U.S. FOOD & DRUG ADMINISTRATION

The impact and future of physiological based PK in biopharmaceutics modeling (PBBM) in support of drug product quality.

UMB CERSI/OPQ/SBIA Conference: Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

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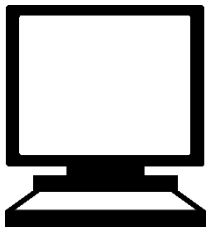
Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

Outline

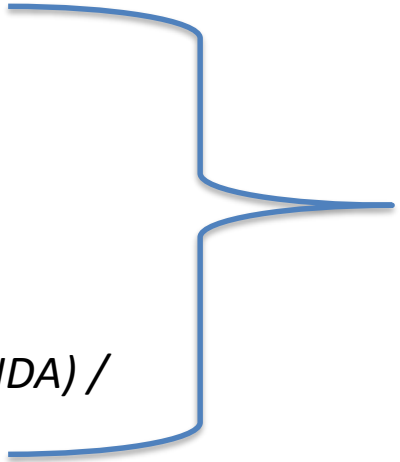
- Past
  - Why are we here
  - What have we done
- Present
  - What are we seeing
  - What are we asking
  - How are we doing it
- Future
  - Expectations
  - Future operational state

Past: Why are we here today?

- Purpose of this workshop:
- Follow on/continuation of UMB CERSI/FDA Conference: Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development, May 16, 2017
- Hope to discuss in various formats the potential pitfalls, benefits, lessons learned, and future opportunities in a safe environment as scientists

Past: Why are we here today?

- Hypothetical development situation:
- *Drug Discovery*
- *Screening*
- *Pre-Clinical Testing*
- *IND Application*
- *Phase I Clinical Trials*
- *Phase II Clinical Trials*
- *Phase III Clinical Trials*
- *New Drug Application (NDA) /*
- *Phase IV*



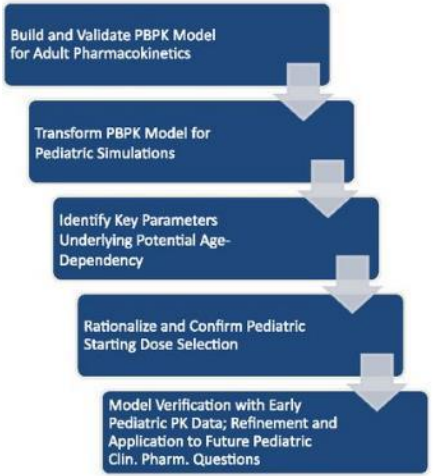
Mechanistic Modeling Can play a role at every step!

Past: Why are we here today?

- Mechanistic modeling can:
  - Reduce costs
  - Guide experiments
  - Guide Formulation/Process Design
  - Predict Outcomes
- Mechanistic modeling and Quality of Medicines (Formulation and Process):

PBPK Modeling

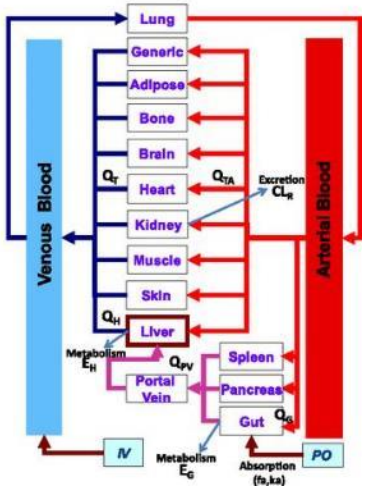
A

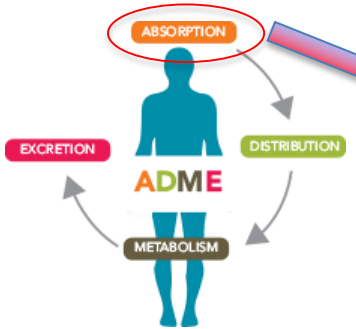


B

Data Inputs	Parameters
Physicochemical	Molecular weight
	Lipophilicity (logP)
	Acid/base character (pKa)
	Polar surface area
	Hydrogen bond donors
	Effective permeability
	Solubility (pH dependence, biorelevant media)
in vitro ADME	Plasma protein binding, extent
	Plasma protein binding, identity of protein/s
	Blood:plasma partitioning ratio
	Intrinsic clearance in liver fractions/hepatocytes
	Enzyme/transporter isoform phenotyping (% contribution)
Clinical PK	Renal clearance
	Total body clearance or apparent clearance

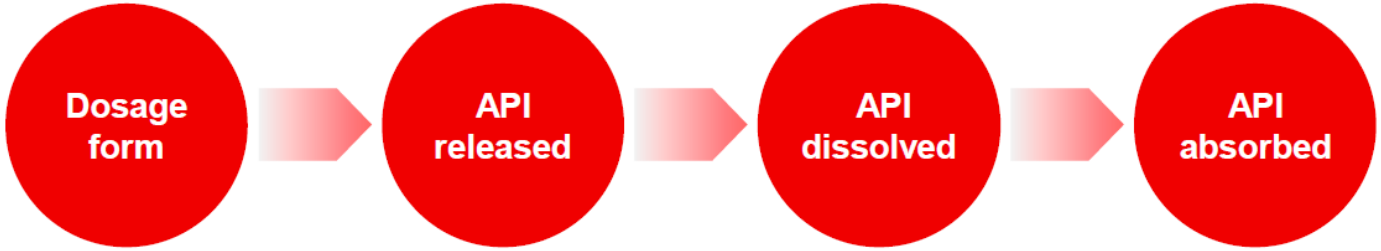
C



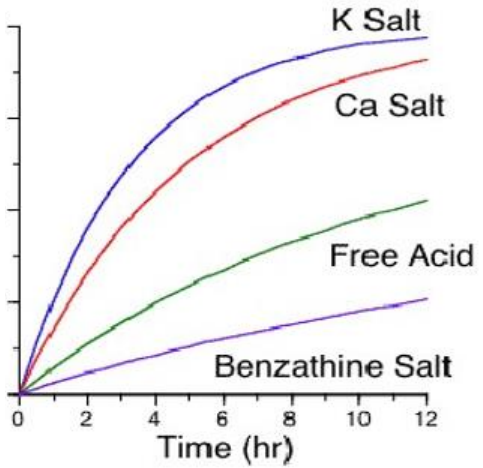


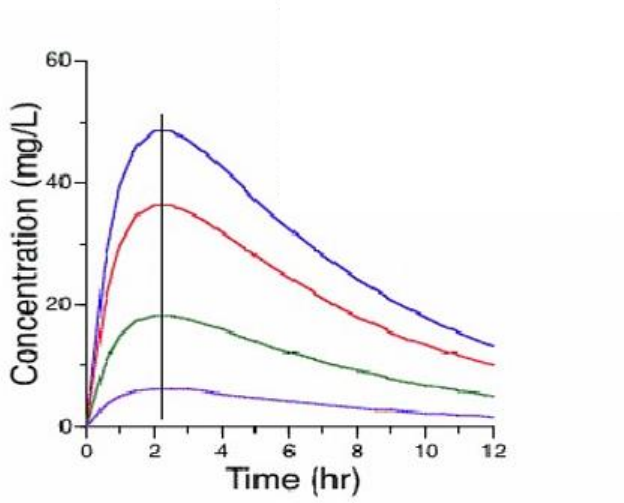
Manufacturing/Process/Formulation Attributes can control this step!

Dissolution: What is it?



- Dissolution is one of the only batch release tests that monitors the rate and extent of in vitro drug release, and this test is often used as a surrogate to ensure consistent in vivo performance.





This is dissolution

This is in vivo

Simple but Effective

Dissolution: What is it?

$$\frac{dW}{dt} = \frac{D}{h} S(C_s - C_b)$$

- dW/dt = dissolution rate
- D = diffusion coefficient
- h = thickness of the stagnant layer surrounding the dissolving particle
- S = the surface area of the solid
- C_s = the concentration of a saturated solution
- C_b = the concentration at any given time of the bulk solution

Present: Where are we today? Dissolution as a QC Test

- The purpose of a QC dissolution method is to detect variations during routine product manufacturing and changes during product storage that might negatively impact product performance (e.g. bioavailabilities or safety/efficacy).
- Variations may be related to API, raw materials, or other critical attributes specific to the manufacturing process.

Present: Where are we today?
Dissolution as a QC Test: Challenges

- Should be discriminatory across strengths/dose
- Robust yet simple such for routine testing
- Able to detect problems in manufacturing (change in CMA/CPPs)
- Route of administration and therapeutic usage must be considered
- Able to reject “non-BE” batches

Present: Where are we today? Dissolution as a QC Test

Three Critical Components:

- Evaluation of the selected method
- Demonstration of discriminating ability
- Selection of acceptance criteria

IR Products

- Setting based on overall data (BE & exhibit batches).
- Collection of complete dissolution profile data (n=12).
- The selection of spec-time point should be where NLT 80% (Q) of drug is dissolved.
- For slow dissolving products, more than one time-point value may be needed.

ER Products:

- Setting based on overall data (BE & exhibit batches)
- Collection of complete dissolution profile data (n=12)
- At least 3 time-points covering the initial, middle, and final phases of the dissolution profile
- Dissolution acceptance criteria range for the initial and middle time points is based on mean target value +10%
- NLT 80% of label amount as a limit for the last time-point.

Setting Acceptance Criteria cont…

ER Products:

- Setting based on overall data (BE & exhibit batches).
- Collection of complete dissolution profile data (n=12).
- At least three spec time-points covering the initial, middle, and final phases of the dissolution profile.
- Dissolution acceptance criteria range for the initial and middle time points is based on mean target value +10%.
- NLT 80% of label amount as a limit for the last time-point.

Simple but Effective

Present: Where are we today?

- Common Themes in FDA/Industry discussions:
  - *Industry:*
  - "You are being too stringent/restrictive"
  - "You are making us throw away good batches"
  - "Lifecycle management will be difficult"
  - "Dissolution is irrelevant/insensitive for our product"

  - *Regulators*:
  - "Your method is not discriminatory"
  - "Your method is not clinically relevant"
  - "Your method cannot ensure batches will maintain efficacy"
  - Post Marketing Commitments Usage

Present: Where are we today?

- Common Themes in **FDA**/Industry discussions:
  - *Industry:*
  - "You are being **too stringent/restrictive**"
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Present: Where are we today?

- Hypothetical:
  - Out of Specification Report
    - Keep on Market or Withdraw?
  - Without some ability to link specifications to in vivo disposition or PD, challenges arise

Present: Where are we today?

- PBPK for Biopharmaceutics Purposes:
  - **What are we using it for?**

Present: Where are we today?

- PBPK for Biopharmaceutics Purposes:
  - **<u>What are YOU using it for?</u>**
    - »PURPOSE should be front and center

Present: Where are we today?

PBPK for "traditional" Purposes in FDA Submissions

- DDI
- Pediatrics
- Hepatic Impairment
- Renal Impairment
- Pharmacogenetics
- Absorption
- Pregnancy
- Other

PBPK for Biopharmaceutics Purposes

- Process/Formulation Changes (SUPAC)
  - E.g. Particle Sizing
- Dissolution Method/AC
- Formulation Variants
- BCS Supportive Information
- Clinically Relevant Quality Specifications
- Other

Present: Where are we today? How are we doing it?

- Issues:
  - Modeling is inherently technical
  - Balancing needs of multiple programs

Present: Where are we today?

- Solution: How are we doing it?
  - CDER Biopharmaceutics Policy Council (MAPP 5017.4)
  - Modeling Committee

Future: Where are we going

- Proliferation of model-based/supported quality specifications
- Increasing flexibility and confidence in dissolution product testing
- Increased alignment of terminologies
- Hope for public recommendations in the near future (in the form of guidance)

Future: Where are we going
Operational expectations

- FDA's format guidance:
  - *Guidance for Industry: Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry (Sept 2018)*
- Model Summary should clearly state the purpose of the model and uses in the regulatory dossier.

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Thank you & Questions?


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