

Product Development Considerations for Generic Transdermal Delivery Systems (TDS)

Complex Generic Drug Product Development Workshop

Session 5: Complex Route of Delivery/Dosage Forms

Topical (Dermatological) and Transdermal

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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.

Equivalence for Generics

- Pharmaceutical Equivalence (PE)
 - Same active ingredient(s) and
 - Same dosage form and
 - Same route of administration and
 - Same strength
- Bioequivalence (BE)
 - No significant differences in rate and extent of absorption at site of action
- Therapeutic Equivalence (TE) of Generic Products
 - PE + BE
 - Expected to have the same clinical effect and safety profile under labeled use

PE for TDS Products

- For TDS products, strength is defined by the nominal drug delivery rate, not drug load, and adjusted by size
- So, compared to the Reference Listed Drug (RLD) TDS product, a generic TDS of the same strength may have a
 - Different drug load
 - Different formulation composition
 - Different residual drug excess
 - Different product size and/or shape
 - Different heat effects due to different drug load and design

Failure Modes for BE/TE

- Failure modes for TE may arise from:
 - Differences in “inactive” ingredients?
 - Differences in dosage form design?
 - Differences in the drug load or size of the TDS?
- These differences may collectively affect
 - Generic TDS **adhesion to skin**
 - Generic TDS **dose proportionality**
 - Generic TDS **heat effects**





Shape Considerations for TDS



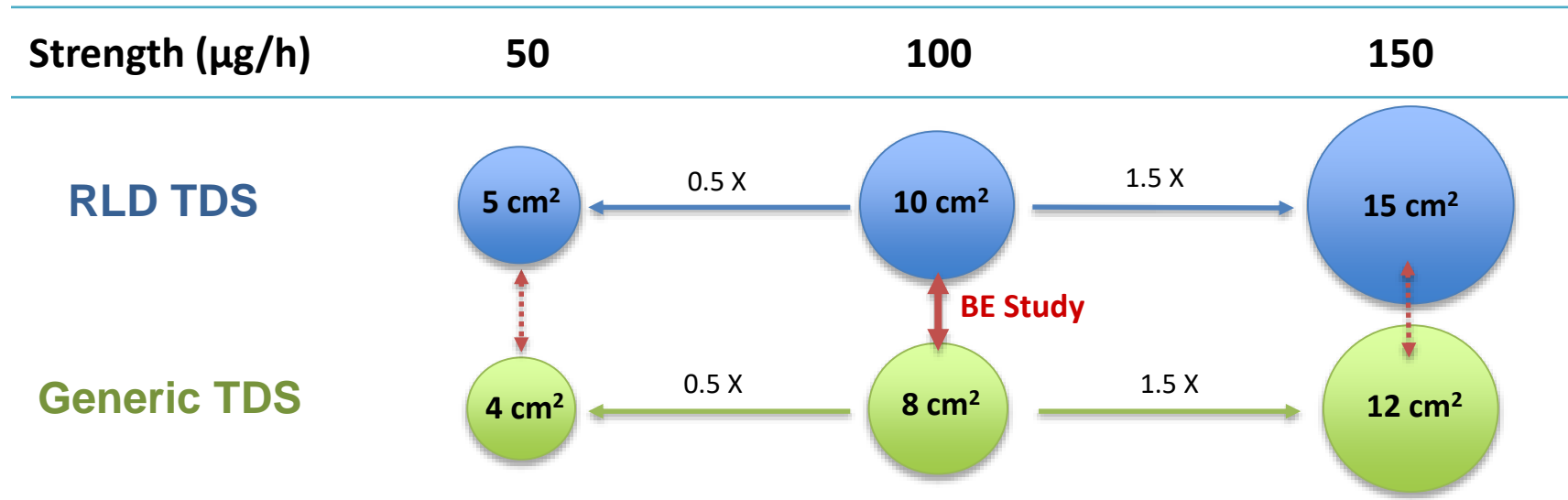
Corners may be more prone to lifting, and a long rectangular TDS may experience different torsional strains depending upon the anatomical site and the orientation in which it is applied.

A generic TDS may have a different formulation, size and/or shape; these differences may affect the TDS adhesion to skin.



Study	Test	Reference	Non-Inferior Adhesion
A			May Fail
B			May Pass

Proportional Similarity of TDS



“The proportional similarity of the formulation across all strengths” means:

- Identical amounts of ingredients per unit of active surface area for all strengths.
- Identical ratios of the active surface areas for the Test and RLD TDS.

Proportionality of Exelon® TDS



- Case Study: Exelon® (rivastigmine) TDS
 - The ratios of ***labeled (nominal)*** strengths are not proportional to the ratios of **actual** active surface areas or of **actual** drug load across all strengths.

	RLD NDA 022083		Nominal Strength
Exelon® TDS	Area (cm ²)	Drug Load (mg)	(mg/24h)
High Strength	15	27	13.3
Mid Strength	10	18	9.5
Low Strength	5	9	4.6
Ratio of High/Mid	1.500	1.500	1.400
Ratio of Low/Mid	0.500	0.500	0.484



- The “proportional similarity of the formulation across all strengths” should be based on the **actual** active surface areas of the Exelon® TDS.

Impact of Heat on TDS Performance



Considerations for various scenarios of heat exposure:

- Early heat
- Late heat
- Continuous heat

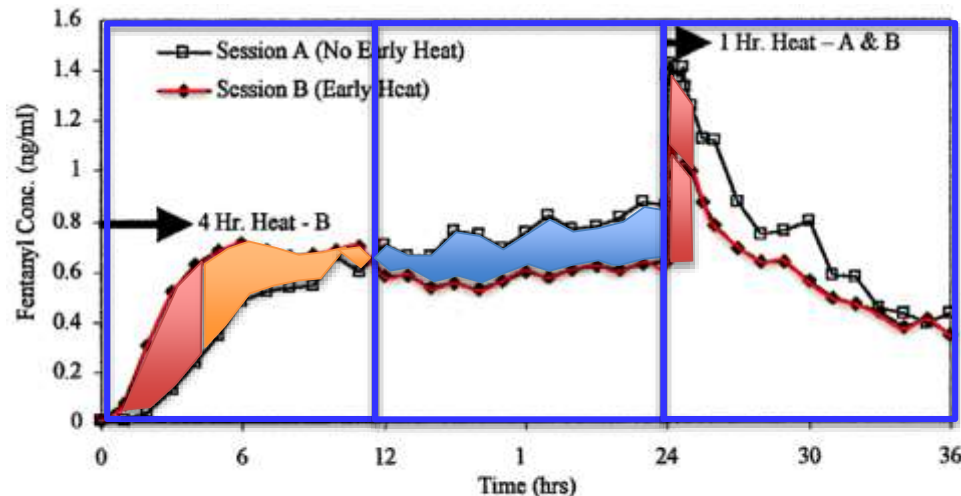


FIGURE SOURCES: <http://www.clinicaladvisor.com/termsandconditions/>
(Authorized non-commercial use) Inset image from the Ortho Evra®
Prescribing Information (package insert)

Figure 1. Mean serum fentanyl concentrations after transdermal fentanyl delivery with and without heat (n = 10).

FIGURE SOURCE: Ashburn et al. (2003) The Pharmacokinetics of Transdermal Fentanyl Delivered With and Without Controlled Heat. Journal of Pain Vol. 4, No 6: 291-297

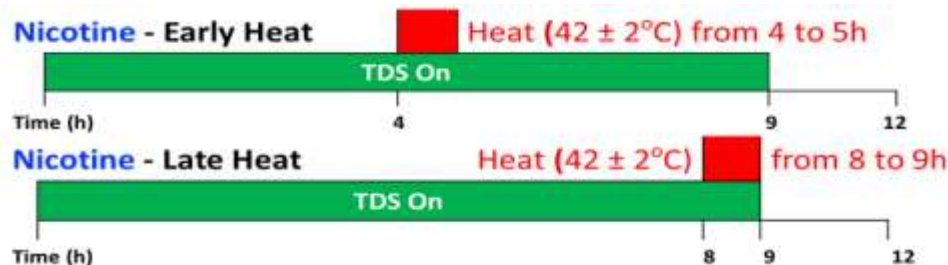
Study of Nicotine TDS Heat Effects



- Two different (pharmaceutically equivalent) nicotine TDS products.

Nicotine TDDS 14 mg/24h	Patch size (cm ²)	Rate/Area (µg/h/cm ²)	Adhesive type	Other inactive ingredients
Nicoderm CQ®	15.75	37	Polyisobutylene	Ethylene vinyl acetate-copolymer, polyethylene between pigmented and clear polyester backing
Aveva	20	29	Polyacrylate/Silicone	Polyester backing

- Two different study designs for heat exposure to nicotine TDS products



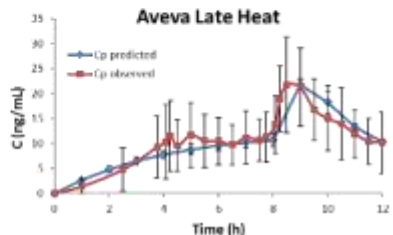
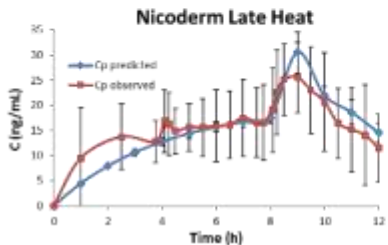
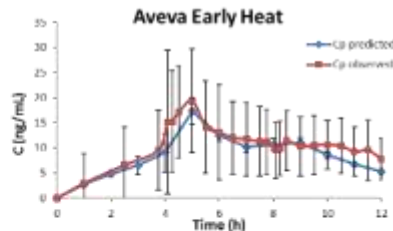
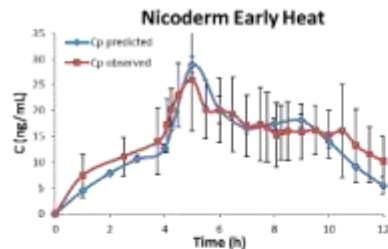
- Harmonized in vivo and in vitro permeation test (IVPT) study designs
- Evaluate whether IVPT results could predict the in vivo results

In Vitro – In Vivo Relationship

- IVPT results were reasonably predictive of Nicotine TDS heat effects in vivo

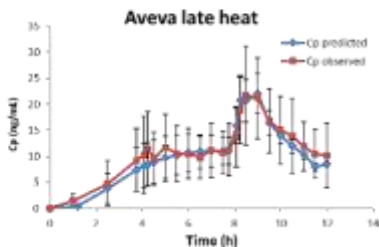
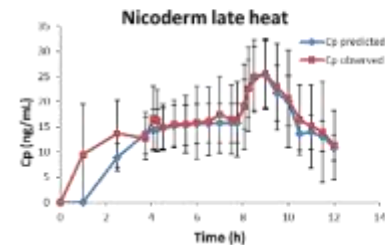
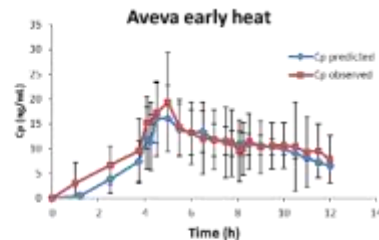
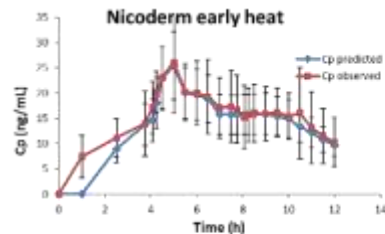
Approach I

(prediction based upon in vitro data only)



Approach II

(including an in vivo-derived heat factor)



Conclusions

- TDS products are complex, and can exhibit unique failure modes for BE/TE.
- Generic TDS products must be therapeutically equivalent for patients, despite any allowable design or formulation differences compared to the RLD TDS.
- Therefore, FDA's BE standards for TDS products comprehensively evaluate potential failure modes for BE/TE to ensure that patients have access to high quality generic TDS.

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