FDA Champions Research to Make Complex Generic Transdermal Products Available to Patients

U.S. Food and Drug Administration – Drug Industry Association Webinar

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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, Bioequivalence & Generics

- Pharmaceutical Equivalence (PE) Means
  1. Same active ingredient(s)
  2. Same dosage form
  3. Same route of administration
  4. Same strength

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N019813	AB	Yes	FENTANYL	FILM, EXTENDED RELEASE;TRANSDERMAL	25MCG/HR	DURAGESIC-25	JANSSEN PHARMS
A077449	AB	No	FENTANYL	FILM, EXTENDED RELEASE;TRANSDERMAL	25MCG/HR	FENTANYL-25	AVEVA
A077154	AB	No	FENTANYL	FILM, EXTENDED RELEASE;TRANSDERMAL	25MCG/HR	FENTANYL-25	MALLINCKRODT INC
A077062	AB	No	FENTANYL	FILM, EXTENDED RELEASE;TRANSDERMAL	25MCG/HR	FENTANYL-25	PAR PHARM INC
A077051	AB	No	FENTANYL	FILM, EXTENDED RELEASE;TRANSDERMAL	25MCG/HR	FENTANYL-25	LAVIPHARM LABS
A076709	AB	No	FENTANYL	FILM, EXTENDED RELEASE;TRANSDERMAL	25MCG/HR	FENTANYL-25	WATSON LABS
A076258	AB	No	FENTANYL	FILM, EXTENDED RELEASE;TRANSDERMAL	25MCG/HR	FENTANYL-25	MYLAN TECHNOLOGIES

TABLE SOURCE: Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, for Fentanyl Transdermal Systems

Equivalence, Bioequivalence & Generics

- Bioequivalence (BE) Essentially Means

  Absence of a significant difference in the rate and extent of availability of the drug between test and reference products

  - For Transdermal Delivery Systems (TDS), this is routinely demonstrated using pharmacokinetic (PK) BE studies

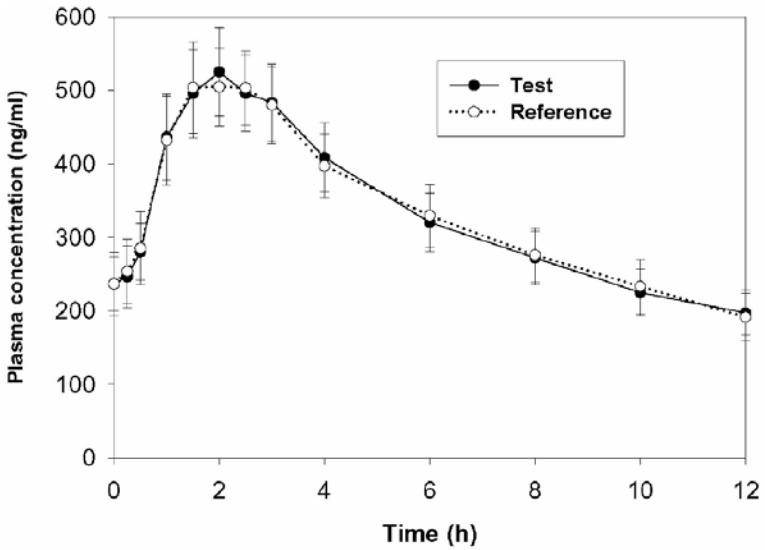


FIGURE SOURCE: Tassaneeyakul et al. (2005) Steady-state bioequivalence study of clozapine tablet in schizophrenic Patients. J Pharm Pharmaceut Sci 8(1):47-53. This is a general example of typical of results from a BE study with PK endpoints.

Equivalence, Bioequivalence & Generics

- For simple generic products, most failure modes for therapeutic equivalence (TE) may be adequately controlled by:
  - Matching the 4 components of PE
  - Demonstrating BE
  - Adequate labeling and cGMP manufacturing
- However, TDS Drug Products are complex, and there are unique/additional issues that must be considered to ensure TE for generic TDS

TE Considerations for Generic TDS

- While the RLD & generic TDS will have the same active ingredient(s)…
- The generic TDS may have
  - Different inactive ingredients
    - Adhesives, impurities, penetration enhancers?
  - Different level of exposure to adhesive impurities?
  - Different irritation/sensitization potential?
  - Different adhesion characteristics? (and impact on PK?)
  - Different heat effects due to product composition?

TE Considerations for Generic TDS

- While the RLD & generic TDS will be the same dosage form…
- The generic TDS may have
  - Different product design?
    - Reservoir or Matrix TDS designs
  - Differentiated failure modes related to the product design?
    - Leakage (bursting) or cold flow
    - Release liner removal issues
    - Abuse potential
    - Crystallization
    - Heat effects
    - Adhesion

TE Considerations for Generic TDS

- While the RLD & generic TDS will be the same strength… “strength” is based on nominal drug delivery rate, not drug load, and adjusted by size
- The generic TDS may have
  - Different drug load?
  - Different residual drug excess?
  - Different product size and/or shape?
  - Different strength when evaluated by different methods?
  - Different heat effects due to different drug load and design?

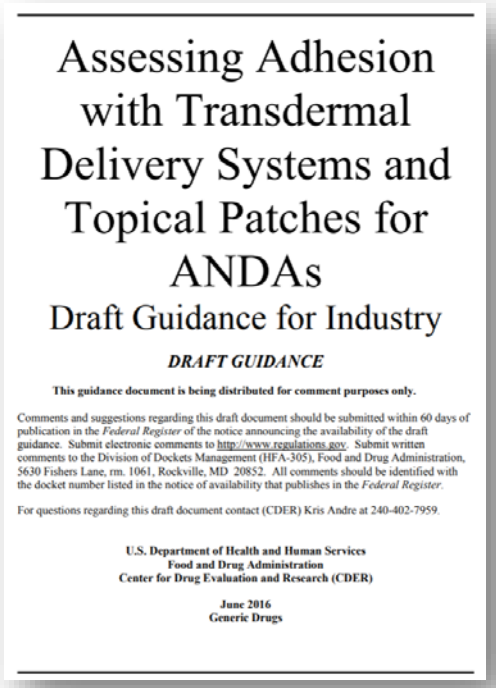
TE Considerations for Generic TDS

- What 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** (Case Study #1)
  - Generic TDS **Heat Effects** (Case Study #2)
  - Other aspects that are outside the scope for today

Regulatory Science Impact: Case #1

Guidance on **TDS Adhesion** Studies

1. Optimizing study design and control parameters
2. Resolving statistical analysis problems



Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs

Draft 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 http://www.regulations.gov. Submit written comments to the Division of Dockets Management (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) Kris Andre at 240-402-7959.

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

June 2016
Generic Drugs

TDS Adhesion

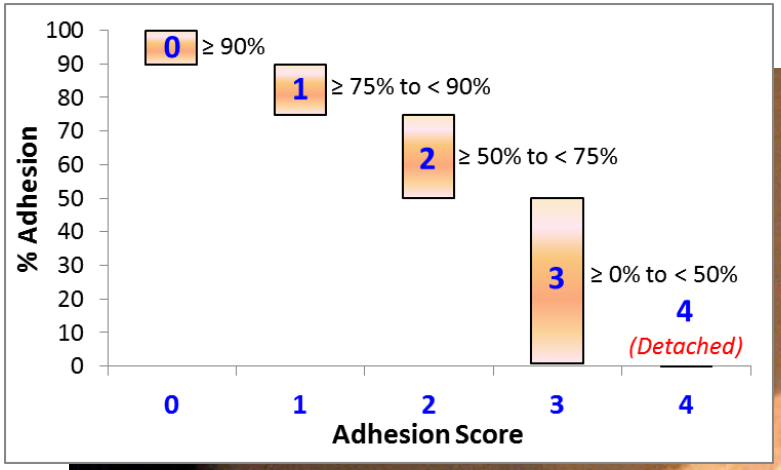


FIGURE SOURCE: https://en.wikipedia.org/wiki/Transdermal_patch (Free Media)

TDS Adhesion

- Evaluating In Vivo TDS Adhesion (The Old Way)
  - Non-inferiority of adhesion for Generic vs. RLD TDS
  - Historically adhesion study designs varied in 23 PSGs
    - Adhesion evaluated with the PK bioequivalence study
    - Adhesion evaluated with the irritation/sensitization study
    - Adhesion evaluated in an independent study
  - Challenges for the statistical data analysis

Revision of TDS Adhesion Recommendations

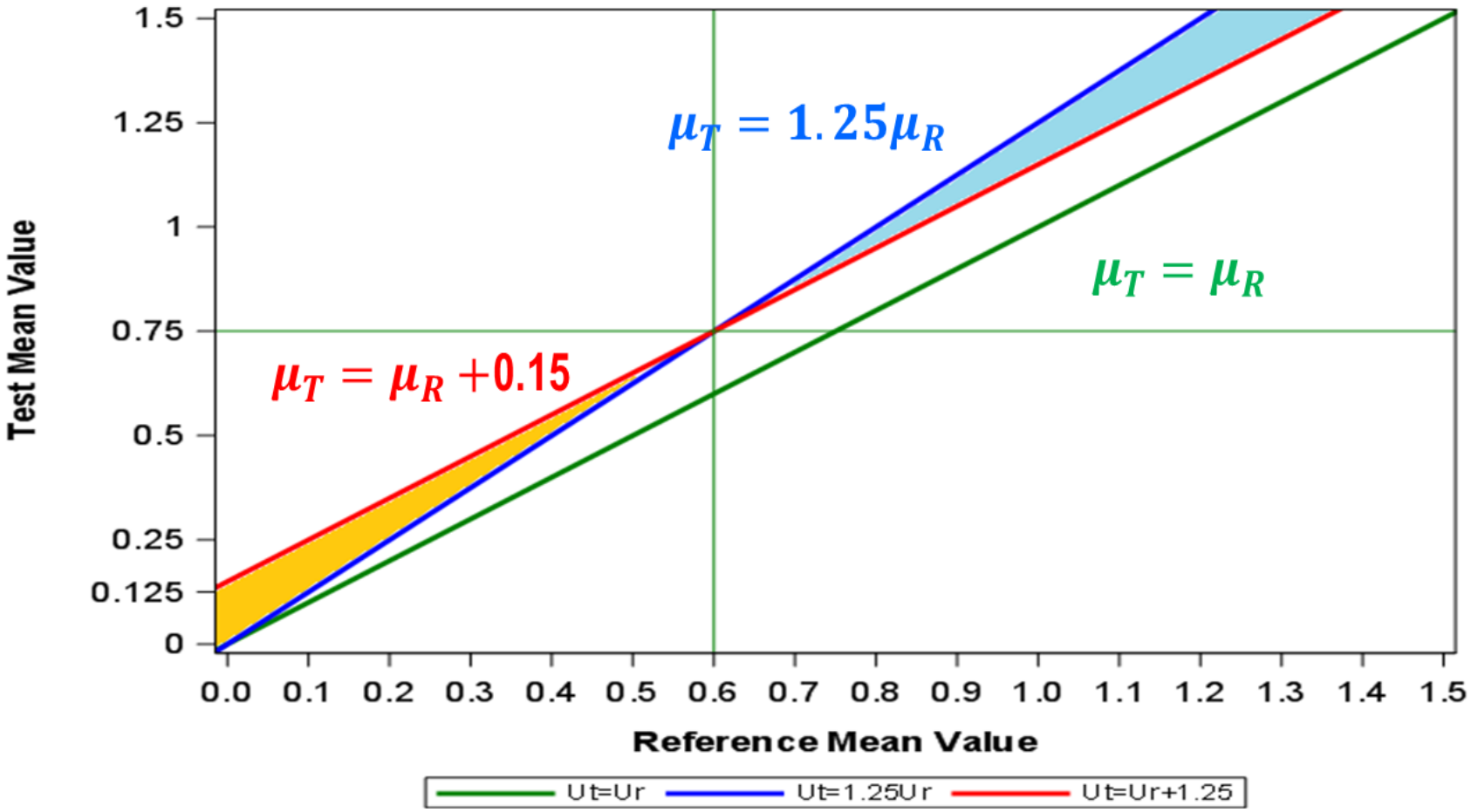
- Numerous regulatory, scientific and study design issues were challenging to harmonize due to inter-dependent considerations, including:
  - Statistical considerations/limitations (highly skewed data)
  - Logistical considerations related to validating any new scoring scale
  - Transition and implementation considerations for Industry and FDA
  - Clinical considerations about when TDS adhesion impacts therapeutic equivalence
  - Bioequivalence considerations about TDS adhesion impacting pharmacokinetics
  - CMC considerations about TDS adhesion as a target product quality attribute
  - Safety considerations about exposure to detached TDS for children and pets
  - Labeling considerations about labeled use conditions vs. adhesion study design
  - Different approaches to evaluating TDS adhesion for NDAs vs. ANDAs
  - Different TDS adhesion study designs deemed acceptable in historical ANDAs
  - Regulatory consistency and backward compatibility of statistical analyses
  - Etc.

Revision of TDS Adhesion Recommendations

- New harmonized recommendations for all TDS products:
  - Revised criteria for evaluation of primary and secondary endpoints
  - New approach for weighting scores across the duration of wear
  - Standardized scoring practices related to the worst observations carried forward
  - Discussed stand-alone adhesion studies or combination adhesion/PK (BE) studies
  - Recommended analysis of and reporting on all samples from adhesion/PK studies
  - Provided a consistent approach to subject inclusion/exclusion from various analyses
  - Discussed tampering with TDS (to prevent lift-off or to re-adhere lifted sections)
  - Discouraged restrictions on normal subject motion/activity during adhesion studies
  - Discussed studies to support labeled use conditions (e.g. ability to shower with TDS)
  - Discussed TDS application to a contralateral anatomical location in the 2nd period
  - Emphasized assessment of to-be-marketed TDS (bridging quality tests as needed)
  - Discouraged the application of numerous TDS on each subject to inflate n for TDS
  - Discussed residual drug analysis
  - New statistical analysis
  - Etc.

Revision of TDS Adhesion Recommendations

- New harmonized recommendations for all TDS products:
  - New statistical analysis (difference of means instead of ratio of means)
  - Margin of 0.15



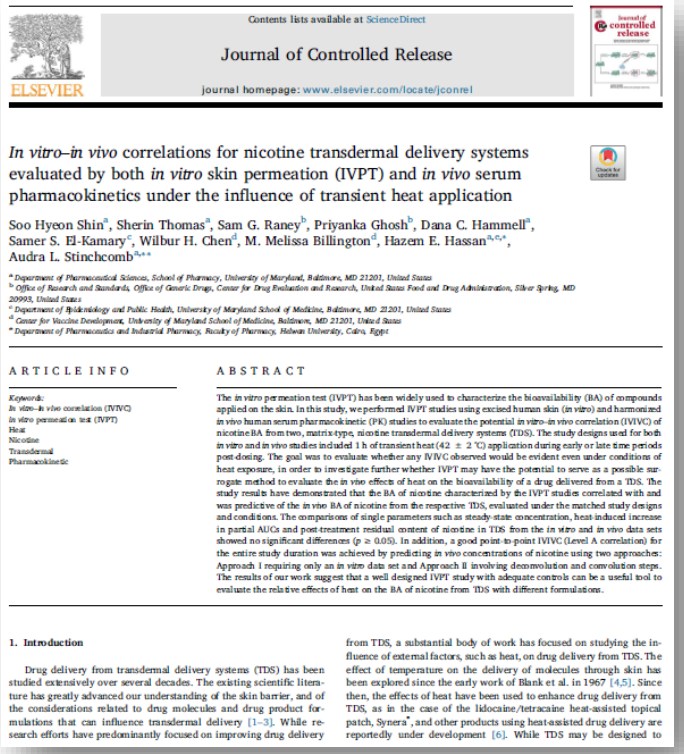
Impact of Revised Recommendations

- Among 33 TDS Adhesion Studies in ANDAs
  - **16 (49%) with TDS that exhibited moderate to poor adhesion** for the RLD and test products **consistently** demonstrated the comparative non-inferiority of the test TDS adhesion, **passing by both the old and new approaches**
  - **5 (15%) with TDS that exhibited moderate to poor adhesion** for the RLD and test products **consistently** failed to demonstrate the comparative non-inferiority of the test TDS adhesion, **failing by both the old and new approaches**
  - **12 (36%) with TDS that exhibited moderate to good adhesion** for the RLD and test products **failed** to demonstrate the comparative non-inferiority of the test TDS **by the old approach**, but **now demonstrated the comparative non-inferiority of the test TDS adhesion by the new approach**

Regulatory Science Impact: Case #2

Evaluation of Generic **TDS Heat Effects**

1. Developing Methods to Study Heat Effects
2. Developing IVIVC for an In Vitro Test System



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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

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ARTICLE INFO

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In vitro permeation test (IVPT)
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Nicotine
Transdermal
Pharmacokinetic

ABSTRACT

The *in vitro* permeation test (IVPT) has been widely used to characterize the bioavailability (BA) of compounds applied on the skin. In this study, we performed IVPT studies using excised human skin (*in vitro*) and harmonized *in vivo* human serum pharmacokinetic (PK) studies to evaluate the potential *in vitro–in vivo* correlation (IVIVC) of nicotine BA from two, matrix type, nicotine transdermal delivery systems (TDS). The study designs used for both *in vitro* and *in vivo* studies included 1 h of transient heat (42 ± 2 °C) application during early or late time periods post-dosing. The goal was to evaluate whether any IVIVC observed would be evident even under conditions of heat exposure, in order to investigate further whether IVPT may have the potential to serve as a possible surrogate method to evaluate the *in vivo* effects of heat on the bioavailability of a drug delivered from a TDS. The study results have demonstrated that the BA of nicotine characterized by the IVPT studies correlated with and was predictive of the *in vivo* BA of nicotine from the respective TDS, evaluated under the matched study designs and conditions. The comparisons of single parameters such as steady-state concentration, heat-induced increase in partial AUCs and post-treatment residual content of nicotine in TDS from the *in vitro* and *in vivo* data sets showed no significant differences ($p \geq 0.05$). In addition, a good point-to-point IVIVC (Level A correlation) for the entire study duration was achieved by predicting *in vivo* concentrations of nicotine using two approaches: Approach I requiring only an *in vitro* data set and Approach II involving deconvolution and convolution steps. The results of our work suggest that a well designed IVPT study with adequate controls can be a useful tool to evaluate the relative effects of heat on the BA of nicotine from TDS with different formulations.

1. Introduction

Drug delivery from transdermal delivery systems (TDS) has been studied extensively over several decades. The existing scientific literature has greatly advanced our understanding of the skin barrier, and of the considerations related to drug molecules and drug product formulations that can influence transdermal delivery [1–3]. While research efforts have predominantly focused on improving drug delivery from TDS, a substantial body of work has focused on studying the influence of external factors, such as heat, on drug delivery from TDS. The effect of temperature on the delivery of molecules through skin has been explored since the early work of Blank et al. in 1967 [4,5]. Since then, the effects of heat have been used to enhance drug delivery from TDS, as in the case of the lidocaine/tetracaine heat-assisted topical patch, Synera®, and other products using heat-assisted drug delivery are reportedly under development [6]. While TDS may be designed to

TDS Heat Effects

FIGURE SOURCE: © http://www.clinicaladvisor.com/termsandconditions/ (Authorized non-commercial use)

TDS Heat Effects

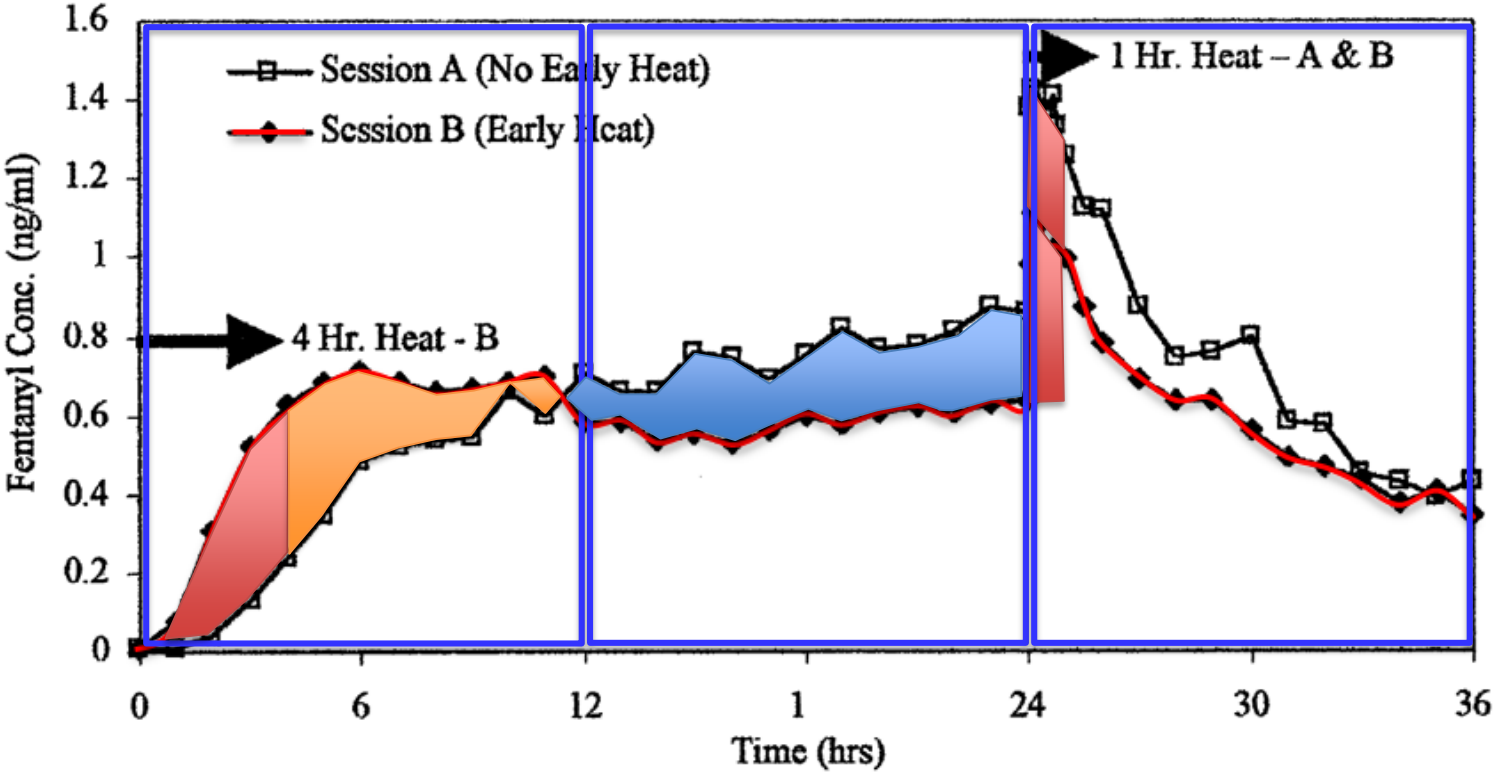
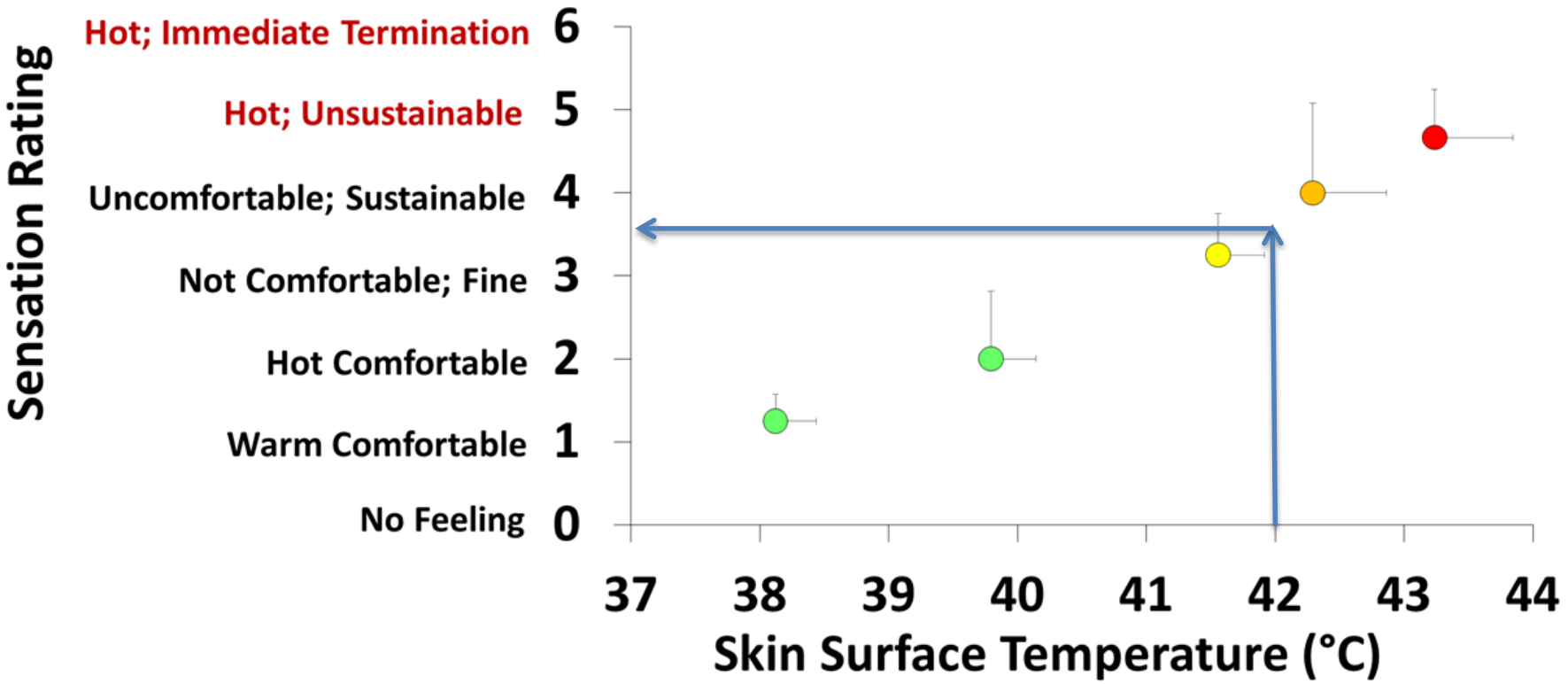


Figure 1. Mean serum fentanyl concentrations after transdermal fentanyl delivery with and without heat (n = 10).

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

TDS Heat Effects Studies

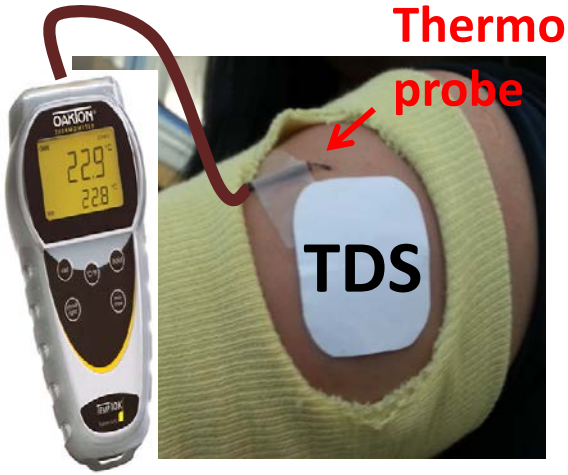
- In Vivo assessment of tolerable temperatures

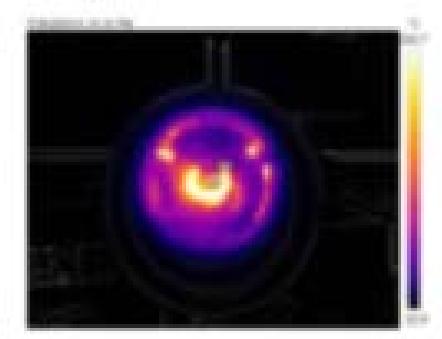


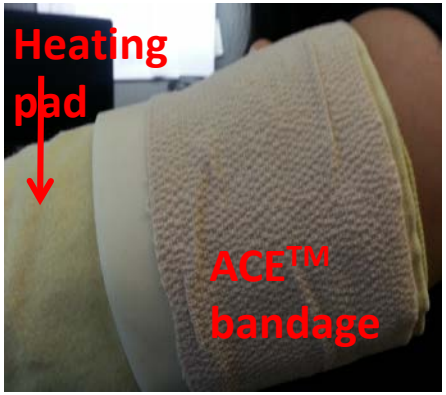
Refer to Zhang et al. (2017) Characterization of Temperature Profiles in Skin and Transdermal Delivery System When Exposed to Temperature Gradients In Vivo and In Vitro. Pharm Res 34: 1491.

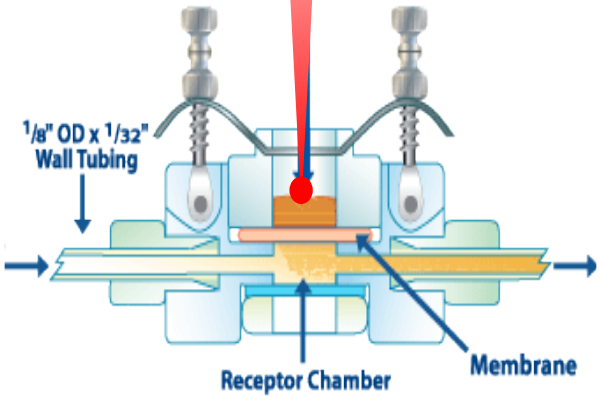
TDS Heat Effects Studies

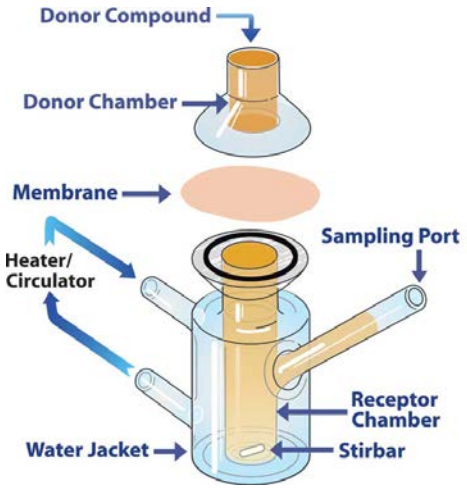
University of Maryland "UMB" (in vivo)	University of Maryland "UMB" (in vitro)	University of Cincinnati "UC" (in vitro)





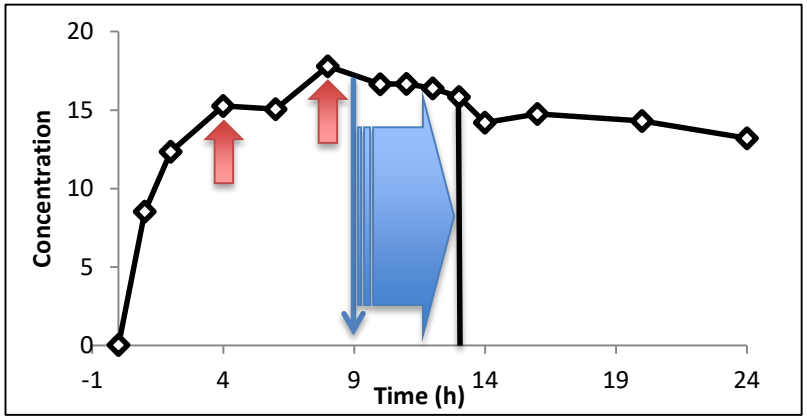


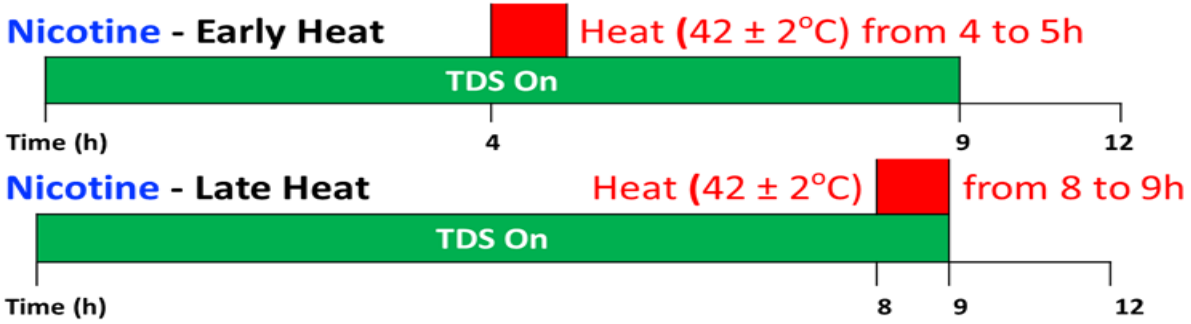




Nicotine TDS Heat Effects Studies

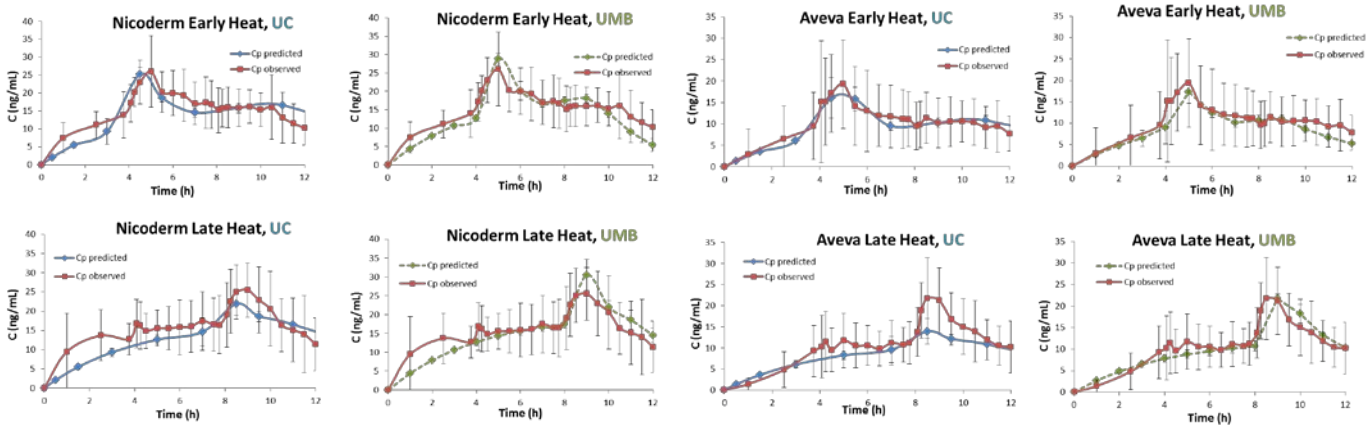
Nicotine TDDS 14 mg/24h	Patch size (cm^2)	Rate/Area ($\mu g/h/cm^2$)	Adhesive type	Other inactive ingredients
Nicoderm CQ®	15.75	37	Polyisobutylene	Ethylene vinyl acetate-copolymer, polyethylene between pigmented and clear polyester backing
Aveva	20	29	Polyacrylate/Silicone	Polyester backing



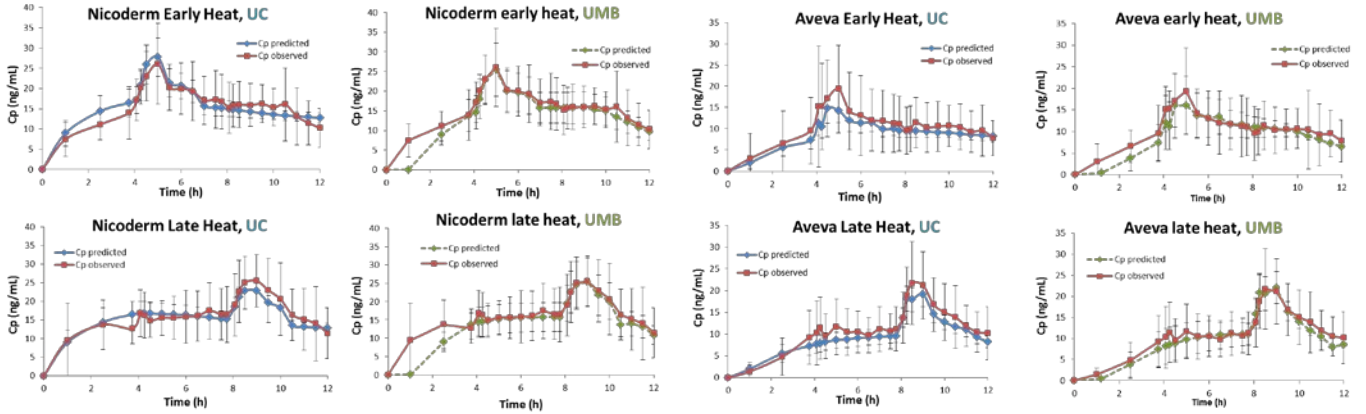


Level A IVIVC/IVIVR for Nicotine TDS

- **Approach I** (prediction based upon in vitro data only)

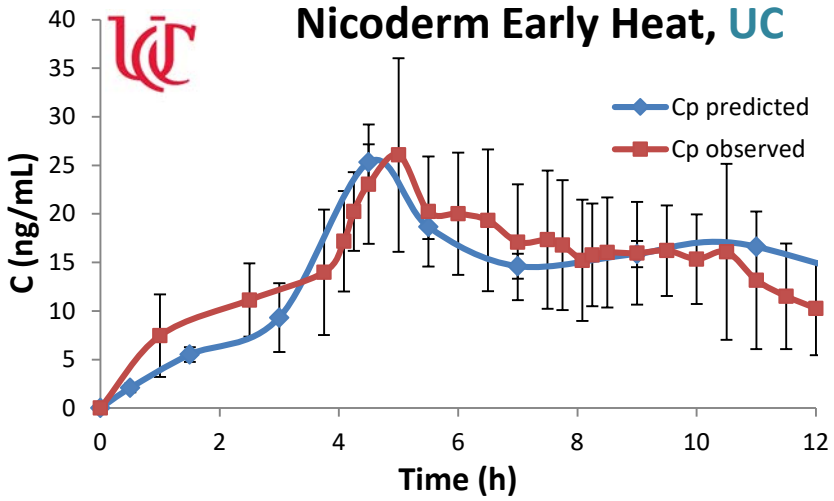


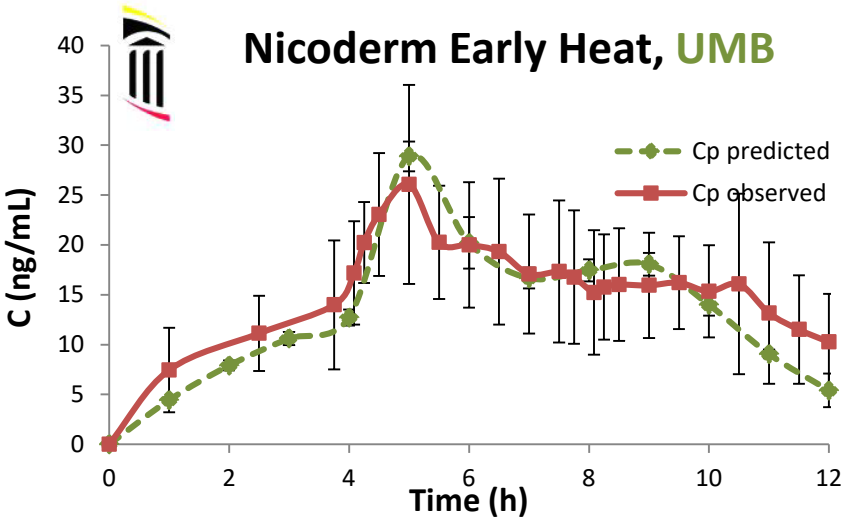
- **Approach II** (including an in vivo-derived heat factor)

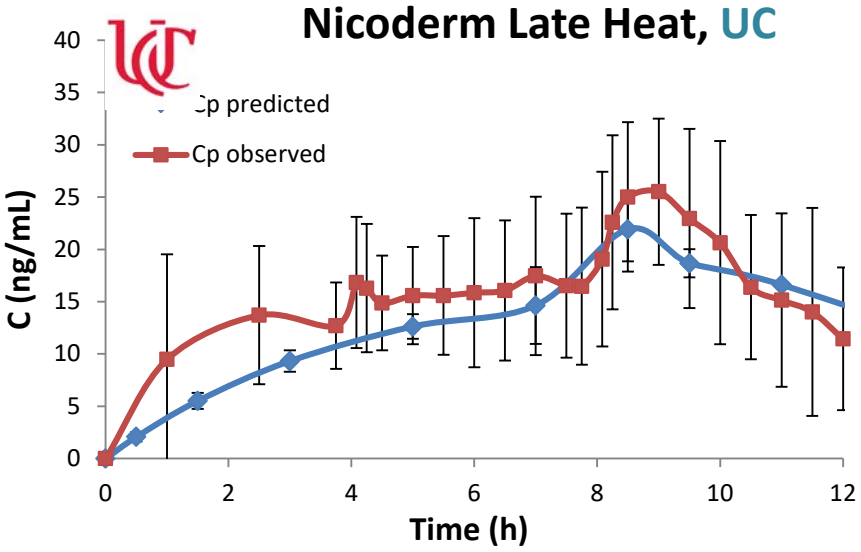


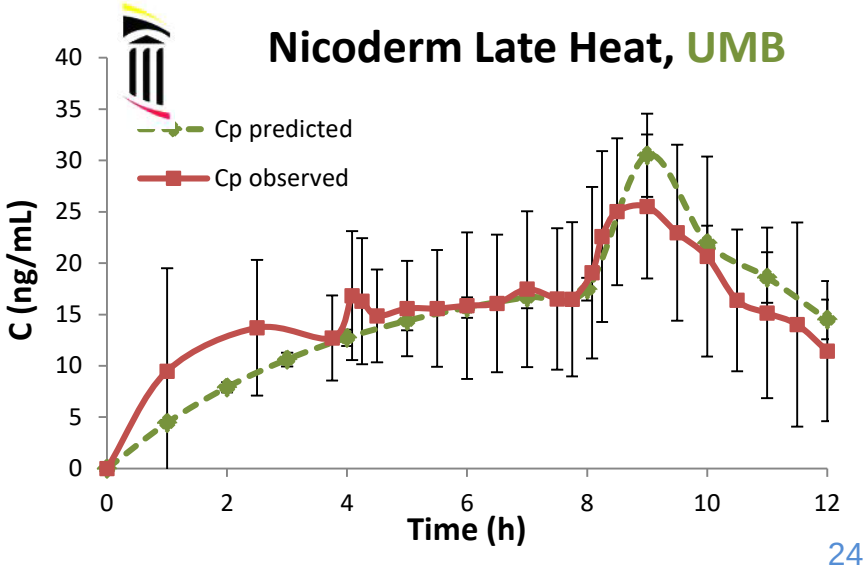
Refer to Shin et al. (2018) In vitro-in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application. J Control Release. 270: 76-88. (Funded, in part, by FDA through award U01FD004946)

Level A IVIVC Approach I for Nicoderm

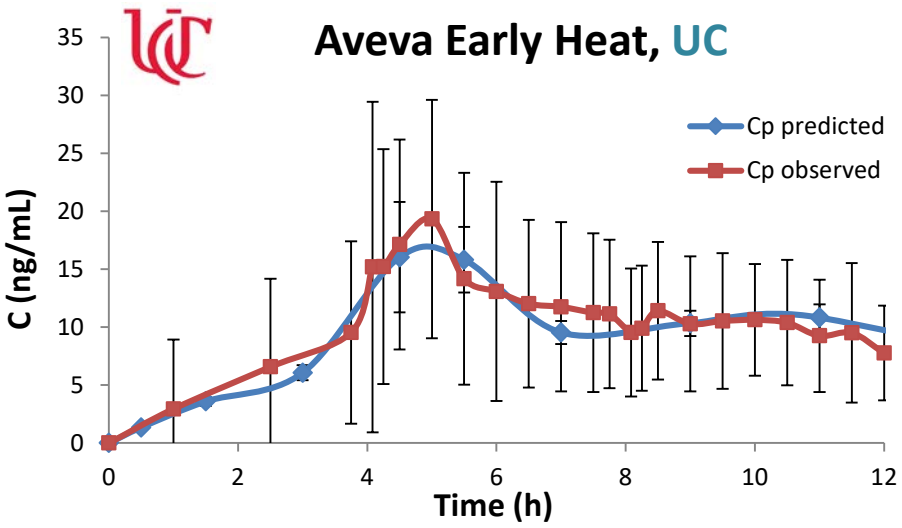


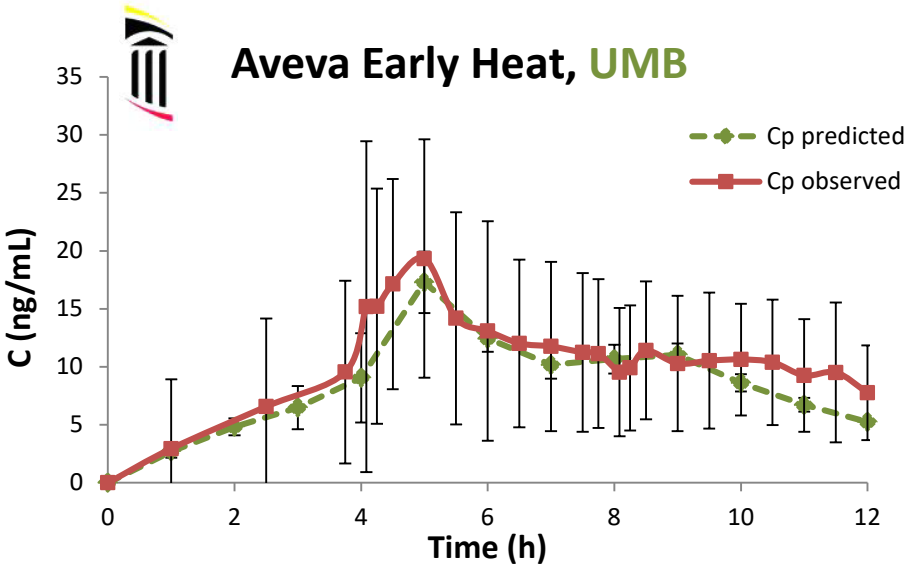


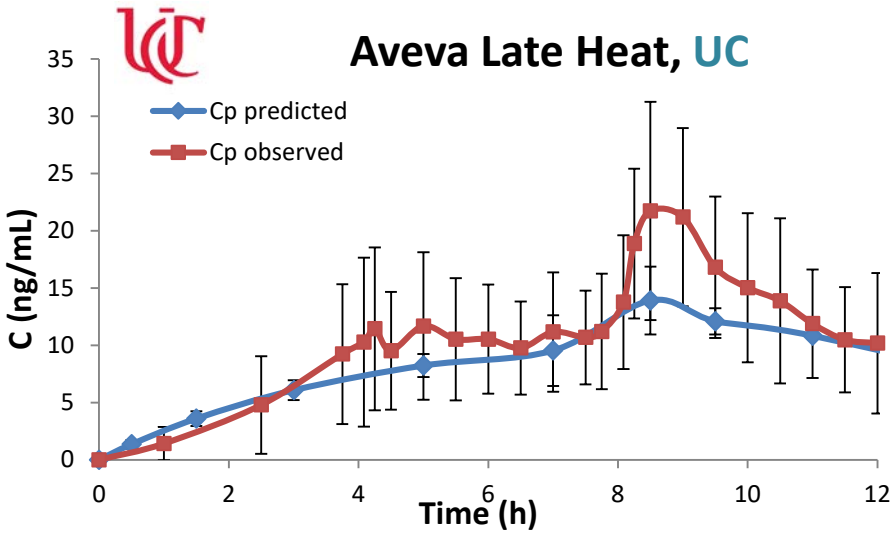


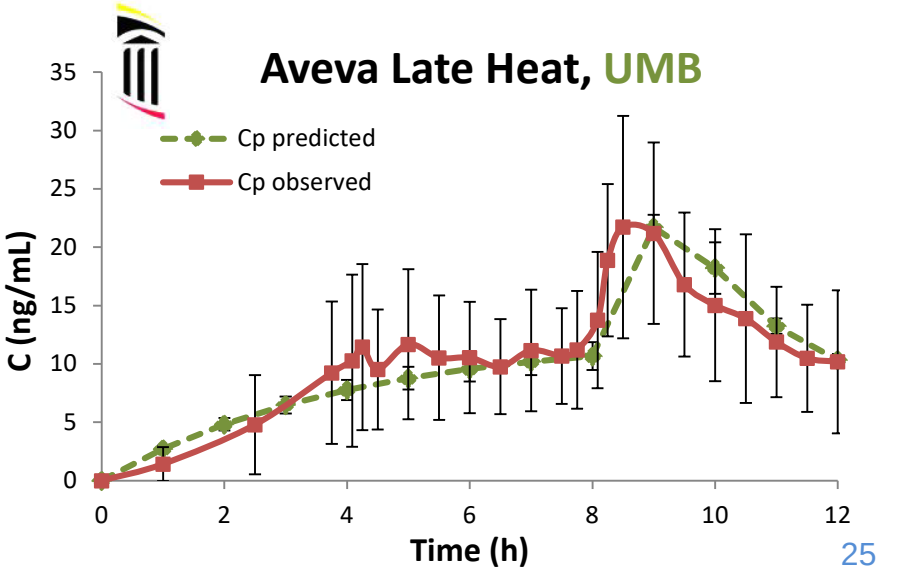


Level A IVIVC Approach I for Aveva

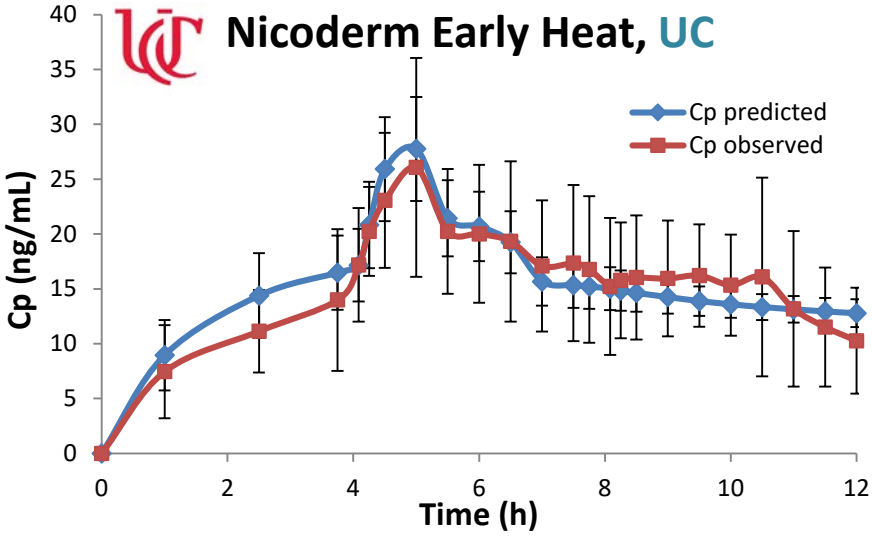


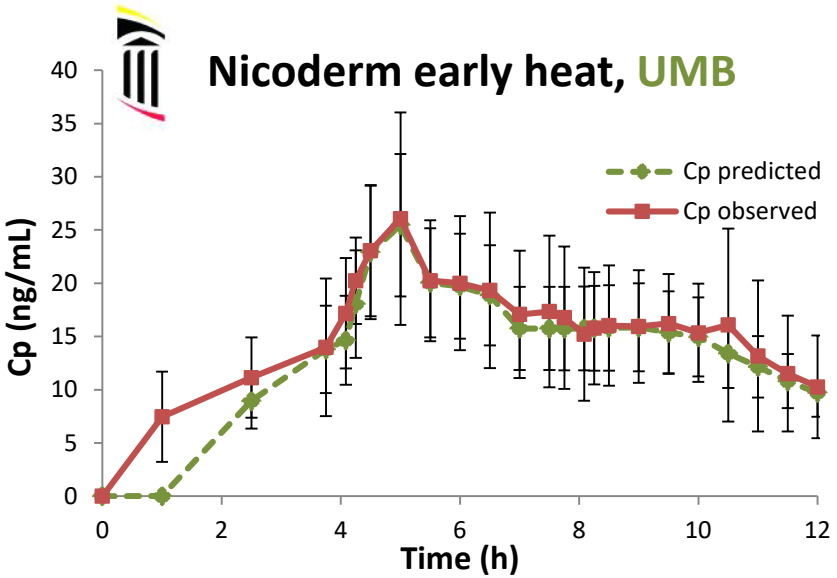


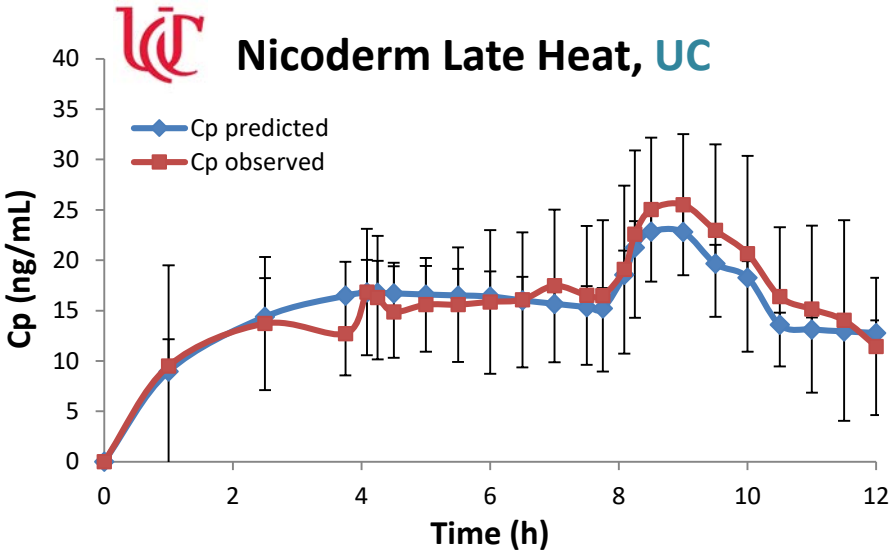


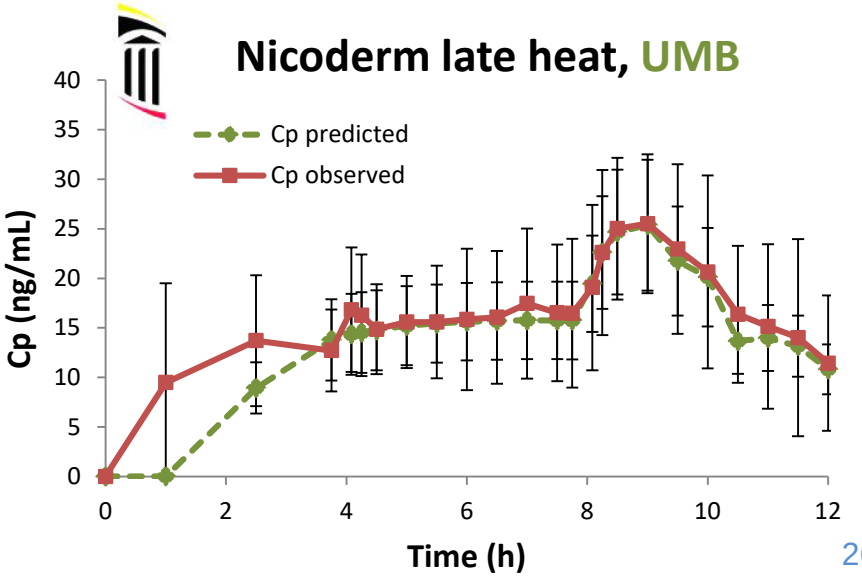


Level A IVIVC Approach II for Nicoderm

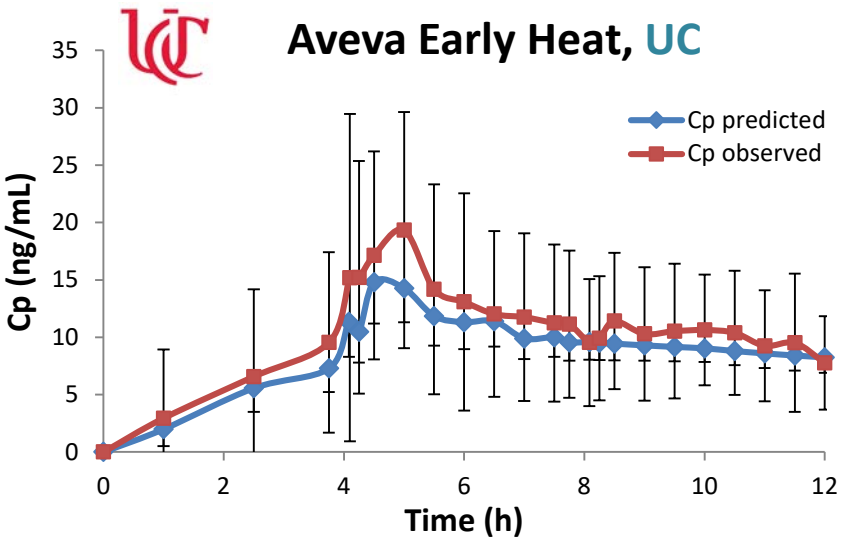


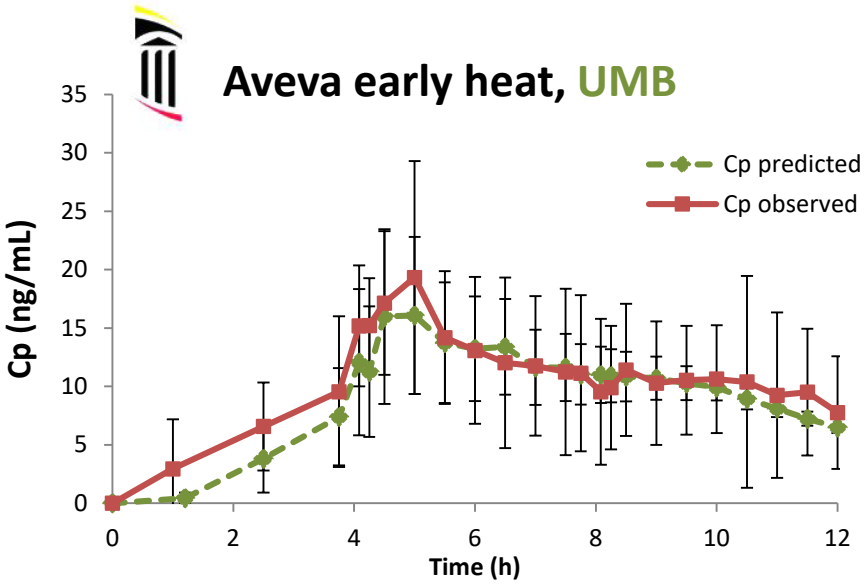


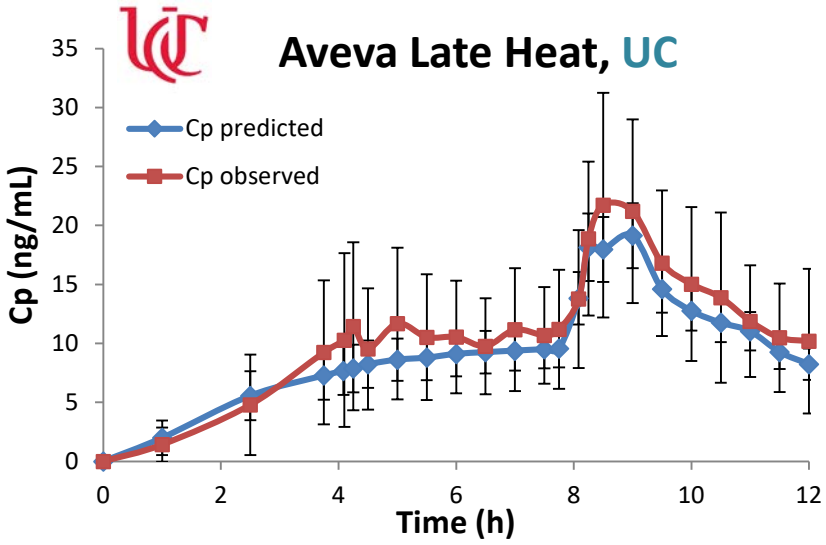


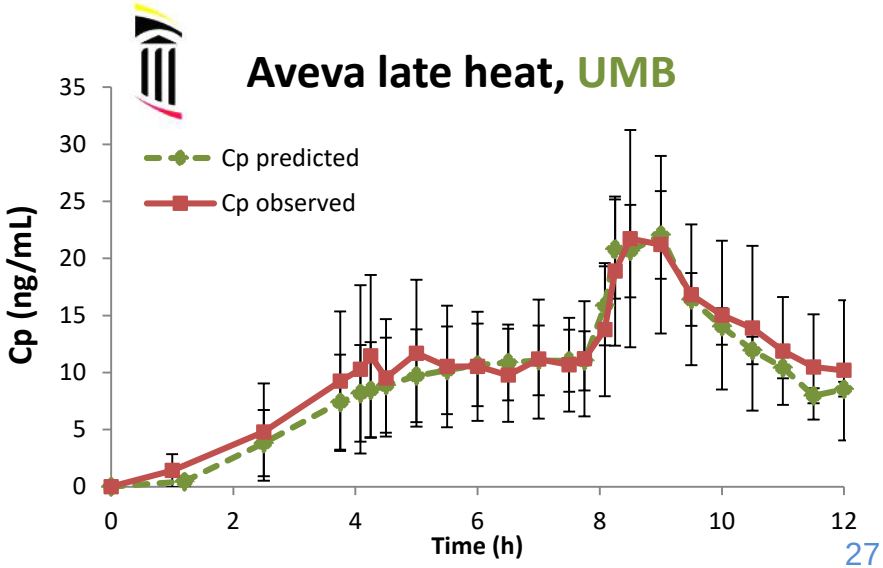


Level A IVIVC Approach II for Aveva









Nicotine TDS Heat Effects Studies

IVIVCs/IVIVRs were developed for

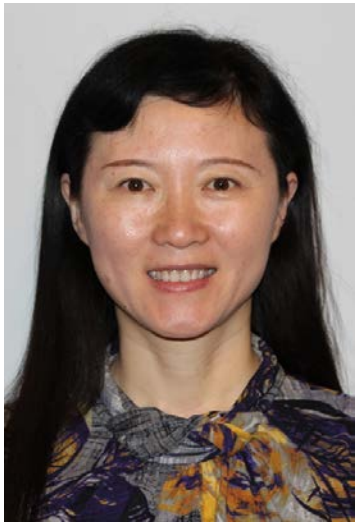
- Different nicotine TDS
- Under normal skin surface temperature
- Under elevated temperature conditions
- At different periods in the duration of product wear
- By independent research groups at different sites
- Using different IVPT apparatus, skin preps & heat application methods
- Using different IVIVC approaches

The results suggest that the IVPT model is able to correlate with and be predictive of in vivo bioavailability for nicotine TDS products exposed to transient heat, when in vitro and in vivo study designs are harmonized.

Conclusions

- TDS are complex drug-device combination products
- The evaluation of generic TDS products involves several unique scientific and technical challenges
- We have successfully reduced a key barrier to generic TDS approval associated with statistical evaluation of non-inferiority for TDS adhesion
- This has supported the approvability of numerous ANDAs for generic TDS products, notably including well-adhering generic TDS
- We are also developing a safe and efficient approach that may help us to evaluate heat effects for generic TDS

Special Acknowledgements



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