to Correlate Quality Attributes to in vivo Performance

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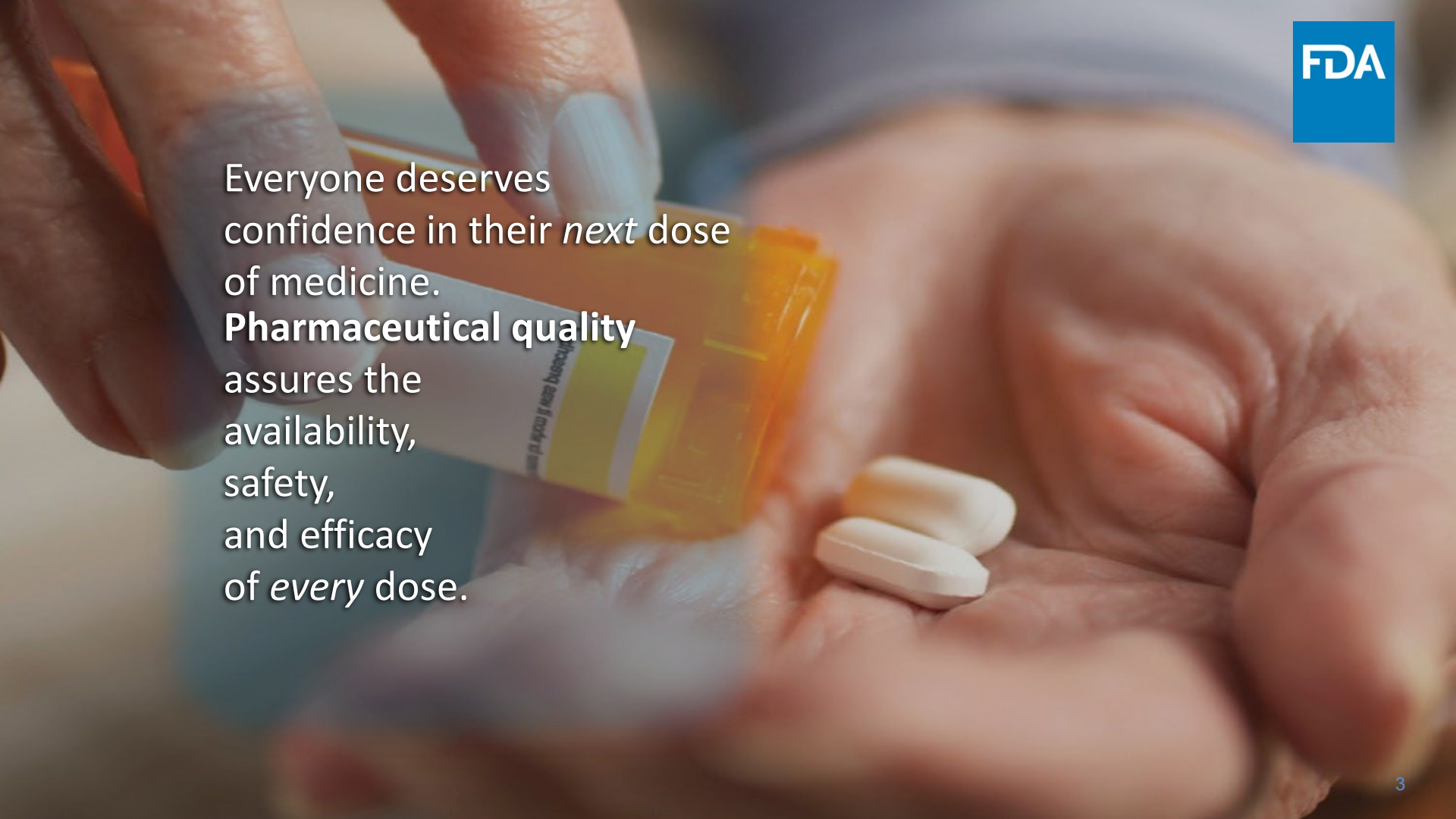
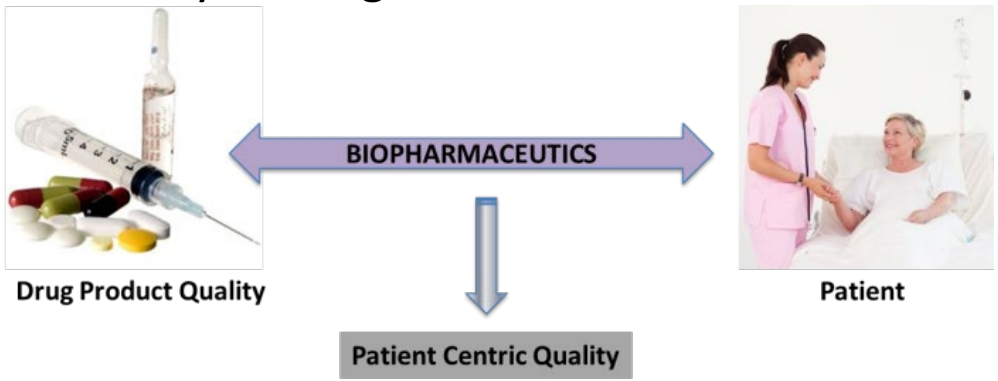

Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

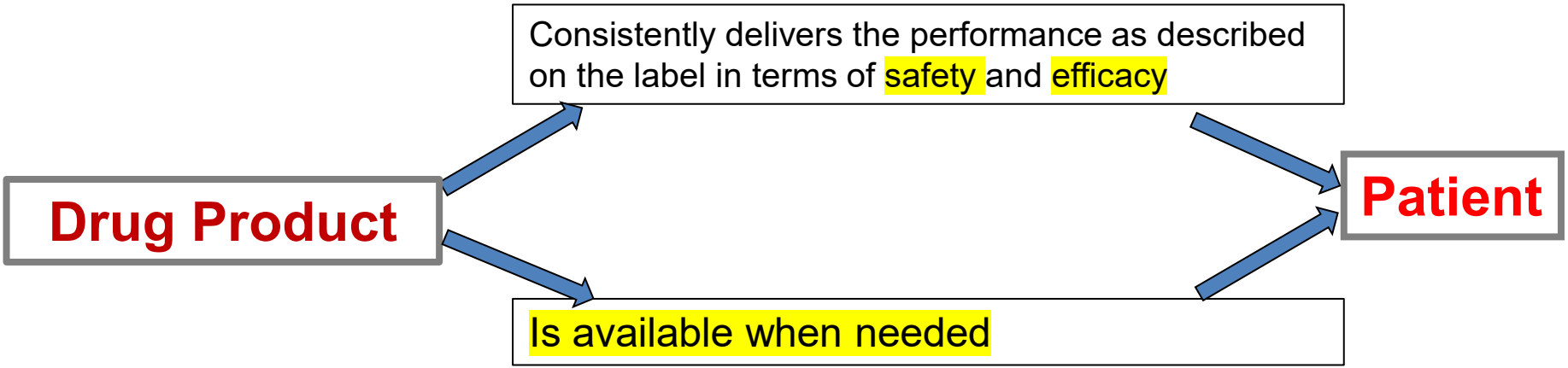
Biopharmaceutics

Biopharmaceutics examines the interrelationship 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



Adapted from B. Rege's "Introduction - Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality: Regulatory and Industry Perspectives" August 29, 2023, M-CERSI/FDA Workshop "Physiologically Based Biopharmaceutics Modeling (PBBM) Best Practices for Drug Product Quality"

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
  - Quality control tests often lack biorelevance
  - Biorelevant test 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

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Patient Centric Quality Standards: Obstacles

- Even more challenging for local acting complex drug products (such as oral inhalation product)

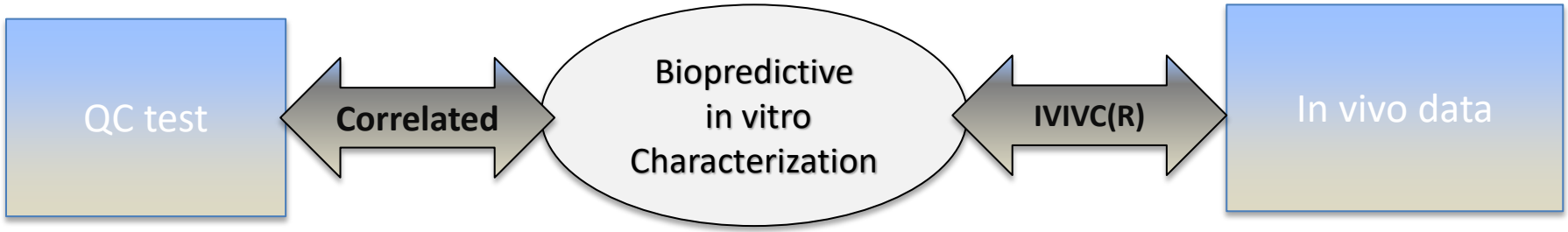
PSG for Albuterol sulfate aerosol inhalation
For Q1/Q2 formulation
Six in vitro tests:
1. SAC
2. APSD
3. Spray pattern
4. Plume Geometry
5. Priming and repriming
6. Realistic APSD
Two in vivo BE studies with PK endpoints (with and without Charcoal block)

For non Q1/Q2 formulation
Five in vitro tests (1-5)
One in vivo PD BE studies

- Identification of clinically relevant quality attributes
- In vitro testing methods and data interpretation
- Lack of meaningful in vivo data to be correlated to in vitro characterization
- Scarcity of IVIVR (C) research

Biopredictive in vitro Characterization

- Biopredictive in vitro characterization refers to laboratory techniques and methods designed to simulate and predict the behavior of pharmaceutical compounds in the human body.

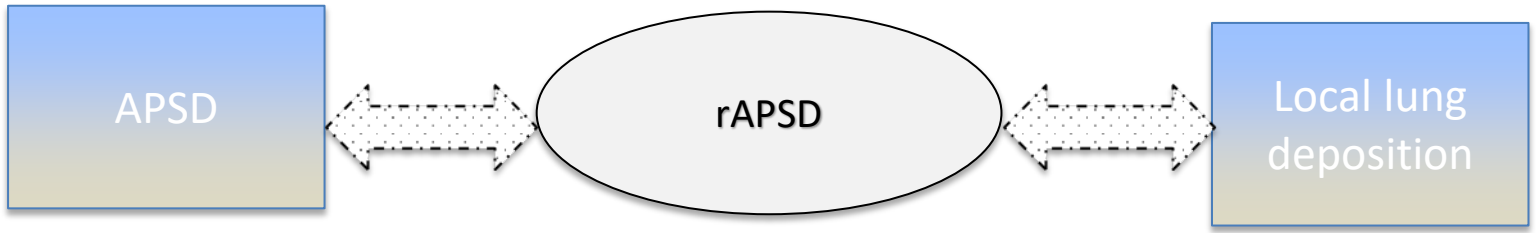


An example: pMDI - APSD vs rAPSD

- used in judging product quality and performance
- USP <601>

- More clinically relevant conditions
- Take patient variability into consideration

- Local bioavailability
- corelated to efficacy



- Lack of research to correlate APSD to rAPSD

- Challenges associated with rAPSD method and data interpretation
- Lack of local lung deposition data

Biopredictive in vitro Characterization

-Research Gaps and Opportunities

Research gaps are obvious!

- Research is needed to correlate in vitro characterization to clinical performance.
- Research is needed to establish safe space for clinically relevant quality attributes.

Research opportunities for

- ✓ Developing and validating biorelevant models
- ✓ Modeling/simulation

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