A Research Strategy to Develop Efficient BE Approaches for Complex Generic Topical Products

FDA-CRCG Workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Topical Product Development

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Code of Federal Regulations (CFR)

- A generic drug product must demonstrate that it is bioequivalent to a reference standard drug product
- Bioequivalence (BE) is

  "*…the absence of a significant difference in the rate and extent to which the active ingredient …becomes available at the site of drug action …in an appropriately designed study.*" - 21 CFR 314.3
- The type of evidence that is considered to be the most accurate, sensitive, and reproducible for determining the bioavailability (BA) or BE of a drug product is

  "*…an in vivo test in humans in which the concentration of the active ingredient …in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time.*" - 21 CFR 320.24

Cutaneous Pharmacokinetics (PK)

- For topical products applied on the skin, 21 CFR 320.24 indicates

  "*…an in vivo test in humans in which the concentration of the active ingredient …in [an] appropriate biological fluid is measured as a function of time*"

  would provide the most accurate, sensitive, and reproducible evidence for BE
- In other words, cutaneous PK based BE approaches are the ideal
  - Several such approaches have been conceived
    - Tape stripping, dermal microdialysis & open flow microperfusion, spectroscopic methods
  - There were fundamental scientific and practical challenges
    - Sampling depth, frequency, duration, reproducibility/variability, PK fundamentals
  - For decades, FDA has supported research to develop such approaches

Efficient Approaches for Topical BE

- In parallel, FDA supported research to develop in vitro BE methods
- 21 CFR 320.24 also lists in vitro evidence that can demonstrate BE

  "*An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data; or … [a] currently available in vitro test acceptable to FDA (usually a dissolution rate test) that ensures human in vivo bioavailability*"
- For topical products, in vitro BE approaches may include an in vitro release test (IVRT) and an in vitro permeation test (IVPT)
  - Notably, IVPT studies are also cutaneous PK based BE approaches
  - This is relevant to today's workshop because numerous scientific advances that supported the regulatory utility of IVPT studies also laid the foundation to make in vivo cutaneous PK approaches feasible, and more efficient
    - Study design considerations, validation approaches, data and statistical analysis methods

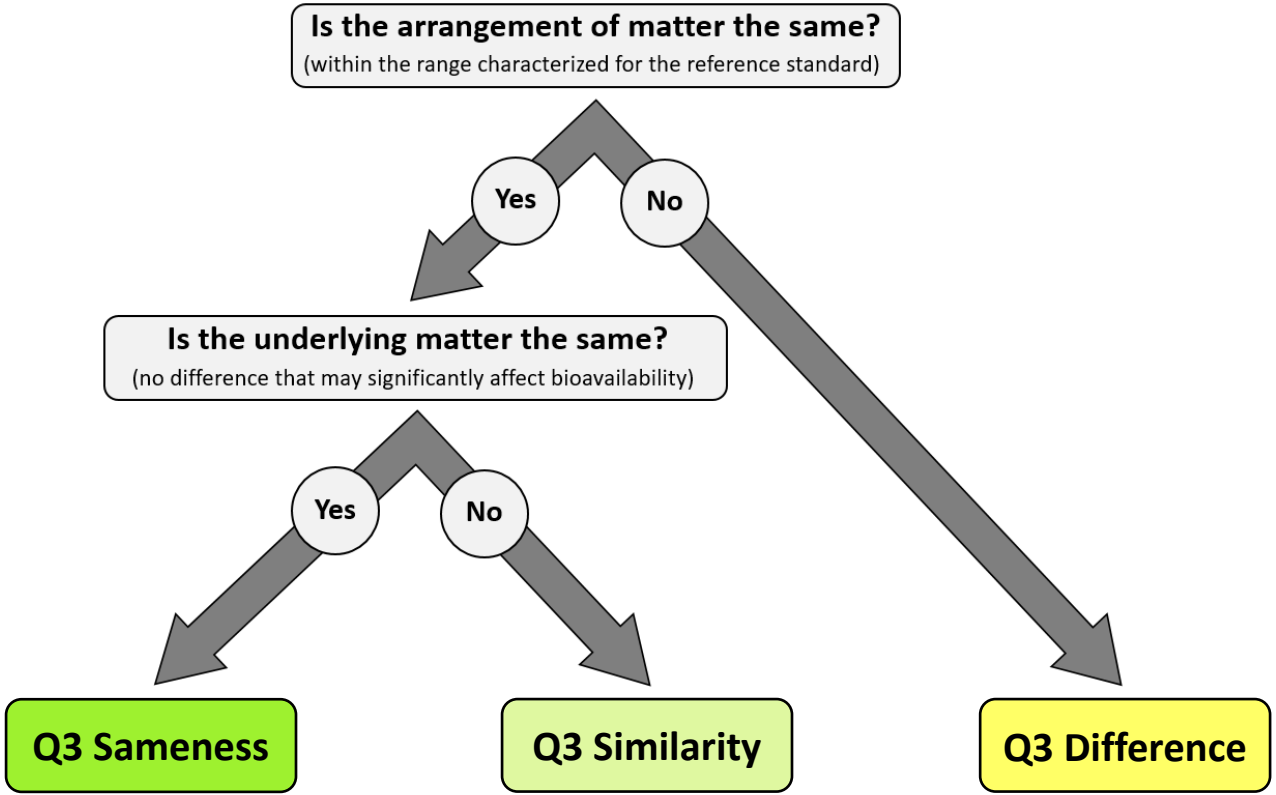
Topical BE Modernization Strategies

- One strategy facilitated the development of topical generics that were precisely matched to the reference standard, within the batch-to-batch variation of the reference standard product
  - To assess this, FDA supported research that developed and optimized
    - In vitro tests to compare physicochemical and structural (Q3) product quality attributes
    - In vitro (IVRT) BE studies to compare the rate of drug release from the dosage form
    - In vitro (IVPT) BE studies to compare the rate and extent of drug permeation into skin
- Another strategy facilitated the development of in vivo cutaneous PK based BE approaches
  - In vivo dermal open flow microperfusion (dOFM) and dermal microdialysis (dMD) methods are currently in an advanced state of development

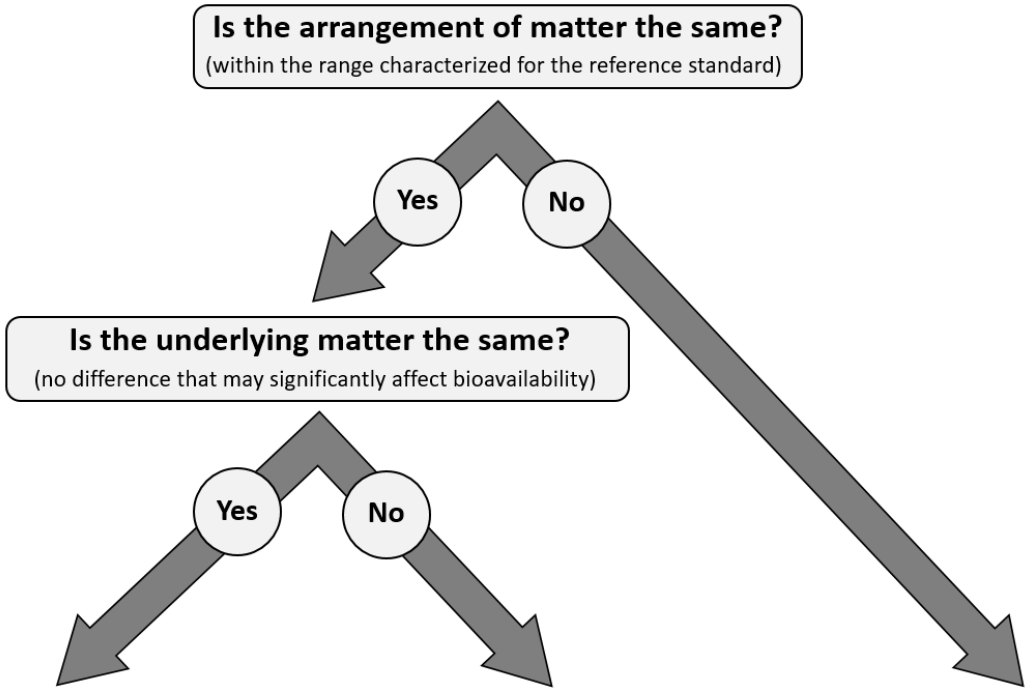
Topical BE Toolkit

- Multiple complementary approaches to address failure modes for BE
  - To establish when there is no significant difference (NSD) in the qualitative (Q1) or quantitative (Q2) composition of two topical formulations
  - To compare Q3 attributes between two topical products
  - To perform IVRT method validation, BE study conduct, and data analysis
  - To perform IVPT method validation, BE study conduct, and data analysis
  - To perform in silico modeling and simulation and support a demonstration of BE
  - To perform in vivo systemic (plasma) PK BE study conduct and data analysis
  - To perform in vivo local (cutaneous) PK BE study conduct and data analysis
- Implementing efficient topical BE standards
  1. Product formulations that have **NSD in Q1, Q2, or Q3** attributes compared to the reference standard are typically eligible for **in vitro based BE** approaches
  2. Product formulations that have **a difference in Q1, Q2, Q3** attributes compared to the reference standard are eligible for **in vivo based BE** approaches

Q3 Draft Guidance for Industry



Product-Specific Guidances (PSGs)



Generally eligible for characterization-based (in vitro) BE approaches in current PSGs

In vivo cutaneous PK dOFM/dMD BE studies?

Generally eligible for traditional in vivo BE approaches in current PSGs

In Vivo Cutaneous PK BE Studies

- Current state (benefits/challenges/opportunities)
  - Ideal type of evidence to demonstrate BE for topical products per FDA CFR
  - Multiple drugs and dosage forms have been studied by multiple researchers
  - Key elements of protocols and operating procedures have been developed
  - Considerations for study designs, controls, and validation are well defined
  - Scientific principles for cutaneous PK BE studies are in an advanced state
  - Study design elements and analytical methods may need optimization
  - Data and statistical analysis procedures may need optimization

The Goal of Today's Workshop

- The sessions of this workshop are intended to help us discuss:
  1. The influence of formulation differences on failure modes for BE in vivo, and potential contexts of regulatory use for in vivo cutaneous PK BE studies
  2. The scientific and practical challenges with conducting and assessing in vivo cutaneous PK BE studies, and the considerations impacting efficiency
  3. The specific procedural and technical methods that we can optimize to ensure in vivo dOFM/dMD studies efficiently mitigate failure modes for BE
- The goal of today's workshop is to:
  - Identify scientifically appropriate, practical, and efficient approaches for conducting and assessing in vivo dOFM/dMD BE studies that generic product developers would likely consider feasible to utilize for the development of topical generic products.

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