Critical Roles for Locally Acting PBPK in Regulatory Decisions

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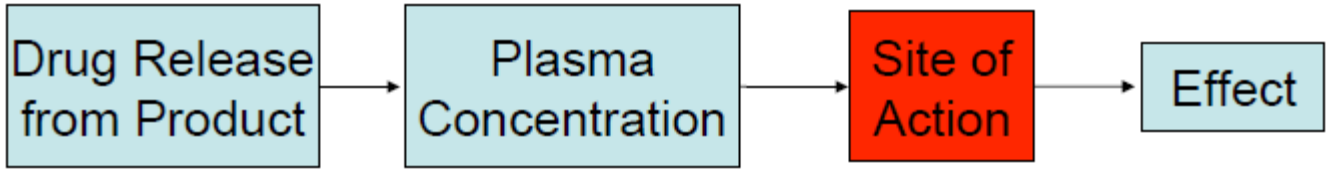
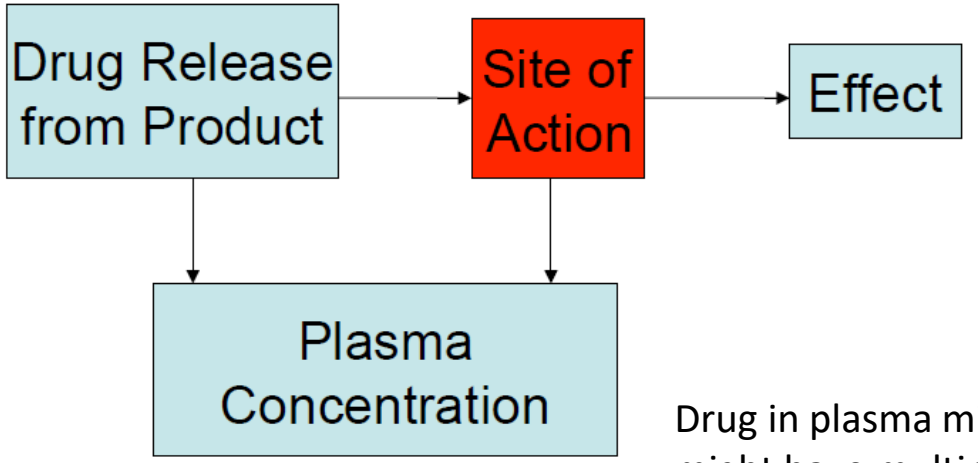
Locally Acting Products

- Systemic Drugs



- Locally Acting Drugs



Examples:
Inhalation and Topical

Drug in plasma might not be detectable or might have multiple routes

FDA Relies on Systemic Exposure for Regulatory Decisions

- New Drug Development
  - Clinical Pharmacology relies on systemic exposure
    - Drug-Drug interactions
    - Exposure-response
    - Population PK analysis
    - Relative BA for bridging studies
- Generic Drug Development
  - PK based bioequivalence supports the approval of the vast majority of generic drugs

All the things FDA and drug developers want to do become more difficult for locally acting products

Approaches for Locally Acting Products

- New Drug Development
  - Rely on safety and efficacy studies
    - Reasonable but not optimal
  - Barrier to product improvement
    - Need to demonstrate BE after formulation change or in product development
- Generic Drug Development
  - Use clinical endpoints for bioequivalence?
    - High cost is a barrier to generic competition
  - Clinical endpoints have high variability/low sensitivity
    - Inefficient detection of formulation differences
  - Unnecessary human testing
    - Often 300-500 patients sometimes larger than original efficacy study

Equivalence Concepts

- **Pharmaceutical Equivalence (PE)**
  - Same active ingredient(s) and
  - Same dosage form and
  - Same route of administration and
  - Same strength

- **Bioequivalence (BE)**
  - No significant difference in rate and extent of drug at **site of action**

- **Therapeutic Equivalence (TE) of Generic Products**
  - Generics must demonstrate PE and BE to the reference product
  - Generics rely on the safety and efficacy of the reference product
  - Generics must have adequate labeling and cGMP manufacturing
  - TE products can be substituted freely

Regulatory Basis for Alternatives

- A 2003 addition to the Federal Food Drug and Cosmetic Act at Section 505(j)(8)(A)(ii) indicates that
  - "For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the **site of drug action**".

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Role of PBPK Models

- PBPK models for the local routes of drug delivery aid development of appropriate BE methods
- Capture the current understanding of the complex interplay between product attributes and human physiology for these routes of delivery
- Routes of Interest
  - Inhalation; Topical dermatological; Ophthalmic; Nasal; GI acting ; Vaginal; Otic
- FDA under GDUFA has funded research to establish these tools

Approaches to Local BE

- Comparative clinical endpoint bioequivalence studies
- Characterization-based approaches (Q3)
- Weight of evidence
  - Combined in vitro and in vivo performance measures

Q1 and Q2 and Q3 Definitions

- Classify product similarity
  - Q1: Same components
  - Q2: Same components in same concentration
  - Q3: Same components in same concentration with the same arrangement of matter (microstructure)
    - Characterization and performance data can support Q3 equivalence
- Used primarily for products that are applied directly to the site of action such as ophthalmic or topical dermatological drug products

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PBPK for Q3 BE

- Characterization approaches are supported by PBPK models that help identify the critical aspects of the microstructure and indicate the sensitivity of drug concentrations at the site of action to measurable product characterizations
- Example: How sensitive is ophthalmic drug delivery to particle size in an ophthalmic suspension?

Beyond Q3

- Q1/Q2/Q3 approaches limits formulation flexibility
  - Could limit generic competition
  - Continuing need for new BE approaches that can expand generic competition
  - Non Q1-Q2 products often need in vivo component of BE
    - Modeling and simulation is critical to the interpretation of in vivo data (esp PK) for locally acting products

Weight of Evidence

- Used for indirect delivery
  - inhalation drug products where the product is delivered by a device that can change the product characteristics significantly between the container and site of action
  - Combination of in vitro and in vivo bioequivalence methods to conclude that the drug delivery to the site of action is equivalent without direct measurement
- Also relevant for non-Q1,Q2 formulations with a potentially significant change in an excipient

FDA BE recommendations for Orally Inhaled Drug Products: weight-of-evidence approach

2013
First product-specific guidance for OIDP published

Device and Formulation Design

Comparative In Vitro Studies

Comparative Pharmacokinetic Studies

Comparative Pharmacodynamics or Clinical Endpoint Studies

2019
First Generic OIDP application approved!

Inhalation Products

- Key challenge: Role of clinical data sets in the weight of evidence
- Inhalation Product Research
  - Role of dissolution, particle size and PK studies
  - CFD modeling of deposition
- Role of PBPK: Understand the connection between in vivo measurements and drug concentration at the site of action

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Summary

- Today you will here detailed presentations on many of these routes of delivery
- The integration of new data and new modeling approaches continues to drive scientific progress
- This scientific progress is the foundation for a future robust pipeline of complex generic products