# 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

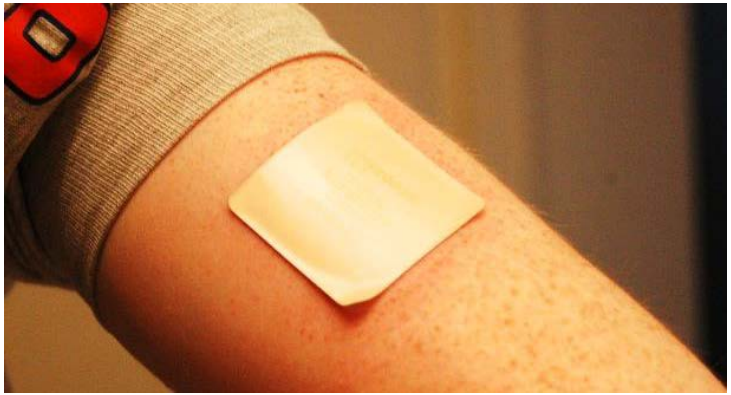
- For TDS products, strength is defined by the nominal drug delivery rate, not drug load, and adjusted by size

- 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

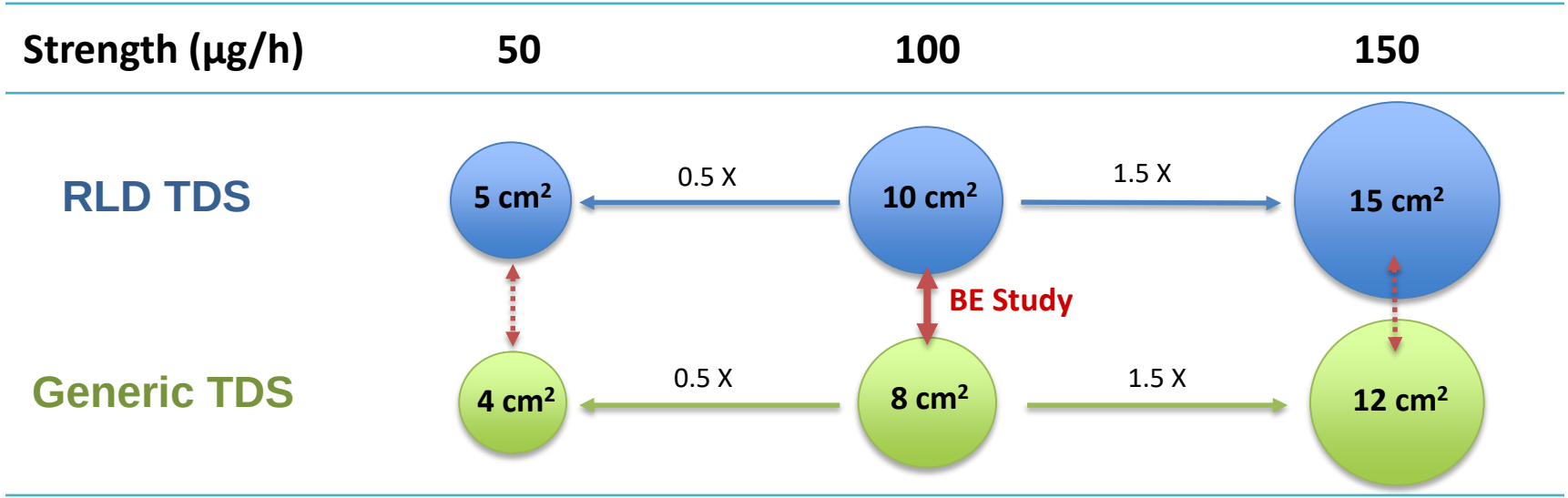


A generic TDS may have a different formulation, size and/or shape; these differences may affect the TDS adhesion to skin.

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.

| 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.


SOURCE: https://www.regulations.gov/document?D=FDA-2017-P-6923-0003

# 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)

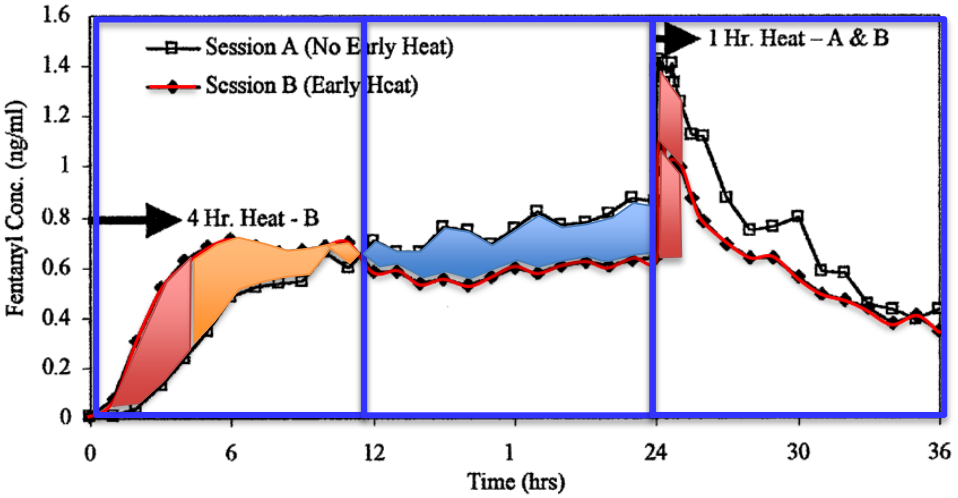



**Figure 1.** Mean serum fentanyl concentrations after transdermal fentanyl delivery with and without heat (n = 10).

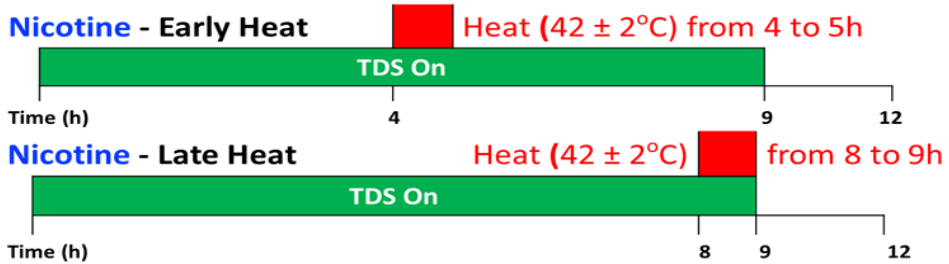
**FIGURE SOURCE**: Ashburn et al. (2003) The Pharmacokinetics of Transdermal Fentanyl Delivered With and Without Controlled Heat. Journal of Pain Vol. 4, No 6: 291-297

# Study of Nicotine TDS Heat Effects

- Two different (pharmaceutically equivalent) nicotine TDS products.

| Nicotine TDDS 14 mg/24h | Patch size ($cm^2$) | Rate/Area ($\mu g/h/cm^2$) | 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

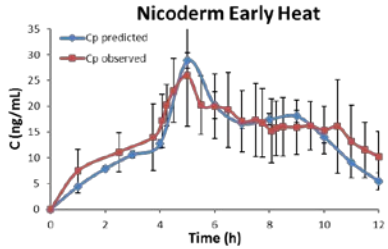


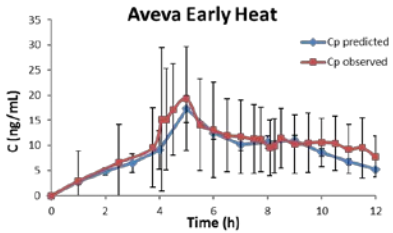

- Harmonized in vivo and in vitro permeation test (IVPT) study designs
- Evaluate whether IVPT results could predict the in vivo results

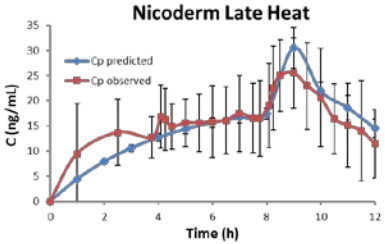
# In Vitro – In Vivo Relationship

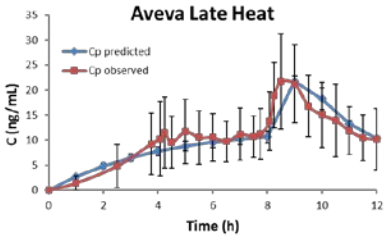
- IVPT results were reasonably predictive of Nicotine TDS heat effects in vivo

Approach I
(prediction based upon in vitro data only)

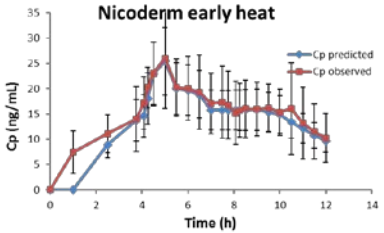


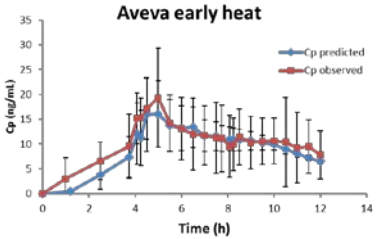



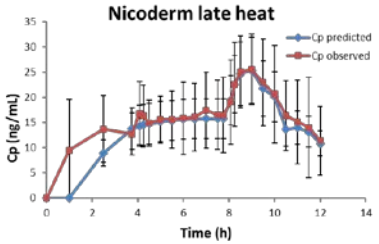



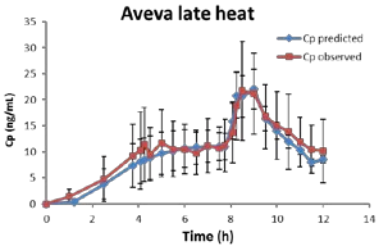




Approach II
(including an in vivo-derived heat factor)






**REFERENCE**: Shin, SH, et al. "In vitro–in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application." *Journal of Controlled Release* 270 (2018): 76-88.

# 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.

# Acknowledgements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