Biopharmaceutics of Non-Orally Administrated Drugs

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Opinions expressed in this presentation are those of the speaker and do not necessarily reflect the views or policies of the FDA

Definition of Biopharmaceutics

"the study of the chemical and physical properties of drugs and the biological effects they produce" (OED)

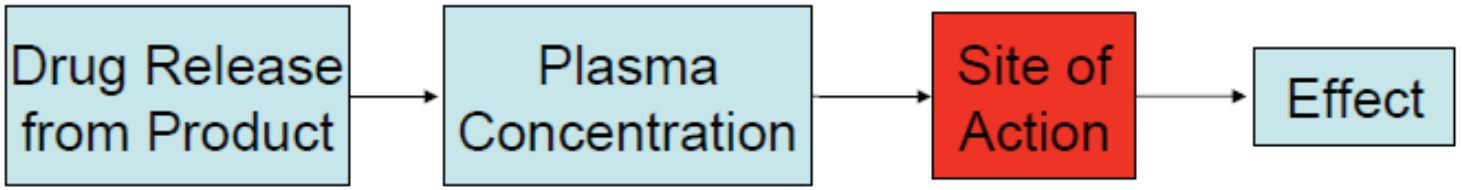
- Example: Biopharmaceutics Classification System
  - For oral dosage forms solubility and permeability are the most important factors

Regulatory Science of Bioavailability, Bioequivalence and Product Performance

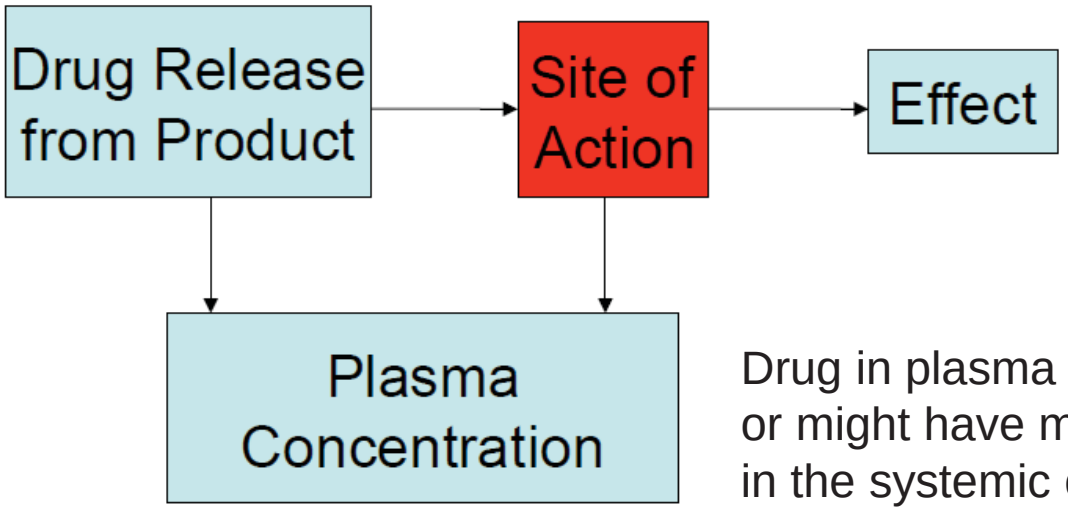
- If your understanding of biopharmaceutics is strong, then you can predict and control bioavailability and bioequivalence through product performance
- Example: For a BCS class I drug with rapid dissolution, in vivo bioequivalence studies are not needed
- What is the state of biopharmaceutics for non-oral dosage forms?

Locally Acting Products

- Systemic Drugs



- Locally Acting Drugs



Examples:
Inhalation and
Topical

Drug in plasma might not be detectable or might have multiple routes to arrive in the systemic circulation

Biopharmaceutics of Locally Acting Products

- Neglected area
- Unfocused pharmaceutical development
- Limits post-approval changes
- Challenges in demonstrating bioequivalence

- New approaches to bioequivalence of topical and inhalation products can illustrate the potential of biopharmaceutics for these dosage forms.

Therapeutic Equivalence

- Approved generics are expected to be Therapeutic Equivalents
  - Have the same clinical efficacy and safety profiles when administered to patients under conditions specified in the labeling.
  - Can be substituted for each other without any adjustment in dose or other additional monitoring
- Success of the generic drug program depends on biopharmaceutics
- Biopharmaceutics allows us to infer therapeutic equivalence without repeating clinical studies

GDUFA Regulatory Science Agreement

- Final agreement letter – September 7, 2011
  - *FDA committed that in the area of regulatory science it will continue, and for some topics begin undertaking various regulatory science initiatives.*
  - *FDA agreed to convene a working group and consider suggestions from industry and other stakeholders to develop an annual list of regulatory science initiatives for review by CDER Director.*

GDUFA
FY 2013 Regulatory Science Accomplishments

- New External Collaborations
  - 20 Grants, 8 Contracts for $17 million in Regulatory Science
- New Internal Collaborations
  - FDA lab (new equipment for Generic Drug Research: $1 million)
  - 25 new ORISE fellows for Generic Drug Research (10 to FDA lab)
- New Guidance for Industry
  - First MDI BE guidance (April), First Ophthalmic Emulsion BE guidance (June), First DPI BE guidance (Sept)
- New Plan for FY 2014 Regulatory Science
  - Public Meeting and comments

GDUFA
FY 2014 Regulatory Science Priorities

http://www.fda.gov/Drugs/NewsEvents/ucm367997.htm

- Post-market Evaluation of Generic Drugs
- Equivalence of Complex Products
- Equivalence of Locally Acting Products
- Therapeutic Equivalence Evaluation and Standards
- Computational and Analytical Tools

GDUFA and Biopharmaceutics

- Many of the GDUFA Regulatory Science Priorities require advances in biopharmaceutics of non-oral dosage forms
- Inhalation Example
- Topical Dermatological Example

INHALATION EXAMPLE

Inhalation Examples

- Complex dosage forms consisting of formulation and device components
  - Defining device similarity for generic dry powder inhalers
  - Demonstrating equivalent local drug delivery in the lung
- Two recent guidance indicate the development of biopharmaceutics for inhalation products
- The first individual product guidance for a MDI has posted (Albuterol Sulfate April 2013)
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf
- First drug specific BE recommendation for DPI: Draft BE guidance for Fluticasone Propionate; Salmeterol Xinafoate (FP/SX) inhalation powder aerosol, published in September, 2013
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf

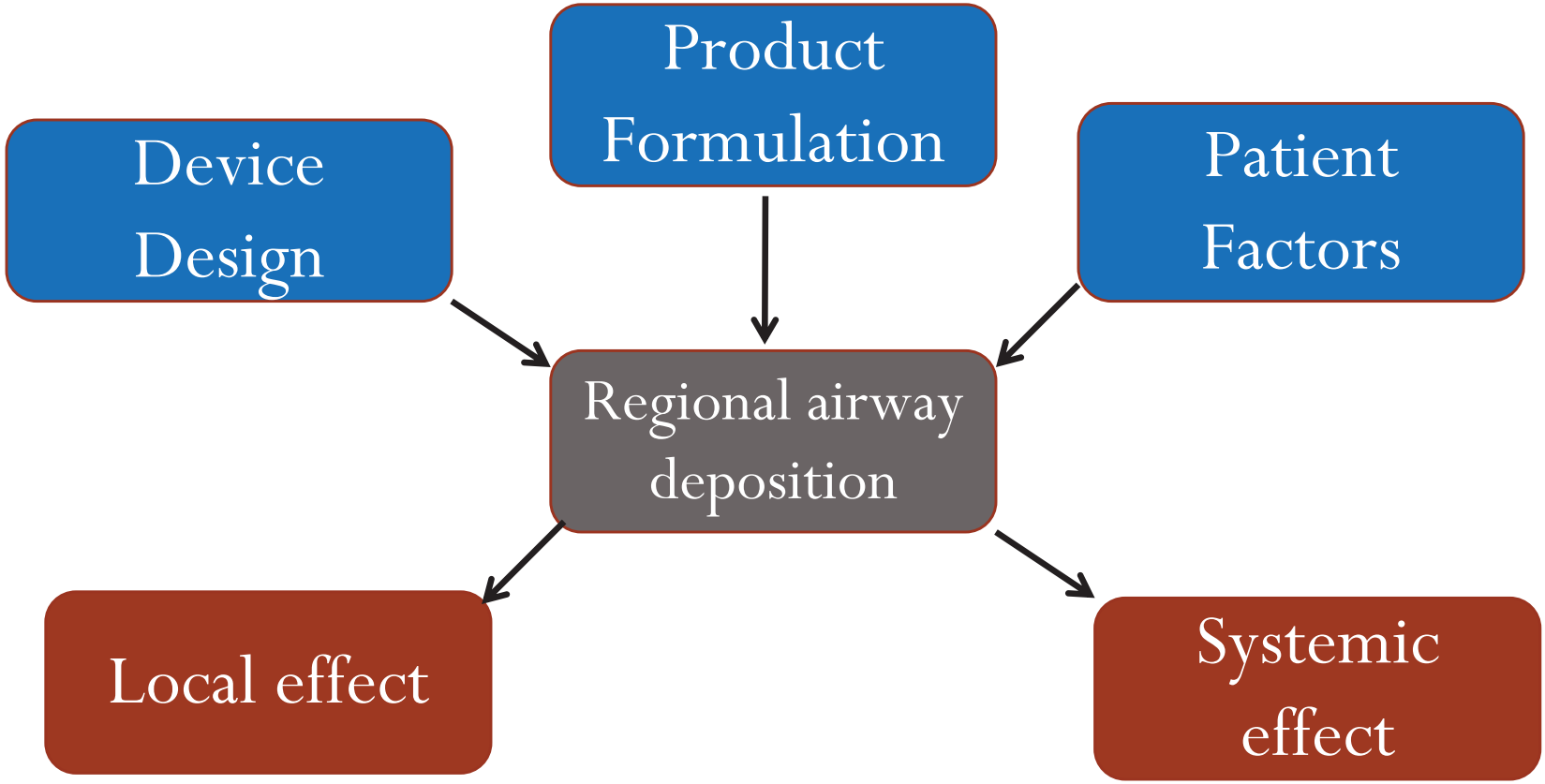
Inhalation Products

MDI

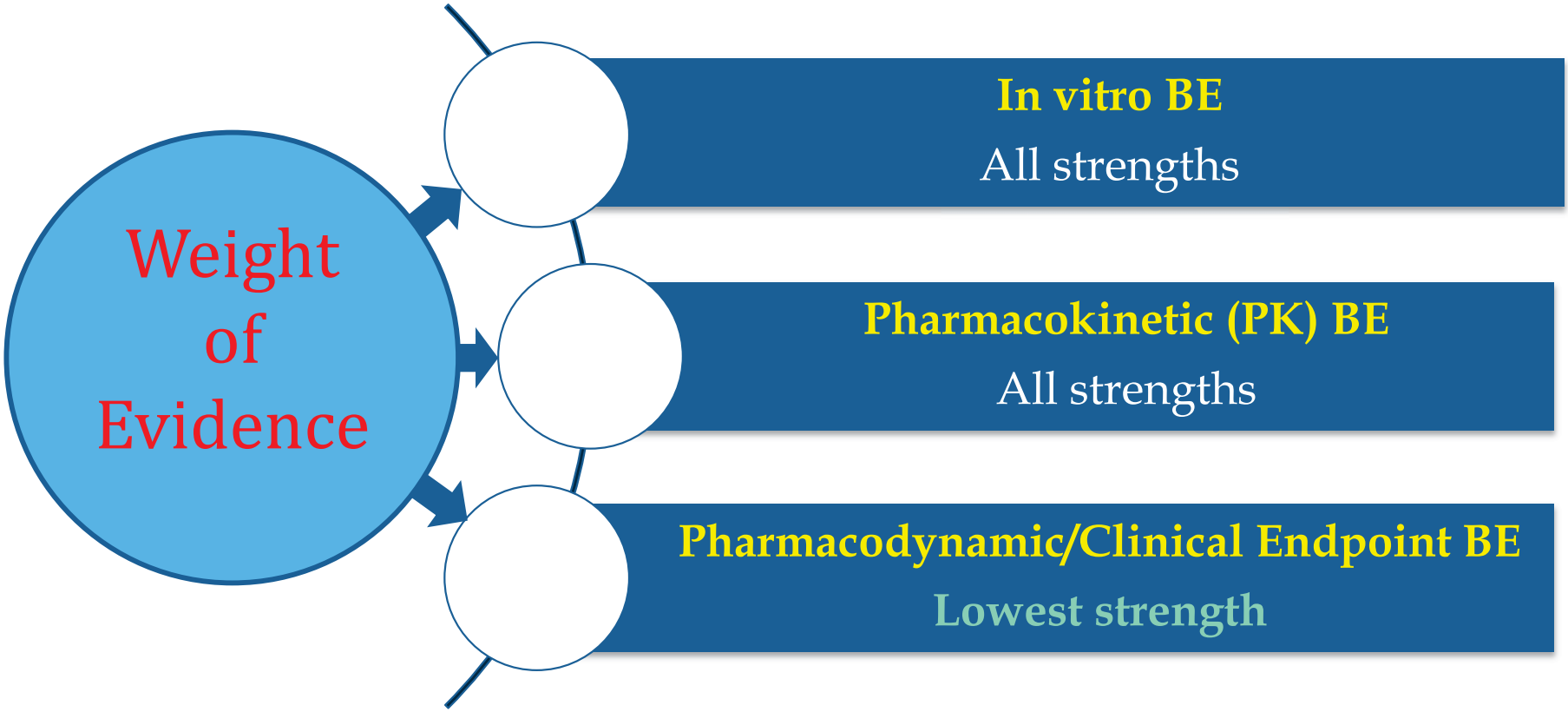
- Picture coming

DPI

Considerations for Generic Inhalation Products



BE Evaluation for Inhalation Products



In Vitro Considerations (MDI and DPI)

- Equivalent Emitted Dose at various lifestages
  - Beginning, middle and end lifestages
  - Range of flow rates for DPI
  - Equivalence criteria
    - Population Bioequivalence (PBE)
- Lifestages
  - Each device is labeled for a fixed number of actuation
  - Product performace should be maintained from the first use to the last use
  - Beginning Lifestage: first set of actuations
  - Middle Lifestage : 50% of labeled number of actuations
  - End Lifestage: labeled number of actuations

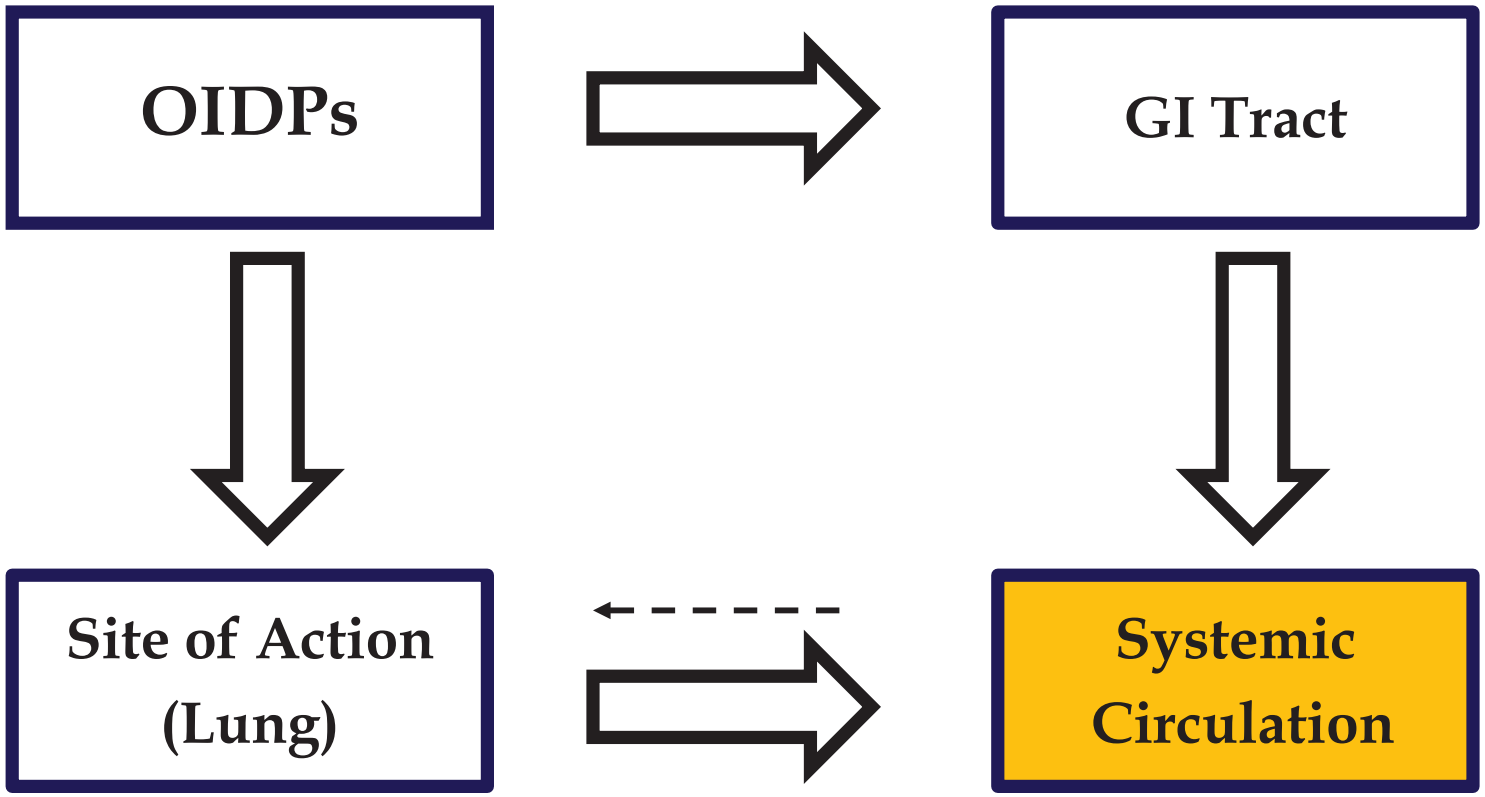
In Vitro Considerations (MDI and DPI)

- Equivalent Aerodynamic Particle Size Distribution
  - Beginning and end lifestages
  - Range of flow rates for DPI
  - Drug deposition on each individual site, to include the mouthpiece adapter, throat, and each stage of the cascade impactor including the filter
  - Equivalence criteria
    - Impactor-sized mass (ISM) based on PBE
    - The CI profiles representing drug deposition on the individual stages of the CI.
      - How to compare?

In Vitro Considerations (MDI)

- Equivalent spray pattern
  - Beginning lifestage
  - Equivalence criteria
    - Qualitative comparison of spray shape
    - Ovality ratio and area or ovality ratio and Dmax based on PBE
- Equivalent plume geometry
  - Beginning lifestage
  - Equivalence criteria
    - Geometric mean ratio of T to R, based on log transformed data, falls within 90-111%
- Equivalent priming and repriming
  - Beginning lifestage (priming) or following storage for specified period of non-use after initial-use
  - Equivalence criteria
    - PBE

Pharmacokinetics of Orally Inhaled Drug Products (OIDPs)



The sampling site for PK studies (plasma) is a compartment that is downstream of the site of action (the lung)

Equivalent Systemic Exposure

- PK BE study design
  - Single-dose studies in healthy subjects
  - Dose based on minimizing the number of inhalations but justified by assay sensitivity
  - PK measurements feasible for inhaled bronchodilators
- Equivalence criteria
  - 90% CI: 80% – 125% for AUC and C_{max}

Equivalent Local Delivery (Albuterol)

- PD study endpoints in asthmatic patients
  - Bronchodilatation or methacholine challenge (bronchoprovocation) endpoint
- Establishment of dose-response
  - Ensures the sensitivity of a pharmacodynamic (PD) study to distinguish potential differences between test and reference products
- Dose scale method for equivalence
  - E_{max} model
  - Equivalence based on "dose scale"
- Equivalence criteria
  - 90% CI: 67-150 % for relative bioavailability
  - For dose-scale analysis power for BE is driven by both within and between subject variability
  - For standard ABE we have methods for reference scaling on the within subject variability
  - These limits provide equivalent assurance of similarity as ABE limits of 80-125%

Equivalent Local Delivery (FP/SX)

- FEV1 endpoint (no PD endpoint with dose response)
- For lowest strength 100/50µg: waiver for other strengths based on successful demonstration of in vitro BE and PKBE
- Design:
  - A randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2 week run-in period followed by a 4 week treatment period of the placebo, T or R product
- Patient population recommended
  - Asthmatics with pre-bronchodilator FEV_1 of ≥40% and ≤85% of the predicted value during the screening visit and on the first day of treatment
  - ≥15% reversibility of FEV_1 within 30 minutes following 360 mcg of albuterol inhalation (pMDI)
- BE endpoints (baseline adjusted):
  1. Area under the serial FEV_1-time curve calculated from time zero to 12 hours ($AUC_{0\text{-}12h}$) on the first day of the treatment – Mainly SX component
  2. FEV_1 measured in the morning prior to the dosing of inhaled medications on the last day of a 4-week treatment –FP+SX combined effect
- Equivalence:
  - the T and R products should both be statistically superior to placebo ($p<0.05$) with regard to the BE study primary endpoints
  - The 90% CIs for the T/R ratios for the primary endpoints should fall within the limits of 80.00-125.00%

Current State of Inhalation Biopharmaceutics

- Extensive product testing covers all relevant performance
- What are the physical properties that drive this performance?
  - Particle size
  - Surface chemistry
  - Device-formulation interactions

Future for Inhalation Biopharmaceutics

- Previous OGD Research Projects
  - Formulation and device modifications
  - PK based approach
  - In vitro DPI studies
  - Modified chi-square ratio approach
  - Modeling and simulations: CFD, PD/clinical trial simulations, pulmonary absorption models
- New GDUFA Research Projects (FY 2013)
  - Predictive dissolution method for orally inhaled drug products
  - Systematic evaluation of excipient effects on the efficacy of metered dose inhaler products
  - Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action

TOPICAL EXAMPLE

Why are Topical Products Complicated?

- Complexity
  - Semi-Solid dosage forms
  - Complex structure of skin
  - Product components affect skin
  - Disease state can change skin
- Failure Modes
  - Application
  - Formulation
  - Physiology
- Application
  - Different spreading on the skin
  - Different area/duration of exposure
- Formulation
  - Drug does not leave formulation
  - Thermodynamic activity is different (suspension v. dissolved drug)
- Physiology
  - Formulations have different effects on stratum corneum
  - One formulation prefers follicular pathway

BE Approaches for Locally Acting Products

- FDA has begun to make different recommendation for Q1 and Q2 formulations for other locally acting drugs: Cyclosporine Ophthalmic emulsion, budesonide inhalation suspension,Vancomycin and Acarbose
- For other locally acting products (inhalation products, GI acting) FDA has recommended "weight of evidence" or combined approaches
  - PK,PD, in vitro for inhalation
  - Dissolution and PK for mesalamine
- Topical drugs have lagged

Q1 and Q2 Identical

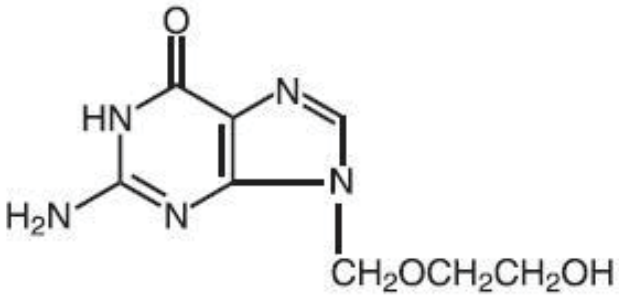
- Q1 and Q2 Definitions: Classify product similarity
  - Q1: Same components
  - Q2: Same components in same concentration
  - Q3: Same components in same concentration with the same arrangement of matter (microstructure)
- Uncertainty Due to Differences in Manufacturing
  - Is the rheology the same?
  - Is the solubility of the drug in the formulation the same?
  - Are excipients released at same rate?
  - Is particle size the same? (suspensions)
- Potential Path Forward
  - In vitro tests are the best evaluation method for manufacturing process
    - Rheology
    - In vitro release (diffusion cell)
    - Particle Size (suspension)

Beyond Q1 and Q2

- Questions for Q1 identical
  - Excipient effect on skin barrier properties can be concentration-dependent
  - Thermodynamic activity could differ
- Questions for different inactive ingredients
  - In vivo test if composition differences in excipients could potentially alter either skin permeability or the solubility of drug in the formulation
  - Would in vitro release test answer this? Are there IVIVC

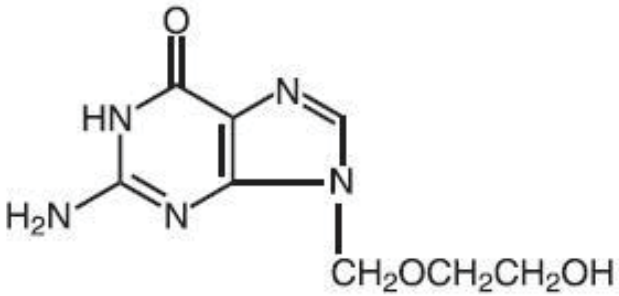
In Vitro Option : Acyclovir Ointment

- Acyclovir – synthetic nucleotide analogue active against Herpes virus
- RLD - Zovirax® (NDA 018604) by Valeant Bermuda
- Generic Equivalent – 5% Acyclovir Ointment (ANDA 202459) by Mylan Pharmaceuticals
- Indication – Initial outbreak of genital herpes or for treatment of lesions caused by Herpes simplex virus
- Mechanism – Converted to Acyclovir triphosphate; stops viral DNA replication



In Vitro Option : Acyclovir Ointment

- Site of Action – Upper skin layer
- RLD Formulation – Simple polyethylene glycol base suspension of the API
- Sensitivity/Feasibility – Low potency drug that may not suitable for clinical endpoint BE studies
- FDA Draft Guidance (published March 2012) can be found here:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm296733.pdf
- Two options for establishing BE –
  - In Vitro Approach
  - Clinical Endpoint Approach



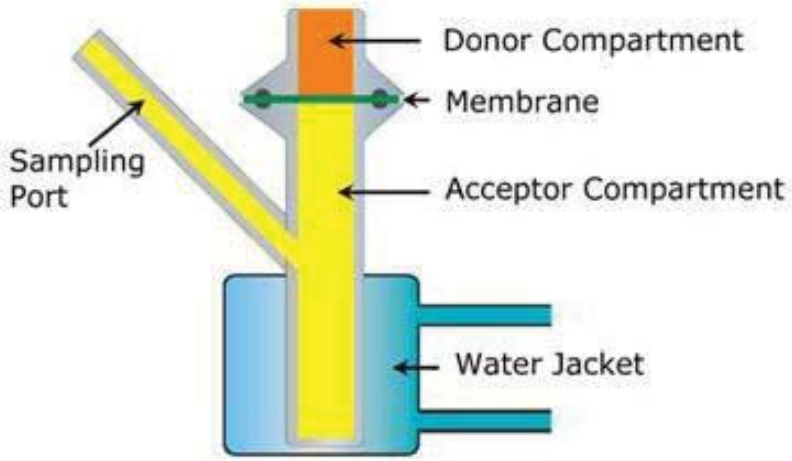
In Vitro Option : Acyclovir Ointment

- Requirements
  - Generic formulation must be qualitatively (Q1) and quantitatively (Q1) the same as the RLD
  - Generic formulation must also be Q3 (same physiochemical attributes) to the RLD
    - Product manufacturing can affect the microstructure of a formulation, and thus impact drug delivery
    - To ensure Q3, generic formulation must demonstrate:
      - Similar release rates
      - Similar critical quality attributes
- If the generic formulation is *not* Q1/Q2 to the RLD, BE may be established through a clinical endpoint study
  - Design - randomized, double blind, parallel, placebo controlled
  - Strength - 5%
  - Subjects – Immunocompromised males and non-pregnant females with recurrent herpes simplex labialis

Establishing Q3 to the RLD

- In Vitro Release Testing
  - Methods described in the FDA Guidance for Industry: SUPAC – SS (semisolids)
  - Dosing – finite versus infinite
  - Choice of membrane:
    - Synthetic – chosen to provide no resistance to drug transport. Under these conditions, rate of appearance in the receptor medium is determined solely by the release rate of the formulation
    - Human cadaver skin – may provide better in vivo correlation, but lower ability to detect formulation differences

Diffusion Cell Schematic

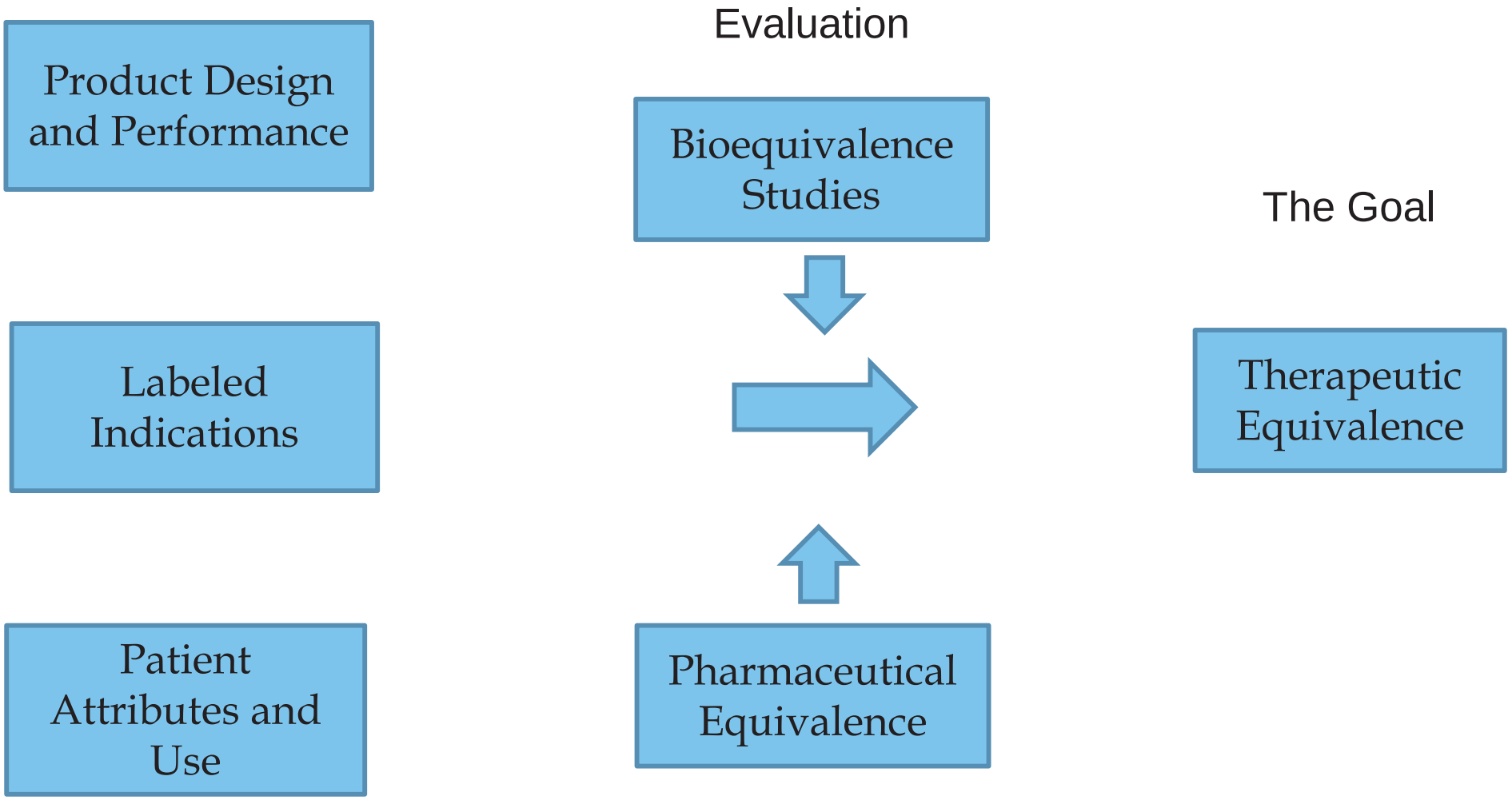


Establishing Q3 to the RLD

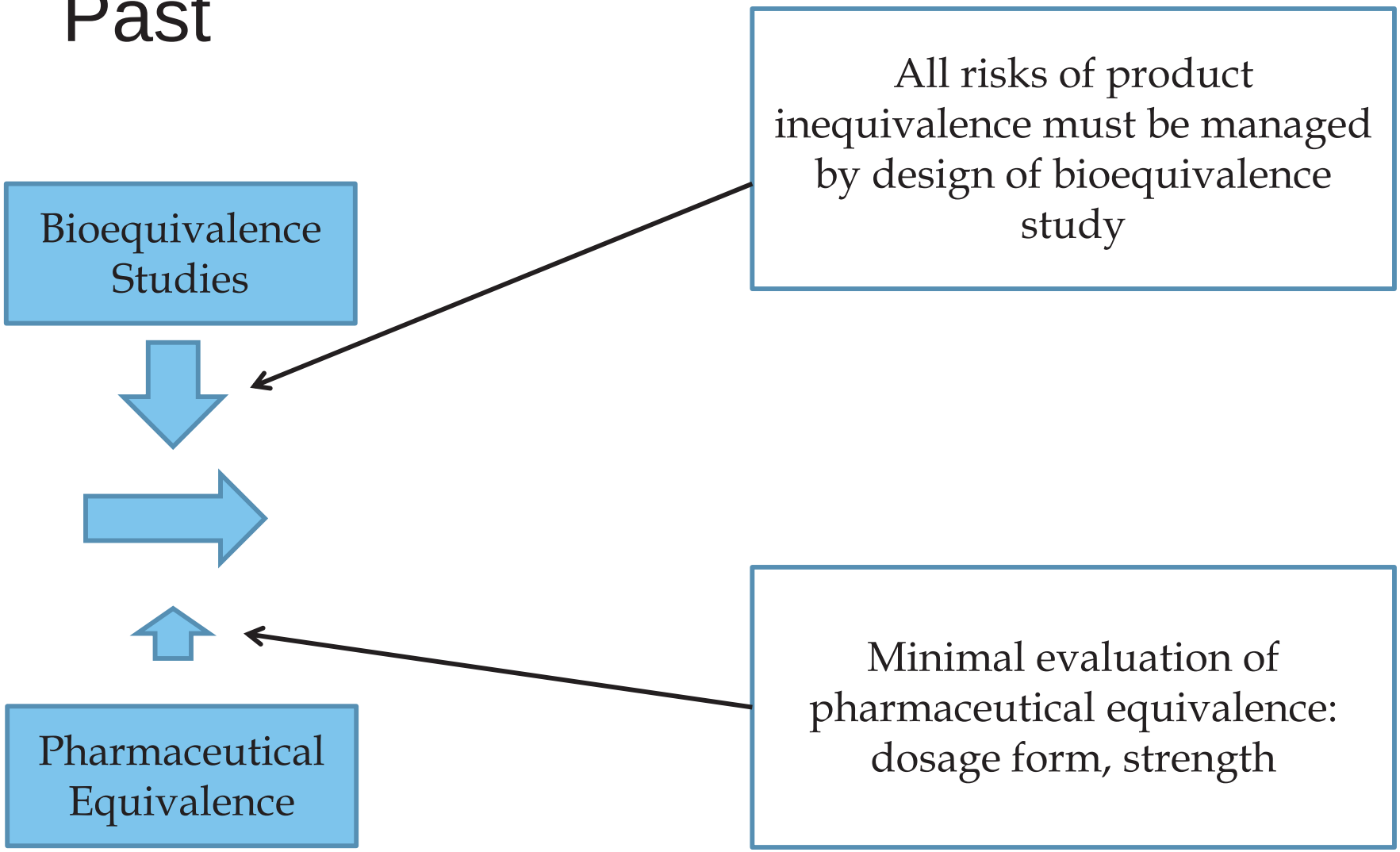
- Critical quality attributes considered for Q3:
  - Particle Size – Differences in particle size can affect API release into the vehicle and subsequent delivery into the skin
  - Viscosity – Differences in viscosity can alter the transport of suspended particles to the skin surface, or diffusion of the free drug
  - Polymorphic form – Different morphic forms of the API can have different skin permeation and retention characteristics
  - PEG molecular weight distribution – Alteration of the PEG molecular weight distribution may affect drug/vehicle interactions, causing changes in the thermodynamic activity of the drug that may affect drug delivery

Evolution of Biopharmaceutics

Determinants of
Therapeutic Equivalence

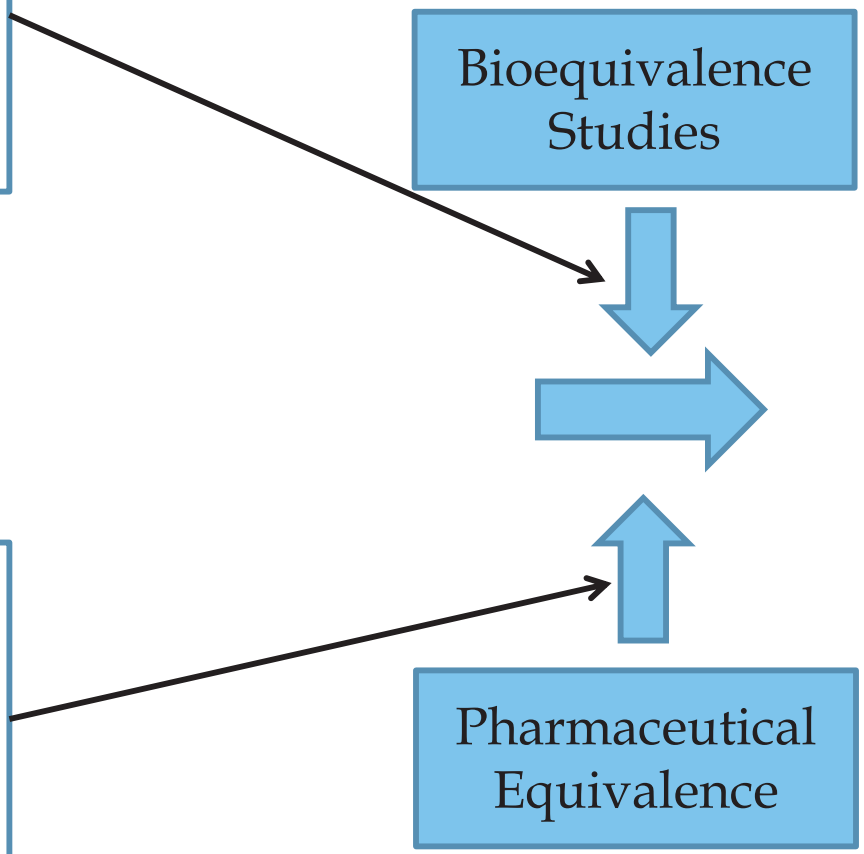


Past


Bioequivalence Studies
All risks of product inequivalence must be managed by design of bioequivalence study
Pharmaceutical Equivalence
Minimal evaluation of pharmaceutical equivalence: dosage form, strength

Future

Design of bioequivalence study complements equivalence in design and performance. Fewer inequivalence risks are managed by BE study



QbD informed evaluation of pharmaceutical equivalence: dosage form, strength, product design and product performance

Conclusions

- You cannot use modern approaches to pharmaceutical development without a biopharmaceutics foundation
- No BCS like classification for inhalation and topical products
- Key formulation variables are known
- Need for in vitro release tests