Dermal PBPK Modeling for a Transdermal Delivery System to Assess the Impact of the Application Site on In Vivo Performance

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 6: Quantitative Methods – Study Design, Model-integrated BE Approaches

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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.

Learning Objectives

- Discuss the general workflow in building and validating a dermal physiologically-based pharmacokinetic (PBPK) model for a transdermal delivery system (TDS);
- Describe the application of the developed model in predicting absorption of an active pharmaceutical ingredient (API) through the skin at an application site other than the one the model was validated for;
- Describe the application of the developed model in predicting the amount of the API remaining in the TDS at the end of the wear period.

Outline

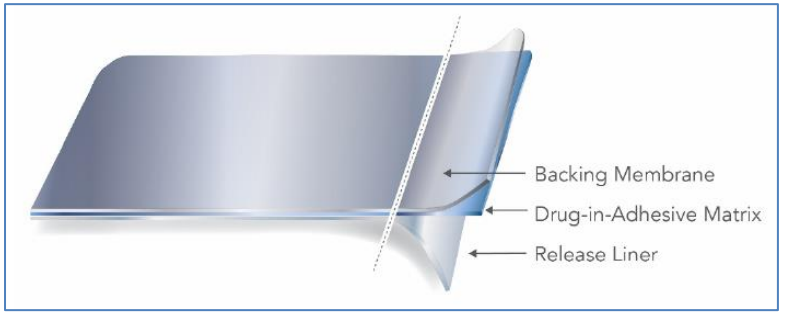
- Transdermal Delivery Systems (TDS)
- In silico methodologies to support drug product development and approval
  - What is dermal Physiologically-based Pharmacokinetic (PBPK) modeling?
- Case Study: Background
- How was Dermal PBPK modeling applied in this case?
  - Model development
  - Model validation
  - Model application
- Take home messages

Transdermal Delivery Systems (TDS)

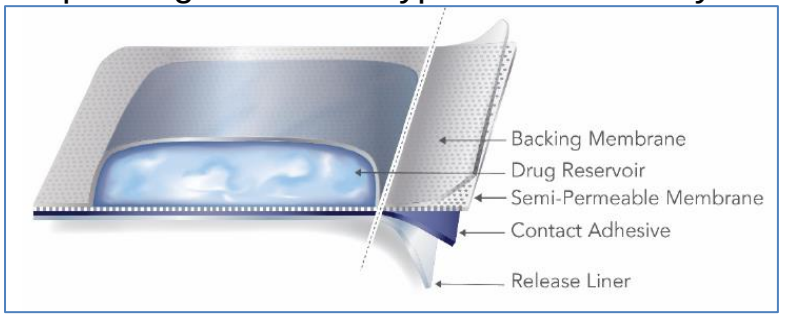
"… designed to deliver the active ingredient (active substance) across the skin and into systemic circulation…"

- Matrix type TDS: active ingredient(s) dissolved or partially suspended in a mixture of adhesives, penetration enhancers, softeners, and preservatives
- Reservoir type TDS: components in liquid or semi-solid form in a heat-sealed area to entrap the active gel between the backing membrane and a microporous membrane

Matrix type transdermal system

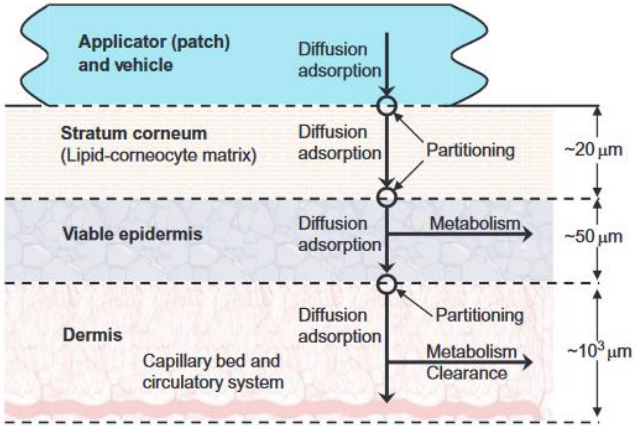


Liquid or gel reservoir type transdermal system

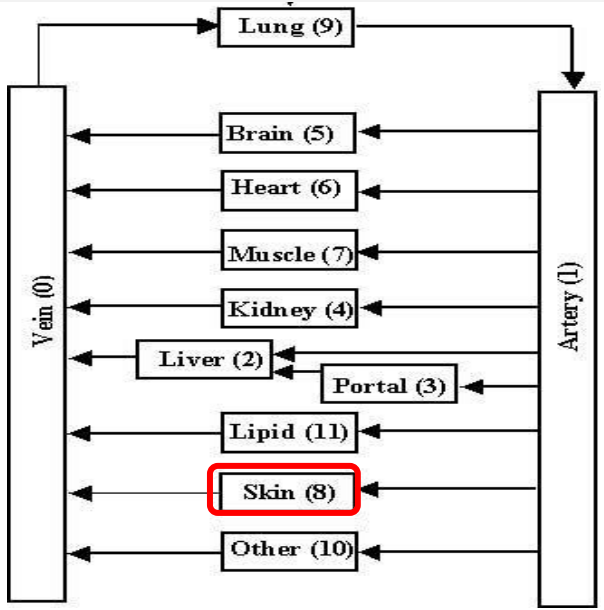


Transdermal and Topical Delivery Systems - Product Development and Quality Considerations | FDA

Modeling skin bioavailability…



Mechanistic PBPK models:
API, formulation and human/animal physiology (variability and population)



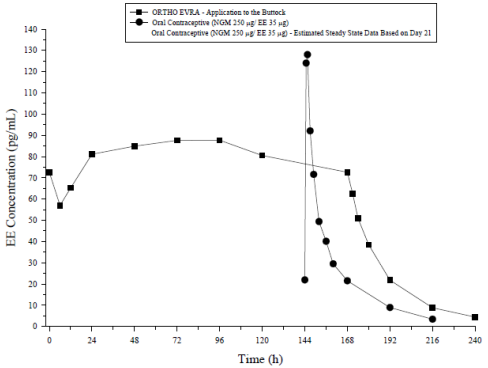
API: Active Pharmaceutical Ingredient

BMC Clin Pharmacol. 2002 Aug 15;2:5. David G Levitt. Clin Pharmacol. 2016 Oct 19;8:163-176. Abd et al.
https://reader.elsevier.com/reader/sd/pii/B9780124080775000109?token=7B6390B968A5B97902A420B977D483BD3FDCA4A2581F89FE99F66732BA808D0E8F0BF98B6BA263D3F277D2A0725D9441

Reference Listed Drug (RLD)

- Ethinyl Estradiol (EE); Norelgestromin Transdermal Extended Release Film, 0.035MG/24HR; 0.15MG/24HR
- Estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch.
- ORTHO EVRA® uses a 28-day (four-week) cycle. Apply a new patch to the upper outer arm, abdomen, buttock or back each week for three weeks (21 total days). Week Four is patch-free.

Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive for 2 Cycles or Application of ORTHO EVRA for 2 Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15-21, ORTHO EVRA: Cycle 2, Week 3]



Mkt.Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	
RX	ETHINYL ESTRADIOL; NORELGESTROMIN	XULANE	A200910	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR	RS
DISCN**	ETHINYL ESTRADIOL; NORELGESTROMIN	ORTHO EVRA	N021180	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR	RLD

https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons

ORTHO EVRA®, (norelgestromin/ethinyl estradiol transdermal system), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021180s048lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200910Orig1s000.pdf

Contains Nonbinding Recommendations

Draft Guidance on Ethinyl Estradiol; Norelgestromin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Ethinyl estradiol; Norelgestromin

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.035 mg/24 hr; 0.15 mg/24 hr
   Subjects: Healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.
   Additional comments:
   - In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *patches* or *extended release films*.
   - Unless otherwise justified, the ethinyl estradiol; norelgestromin TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference product, and worn for 7 days. Applicants should randomize subjects to receive either the test or reference product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021180.pdf

Case Study: Background

- A generic TDS (Test) was developed with API loaded amount that was lower than the respective API amount in the Reference Standard (RS).
- Bioequivalence (BE) was demonstrated between the RS and Test products following TDS application to the abdomen in agreement with the current product-specific guidance (PSG) recommendations.
- Literature reports no impact of anatomical site on the EE systemic exposure following application of the RLD.

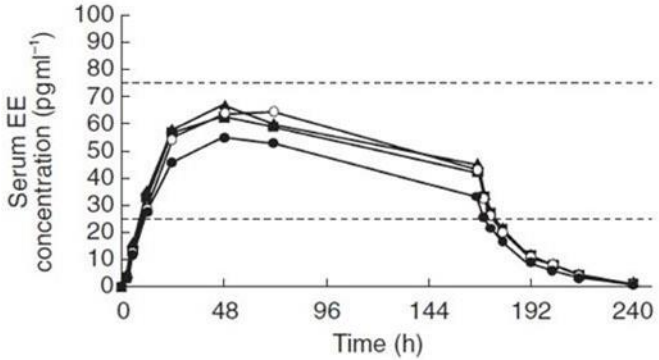


Figure 2 Mean serum concentration *vs* time profile of ethinyl oestradiol (EE) following successive applications of the contraceptive patch for 7 days at each of the four anatomical sites (● abdomen; ▲ arm; ■ buttock; ○ torso). Dashed horizontal lines indicate reference range.

Br J Clin Pharmacol 2002 Feb;53(2):141-6. Abrams et al..

Case Study: Question

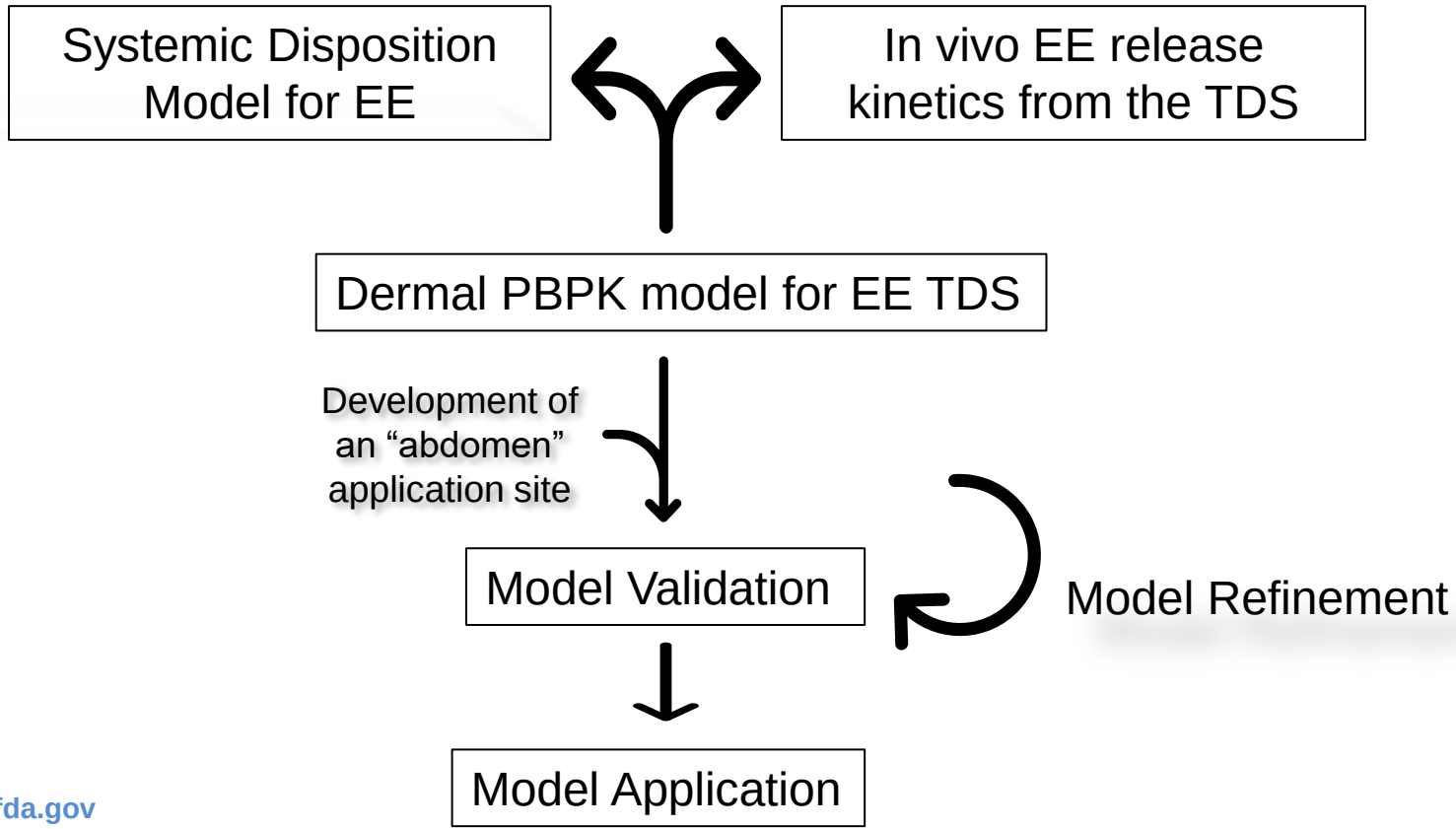
What is the impact of the application site on the API amount delivered into the systemic disposition over the TDS application period and can it result in dose depletion when the API loaded amount differs between the RS and the Test products?

The Agency internally used Modeling and Simulation approaches to assess the potential need for conducting an in vivo BE study with PK endpoints in female healthy volunteers with back as the application site.

Model Assumptions

- TDS releases API at the same rate regardless of the application site, which is consistent with the current knowledge of TDS function. Differences in PK exposure following application at different application sites would be the result of differences in skin physiology between application sites.
- Parameters contributing to variability besides application site include number of subjects, study-to-study differences in skin physiology and drug distribution and elimination, and study conduct (e.g., how TDS was applied and conditions at which TDS was applied).
- Potential impact of adhesion on drug product performance is beyond the scope of this work and was not consider here.

Model Development and Validation Workflow



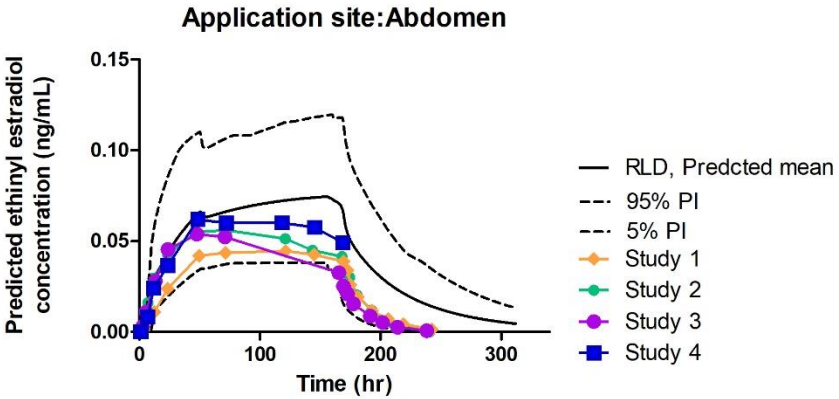
Model Development

- Systemic disposition model for intravenously administered EE:
  - EE physicochemical parameters and PK characteristics used for the development of the systemic disposition model
  - Literature (Ezuruike et al, 2018, Drugbank, PubChem)
  - Validation: Back et al.,1987 and in-house data
- Dermal PBPK model developed for EE applied as a TDS
  - QSAR models except diffusion in viable epidermis and dermis which were optimized against systemic PK data for the TDS
  - Validation: literature, in-house data
- EE release from the TDS was empirically obtained by deconvoluting the systemic PK data
  - Methods that mechanistically model API release from the TDS did not perform well

Contraception. 1987 Oct;36(4):471-9 Back et al.
Clin Pharmacol Ther. 2018 Dec;104(6):1229-1239. Ezuruike et al

Application Site: Abdomen

- The “abdomen” was not available as an application site within the modeling platform used
- Development and validation of the “abdomen” as an application site leveraging RLD data



RLS: Reference Listed Drug, PI: prediction interval

Parameter	Value (CV%) males/females	Source
Stratum corneum, skin surface pH	5.29 (10%)/5.98 (10%)	Bailey et al.,2012
Viable epidermis, thickness (µm)	99.8 (50%)	Wei et al., 2017
Dermis, thickness (µm)	2284 (50.1%)	Wei et al., 2017
Subcutis, thickness (µm)	17 (30%)/22 (30%)	Derraik et al., 2014, Lancerotto et al.,2011
Muscle, thickness (µm)	8 (30%)/4 (30%)	Tanah et al., 2016

NDA 021180, Clinical pharmacology and Biopharmaceutics review, Reviewer: Dhruba J. Chatterjee, Ph.D, date: 11/16/01.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/021-180_Ortho%20EVRA_biopharmr.pdf
ANDA 200910, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200910Orig1s000.pdf
Br J Clin Pharmacol 2002 Feb;53(2):141-6. Abrams et al., Contraception. 2001 Nov;64(5):287-94. Abrams et al.

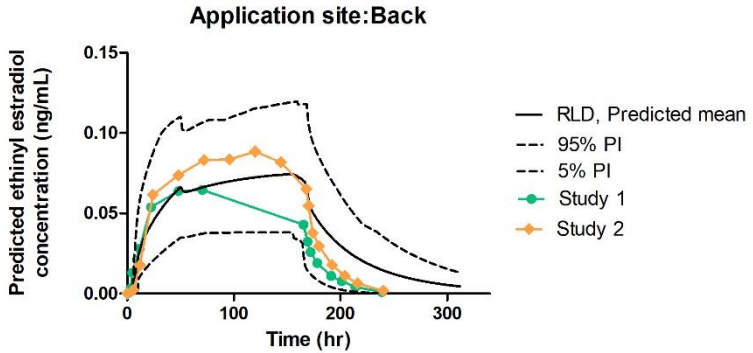
Lasers Surg Med. 2012 Feb;44(2):131-42. Bailey et al.
Sci Rep. 2017 Nov 21;7(1):15885. Wei et al.
PLoS One. 2014 Jan 21;9(1) Derraik et al.
J Physiol Anthropol. 2016 Aug 23;35(1):17. Tahan et al.

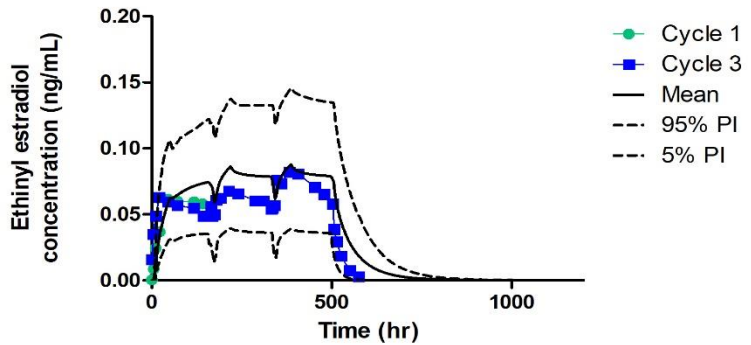
Model Validation/Refinement

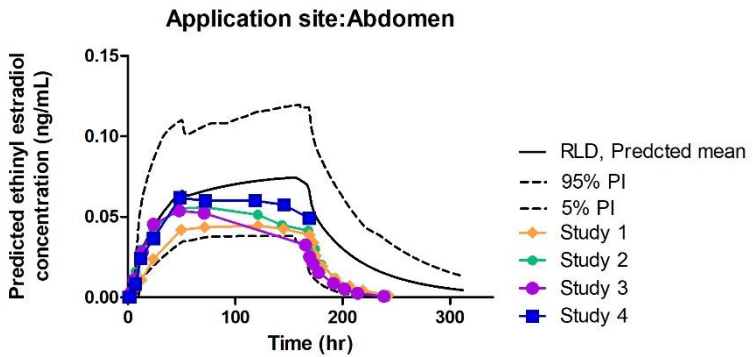
- The dermal PBPK model was validated against literature and in-house data on the systemic API exposure.
  - Dose proportionality study: range of application areas for TDS
  - Steady state (cycle 1-3) vs single dose
  - Over the time period of 3 weeks
  - Across different studies

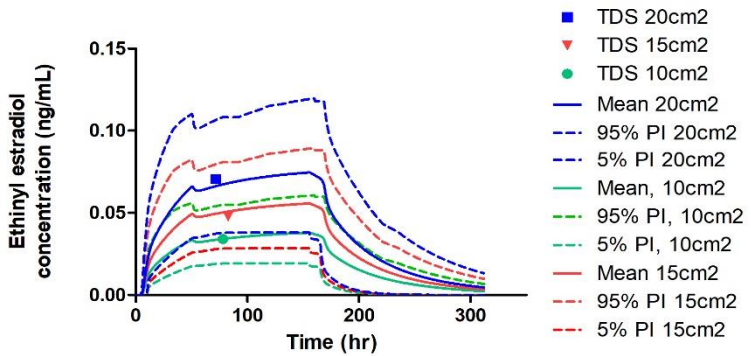
NDA 021180, Clinical pharmacology and Biopharmaceutics review, Reviewer: Dhruba J. Chatterjee, Ph.D, date: 11/16/01. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/021-180_Ortho%20EVRA_biopharmr.pdf
ANDA 200910, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200910Orig1s000.pdf
Br J Clin Pharmacol 2002 Feb;53(2):141-6. Abrams et al., Contraception. 2001 Nov;64(5):287-94. Abrams et al.

Acceptable Model Performance









NDA 021180, Clinical pharmacology and Biopharmaceutics review, Reviewer: Dhruba J. Chatterjee, Ph.D, date: 11/16/01.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/021-180_Ortho%20EVRA_biopharmr.pdf
ANDA 200910, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200910Orig1s000.pdf
Br J Clin Pharmacol 2002 Feb;53(2):141-6. Abrams et al., Contraception. 2001 Nov;64(5):287-94. Abrams et al.

PI: prediction interval

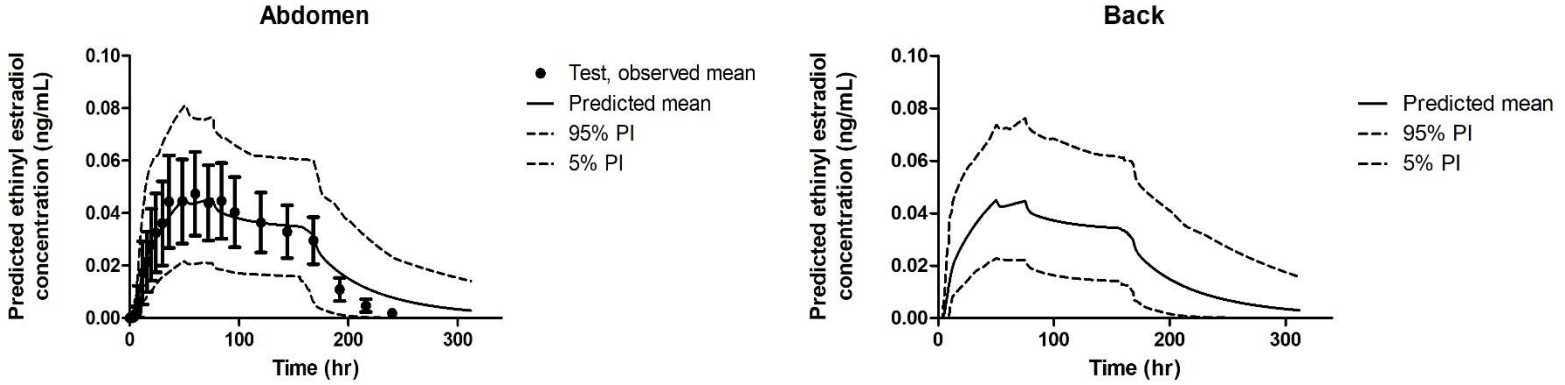
Model Application

The validated model was used to:

- develop dermal PBPK models for the RS and the Test product
- predict API exposure following application for the Test product on the anatomical site developed and assess the risk for dose depletion at the end of the application period.

Exposure Following Application on the Back was Predicted

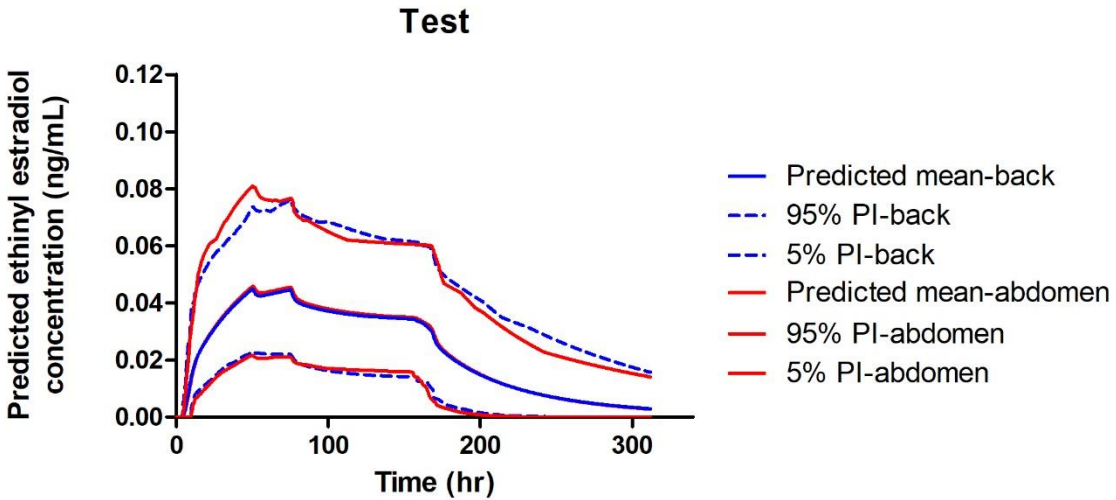
- Dermal PBPK model developed for the Test product
  - Leveraged the dermal PBPK model for the RLD
  - EE release rate obtained by deconvoluting systemic PK data for the Test product (abdomen site)



PI: prediction interval

Exposure Following Application on the Back and Abdomen

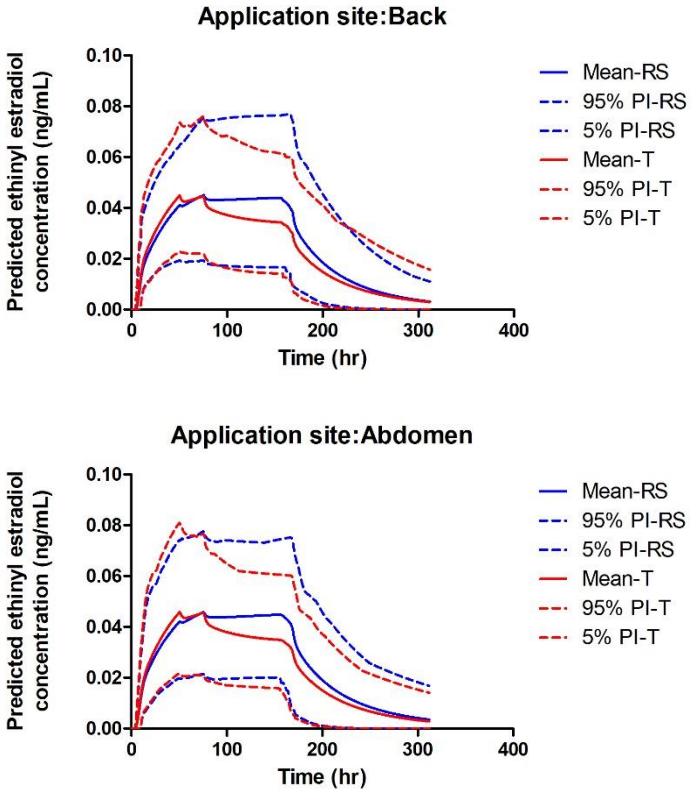
- Exposure following application of the Test product on the back or abdomen were predicted to be comparable



PI: prediction interval

VBE assessment between the Test and RS

- Test and RS are expected to be bioequivalent leveraging the developed models within the scope of a virtual bioequivalence (VBE) assessment.
- No EE depletion is expected for the Test drug product when the product is applied on the back of healthy volunteers under the labeled use conditions.



RS: Reference Standard. T: Test, PI: prediction interval

Conclusion

The validated dermal PBPK model was used to predict the API exposure following TDS application to an anatomical site other than the other evaluated in the in vivo BE study with PK endpoints and to assess the potential for API depletion during the application period.

- Modeling and simulation approaches with a VBE assessment component can be used to support product development and approval for transdermal and dermatological drug products.
  - Provide insight on the effect of important formulation attributes that may influence skin permeability of API
- Modeling and simulation approaches coupled with a VBE assessment supporting an Abbreviated New Drug Application (ANDA):
  - Early interaction between industry and regulatory agency should be initiated through the pre-ANDA meeting request program, GDUFA II.[1]

[1] Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-anda-applicants-complex-products-under-gdufa-guidance-industry

Generic Drug User Fee Amendments: Regulatory Science/Research

Grant	Grant Duration	Institute	Grant No.
Development and validation of dermal PBPK modelling platform towards virtual bioequivalence assessment considering population variability	2014-2018	Simcyp, Ltd	1U01FD005225
Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	2014-2019	University of South Australia	1U01FD005232
Characterization of key system parameters of mechanistic dermal PBPK models in various skin diseases and performance verification of the model using observed local and systemic concentrations	2018-2020	Simcyp, Ltd	1U01FD006521
Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations	2018-2020	SimulationsPlus, Inc	1U01FD006526
Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems	2018-2020	University of Queensland	1U01FD006522
PBPK and Population Modeling Seamlessly Linked to Clinical Trial Simulation in an Open-Source Software Platform	2018-2021	Children's Hospital of Los Angeles	1U01FD006549
Progressing integration of in vitro topical formulation characterisation, release and permeation data to the next level - PBPK based extrapolation to bioequivalence assessment in virtual populations	2021-2023	Certara UK,Ltd	1U01FD007323
Dermal Drug Product Quality and Bioequivalence Assessment through Advanced MAM and PBPK Simulation	2021-2023	SimulationsPlus, Inc	1U01FD007320
Quantitative Expression and Inter-Individual Variability of Skin Proteins Involved in Drug and Excipient Metabolism and Transporters Using Targeted and Label Free LC MS/MS Proteomics	2021-2023	University of Manchester	1U01FD007348

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Questions?

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Division of Quantitative Methods and Modeling
Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA

Challenge Question

What are the key elements of the model development and validation workflow presented here:

A. Systemic Disposition Model for EE

B. In vivo EE release kinetics from the TDS

C. Dermal PBPK model for EE TDS

D. Model validation and refinement

E. All of the above


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ADMINISTRATION

To OGDP: not to be included in the actual presentation

- This presentation summarizes the work done within the scope of a consult to DQMM for ANDA 213950, a generic to XULANE® (NGMN and EE) TDS (RS)/ ORTO EVRA TDS (which is the RS, discontinued RLD). The modeling work was used to "predict the API exposure following TDS application to an anatomical site other than the other evaluated in the in vivo BE study with PK endpoints and to assess the potential for API depletion during the application period." The product was approved on Feb 25, 2021.

- However, Amneal's passing fasting study (pivotal) was conducted at Synchron Research Services Pvt. Ltd. (Synchron). Due to a data integrity issue with this CRO, their product was downgraded to BX based on the Orange Book. They redid their fasting study and is currently under review. The OB review 213950/S-004 does not note any issues and provides a very good overview of the regulatory history. Bioequivalence Review (fda.gov) None of the data from this second study was utilized for this presentation. Only data (mean PK profiles) from the Feb 25, 2021 approved product were utilized for this model.

- All other study data provided in the figures (slides 14, 16,18) are on the RLD available in the public domain, on the RS available in the public domain (drugs@fda) and the mean PK profiles of ANDA 213950 approved on Feb 25, 2021 (slide 18). So when using the "in-house" data term, I am referring to the mean PK profiles from ANDA 213950. Everything else is in the public domain (literature and Clin Pharm Review at Drugs@fda).

- Teva has an approved product ANDA 213977 with the exact same in vivo PK study parameters; abdomen was the application site. However, the API depletion concern did not exist for Teva. The Teva mean PK profiles were used for the internal modeling work, but are not presented or mentioned in this presentation.

This Event has CME !!

- Because this event includes CE for physicians, nurses, and pharmacists; there are additional requirements for the design of your slides:
  - There must be a list of learning objectives near the beginning of your slides (details on next slide).
  - There must be at least two “Challenge Questions” posed to the audience during or at the end of your presentation (more information in later slides)
  - You are encouraged to include audience activities and interaction (such as review of a case study) to make the learning more interactive.
  - *[BTW – You slides really should never be as verbose as many of the “directions” slides in this template.]*

Learning Objectives

- For CME events, this slide takes the place of the usualc“Overview” slide (which prepares your audience!)
- It should still list a brief overview of the talk, but use learning objective statements (that start with a verb), such as:
  - “Describe the overall steps in the Drug Life Cycle from initial testing through the IND and NDA and into post-market”
  - “List the 10 most common errors made when submitting in eCTD format”
- To learn more, see ***CDER DLOD’s Learning Objective Guidance***

Standard Content Slide

- Try to have no more than four bullets
- Try to have fewer than 8 words per bullet
- Since you will be saying lots of words
- Your slides do NOT need to be wordy

Poll Question #1

If you want to include an Adobe Connect Poll question in your presentation, what should you do?

A. Use this slide as the template

B. Read the directions in the “Notes” section for this slide

C. Insert the Poll question wherever it best fits in the flow of your presentation

D. All of the above

Bring in Bullets 1-by-1

- Use fade “Animation” to display your bullets
- One click at a time
- To better focus on each bullet as you discuss it
- View this slide in “Slideshow” mode to see it in action!
- If having all the bullets come up at once is better for how you want to tell your story, you can remove the bullet animation from the slide

You might create sections for longer talks..

The Next Momentous Section

Yet Another Standard Content Slide

- Try to have no more than four bullets
- Try to have fewer than 8 words per bullet
- We know that is *really* difficult for CDER talks
- It is an ideal – like driving 55 MPH
- Try to use the *minimum* number of words while still **briefly** stating your idea

Including Challenge Questions

- CE requires each speaker include at least two challenge questions for their talk.
- These must be difficult enough so that the audience would need to attend the presentation to know the answers.
- Best practices:
  - Place questions throughout the presentation or at the end.
  - Create a multiple-choice question with four feasible choices.
  - Do not use “All of the Above” or “Both B & C” as answer choices.
  - True/False questions are OK, but not encouraged
  - Read the question to the audience; then click to show and read each choice; then ask “Raise your hand if you think it is A”, “Raise your hand if you think it is B”, etc.
    - Then click one more time to show the green box around the correct answer
- Use the next two slides as a template for your Challenge Questions (be sure to test it in “Slideshow” mode)

Challenge Question #1

Labeler Code Information including the name, physical address, email address and other contact information must be updated within:

A. 60 days

B. 90 days

C. 30 days

D. Every June and December

Challenge Question #2

Which of the following statements is NOT true?

A. The indicated population must mirror the studied population (i.e., population described in the CLINICAL STUDIES section).

B. There may be instances when it is necessary to include information in the INDICATIONS AND USAGE section that is discussed in greater detail elsewhere in the labeling.

C. In most cases, limitations of use will identify a particular patient population in which a drug should generally not be used.

D. Indications approved under accelerated approval must include a reference to the CLINICAL STUDIES section.

Resources

- Optional: If you do want to include a list of resources, you should list the titles and directly hyperlink them such as:
- Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format
- Pregnancy and Lactation Labeling Final Rule
- Prescription Drug Labeling Resources
- FDALabel: Full-Text Search of Drug Labeling
- Drugs @FDA
- FDA Office of Women's Health Pregnancy Registry Website
- LactMed (National Library of Medicine)

Summary

- End with a brief summary of the main points
- This way you “tell them what you told them”
- It will reinforce learning
- And it segues into the Q&A

Questions?

Bosepheous G. Pandemonium
Captain, US Public Health Service
Best Division By Far, Office of Greatness
CDER | US FDA

[Optional Link to Relevant Webpage, Email, Etc.]

Closing Thought

To end on a ***strong*** note, leave them with a “call to action” statement that summarizes what they should do with what they just learned.


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