Irritation and sensitization potential of approved topical and transdermal delivery systems – A retrospective study

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Purpose

Topical and transdermal delivery systems (TDS) are dosage forms designed to adhere to the skin for convenient, prolonged, and steady delivery of an active pharmaceutical ingredient (API). However, TDS use may result in skin irritation and sensitization (I/S) reactions due to occlusion of the application site throughout the prolonged wear period or reaction of the skin site to TDS components.

Therefore, FDA product-specific guidances (PSGs) recommend that the demonstration of therapeutic equivalence of generic TDS with respect to their reference listed drug (RLD) be generally based on in vivo comparative assessments of three key attributes, including bioequivalence based on pharmacokinetic endpoints, non-inferiority assessments of adhesion performance, and **I/S potential**. The overall goal of this study is to correlate product composition and physical differences in TDS with clinical safety and therapeutic performance attributes, i.e., I/S potential.

The relevant guidances typically recommend that applicants evaluate skin I/S compared to the reference standard (RS) in a single study, provided that a sufficient number of subjects are included to evaluate sensitization. Applicants typically need to enroll an adequate number of subjects to ensure that at least 200 evaluable subjects are included in their per protocol (PP) population; however, for irritation only studies, the number of evaluable subjects in the PP population can vary. In this study we **conducted a risk-based analysis to identify if TDS containing certain components are more prone to I/S compared to others**.

To address these outstanding questions, as a starting point, we reviewed data from approved ANDAs.

Methods

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. For each of the irritation, and sensitization evaluations conducted within these approved ANDAs, factors related to the study conduct (e.g., the number of studies conducted, study outcome, reason for initial study failure (if applicable), size and site of TDS application during the study), and product information (e.g., inactive ingredients, size, shape, etc.) for the proposed generic TDS and the corresponding RLD, as well as corresponding PSG recommendations, were collected.

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.

30 TDS ANDAs approved during GDUFA I and II (10/01/2012 – 09/30/2022) identified from the Orange Book

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Irritation, and sensitization study failures in ANDAs identified from FDA Reviews available in FDA internal databases

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FDA Review documented reasons for initial study failures collected and analyzed

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Potential correlations between initial study failures and product factors (e.g., inactive ingredients, TDS size and shape, application site studied) were analyzed

Inactive ingredients in the dataset (from product labeling)

Limited instances of study failures

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

FDA review documented reasons for study failures

ANDAs containing a failed study were subsequently approved based on reassessment of the original study or additional datasets.

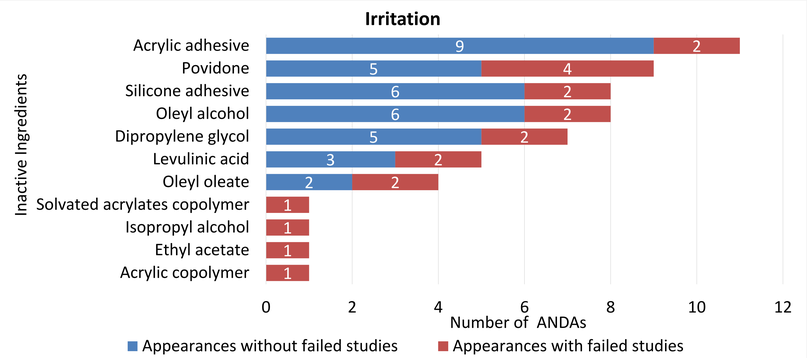
Sensitization

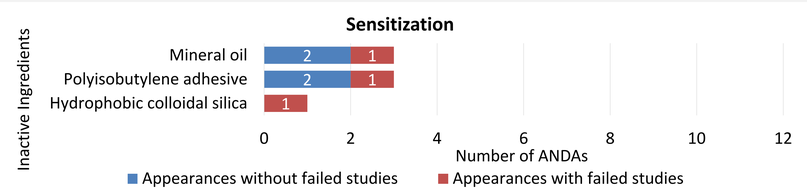
API	Reason for study failure	Subsequent approval supported by
Methylphenidate	FDA disagreed with the applicant's interpretation of the sensitization data.	Since API is known to cause sensitization reactions when applied to the skin, the data were found to be acceptable and PSG for this drug product was subsequently updated in Oct 2018 to remove recommendation of sensitization evaluation.

Irritation

API	Reason for study failure	Subsequent approval supported by
Buprenorphine	The positive control system did not appear to have functioned as anticipated, as it failed to produce sufficient irritation.	A new study that addressed the specific limitation related to study design, and the product was not reformulated
	The applicant hypothesized that the dry, arid climate of one of the clinical sites impacted the positive control system, and it failed to produce sufficient irritation. (FDA did not accept this argument.)	
Estradiol	The sample size of the study was relatively small, raising questions about the power of the study.	
Estradiol	Appeared to be a general product failure, as no specific causes were identified.	A new standalone study was conducted, and the product was not reformulated

Analysis of potential correlation between I/S study failure and product





Note: A total of 67 inactive ingredients in the 30 ANDAs were reviewed in this study. The inactive ingredients that are summarized in the graph above are limited to those that are present in ANDAs that originally contained a failed study but were subsequently approved based on reassessment of the original study or additional datasets. The data are represented to illustrate the number of times the inactive ingredient was used in a product that had a failed study compared to the total number of times the inactive ingredient has been used across the 30 ANDAs. The data are grouped based on the nomenclature in the drug product labeling.

Conclusions

The analysis of the approved ANDAs over the last decade suggests that, in general, TDS products appear to be well designed, with limited instances of study failures being observed across the I/S studies reviewed.

The reason for observed failures during evaluation of I/S studies were not specifically attributed to any product-related factors, particularly the inactive ingredients.

Further research is warranted to understand how inactive ingredients (including the backing membrane) within a formulation may influence the I/S potential of a prospective generic TDS.

Disclosure and Acknowledgements

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