U.S. FOOD & DRUG ADMINISTRATION

Challenges and Strategies in Establishing an *In Vitro-In Vivo* Link

UMB CERSI/FDA Conference: Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development

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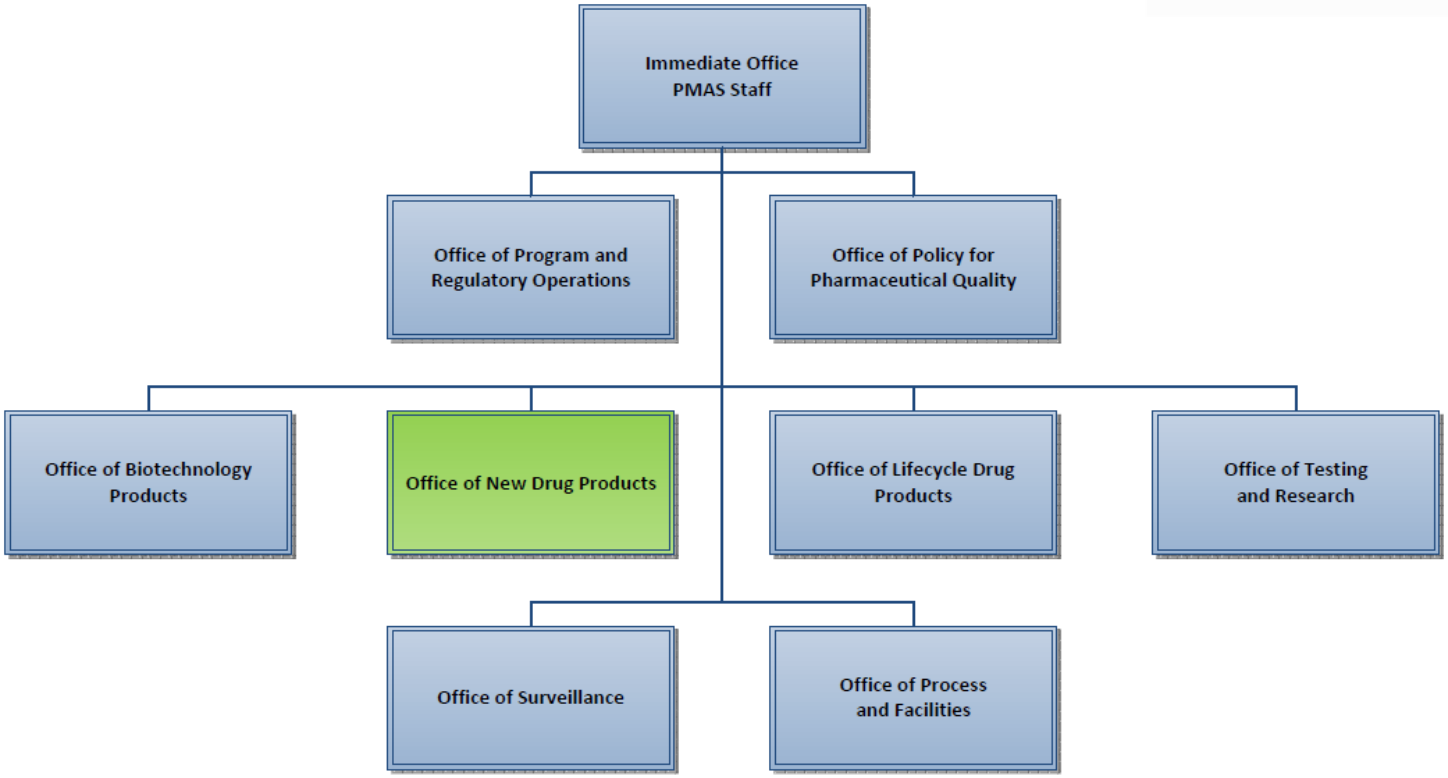
Paul Seo, Ph.D.
Division Director
OPQ/ONDP/Division of Biopharmaceutics

Outline

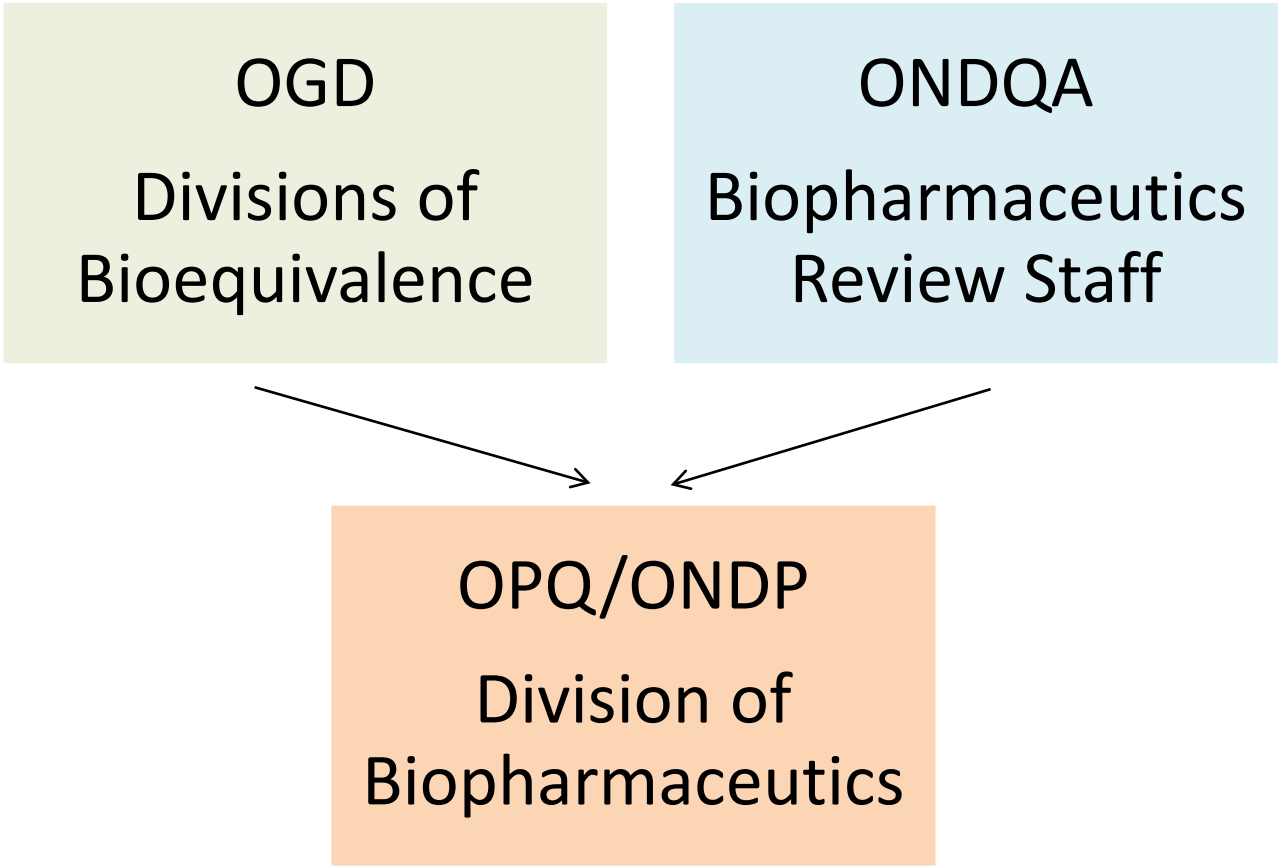
- Division Organization and Responsibilities
  - OPQ Standup
  - A historical perspective
- Clinical Relevance/Specifications and Dissolution
- Current State
- In Silico Modeling: PBPK
- Challenges
- Conclusions/Questions

THE OFFICE OF PHARMACEUTICAL QUALITY



A historical perspective

- Biopharmaceutics discipline at FDA



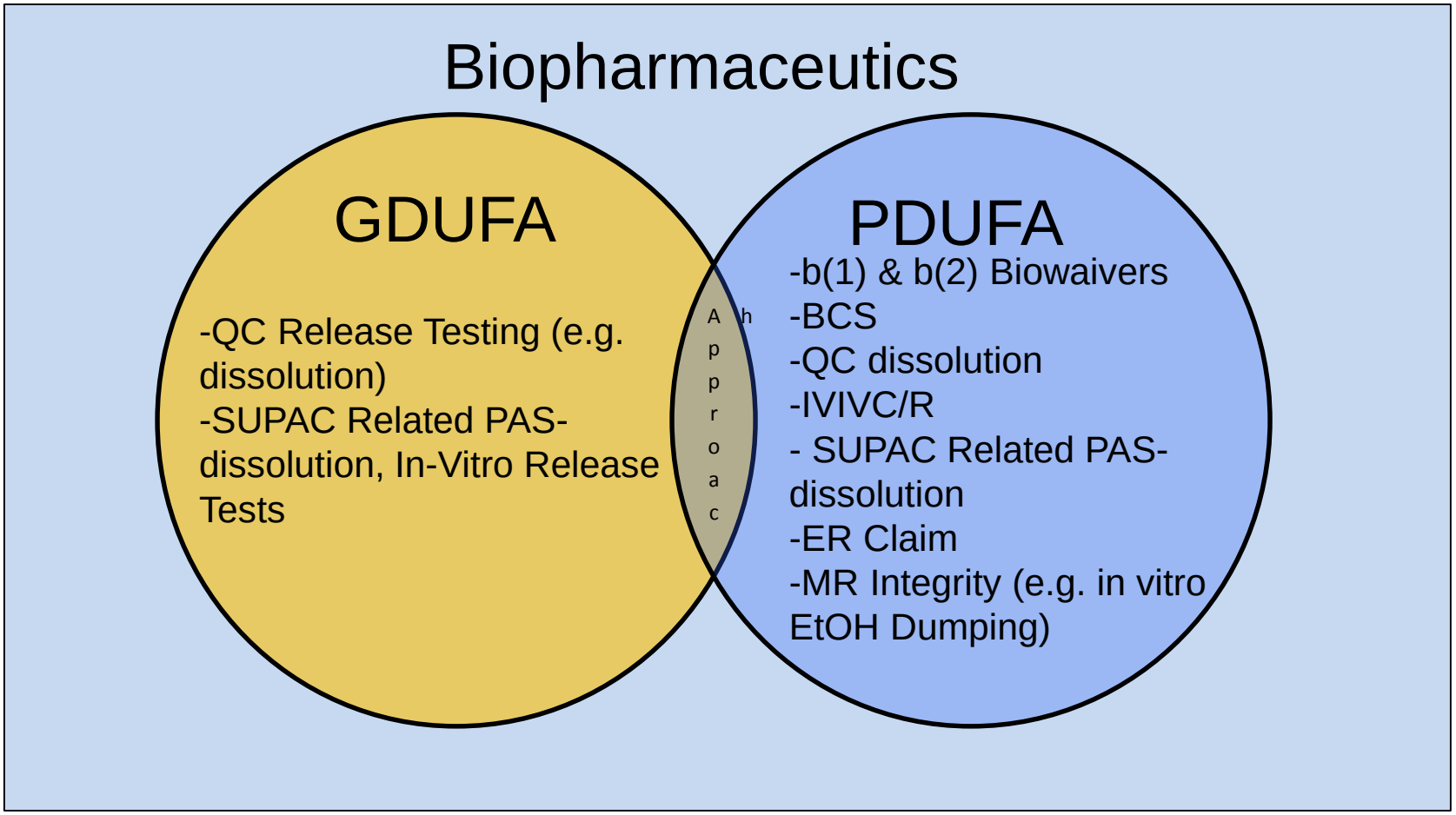
Organizational Strategy: Biopharmaceutics

- Reorganization to OPQ was a prime opportunity to align functions and strategy

- Main Objectives for Biopharmaceutics:
  - Review Work
    - ANDAs/NDAs/Combination Products/Consults
  - Clinical Relevance and Linking Biopharmaceutics to the patient

Division Organization

- 2 Primary Review Branches
- 1 Support and Research Branch
- Review Branches Organized by Therapeutic Area
- Support and Research Branch focuses on issues that support review functions (e.g. in silico modeling, IVIVC/R, PKPD, PBPK)


Biopharmaceutics
GDUFA
-QC Release Testing (e.g. dissolution)
-SUPAC Related PAS-dissolution, In-Vitro Release Tests
Approach
PDUFA
-b(1) & b(2) Biowaivers
-BCS
-QC dissolution
-IVIVC/R
- SUPAC Related PAS-dissolution
-ER Claim
-MR Integrity (e.g. in vitro EtOH Dumping)

Biopharmaceutics Definition

- Biopharmaceutics examines the interrelationship of the physical/chemical properties of the drug, the dosage form (drug product) in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. The importance of the drug substance and the drug formulation on absorption, and in vivo distribution of the drug to the site of action, is described as a sequence of events that precede elicitation of a drug's therapeutic effect.[1]

- Applying this definition to the regulatory perspective

[1]Applied Biopharmaceutics & Pharmacokinetics 6th Edition, Shargel, Wu-Pong, Yu.

Audience Participation

- Cotton
- Carpet
- Snow
- Other

Audience Participation

- Cotton
- Carpet
- Snow
- Other

Audience Participation

- Coconut
- Tree Bark
- Pencil
- Other

Audience Participation

- Coconut
- Tree Bark
- Pencil
- Other

Audience Participation

- Tomato
- Inflamed Gums
- Candle Wax
- Other

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Moral of the Quiz

- As scientists (regulatory or otherwise), its easy to become “lost” in the details
- Need a high level panoramic view to link to the patient
- Clinical relevance is a large topic needing a large view-point on patient needs and impact
  - Safety, Efficacy, Availability, Pharmaceutical Elegance, etc.
  - Technical and Regulatory Considerations (e.g. Clinically relevant specifications)

Clinical Relevance

Clinically Relevant Specifications (CRS)

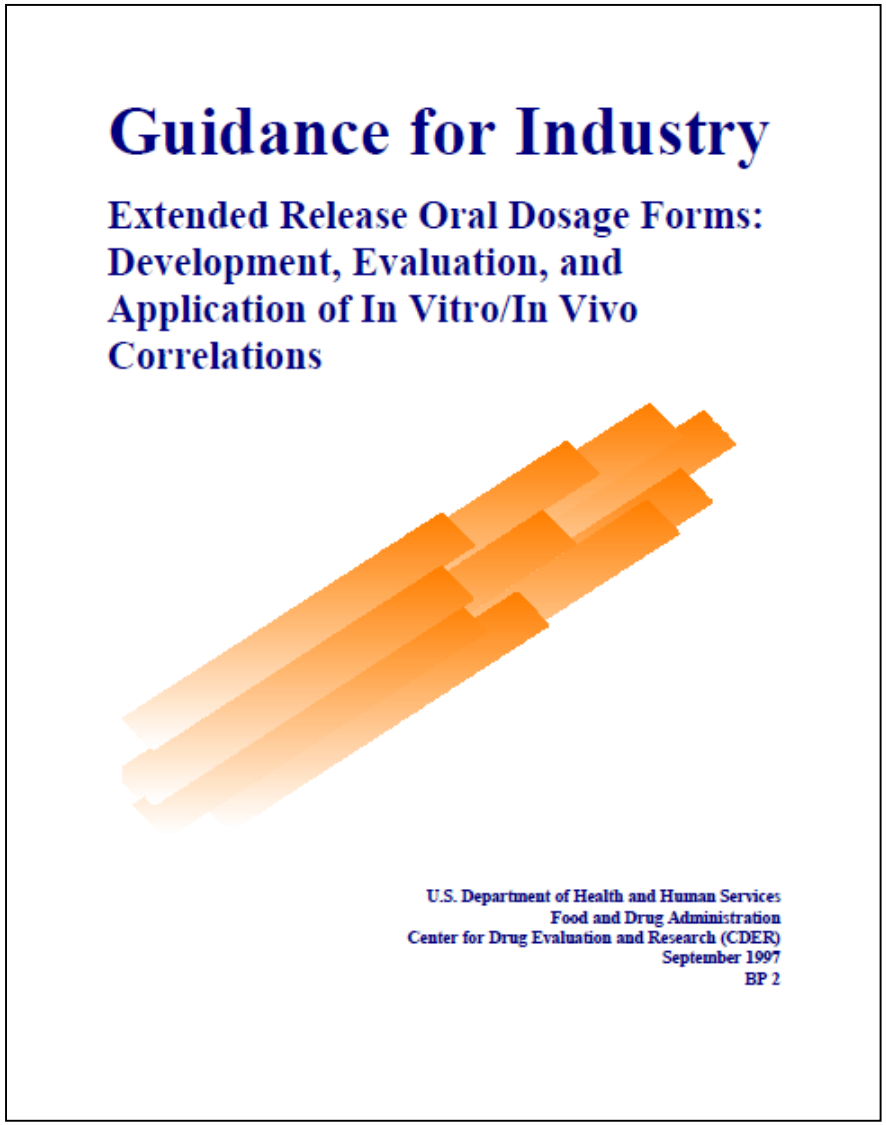
- CRS are those specifications that ensure the delivery of the intended dose of drug to the site of action or is available to the physiological system (the patient) to assure consistent safety and efficacy for the marketed product relative to those achieved by the clinical trial formulation

- Signified by test methods and acceptance criteria that are able to identify and reject drug product batches that are likely to perform inadequately in the indicated patient population.

Dissolution Testing: The little engine that could…

- Pharmaceutical Development
- Stability Studies
- Biowaivers
- Interchangeability Evaluation
- Routine QC
- SUPAC
- Various DF: Tablets, Capsules, Implants, Powders, inserts, suspensions, etc.

IVIVC/R-Current State



- *IVIVC Guidance is approximately 20 years old*
  - *FDA has recommended use of IVIVC for same timeframe*
- *Based on sound science*
- *Since 2008, approximately 54 IVIVCs submitted (PDUFA Space)*
- *Primarily for solid oral dosage forms (74%)*

IVIVC/R-Current State

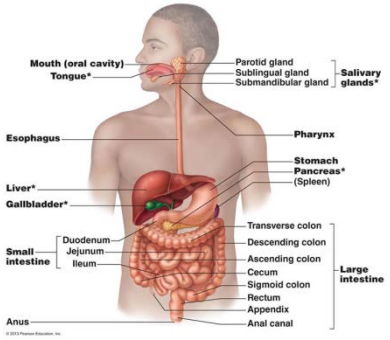
- *Why not more IVIVCs?*
  - *Possibly due to:*
    - *IVIVC is "Difficult"*
    - *Low Acceptance Rates, approximately 40%*
    - *Resource Barriers (Knowledge, Cost and Time)*
    - *Ethical Considerations*
    - *Seen as all or nothing approach*

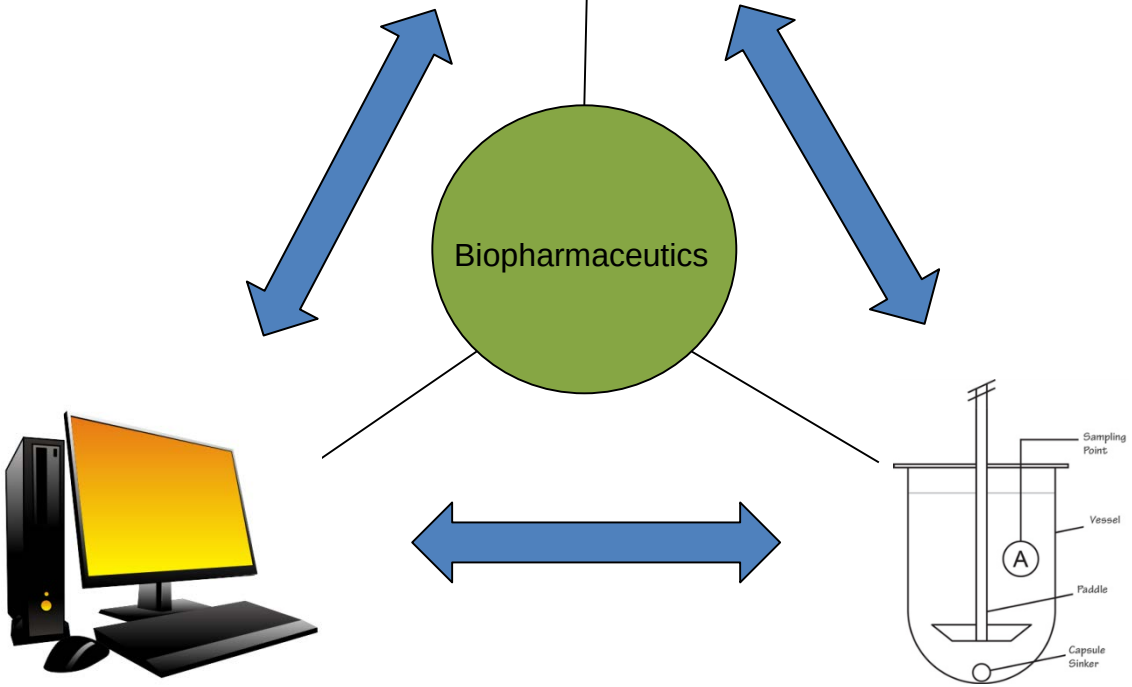
IVIVC/R-Current State

- Some common reasons for unsuccessful IVIVCs:
  - Traditional Dissolution methods may be non-sensitive (i.e. may need physiologically relevant dissolution testing)
  - Formulation variants do not provide adequate change in release profile
  - Formulation variants are not appropriate (e.g. release controlling excipient addition/deletion)
  - Lack of *a priori* planning of IVIVC

Suarez-Sharp S, Li M, Duan J, Shah H, Seo P. Regulatory Experience with In Vivo In Vitro Correlations (IVIVC) in New Drug Applications. AAPS J. August 2016.

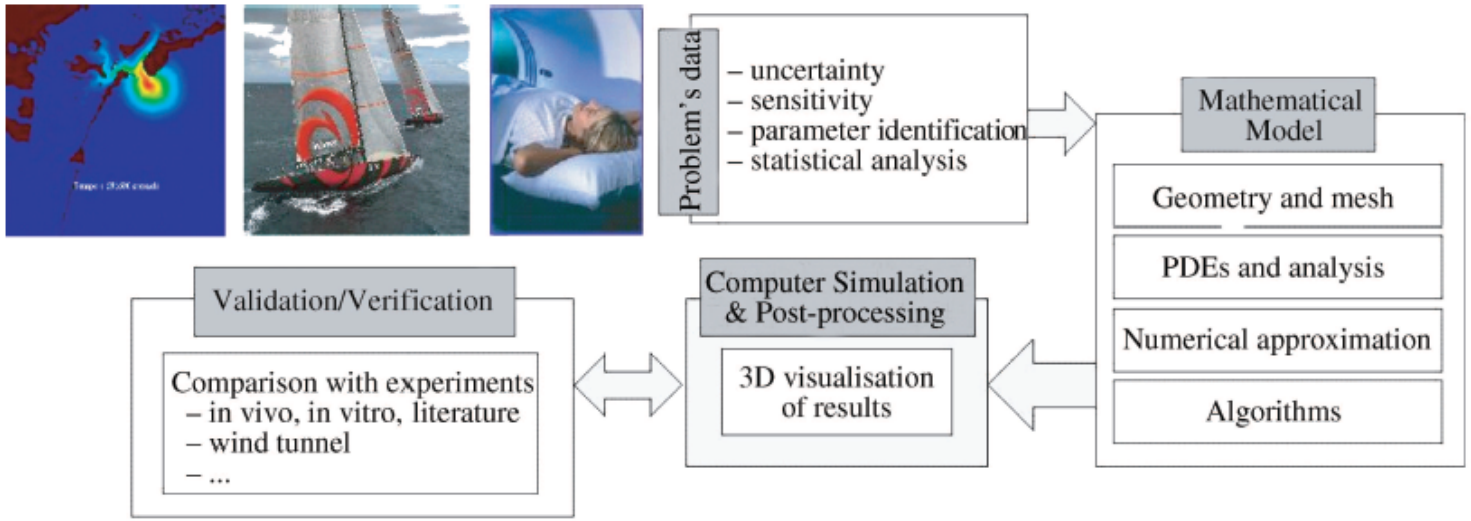
Establishing the Link





Emphasis on In Silico Modeling

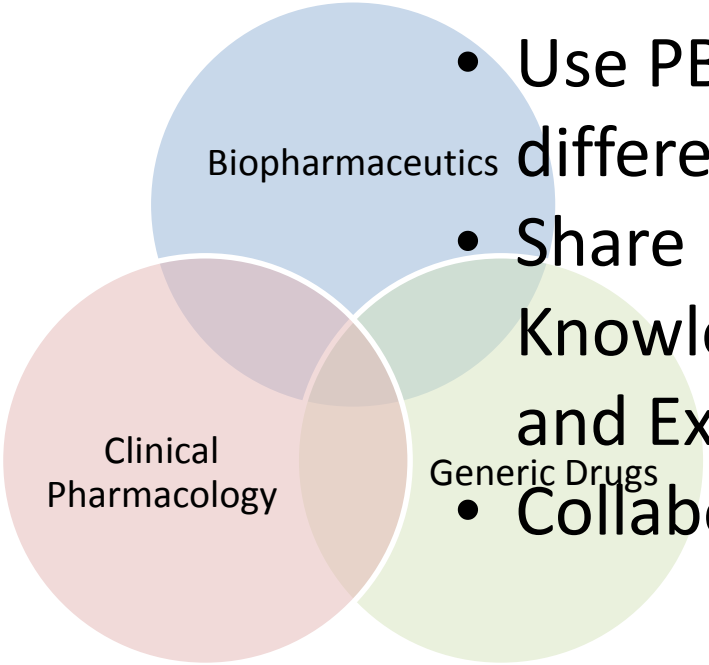
- Modeling: "Fit for use/purpose"
  - Pharmaceutical R&D, Engineering, Physics, Quantum Mechanics, etc.



Quarteroni A., "Mathematical Models in Science and Engineering," Notices of the American Mathematical Society, Vol 56, No.1. Jan 2009.

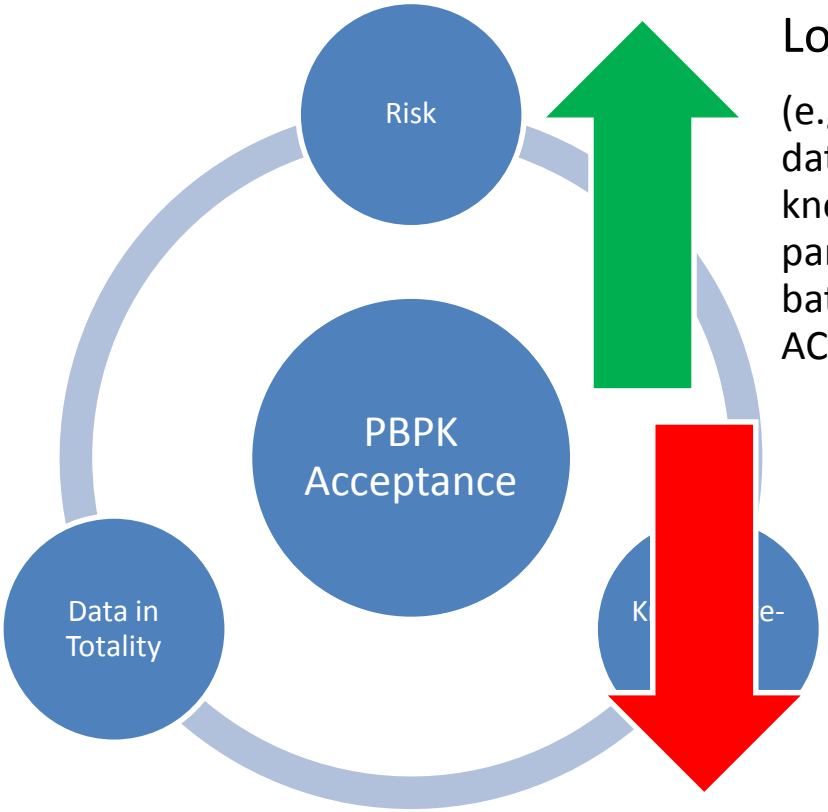
Physiologically Based Pharmacokinetic Modeling (PBPK)

- Alignment with PDUFA 6: Advancing Model Informed Drug Development (MIDD)
- PBPK



- Use PBPK for different means
- Share Knowledgebase and Experience
- Collaborate

PBPK in Biopharmaceutics



Lower Risk

(e.g. larger dataset/ knowledgebase, particle sizing, batch release AC)

Higher Risk

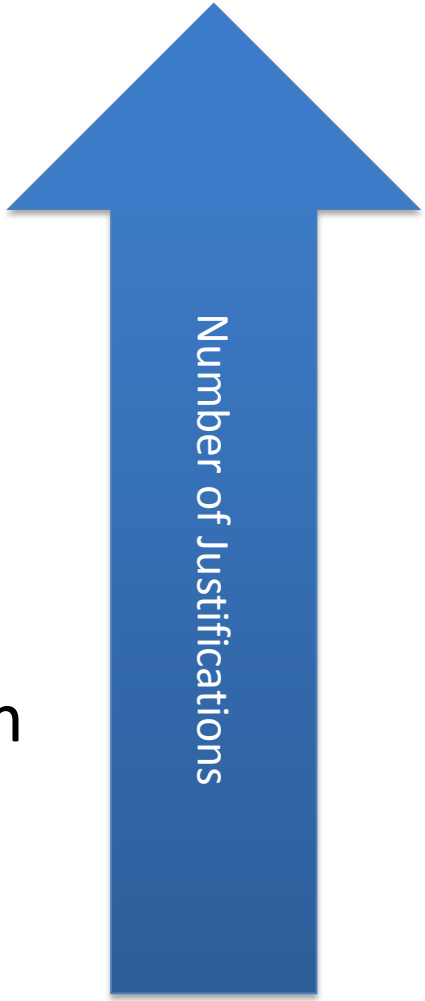
(e.g. more unknowns, larger impact, full biowaivers)

PBPK Approaches So Far

- Since 2009, 19 NDA submissions involved PBPK modeling/simulations to support Biopharmaceutics
- Approximately 75% of the PBPK models were found acceptable from Biopharmaceutics perspective
- Exploring ways to apply approaches to low-risk/high reward ANDAs
- Model added as supportive data to make Biopharmaceutics assessment

PBPK Case Examples

- Wide array of uses to justify:
  - Dissolution Method/Acceptance Criteria
  - Particle Size Distribution Setting
  - IVIVR
  - Risk Assessment
  - Oral Absorption in Special Population
  - Supportive evidence of BCS Classification
  - Effect of Gastric pH
  - Effect of Food



PBPK Case Examples

- Dissolution Method Acceptance Criteria
  - Justify a biorelevant method/AC and discriminatory capability
  - Allowed widening of specifications but allowed for ability of dissolution method to reject non-BE batch

- Biorelevant Specifications of Critical Material Attributes and Critical Process Parameters
  - Justify CMA specifications for particle size and polymorphic form
  - Justify CPPs for milling method and pressure force/hardness, dwell time

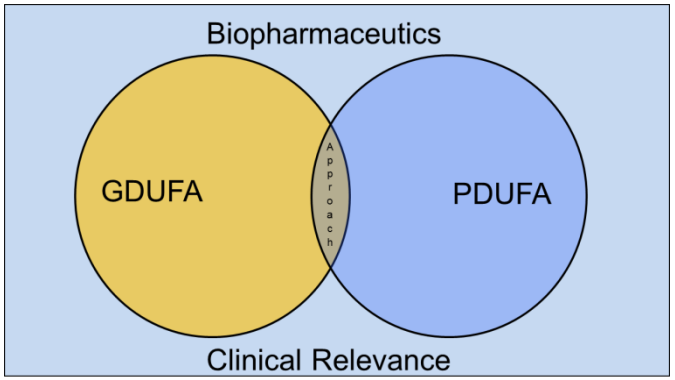
- SUPAC and risk assessment
  - SUPAC level 3 change requiring a bioequivalence study
  - Comparison of pre- and post-change products using previously established PBPK model
  - Totality of data used to make the biopharmaceutics assessment of SUPAC change (e.g. quality, clinical, model predictions, dosage form, risk)

Challenges

- What happens when applications/dossiers do not link relevant quality attributes to *in vivo* data?
  - If risk/benefit to protect public health, information requests are becoming more common for quality-in vivo impact
  - Rely on quality parameters at hand (traditional pharmaceutics)
    - Batch to batch consistency and sameness
    - Often seen as “Regulatory inflexibility”

Challenges

- Functional and Logistical Challenges
  - Workloads
  - Staffing
  - Complexity
  - Cross-Program: PDUFA and GDUFA are Dramatically Different
    - Regulations
    - Approaches
    - Timelines and Deliverables
  - Training



Challenges

- NDAs
  - Reluctance to attempt PBPK upfront
  - Reluctance to submit early development data
- ANDAs
  - No real avenue for engagement prior to submission
  - Quantity of Reviews to apply PBPK
- Setting Model criteria is application specific
- Software limitations (e.g. wide array of software available, ease of training/use, data handling capabilities)

Future Directions

- Hoping to provide more clarity through future publications
- Once sufficient knowledgebase and experience is gathered, a draft guidance can be established
- Regular use of IND written responses to recommend and promote collaboration of PBPK based model building and PBPK-IVIVC/R
- Risk/Reward and high-impact ANDAs to be selected for PBPK Biopharmaceutics Application

Conclusions

- The ultimate stakeholder – the patient
- Clinical Relevance discussion falls into “2 buckets”
  - Patient-focused quality review is often a broad and challenging discussion that involves multiple stakeholders and transparent communication about uncertainty
  - PBPK is a promising tool in the Biopharmaceutics space to support clinically relevant specifications
  - Clinical relevance is an evolving thought processes/flexible (case by case)

- Early collaboration is key and makes for a stronger application

The future…

Acknowledgements

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