

FY2018 GDUFA Science and Research Report: Drug-Device Combinations

This section contains only new information from FY2018. For background scientific information and outcomes from previous years on this research topic, please refer to:

- FY2015 GDUFA Science and Research Reports:
Transdermal Drug Products
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503041.htm>)
Locally-Acting Orally-Inhaled and Nasal Drug Products
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503040.htm>)
- FY2016 GDUFA Science and Research Reports:
Transdermal Drug Products
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549168.htm>)
Locally-Acting Orally-Inhaled and Nasal Drug Products
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549167.htm>)
- FYs 2013-2017 GDUFA Science and Research Reports:
Transdermal Drug Products
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm605293.htm>)
Drug-Device Combinations
(<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm>)

Introduction

When a generic drug-device combination product is approved in an abbreviated new drug application (ANDA), FDA has concluded that it is therapeutically equivalent to its reference listed drug (RLD). This means the generic combination product is expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in the product labeling and can be freely substituted for its RLD. For drug-device combination products (**Figure 1**), our research programs focus on two aspects of substitution: patient use of drug-device combination products and product performance (especially drug delivery).

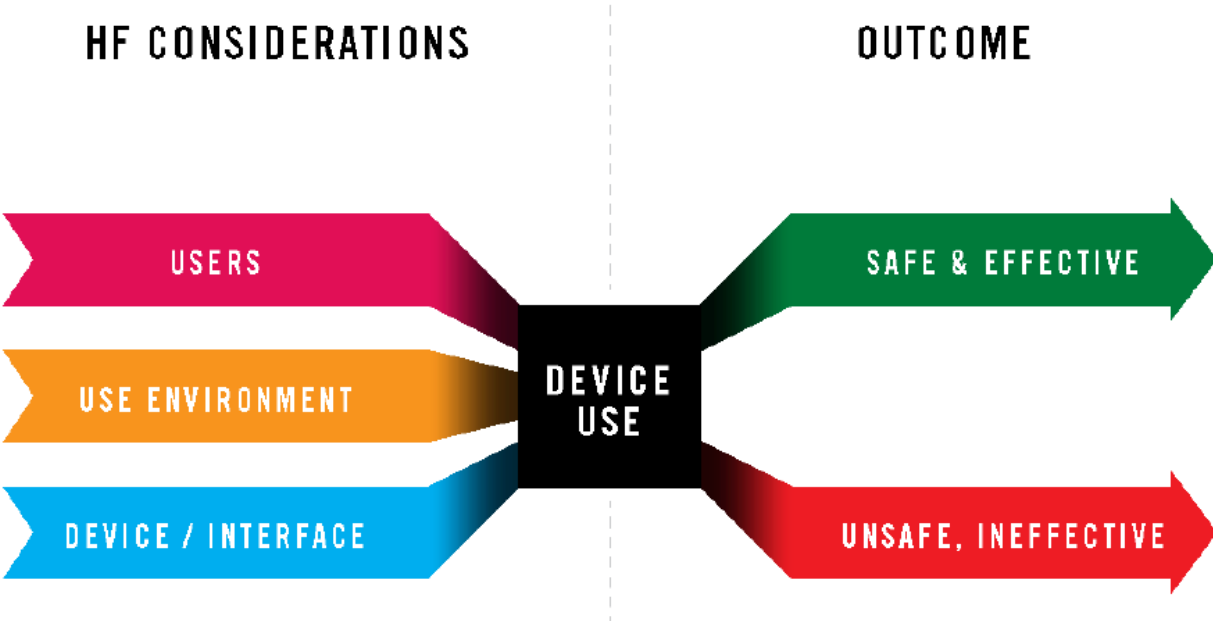
FDA considers whether the end-user (e.g., the patient or caregiver) can use the generic drug-device combination product when it is substituted for the RLD without additional intervention of the health care provider and/or without additional training prior to use. FDA recognizes that a potential applicant of a proposed generic drug-device combination product may develop a user interface with differences from that approved for the RLD product. In the newly published guidance on this topic, FDA recommends that potential applicants conduct comparative (also known as “threshold”) analyses to assess these differences. The FDA published a draft guidance entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry* (January 2017),¹ which details comparative analyses that can be used to identify and assess differences in design between the user interface of a proposed drug-device generic combination product and the user interface of its RLD. Such differences in the design of the interface of a proposed generic combination product and the RLD are evaluated during the ANDA review process (**Figure 2**).

Figure 1: Examples of FDA-approved Drug-Device Combination Products.

¹ CDER/FDA. Draft Guidance for Industry (2017): Comparative analyses and related comparative use human factors studies for a drug-device combination product submitted in an ANDA. [<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf>.]



Figure 2: Relationship Between User Interface Considerations, Device Use and Outcomes.



Source: <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/humanfactors/ucm320901.pdf>

Research

FDA awarded a contract to a group in the Imperial College London to develop a systematic way to evaluate patient perception of dry powder inhaler (DPI) airflow resistance, evaluate patient preferences for a particular airflow resistance range, and determine whether the patient preference for this range varies with disease/severity or class of drug product. This contract is several months into its first year, with the contractors having drafted a literature review on the evaluation of FDA- and European Medicines Agency- (EMA)-approved DPI reported resistances, as well as a draft clinical study protocol and informed consent documentation. This research seeks to further assess whether certain identified differences may impact the clinical effect or safety profile of generic drug-device combination products when compared to RLD counterparts. By better understanding these issues, we hope to assist applicants in the development of complex generic drug-device combination products.

One class of drug-device combination products are transdermal and topical delivery systems (collectively, TDS) that adhere to the skin and deliver drugs into the systemic circulation. These TDS products may be broadly categorized as having either a reservoir or a matrix design (**Figure 3**). Generic TDS are compared to their RLD with respect to systemic bioequivalence, adhesion to the skin, and the potential for causing skin irritation and/or sensitization. The ultimate intent of our research program with TDS is to develop more efficient regulatory standards for prospective generic TDS products. This includes establishing an in vitro – in vivo relationship (IVIVR) between In Vitro Permeation Test (IVPT) studies using excised human skin mounted on diffusion cells and in vivo systemic pharmacokinetics (PK) studies, and evaluating the impact of the Agency’s recently revised statistical approach for assessing the non-inferiority of generic TDS adhesion, which was published in a draft guidance in 2016. A revised draft guidance was published in 2018.²

Drug recrystallization and crystal growth in transdermal delivery systems (TDS) may adversely affect the quality and the efficacy of a drug product. Independently, the presence of crystals in TDS during the shelf life of the product may adversely affect the quality or performance of the TDS. An internal FDA project aimed to understand the effects of drug recrystallization on drug release and permeation kinetics, as well as on TDS physical characteristics. The results from this project elucidated that drug recrystallization in TDS significantly ($p < 0.05$) reduces tack, peel, and shear strengths. Furthermore, recrystallization significantly deteriorates the viscoelastic properties of the adhesive matrix and reduces the drug release and permeation through the skin. A novel in vitro analytical method based on Raman mapping coupled with multivariate image analysis using multivariate curve resolution-alternating least squares was developed as a non-destructive tool for identifying crystals formed. The outcomes of this research illustrated how TDS can be evaluated during product development to assess the risk of drug recrystallization in TDS, so that it can be analyzed, mitigated, and controlled during development, throughout manufacturing, and over the shelf-life of brand and generic drug-in-adhesive TDS products.

Figure 3. Illustrations of a Reservoir TDS and a Matrix TDS.

A)

B)

² Draft Guidance for Industry: Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs (October 2018) available online at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf>.

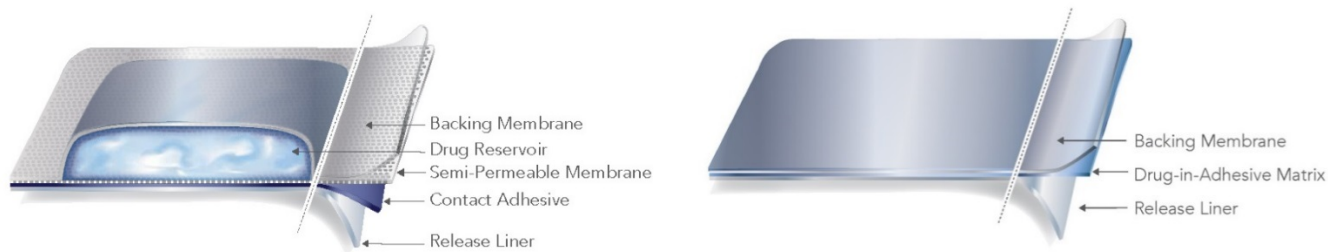


Figure 1: Figure A) Typical reservoir TDS have a raised pouch containing a reservoir of drug that is dissolved or suspended in a gelatinous formulation, with a relatively flat underside that adheres to the skin. Additional layers are also depicted in the figure, although the layers included in the design of a reservoir TDS can vary for different products. Figure B) Typical matrix TDS are slim in profile because the drug load is formulated directly into the adhesive matrix in a thin film that adheres the TDS to the skin. Again, the layers included in the design of a matrix TDS can vary for different products.

The results of the transdermal research performed during FY2018 confirmed the general utility of the IVPT methodology to compare heat effects between prospective generic TDS products and their designated RLD TDS products. Research performed at the University of Maryland (Baltimore) evaluated IVIVRs between IVPT results and systemic PK results for nicotine (**Figure 4**), fentanyl, lidocaine, buprenorphine, oxybutynin, and rivastigmine TDS products. These studies not only evaluated IVIVRs, they also evaluated the utility of IVPT as a surrogate method by which to evaluate the effects of heat (e.g., from heating blankets) on the rate and extent of drug delivery from both types of TDS (topical and transdermal), as well as from transdermal gel products. In silico research performed at the University of South Australia also showed very promising results, suggesting that physiologically based PK modeling and simulation can closely approximate the observed rate and extent of drug delivery from different nicotine TDS.

Figure 4. Predicted vs. Observed Nicotine In Vivo PK Profiles Using Two Different IVIVR Approaches.

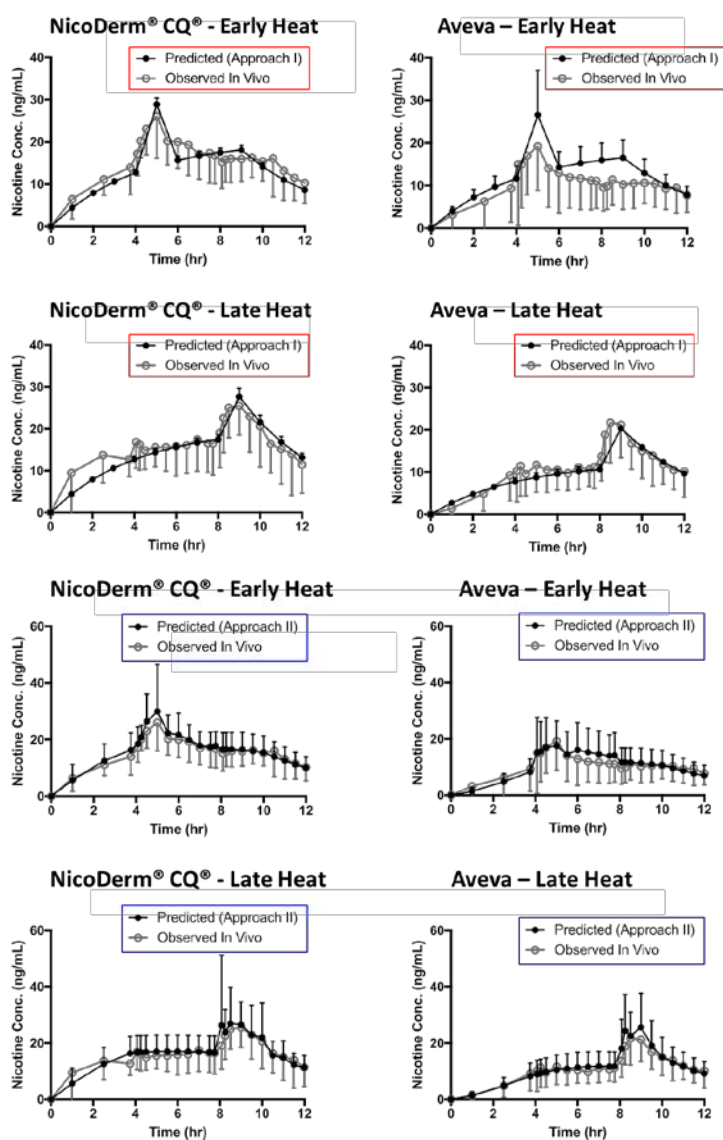


Figure 2: Predicted vs. observed nicotine in vivo PK profiles using two different IVIVR approaches were evaluated for their utility in predicting in vivo serum concentrations for two nicotine TDS. Approach I utilized only in vitro parameters for prediction. Approach II included one parameter from the in vivo study, which corrected for the differences in individual skin permeability between the in vitro and in vivo populations. The in vitro (IVPT) results were able to correlate with and be predictive of the in vivo results in each instance, without significant differences compared to the observed in vivo data. No significant difference ($p > 0.05$) was found among the different IVIVR approaches. Adapted from Shin S, Thomas S, Raney SG, Ghosh P, Hammell DC, El-Kamary SS, Chen WH, Billington MM, Hassan HE, Stinchcomb 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. 2018; 270:76-88.

Independently, research performed within the Agency demonstrated that the FDA’s recently revised approach to evaluating the non-inferiority of TDS adhesion was very effective at increasing the power of these studies, allowing them to be successfully completed with dozens to hundreds (instead of thousands) of subjects. As part of this research, the FDA’s approach to evaluating TDS adhesion was compared with the approach recommended by the EMA and revealed that the FDA and EMA approaches were generally similar and that the outcomes were frequently consistent, although the FDA approach did offer a greater ability discriminate differences in the temporal profile of adhesion.

Research Projects and Collaborations

New Grants and Contracts

- New Contract (HHSF223201810113C) *Formative Research Study to Understand the Impact of Generic Substitutes for Various Patient and Caregiver Populations* with Monica Scales at RTI International

Continuing Grants and Contracts

- Active Grant (U01FD004955) *Heat Effect on Generic Transdermal Drug Delivery Systems* with Audra L Stinchcomb at University of Maryland
- Active Contract (HHSF223201710072C) *Patient’s Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London
- Active Grant (U01FD004275) *Effects of Chemical Penetration Enhancers in Drug-in Adhesive Transdermal Drug Delivery Systems on In-Vitro Skin Permeation Studies* with the National Institute for Pharmaceutical Technology and Education
- Active Grant (U01FD005225) *Development and Validation of Dermal PBPK Modeling Platform Toward Virtual Bioequivalence Assessment Considering Population Variability* with Sebastian Polak at Simcyp, Ltd.

Active FDA Research

- *Characterization of Transdermal Drug Delivery System by Coupled Scanning Electron Microscopy-Raman Spectroscopy*
- *Development of a Novel Bio-Relevant In Vitro Skin Permeation Test (IVPT) for Hydrophobic Drugs Using in-Line Flow Through Diffusion Cells (FTC)*
- *Development of New BE Methods for Transdermal Adhesion*

- *Development of Auto Injector BE Standards*
- *Development of a Biorelevant In Vitro Permeation Method for Generic Transdermal Gel Products.*

Outcomes

Product-Specific Guidances

- *New Draft Guidance for Epinephrine Intramuscular, Subcutaneous Injectable.* FDA Guidance Posting. Oct. 19, 2017. [Link to Posting.](#)
- *New Draft Guidance for Epinephrine Intramuscular, Subcutaneous Solution.* FDA Guidance Posting. July 20, 2018. [Link to Posting.](#)

Publications

- Choi, S. H., Wang, Y., Conti, D. S., Raney, S. G., Delvadia, R., Leboeuf, A. A., and Witzmann, K. *Generic Drug Device Combination Products: Regulatory and Scientific Considerations.* Int J Pharm. (2018) **544**(2):443–454. doi: [10.1016/j.ijpharm.2017.11.038](#). PMID:[29170118](#).
- Sarpatwari, A., Lee, M. P., Gagne, J. J., Lu, Z., Dutcher, S. K., Jiang, W., Campbell, E. G., and Kesselheim, A. S. *Generic Versions of Narrow Therapeutic Index Drugs: A National Survey of Pharmacists' Substitution Beliefs and Practices.* Clin Pharmacol Ther. (2018) **103**(6):1093–1099. doi: [10.1016/j.jpba.2009.11.017](#). PMID: [29165800](#).
- Shin, S., Thomas, S., Raney, S., Ghosh, P., Hammell, D., El-Kamary, S., Chen, W., Billington, M., Hassan, H., and Stinchcomb, A. *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. (2018) **270**:76–88. doi: [10.1016/j.jconrel.2017.11.034](#). PMID: [29175139](#).
- Zhang, Q., Murawsky, M., LaCount, T., Kasting, G., and Li, S. *Transepidermal Water Loss and Skin Conductance as Barrier Integrity Tests.* Toxicol In Vitro. (2018) **51**:129–135. doi: [10.1016/j.tiv.2018.04.009](#). PMID: [29698667](#).

Presentations

- Lionberger, R. *Closing Remarks.* Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 13, 2018.
- Raney, S. *FDA Champions Research to Make Complex Generic Transdermal Products Available to Patients.* Presentation at DIA Webinar. Silver Spring, MD, Apr. 25, 2018.
- Stinchcomb, A. *Characterizing In Vitro Bioavailability of Acyclovir and Metronidazole Topical Products, and In Vitro-In Vivo Correlation Results with Transdermal Systems.* Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.
- Witzmann, K. *Overcoming Barriers to Entry for Complex Generic Oral Inhalation Drug Products.* Presentation at DIA Webinar. Silver Spring, MD, Mar. 15, 2018.
- Witzmann, K. *The Role of Comparative Analyses for Evaluation of Generic Drug-Device Combinations in an ANDA.* Presentation at RDD 2018. Tuscon, AZ, Apr. 26, 2018.
Witzmann, K. *Overview of Regulatory and User-Interface Considerations, and the Role of Comparative Analyses, in Developing a Generic Drug-Device Combination Product in an ANDA.* Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.

Posters

- Mohamed, L.A., Kamal, N., Alayoubi, A., Cruz, C.N., Ashraf, M., and Zidan, A.S. *“Snowflakes” in Transdermal Systems: Effects of Drug Crystallization on TDS Performance*. Poster Presentation at 2018 Controlled Release Society Annual Meeting & Exposition. New York City, NY, July 22-24, 2018.
- Mohamed, L.A., Kamal, N., Alayoubi, A., Cruz, C.N., Ashraf, M., and Zidan, A.S. *Development and validation of IVIVC Model for Testosterone Transdermal Gel Products*. 2018 Controlled Release Society Annual Meeting & Exposition, July 22-24, 2018 at the New York Hilton Midtown, New York City, New York, U.S.A.
- Ramezanli, T., Ghosh, P., Zhang, Y., Luke, M., Shin, S., Hassan, H., Stinchcomb, A., Zhang, Q., and Raney, S. *Developing In Vitro-In Vivo Correlations (IVIVCs) for In Vitro Permeation Test and In Vivo Pharmacokinetic Studies to Evaluate the Effects of Heat on Nicotine Transdermal Delivery Systems*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 28, 2017.
- Shin, S., Yu, M., Thomas, S., Hammell, D., Ghosh, P., Raney, S., Hassan, H., and Stinchcomb, A. *Evaluation of Level A In Vitro-In Vivo Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems with Transient Heat Exposure by Using Multiple Approaches*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Shukla, S., Thomas, S., Hammell, D., Bunge, A., Hassan, H., and Stinchcomb, A. *In Vivo Evaluation of Lidocaine Bioavailability from Two Topical Patch Products by Pharmacokinetic and Skin (Tape) Stripping Analyses*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Sun, W., Grosser, S., Kim, C., and Raney, S. G. *A Comparison of the European Medicines Agency (EMA) and United States Food and Drug Administration Approaches to Assessing/Comparing In Vivo Adhesion for Transdermal Delivery Systems(TDS)*. Poster Presentation at the 3rd GBHI Conference. Amsterdam, NE, Apr. 10, 2018.
- Thomas, S., Ghosh, P., Raney, S., Hammell, D., Hassan, H., and Stinchcomb, A. *In Vitro Evaluation of a Buprenorphine Transdermal Delivery System with Transient Heat Exposure and the Correlation of In Vitro Results with Existing In Vivo Results*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- W, S., Grosser, S, Kim, C., and Raney, S. *Impact of the Statistical Approach in the United States Food and Drug Administration (US FDA)’S 2016 Draft Guidance on Assessing Adhesion with Transdermal Delivery Systems (TDS) for Abbreviated New Drug Applications (ANDAs)*. Poster Presentation at the 3rd GBHI Conference. Amsterdam, NE, Apr. 10, 2018.
- Yu, M., Thomas, S., Hammell, D., Hassan, H., and Stinchcomb, A. *A Fully Validated LC MS/MS Method for Simultaneous Determination of Oxybutynin and Its Metabolite N-Desethyloxybutynin in Human Serum*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.