Establishing Equivalence of TDS and OIDPs

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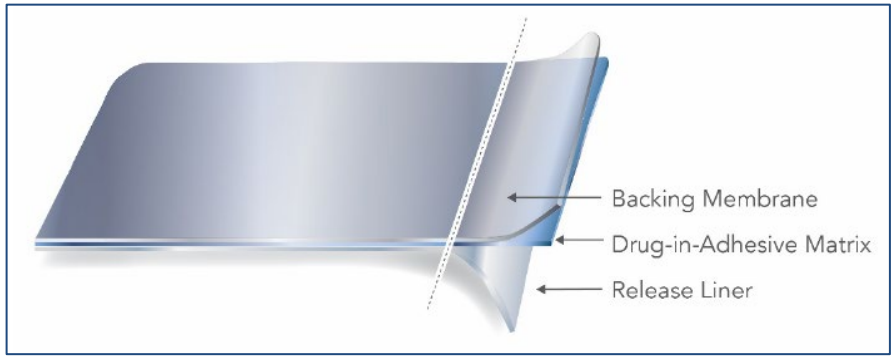
Transdermal Delivery Systems (TDS)

- "… designed to deliver the active ingredient (active substance) across the skin and into systemic circulation…"
- "TDS are combination products"



FDA Guidances for Generic TDS

Product-Specific Guidances (PSG)

Active Ingredient: Buprenorphine

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence study with pharmacokinetic 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

   Waiver request of in vivo testing: The 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr and 15 mcg/hr strengths of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 20 mcg/hr strength TDS, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the TDS formulation across all strengths.

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

PSG_021306 (Jun 2020)

Recent PSGs include recommendations related to device:

Additional information:

Device:

The reference listed drug (RLD) product is a transdermal delivery system and a drug-device combination product.

FDA recommends that prospective applicants examine the external critical design attributes of the RLD device when designing the test device.

User Interface Assessment:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.*[a]

PSG_212268 (May 2022)

FDA Guidances for Generic TDS

General Guidances

Recommendations

Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Melissa Mannion at 301-796-2747.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

low, the adverse reactions could affect thousands of individuals. To evaluate this I/S potential, applicants should compare the T and R TDS products in at least 200 evaluable subjects (see section IV.A.), and the study should be conducted under provocative conditions (repeated removal and reapplication of the TDS on the same skin site) to maximize the potential for the occurrence of an irritation and/or sensitization reaction in the subject population during the study.

In some circumstances, an in vivo study to assess the sensitization potential of a TDS product submitted in an ANDA may not be necessary if adequate justification is provided or FDA has determined that conducting a sensitization assessment is unnecessary or unethical (e.g., where the active ingredient is known to be a skin sensitizer or based on information/data related to the components and composition of TDS products) to show that the T product is not likely to be more sensitizing than the R product.

Internal Research

Active Ingredient

Buprenorphine
Clonidine
Estradiol
Ethinyl estradiol; Norelgestromin
Fentanyl
Lidocaine
Methylphenidate
Oxybutynin
Rivastigmine
Scopolamine

Inactive Ingredients from product labels

Approved ANDAs 2012-2022
Data obtained from publicly available product labels

Internal Research

RLD/RS used in the reviewed ANDA studies		ANDA Information		
RLD	**API**	**Applications**	**Irritation failures**	**Sensitization failures**
N021306	Buprenorphine	5	2	--
N018891	Clonidine	1	--	--
N020538	Estradiol	2	1	--
N203752	Estradiol	2	1	--
N021180	Ethinyl Estradiol; Norelgestromin	1	--	--
A200910	Ethinyl Estradiol; Norelgestromin	2	--	--
N019813	Fentanyl	1	--	--
N020612	Lidocaine	5	--	--
N021514	Methylphenidate	1	--	1
N021351	Oxybutinin	1	--	--
N022083	Rivastigmine	5	--	--
N017874	Scopolamine	4	--	--
Total		30	4	1

Generic TDS drug products approved during Generic Drug User Fee Amendment (GDUFA) I and II (from 10/01/2012 – 09/30/2022) were identified based on their listed approval dates in the Orange Book. Failed studies are defined in this research as studies that were determined to be inadequate during assessment. ANDAs containing a failed study were subsequently approved based on reassessment of the original study or additional datasets.

Potential Research Considerations

What kind of studies are being conducted/or can be used during product development to de risk prospective generic TDS products (irritation/sensitization perspective)?

Orally Inhaled Drug Product (OIDP)

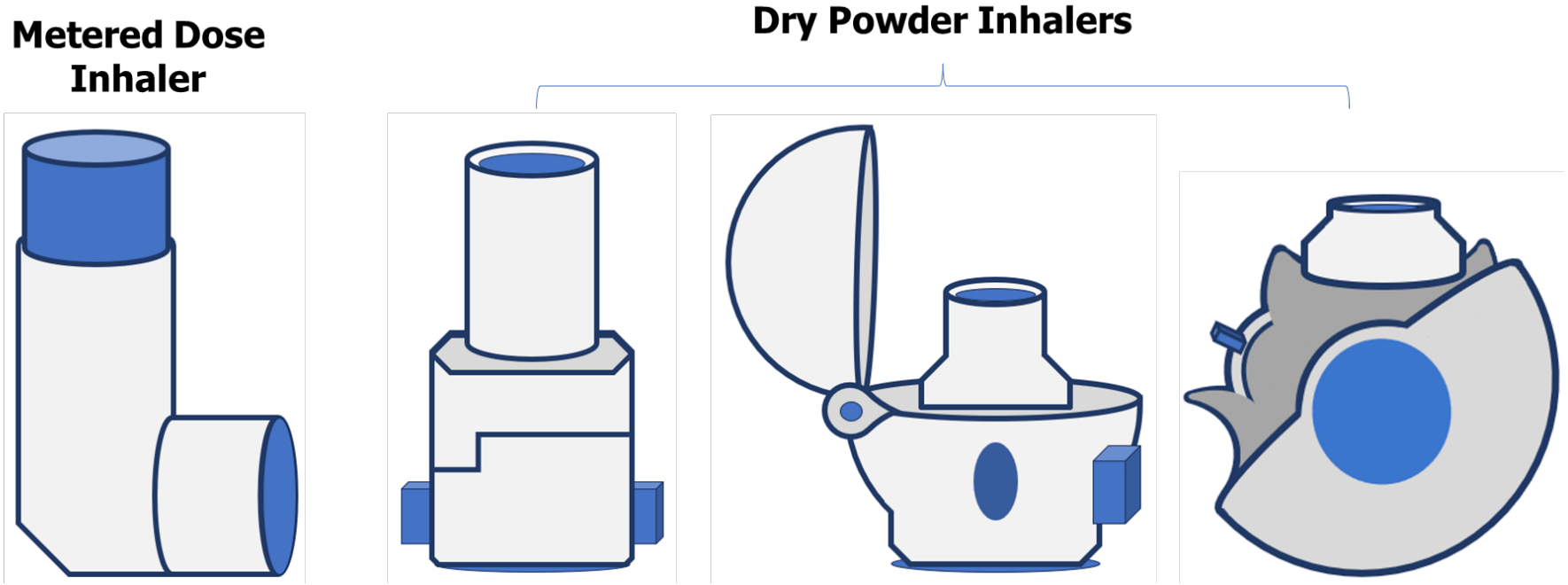


Figure courtesy David McChesney, PharmD, M.S.

Locally-Acting OIDP PSGs

Draft Suspension MDI PSGs (Feb 2024)

- *Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol, Metered*
- *Budesonide; Formoterol Fumarate; Glycopyrrolate Inhalation Aerosol, Metered*

Draft DPI PSGs (May 2024)

- *Fluticasone Propionate; Salmeterol Xinafoate Inhalation Powder*
- *Salmeterol Xinafoate Inhalation Powder*
- *Tiotropium Bromide Inhalation Powder*
- *Formoterol Fumarate Inhalation Powder*

Draft Suspension MDI PSGs (Aug 2024)

- *Fluticasone Propionate; Salmeterol Xinafoate Inhalation Aerosol, Metered*
- *Albuterol Sulfate Inhalation Aerosol, Metered*
- *Levalbuterol Tartrate Inhalation Aerosol, Metered*

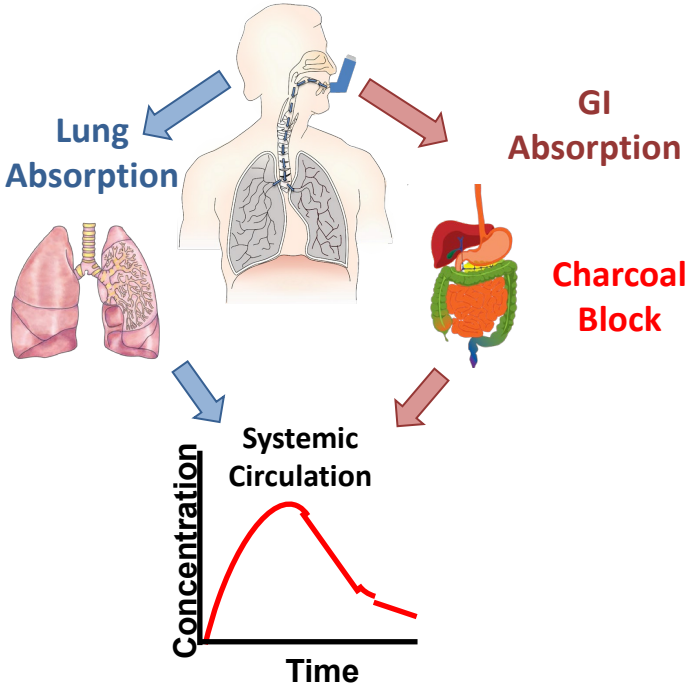
Draft Suspension MDI PSGs (Nov 2024)

- *Mometasone Furoate; Formoterol Fumarate Inhalation Aerosol, Metered*
- *Budesonide; Formoterol Fumarate Inhalation Aerosol, Metered*

BE Approach (Option 1)

- **Formulation Sameness**
- **Conventional In Vitro BE Studies**
- **Alternative In vitro BE Studies**
- **Comparative Characterization Studies**
- **In Vivo Studies**
  - In Vivo PK BE Study
  - ***In Vivo PK BE study with Charcoal Block***
- **Additional Information**
  - Optional Computational Modeling study
  - Device similarity to the RLD

In Vivo Charcoal Block PK BE Study



Drug absorption into the systemic circulation following dosing with certain OIDPs can occur through both lung absorption as well as gastrointestinal (GI) absorption. Dosing with charcoal can block GI absorption.

- For OIDPs, a portion of the emitted dose may be swallowed rather than inhaled and end up in the GI tract.
- For drug products where gut absorption provides a **significant** contribution to the observed systemic drug levels, ***charcoal block PK studies*** provide one method for distinguishing between which portion of the dose is due to pulmonary absorption as compared to GI absorption.
- Currently, a charcoal block PK study is recommended in **certain** OIDP PSGs (i.e., ***where an API has significant gut absorption***), as part of an alternative BE approach to conducting a CCEP BE study.

In Vivo Charcoal Block PK BE Study

- **PSG Recommendations:**
  - Similar to the conventional PK BE study without charcoal dosing in many aspects.
    - ***Healthy*** adult male and female subjects.
    - ***Minimum number of inhalations*** to sufficiently characterize the PK profile with a sensitive analytical method.
    - Dose administration should follow the approved labeling instructions.
    - ***Bio-IND*** may be needed if the administered dose is **above the maximum labeled single dose**.
  - The selected ***charcoal dose*** should be justified in the ANDA.
  - **BE:** 90% CI for the T/R ratio for AUC and C_{max} being between 80 – 125%.

Before conducting a charcoal block PK study, prospective applicants are strongly encouraged to discuss their study design and BE strategy (including potential alternative approaches to the charcoal block PK study) with the Agency (PDEV meetings)

Potential Research Considerations

Problem	Questions
• For the majority of OIDP PSGs that include PK BE studies, the drug dose is based on the minimum number of inhalations to sufficiently characterize the PK profile with a sensitive analytical method. • There is uncertainty with whether changes to the drug dose will impact the amount of charcoal needed to block GI absorption.	• What is the appropriate dose for charcoal block? If more than one dose of charcoal is administered, should the same amount be used for each dose? • What methodologies are suitable for determining the charcoal block dose?

Potential Research Considerations

Problem	Questions
• While literature has shown that, in general, charcoal-block PK studies involve dosing charcoal more than once, there is uncertainty with the number of doses that are sufficient for blocking GI absorption. • The Tmax for GI absorption can vary between OIDPs, which could affect the optimal timing for dosing the charcoal.	• How often should charcoal be dosed during the PK BE study? • What time(s) are optimal for dosing charcoal during the PK BE study and can these be generalized across OIDPs?

Potential Research Considerations

Problem	Questions
• While the goal of the charcoal-block PK study is to provide evaluation of the pulmonary dose, there is uncertainty as to whether other methods or sources of data can provide a similar level of evaluation for differences in the pulmonary dose between products.	• Are there alternative ways to evaluate the pulmonary dose aside from charcoal block?

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