OGD Research Program

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Definition of a Generic Drug

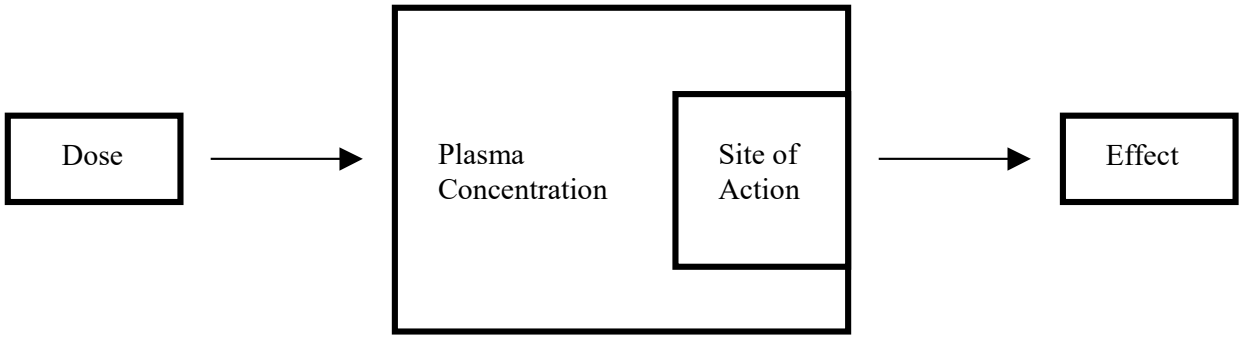
- Approved Generic Products are **Therapeutically Equivalent** to a Reference Listed Drug
  - Interchangeable with the reference drug
    - Same strength, dosage form, route of administration
  - Same clinical and safety profile when administered according to the label
  - Comparable in quality with the reference drug

Therapeutic Equivalence

FDA considers products to be therapeutically equivalent if they are:

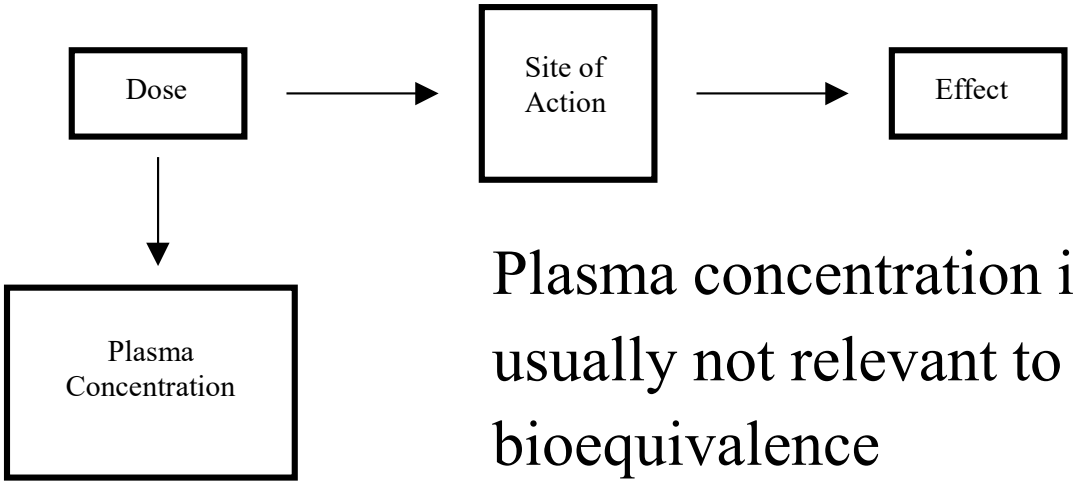
- Safe and Effective
- Pharmaceutical Equivalents
  - Same active ingredient, dosage form, route of administration, strength, purity, quality
- Bioequivalent
  - the rate and extent of absorption are not significantly different when administered at the same molar dose under similar experimental conditions
- Adequately Labeled
- Manufactured via cGMP

Systemic Drugs



- When the plasma concentration is equivalent to the site of action
  - Bioequivalence methods well established
  - OGD is highly optimized
    - 373 approvals in FY 2003
  - Still some scientific challenges at the edges

Locally Acting Drugs



Plasma concentration is usually not relevant to bioequivalence

21 CFR 320.24 allows alternatives:

- in vivo pharmacodynamics
- in vivo clinical comparisons
- in vitro comparisons
- other appropriate approaches

Need for OGD Research Program

OGD Research Program

- Respond to scientific challenges in ANDAs
  - Impurities
  - Polymorphism
  - Complex Drug Products
  - Endogenous Drug Products
- Scientific basis for future generic products
  - Topical
  - Nasal
  - Inhalation
  - Liposomes

Polymorphism

- Scientific symposium on polymorphism, June 7, 2002
- FDA ACPS support, October 21-22, 2002
- GPhA/OGD joint meeting, February 6, 2003
- CMC CC review, March 19, 2003
- Scientific Consideration: *Pharm. Res.,* April, 2003
- Guidance to be issued?

Polymorphism in the Final Rule

- ANDA must demonstrate that a drug product containing the polymorph will perform the same as the drug product described in the NDA.
  - Description of the polymorphic form of the DS
  - Executed batch record
  - Demonstration of BE
  - Relevant CMC
  - Comparative in vitro dissolution testing

Impurities

- OGD Impurity Working Group
  - To provide a scientific perspective on Drug Substance and Drug Product Impurities in Abbreviated New Drug Applications (ANDAs)
  - To propose recommendations for ANDAs on identification, qualification, and acceptance criteria establishment of drug substance and drug product Impurities

Complex Drug Substances

- Low molecular weight heparin (LMWH)
  - Product contains a distribution of molecular species
  - Pharmaceutical equivalence requires the “same” active ingredient
  - Developed criteria to evaluate claims that two LMWH product contain the same active ingredient

Endogenous Drug Products

- The Challenge
  - If the drug substance is present in the body naturally, then bioequivalence based on plasma concentrations may not be correct
- Evaluate BE methods
  - Baseline correction methods
  - Role of feedback control
  - PK/PD modeling

Key Scientific Challenge

- Bioequivalence of locally acting drugs
  - Examples
    - Topical
    - Nasal Spray Suspensions
    - Inhalation
  - Current FDA guidances require clinical testing
  - Target research to provide a scientific basis for *in vitro* or *in vivo* bioequivalence methods

Topical Products

- *In Vitro* Method
  - Explore various approaches to develop methods to determine BE of topical products
    - Formulation Characterization (Q3)
    - Dermatopharmacokinetics (DPK)

Development of Q3 Concept

- In vitro methods to assess structural similarity of topical products
  - Q1: Qualitative similarity in composition
  - Q2: Quantitative similarity in composition
  - Q3: Structural similarity
    - Describe the physical attributes and state of the product
    - Reflect changes in manufacturing or physical state of starting materials

DPK: Improvement of Methodology

- Objectives
  - Develop and demonstrate an improved skin stripping methodology for studying dermatopharmacokinetics of topical dermatological products in the stratum corneum of human subjects *in vivo*.
  - Provide the basis for a new bioequivalence guidance for topical anti-fungal products.

Nasal and Inhalation Product BE

- Nasal and Inhalation BEs
- Nasal BE - Draft guidance (revised 2003)
  - in vitro BE methods for nasal spray **solutions**
  - no BE methods for nasal spray **suspensions**
- Inhalation BE - No guidance
  - Received several control correspondence
- Sept 2003 Symposium: *Pharmaceutical aerosols and sprays*

Imaging Techniques

- Imaging is a critical technology for locally acting products
- Link between *in vitro* test and *in vivo* performance
  - Directly measure DPK of topical drug products
  - Distribution of particles in the lung
- Scientific challenges in tagging or labeling complex formulations