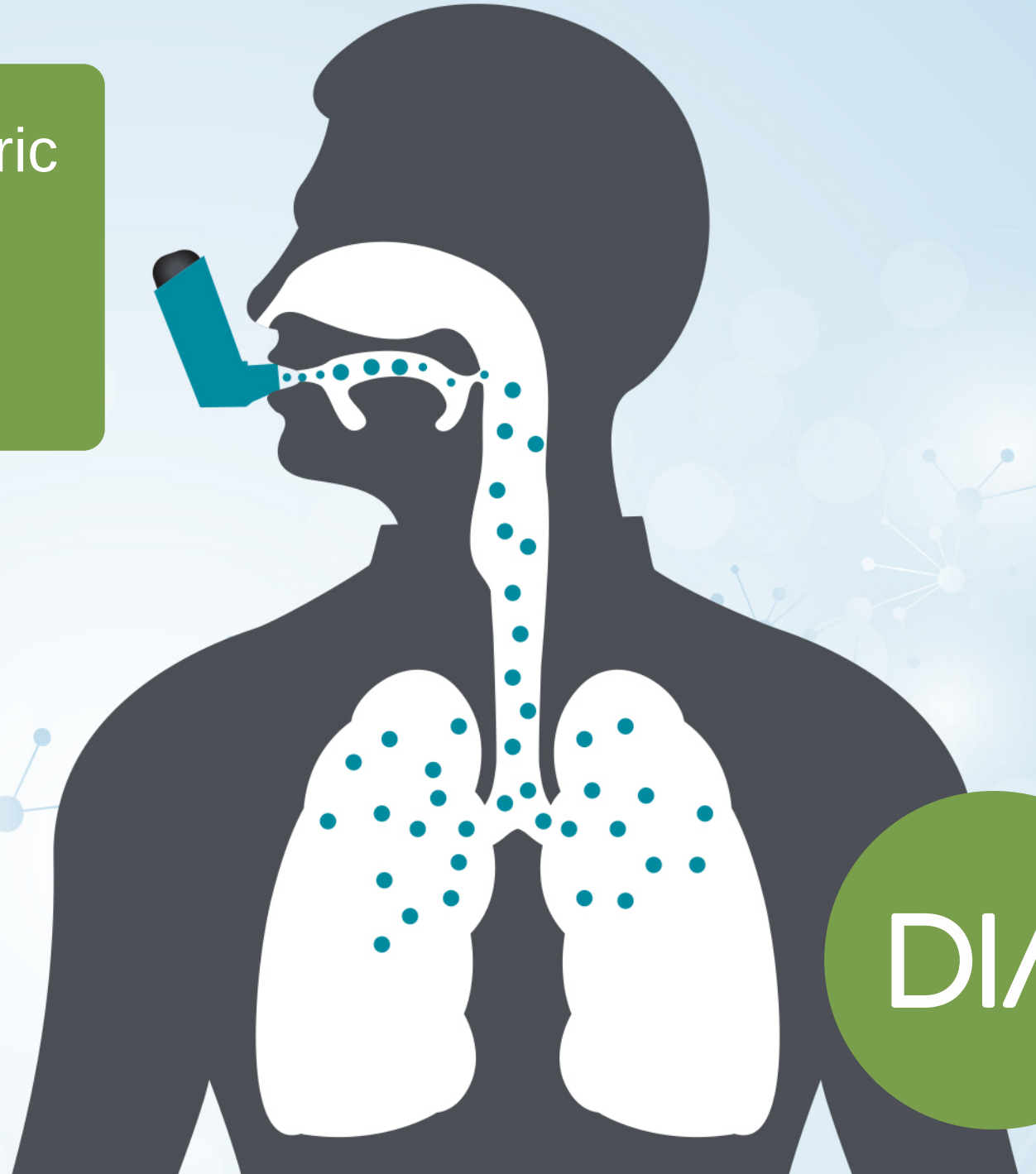
Complex Drug-Device Generic Combination Products

October 9-10
Sheraton Silver Spring, MD



DIA

Facilitating Patient Access to High-Quality Generic Transdermal Products: The Role of FDA and GDUFA

Scientific Research, Development, and Regulatory Considerations for Complex Generic Transdermal Products

DIA-FDA Complex Drug-Device Generic Combination Products Meeting

October 10, 2018 | Silver Spring, MD

DIA

Speaker Disclaimer

The opinions and conclusions expressed in this forum are the viewpoints of the speaker(s) and do not necessarily reflect the official position of the U.S. Food and Drug Administration.

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 when administered to patients under the conditions specified in the labeling

PE for TDS Products

- **For Transdermal Delivery System (TDS) drug-device combination products, strength is not defined by drug load but by nominal drug delivery rate, and strengths are adjusted by size**
- **Compared to the Reference Listed Drug (RLD) product, a pharmaceutically equivalent TDS of the same strength may have a**
  - Different drug load
  - Different “inactive” ingredients (including different adhesives)
  - Different dosage form design and formulation
  - Different product size and/or shape

Failure Modes for BE/TE

- **Failure to demonstrate BE may arise from:**
  - Differences in “inactive” ingredients
  - Differences in dosage form design and formulation
  - Differences in the drug load or size/shape of the TDS
- **These differences may have the potential to affect**
  - The rate and extent of drug delivery/absorption (BE)
  - The adhesion of the TDS to the skin
  - The irritation/sensitization potential of the TDS
  - Other TDS product attributes
    - The control of drug delivery when exposed to heat (heat effects)
    - Transparency, size, metal content, etc.

Assessment of Prospective Generic TDS Products

- **To ensure that generic TDS have the same rate and extent of absorption at the site of action, FDA recommends that applicants demonstrate BE, conducting key comparative product characterizations:**
  - An in vivo comparative BE study with pharmacokinetic endpoints
  - An in vivo comparative adhesion study
  - An in vivo comparative irritation/sensitization study
  - An in vitro comparative heat effects study
- **FDA routinely conducts and supports research to develop and/or revise scientific evidence-based regulatory standards.**

The Regulatory Impact of Scientific Research

- **Case Study #1: Assessing Generic TDS Adhesion**
  - Optimization of the study design and control parameters
  - Resolution of statistical analysis problems
- **Case Study #2: Assessing Generic TDS Heat Effects**
  - Development of methods to study TDS heat effects
  - Demonstration of the clinical relevance of an in vitro approach
- **Regulatory Impact of Scientific Research**
  - Standardization of product development for all TDS products
  - Reduction in study burden for industry
  - Increase in availability of generic TDS

Case Study #1: Assessing Generic TDS Adhesion

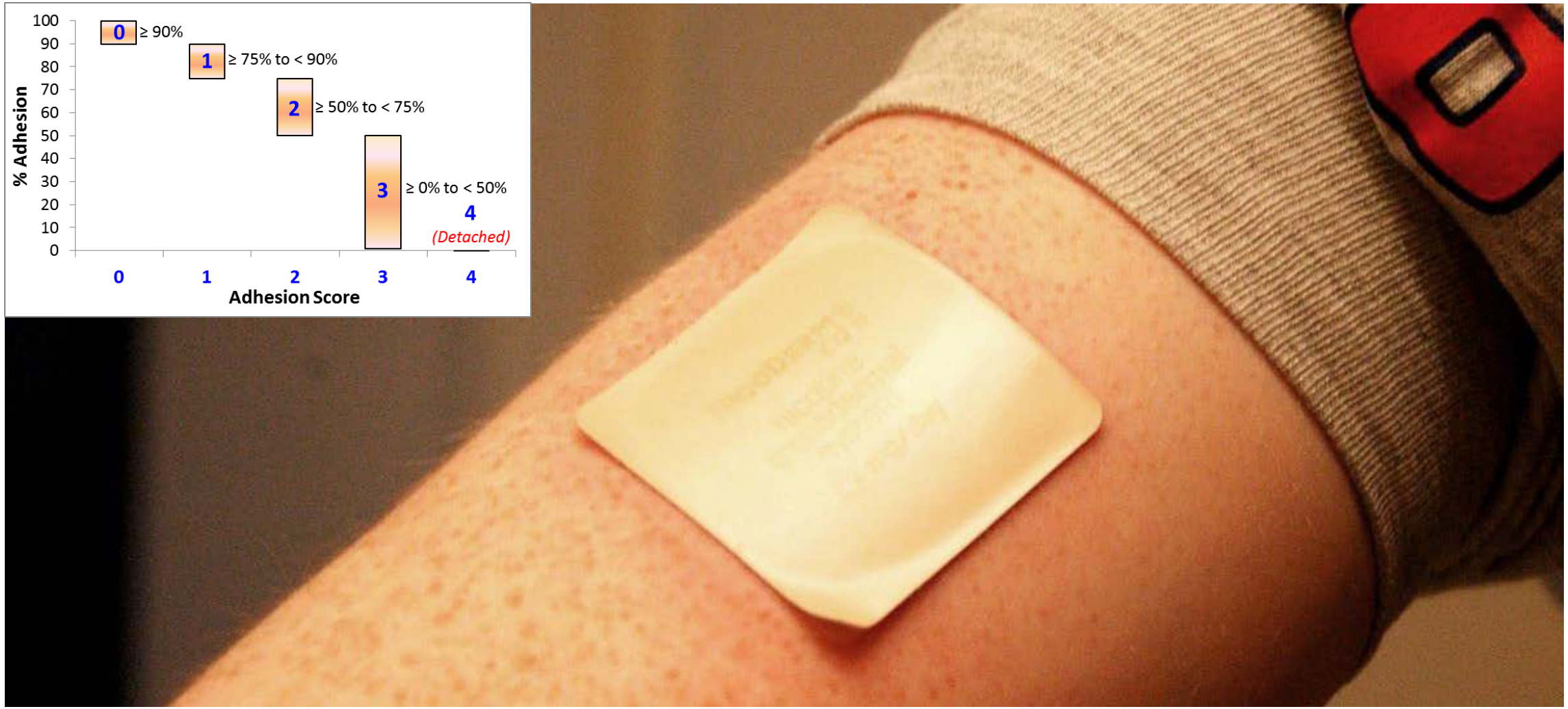


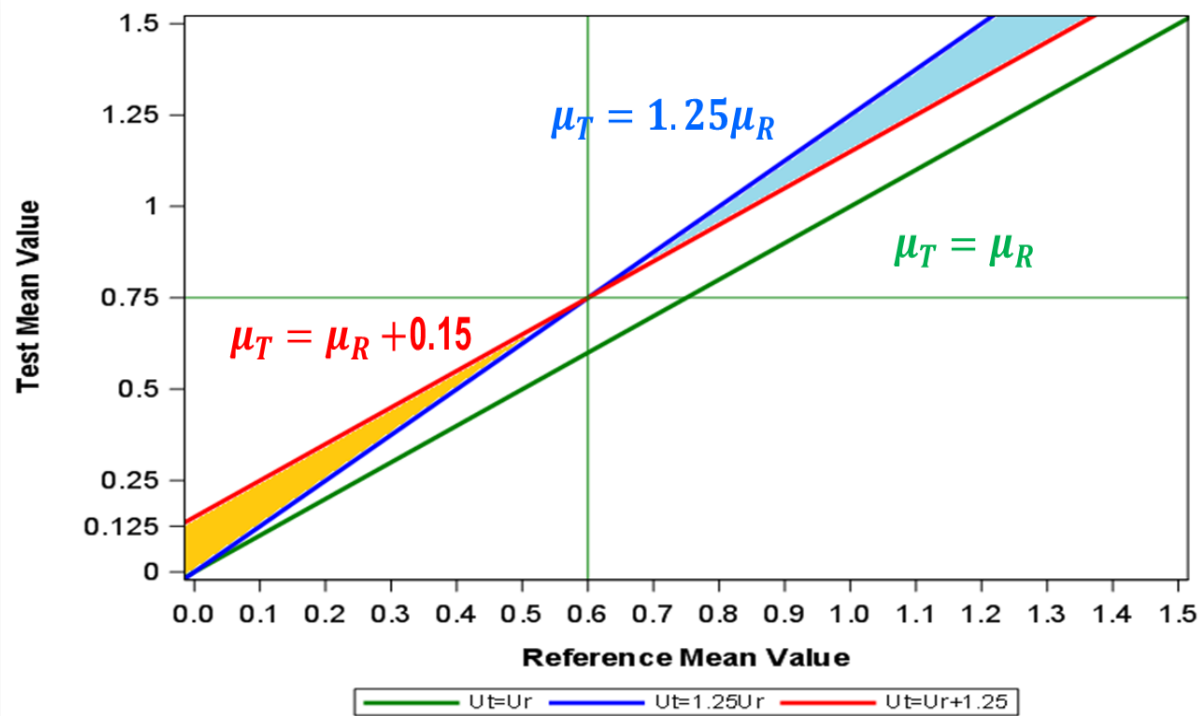
FIGURE SOURCE: https://en.wikipedia.org/wiki/Transdermal_patch (Free Media)

Case Study #1: Assessing Generic TDS Adhesion

- **Assessing TDS adhesion (historically)**
  - Study designs varied across two dozen Product-Specific Guidances (PSGs)
  - Results were difficult to interpret due to insufficient study controls
  - Major issue with statistical analysis of non-inferiority for well-adhering TDS
- **Draft guidance for industry on assessing generic TDS adhesion**
  - Published June, 2016
  - 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
    - Emphasized assessment of to-be-marketed TDS

Case Study #1: Assessing Generic TDS Adhesion

- **New statistical analysis approach:**
  - Based upon a difference of means (DOM) instead of ratio of means (ROM)
  - Margin of 0.15



Case Study #1: Assessing Generic TDS Adhesion

- **Regulatory impact of scientific research**

  Among 40 TDS adhesion studies submitted in ANDAs

  - **47.5%** (19) consistently passed by both the old and new approaches
    - These had moderate or poor adhesion for the RLD
  - **12.5%** (5) consistently failed by both the old and new approaches
    - These had moderate or poor adhesion for the RLD
  - **2.5%** (1) passed the old approach, but failed NI by the new approach
    - This had poor adhesion for the RLD
  - **37.5%** (15) failed the old approach, but passed NI by the new approach
    - These had moderate or good adhesion for the RLD

  Resulting in generics approved for fentanyl, rivastigmine & estradiol TDS

BREAKING NEWS! New and Revised TDS Guidances Posted

- **New and revised guidances for TDS products**

  27 harmonized, inter-related guidances posted in October of 2018, including:

  - 1 revised draft guidance to evaluate TDS ***adhesion***
  - 1 new draft guidance to evaluate TDS ***irritation/sensitization (I/S) potential***
  - 2 ***new PSGs*** for TDS products
  - 23 ***revised PSGs*** for TDS products

BREAKING NEWS! New and Revised TDS Guidances Posted

- **Revised draft guidance on evaluating adhesion**

  Draft Guidance for Industry on *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* includes:

  - An option to use alternative scales & scoring approaches
  - Numerous other clarifications and minor enhancements

- **New draft guidance on evaluating the I/S potential**

  Draft Guidance for Industry on *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* includes:

  - An adoption of the DOM non-inferiority statistical approach (margin of 0.20)
  - An option to use alternative scales and scoring approaches
  - An option to not conduct a sensitization study in certain situations
  - Numerous other clarifications and minor enhancements

Case Study #2: Assessing Generic TDS Heat Effects

- **Considerations for various scenarios of heat exposure:**
  - Early heat
  - Late heat
  - Continuous heat

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

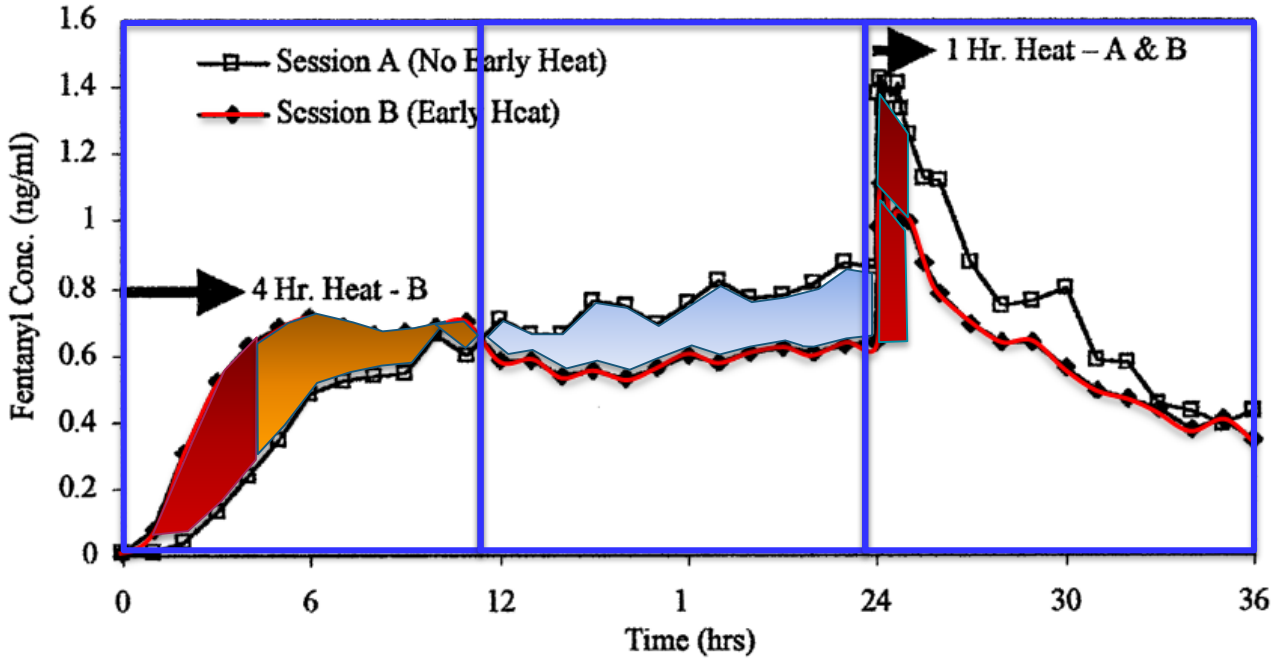


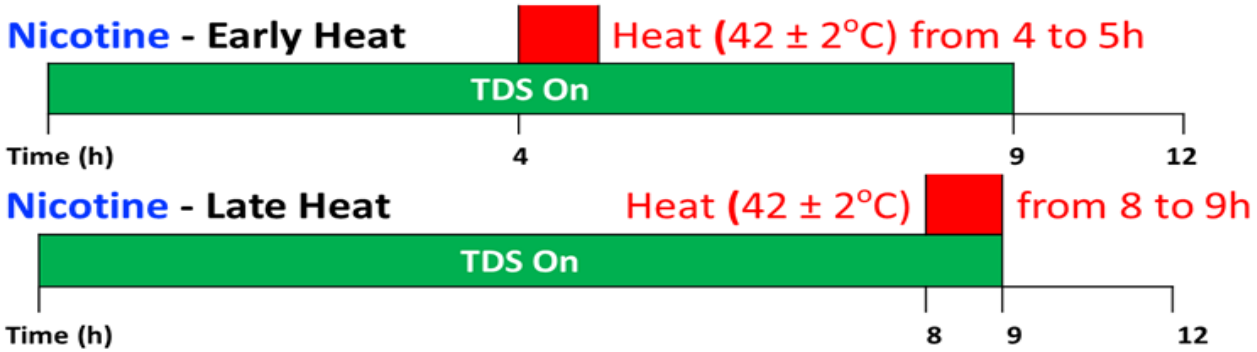
FIGURE SOURCE: Ashburn et al. (2003) The Pharmacokinetics of Transdermal Fentanyl Delivered With and Without Controlled Heat. Journal of Pain Vol. 4, No 6: 291-297

Case Study #2: Assessing Generic TDS Heat Effects

- **Two different nicotine TDS products (PE but not BE)**

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 nicotine TDS heat exposure**



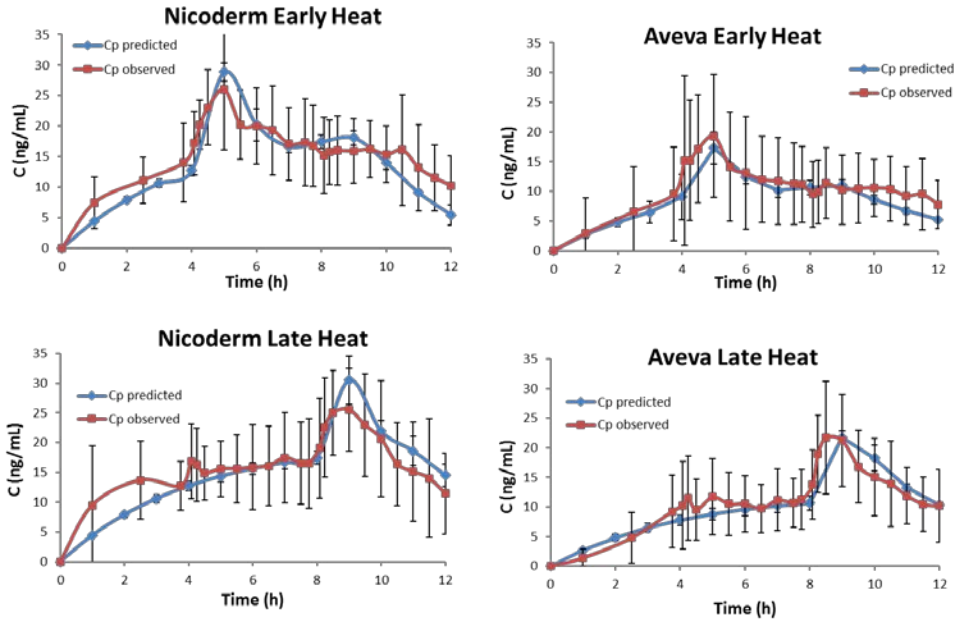
- **Study designs harmonized in vivo and in vitro**

Case Study #2: Assessing Generic TDS Heat Effects

- **In Vitro Permeation Test (IVPT) results reasonably predicted nicotine TDS heat effects in vivo**

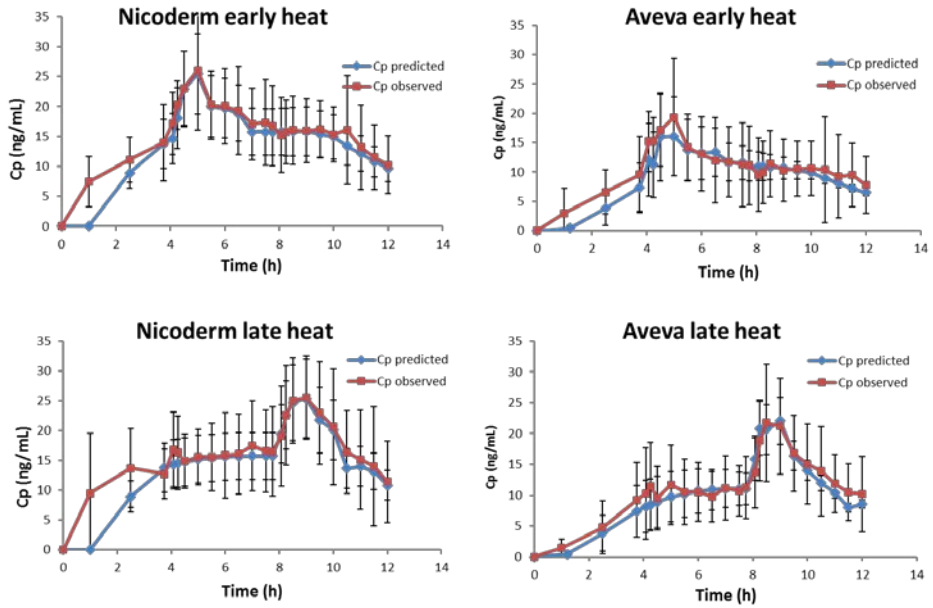
Approach I

(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.

Case Study #2: Assessing Generic TDS Heat Effects

- **Regulatory impact of scientific research**

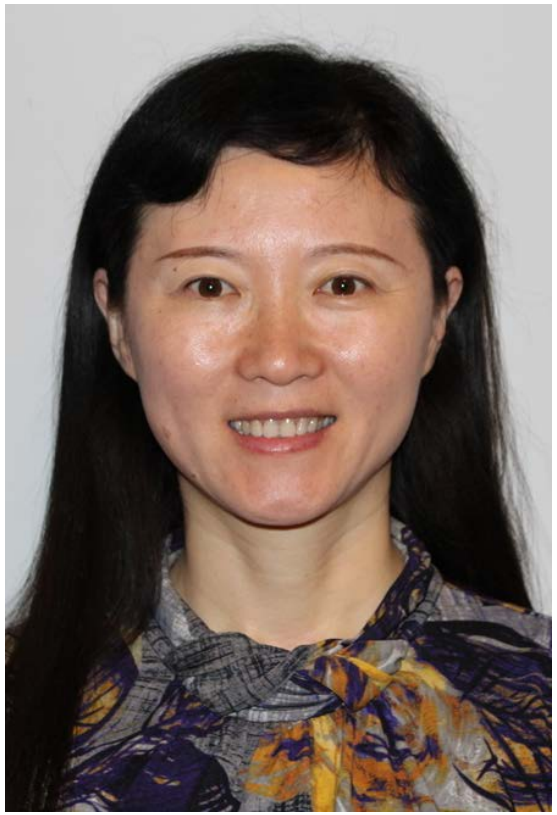
  IVIVCs/IVIVRs were successfully developed for

  - Different nicotine TDS
  - Under both, normal and elevated skin surface temperature
  - At different periods in the duration of product wear
  - By independent research groups at different study sites
  - Using different IVPT apparatus, skin preps & heat application methods
  - Using different IVIVC approaches
  - Illustrating an efficient in vitro approach to support the development of high quality, generic TDS products for patients

Conclusions

- TDS products are complex, and can exhibit unique issues relevant to demonstrating BE.
- Generic TDS products must be bioequivalent and therapeutically equivalent to the RLD.
- Generic TDS products may contain certain allowable design/formulation differences compared to the RLD TDS.
- Scientific research and innovation can streamline product development and reduce barriers/burdens for assessing BE.
- Collaboration among academia, industry and the FDA can facilitate patient access to high quality generic TDS products.

Special Acknowledgements



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