

T A B D

Bioequivalence of Topical Drug Products

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Introduction

- Products applied locally to the skin to treat diseases of the skin
- Types of products
 - Creams
 - Ointments
 - Gels
 - Solutions
 - Suspensions
 - NOT transdermals

Evolution of Scientific Thinking

- Early regulatory approaches to generic topicals
 - Pharmaceutical equivalents
 - Waivers of in vivo studies
- Evidence of non-therapeutically equivalent generic topical corticosteroid products
 - Stoughton, Arch Dermatol 1987;123:1312-4
- Change to in vivo BE testing
- Guidances
 - Topical Dermatologic Corticosteroids: In Vivo Bioequivalence - 2 June 1995

Definition of Bioequivalence

- Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions

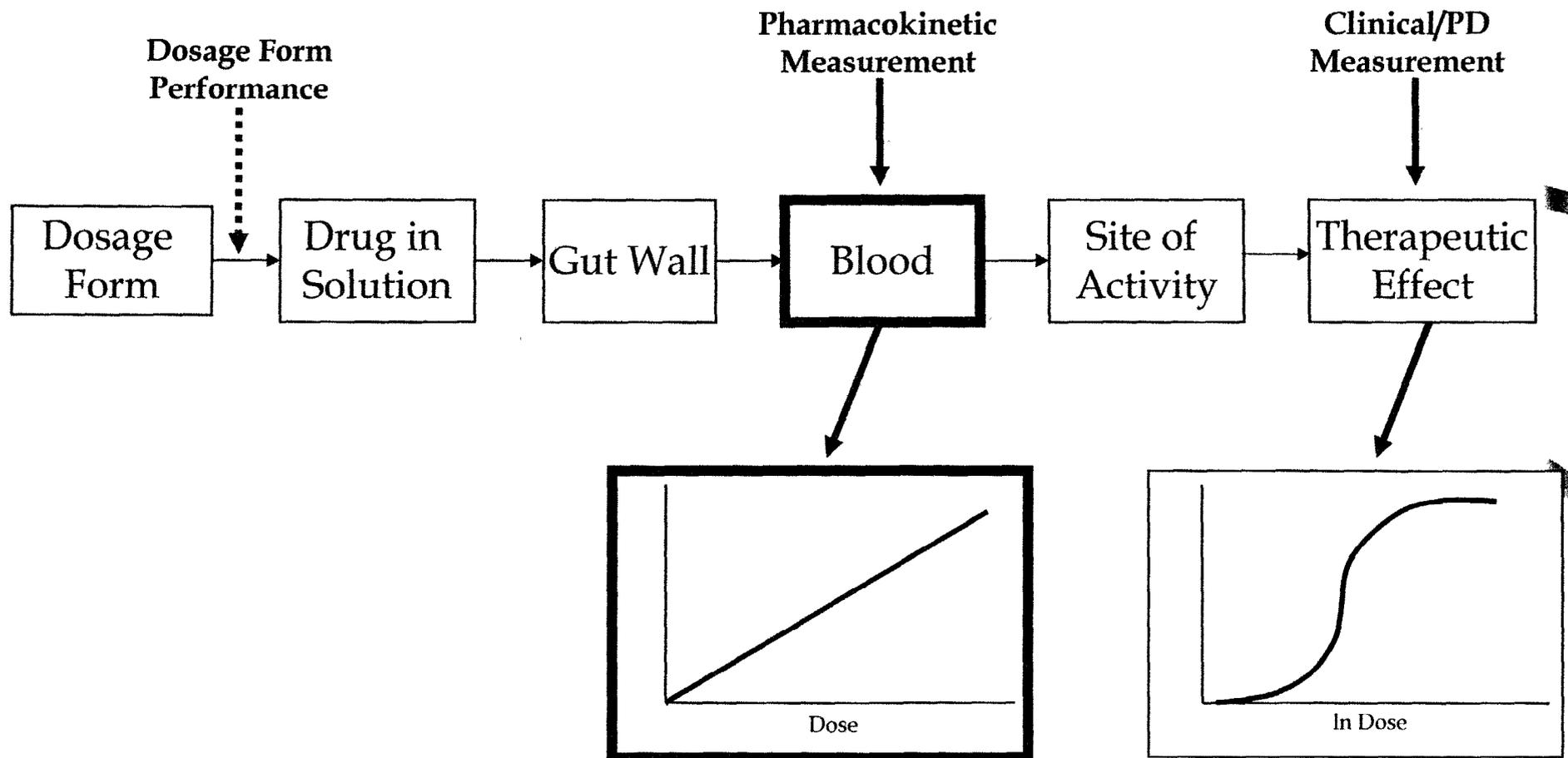
Purpose of BE

- Therapeutic equivalence (TE)
- Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring.
- The most efficient method of assuring TE is to assure that the formulations perform in an equivalent manner.

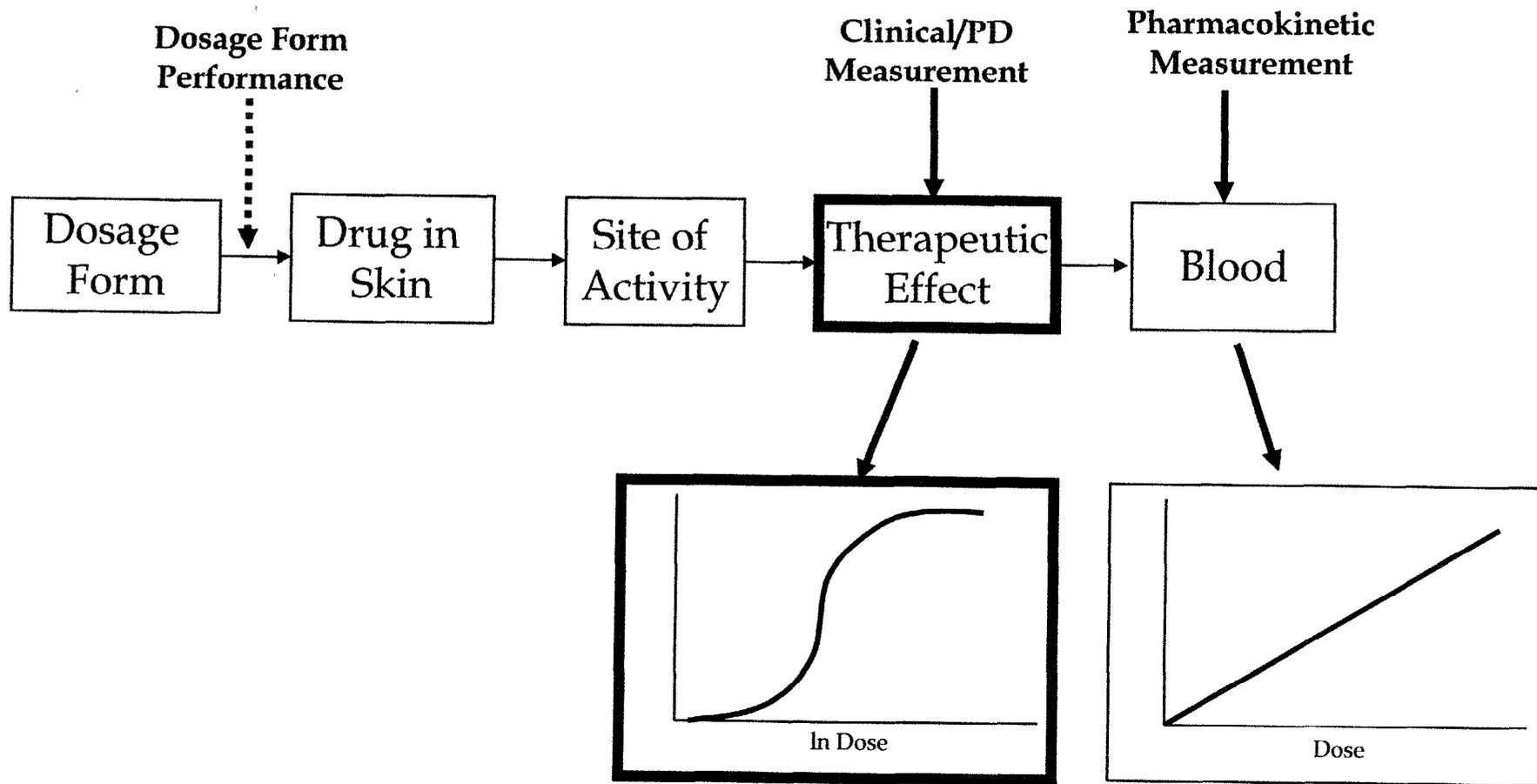
Approaches to Determining Bioequivalence (21 CFR 320.24)

- In vivo measurement of active moiety or moieties in biologic fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

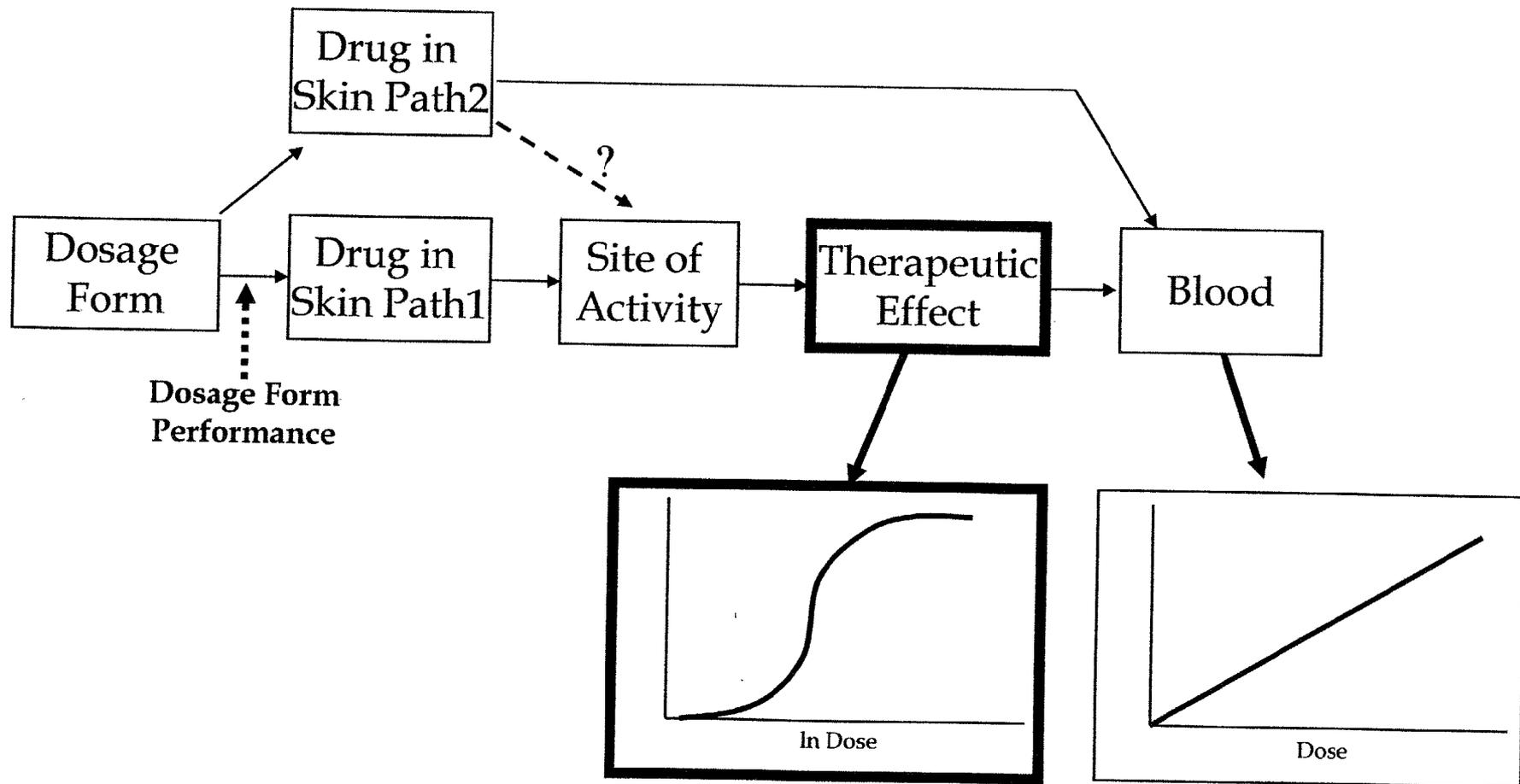
Model of Oral Dosage Form Performance



Simplistic Model of Topical Dosage Form Performance



Model of Topical Dosage Form Performance



Topical Corticosteroids

- Guidance: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence - 2 June 1995
- Pharmacodynamic measurement
- “Blanching” effect
- Dose controlled through duration of application (dose-duration)
- Dose-effect relationship established during each study

Dermatopharmacokinetics

- Product placed on skin and removed at several timepoints
- “Skin stripping” with tape
- Kinetics of drug penetration into stratum corneum studied
- Problems
 - Studied only one “pathway”
 - Not proven to be related to drug availability at the site of activity
 - Different results from different labs

Special Considerations for BE of Topical Products

- Semi-solid topical products are complex dosage forms
- The skin is not a homogeneous “slab” of tissue
 - Several pathways through the skin into the body
 - Stratum corneum
 - Sweat glands
 - Hair follicles

Special Considerations for BE of Topical Products

- Plasma concentrations are not an accurate measure of drug availability at the site of activity
- Surrogate measures may not always adequately reflect availability at the site of activity
- Clinical/PD measures for BE determination
 - Variable
 - May lack sensitivity
 - Limited ability to control dose