Innovation and Harmonization of Bioequivalence Standards for Generic Topical and Transdermal Products

Complex Generic Drug Product Development Workshop

Session 2: Scientific and Regulatory Advances for Generic Topical and Transdermal Product Development

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Priyanka Ghosh, PhD

Pharmacologist

Division of Therapeutic Performance, Office of Research and Standards

Office of Generic Drugs |CDER | U.S. FDA

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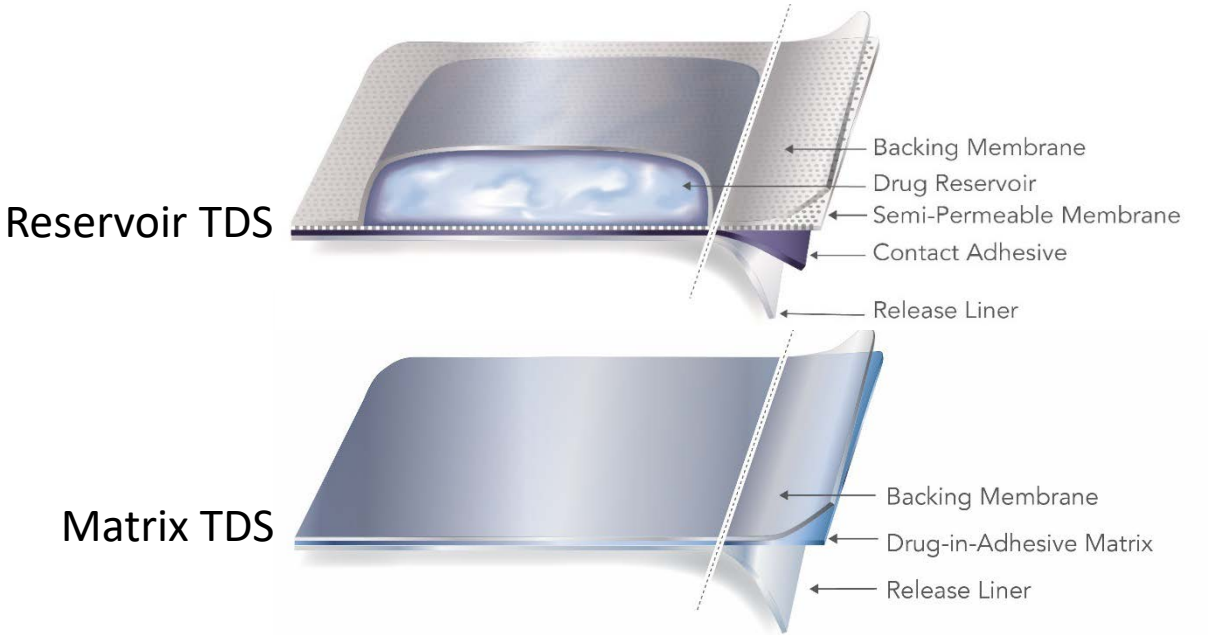
Outline

Transdermal and Topical Delivery Systems

- General Guidances
- Product-Specific Guidances

Topical Dermatological Drug Products

- Product-Specific Guidances

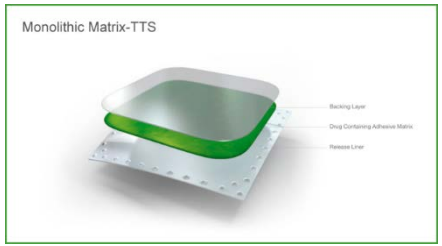


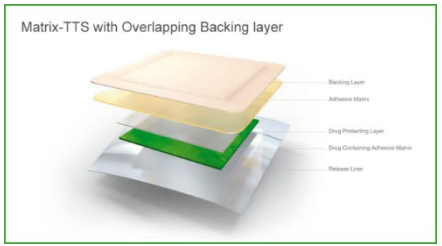
Transdermal and Topical Delivery System (TDS)

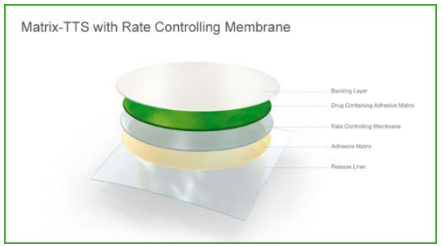
For additional information, please see the draft guidance for industry, ANDA Submissions – Refuse-to-Receive Standards

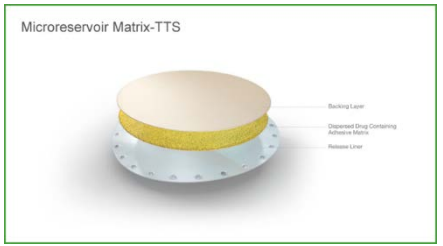
TDS products

- Design variation even among “Matrix” TDS









The graphic is adapted from https://ltslohmann.de/en/technology/transdermal-therapeutic-systems/

Generic TDS products

- Compared to the reference product, a generic TDS may have
  - Different failure modes related to product design
    - Adhesion (Differences in size/shape/composition)
    - Irritation (Differences in composition)
    - Heat effects (Differences in composition)
    - Abuse potential (Differences in drug load)
    - Crystallization
    - Cold flow, Etc.

Evaluation of Bioequivalence for TDS

- In Vivo Studies for Demonstration of Bioequivalence (BE) for TDS
  - An in vivo comparative BE study with pharmacokinetic endpoints [1]
  - An in vivo comparative adhesion study [2]
  - An in vivo comparative irritation/sensitization study [3]

For additional information, please see the following draft guidances for industry,

1. Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA
2. Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs
3. Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs

General Guidance on Adhesion

Draft guidance on assessing generic TDS adhesion

- Published June, 2016
  - Study design considerations
  - Introduced a new statistical analysis approach
    - Revised criteria for primary and secondary endpoints
  - Discussed numerous critical study controls, for example
    - Discouraged tampering with TDS
    - Discouraged restrictions on normal subject motion
- Revised October, 2018 (incorporating feedback from stakeholders)
  - Clarity related to how data should be collected and analyzed
  - Potential use of alternative scales

General Guidance on Irritation

Draft guidance for industry on assessing generic TDS irritation and sensitization

- Published October, 2018
  - Study design considerations
  - Introduced a new statistical analysis approach
  - Introduced concepts for when a sensitization study may not be appropriate
  - Discussed numerous critical study controls, for example
    - Discouraged restrictions on normal subject motion
    - Potential for use of alternative scales

Product-Specific Guidances (PSG) for TDS

- 27 PSG's (new and revised) published since October 2018

Active Ingredient: Buprenorphine

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mcg/hr
   Subjects: Males and non-pregnant, non-lactating females, general population
2. Type of study: Adhesion study
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mcg/hr
   Subjects: Males and non-pregnant, non-lactating females, general population
3. Type of study: Skin irritation and sensitization study
   Design: Randomized, evaluator-blinded, within-subject repeat in vivo
   Strength: Vehicle TDS and positive control (TDS containing the active pharmaceutical ingredient should not be used in this study due to safety concerns)
   Subjects: Males and non-pregnant, non-lactating females, general population

For additional information, please see the draft guidance for industry on Buprenorphine TDS

Product-Specific Guidances (PSG) for TDS

- BE study with pharmacokinetic (PK) endpoints
  - Integration of PSG's with external references e.g., product label

> Unless otherwise justified, the buprenorphine TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference listed drug (RLD) product, and worn for 7 days. Applicants should randomize subjects to receive either the test or RLD product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.

Product-Specific Guidances (PSG) for TDS

- BE study with PK endpoints
  - Data collection and analysis of PK study

> Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the PK may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the PK study. The PK samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.

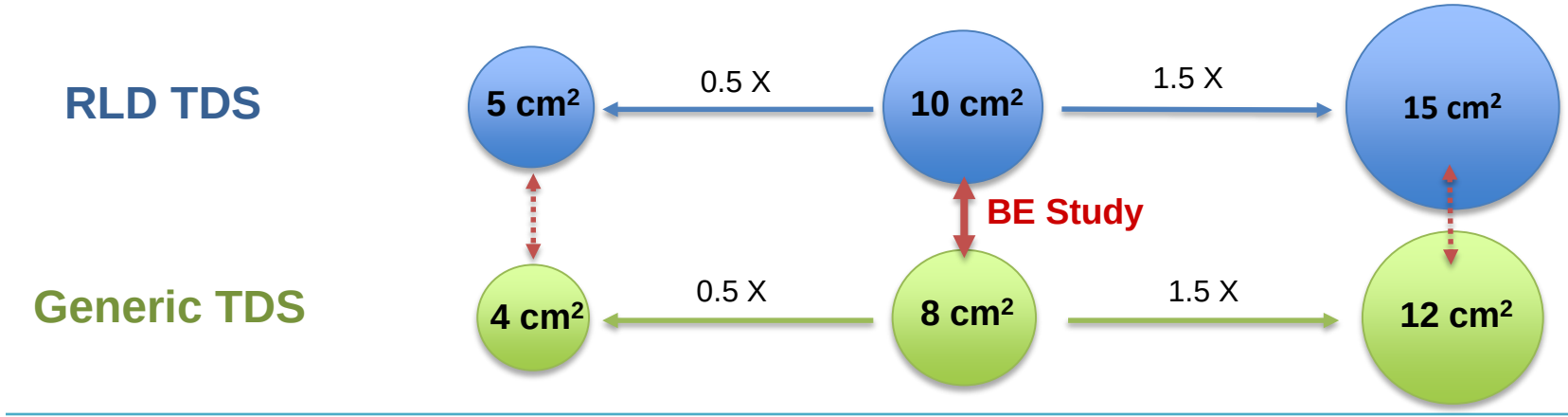
Product-Specific Guidances (PSG) for TDS

- Waiver request of in vivo testing
  - Proportionality of a TDS

Waiver request of in vivo testing: The 4.6 mg/24 hr and 13.3 mg/24 hr strengths of the TDS may be considered for a waiver of in vivo BE testing based on (i) an acceptable BE study with the 9.5 mg/24 hr strength TDS, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the TDS formulation across all strengths.

NOTE: The proportional similarity of the TDS formulation across all strengths means i) that the amounts of active and inactive ingredients per unit of active surface area are the identical for the different strengths of the test product, and ii) that the ratios of the active surface areas of each strength of the test product compared to the 9.5 mg/24 hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the RLD product compared to the 9.5 mg/24 hr strength of the RLD product.

Proportionality of TDS



Product-Specific Guidances (PSG) for TDS

- Dissolution studies
  - Simplifying language related to conduct of dissolution study

> **Dissolution test method and sampling times:** Comparative dissolution testing should be conducted on 12 dosage units each, of all strengths of the test and RLD products. Information on a dissolution method for this drug product can be found on the FDA Dissolution Methods web site, accessible at: http://www.accessdata.fda.gov/scripts/cder/dissolution/.

Product-Specific Guidances (PSG) for TDS

- Adhesion study
  - Alignment with general guidance

> The applicant may elect to evaluate the PK BE (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the BE, and independently, the comparative assessment of adhesion.

  - Selection of population for analysis of PK and adhesion data

> Applicants should prespecify their inclusion criteria for the statistical analysis of PK endpoints and perform their primary PK analysis on the PP population. For the primary PK parameters, applicants should calculate the geometric mean ratios for the T/R treatments and the two-sided 90% confidence intervals.

Product-Specific Guidances (PSG) for TDS

- Irritation and/or Sensitization(I/S) study
  - Selection of size and duration of wear for I/S study

All test articles (i.e., one-half of the 4.6 mg/24 hr test product[1], one-half of the 4.6 mg/24 hr RLD product, one-half of the optional vehicle TDS[2] and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended for dosing in the approved labeling for the RLD product.

Sequential TDS applications should be made to the same application site every 24 hours, for a total of 21 consecutive days. The TDS applied on Day 21 should be removed on Day 22.

Guidances for TDS

- Residual drug

  – Recommendation related to assessment of residual drug

> Applicants should collect and analyze PK samples from all subjects in the PK subpopulation, regardless of the subjects' TDS adhesion scores, and report the sample concentrations for all time points as well as the PK results for all subjects in the PK study. All TDS units that are removed at the end of (or which detach during) the in vivo adhesion and/or PK BE study should be retained for analysis of residual drug content.[8]

For additional information, please see the following draft guidance for industry, Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs

Guidances for TDS

- 27 PSG's have been published
  - Consistent structure and recommendations across all PSG's
  - Clarity related to strength/size/duration of the study
  - Clarity related to waiver of in vivo testing
  - Removal of studies that don't impact an assessment of BE for a specific product e.g., sensitization study
  - Repetitive information was migrated to the general guidances
- Harmonized recommendations across all PSG's in alignment with the general guidances with the goal of increasing the efficiency of TDS product development programs

Topical Dermatological Drug Products

PSG's for Topical Dermatological Products

Potential ways to establish BE for complex topicals:

- Comparative clinical BE studies
  - Clinical (efficacy) endpoint
  - Pharmacodynamic endpoint (e.g., vasoconstrictor studies)
- Characterization-based BE studies
  - in vitro
  - in vivo PK studies

PSG's for Topical Dermatological Products

A Modular and Scalable Approach to BE Evaluation

- Sameness of inactive ingredient components and quantitative composition e.g. qualitative **(Q1)** and quantitative **(Q2)** sameness
- **Q3** (Physical & Structural Characterization) as relevant to the nature of the product
- **IVRT** (In Vitro Release Test)
- **IVPT** (In Vitro Permeation Test) or another bio-relevant assay may be appropriate for some products
- In Vivo systemic **PK** studies may be appropriate for some products

PSG's for Topical Dermatological Products

- Formulation
  - What do we mean by no difference in inactive ingredients

1. In vitro option:

To qualify for the in vitro option to demonstrate bioequivalence for metronidazole topical gel, 0.75% the following criteria should be met:

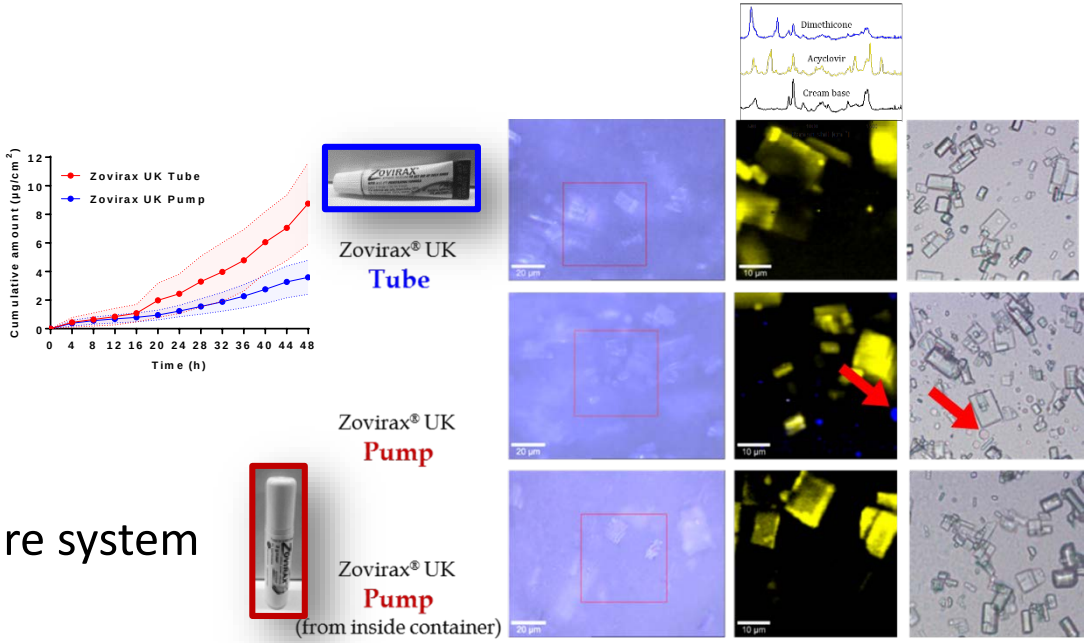
A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*[1], the bioequivalence of the test product with respect to the reference product may be established using the in vitro option if the criteria below are also satisfied.

PSG's for Topical Dermatological Products

- Q3
  - Example of Q3 recommended for single phase systems
    - Appearance
    - Microscopy
    - Particle size
    - Polymorphic form
    - Drying rate (weight loss)
    - Specific gravity
    - Rheology
    - pH
    - Etc.

PSG's for Topical Dermatological Products

- Q3
  - Example of Q3 recommended for multi phase systems
    - Appearance
    - Microscopy
    - Particle size
    - Polymorphic form
    - Drying rate
    - Specific gravity
    - Rheology
    - pH
    - Water activity
    - Globule size
    - Impact of container closure system
    - Etc.



Prof. Michael Roberts FDA Award U01-FD005226

PSG's for Topical Dermatological Products

- IVRT

> The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

  - IVRT method development
  - IVRT method validation
  - IVRT pivotal study

- If a test product is being developed for packaging in multiple container closure systems (CCS), IVRT may need to be conducted using dispensed product from each CCS compared to product dispensed from the corresponding packaging configuration of the reference product

PSG's for Topical Dermatological Products

- IVPT

> The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

  - IVPT method development
  - IVPT method validation
  - IVPT pilot study
  - IVPT pivotal study

- Clearly outline all data analysis including the statistical analysis plan within the study protocol

Generic Topical Product Development

- If a PSG is available
  - Follow the recommendation in the PSG to establish BE
  - Submit a pre-ANDA meeting request when you propose an alternative BE approach
  - Submit controlled correspondence (CC) for questions related to appropriateness of a formulation for a specific BE approach, etc.

- If PSG is Unavailable

  Steps toward the development of a generic topical product
  - Identify the reference listed drug (RLD)
  - Identify the studies proposed to support a demonstration of BE appropriate to the complexity of the dosage form

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Guidance Development Teams

Transdermal and Topical Dermatological Guidance Development Teams

- Office of Generic Drugs
  - Office of Research and Standards
  - Office of Bioequivalence
  - Office of Generic Drug Policy
- Office of Pharmaceutical Quality
  - Office of Lifecycle Drug Products


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