

FYs 2013 - 2017 GDUFA Science and Research Report: Transdermal Drug Products

Introduction

Transdermal products are one of the most common and important classes of drug products due to their unique advantages relative to other dosage forms and routes of administration. They can provide sustained drug delivery for several days (to improve patient compliance), avoid first pass metabolism of a drug by the liver, be administered to a patient who is sleeping, unresponsive, or unable to swallow oral medications and be removed at any time to halt drug delivery, if needed.

Transdermal drug products are administered to the skin, through which the drugs permeate into the systemic circulation and are delivered throughout the body to the site of action. Transdermal products are most frequently developed as transdermal delivery systems (TDS), also known as patches. These TDS are usually designed using pressure sensitive adhesives, and can be adhered to the skin for specified durations of wear. TDS are complex drug-device combination products that may be broadly categorized as having either a reservoir or a matrix design (see Figure 1). However, transdermal products can also be semisolid products (e.g., testosterone transdermal gels). These gels are also sometimes developed as a different type of drug-device combination product, one involving a metered dose pump. Overall, transdermal products are used to treat a wide variety of conditions and diseases, including moderate to severe vasomotor symptoms due to menopause, dementia of the Alzheimer's type, attention deficit hyperactivity disorder, major depressive disorder, management of chronic pain, prevention of nausea and vomiting, prevention of angina pectoris, and several others. Therefore, the availability of high-quality, safe, effective and affordable generic transdermal products is essential to millions of patients.

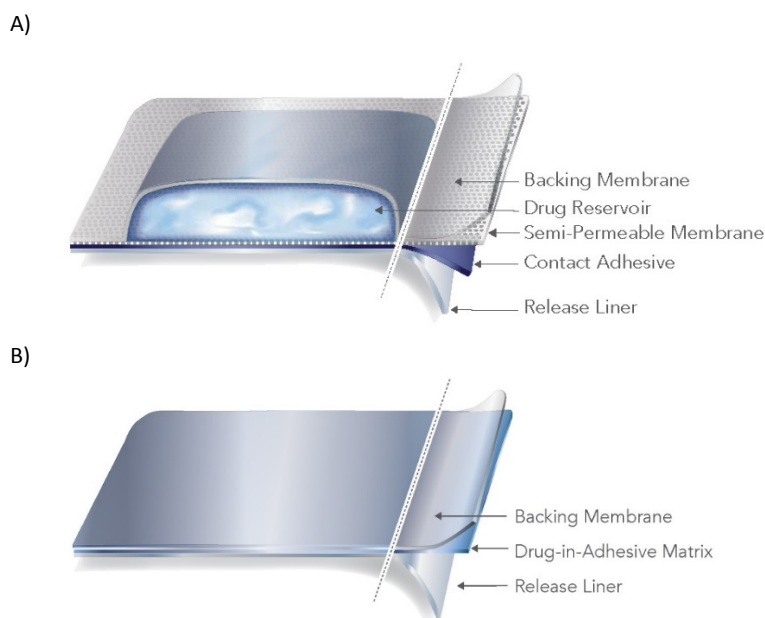


Figure 1: Illustrations of A) a reservoir TDS and B) a matrix TDS: Figure 1A) Typical reservoir TDS have a raised pouch containing a reservoir of drug that is dissolved or suspended in a gelatinous formulation, with a relatively flat underside that adheres to the skin. Additional layers are also depicted in the figure, although the layers included in the design of a reservoir TDS can vary for different products. Figure 1B) 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.

Prior to the implementation of the Generic Drug User Fee Amendments (GDUFA) research program in 2012, several TDS products lacked generic competition. For example, scopolamine TDS, the oldest transdermal product, had been on the market since 1979 with no approved generics. The development of the brand name Reference Listed Drug (RLD) products necessitated the innovator TDS manufacturers to address special considerations related to product quality (e.g., leakage, bursting, cold flow) and performance (e.g., adhesion to the patient's skin) that were somewhat unique to this class of dosage form. Therefore, developing high quality, therapeutically equivalent generic TDS also involved special considerations beyond the pharmacokinetics of the drug.¹ The complexity of the TDS dosage form, and the associated challenges related to product development and manufacturing may, have contributed to the limited availability of generic transdermal products prior to 2012.

For example, while a TDS should adhere to skin in a uniform and consistent manner throughout the duration of patient wear, there are some RLD TDS that may exhibit a partial loss of adhesion (e.g., lifting at the edges in response to daily activities) during patient wear. Independently, the occlusiveness of the RLD TDS and the nature of the TDS formulation may have had the potential to cause skin irritation and/or sensitization reactions. These complex quality and performance considerations for RLD TDS arose under normal conditions of labeled use. Independently, exposure to conditions (such as heat in a sauna or from a heating blanket) which are outside the RLD product's labeled use parameters might increase the rate and extent of drug delivery and lead to overdosing or other unintended consequences.²

As with the development of any generic product, complex quality and performance attributes must be assessed in comparison to the RLD or Reference Standard (RS)³ product. Indeed, FDA-approved generic and RLD/RS TDS products may have certain differences in composition, which may have the potential to influence drug delivery, adhesion, irritation, and/or sensitization. In fact, generic manufacturers are encouraged to minimize the residual surplus of drug remaining in the product when it is ultimately disposed, relative to the equal or greater excess of drug that remains in the RLD/RS and other similar products. Considering these potential differences between an RLD/RS TDS product and a prospective generic TDS, the quality and performance characteristics of all generic TDS products are carefully evaluated prior to approval. For example, in addition to demonstrating bioequivalence (BE) in the rate and extent of drug delivery under labeled use conditions, the in vivo adhesion to skin and the potential for skin irritation and/or sensitization of a generic TDS must be demonstrated to be no worse than that for the RLD/RS TDS product.

When GDUFA was implemented, FDA recognized the unique challenges associated with evaluating therapeutic equivalence for generic TDS products, which arose from complex technical and scientific issues for these products. For example, FDA was aware of specific issues related to determining statistical non-inferiority (NI) for TDS adhesion, irritation and sensitization in clinical studies. FDA was also aware of the potential effects of high temperatures on TDS products, in general, and that differences between the RLD/RS and generic TDS products in composition or design could mean that the TDS products may respond differently to heat. This consideration warranted evaluation, however, there was no established approach for performing such studies at the time.

Accomplishments (2012-2017)

¹ Strasinger C, Raney SG, Tran DC, Ghosh P, Newman B, Bashaw ED, Ghosh T, Shukla CG. Navigating sticky areas in transdermal product development. *Journal of Controlled Release*. 2016;233:1-9

² Hao J, Ghosh P, Li SK, Newman B, Kasting GB, Raney SG. Heat Effects on Drug Delivery Across Human Skin. *Expert Opinion on Drug Delivery*. 2016;13(5):755-768.

³ For information about the differences between RLDs and RS, please review FDA's Guidance for Industry, [Referencing Approved Drug Products in ANDA Submissions](#).

Under GDUFA, the FDA developed innovative approaches that had the potential to reduce the scientific challenges and regulatory barriers impacting the availability of generic TDS products. These innovative approaches can be broken into four research initiatives.

1. The first initiative aimed to develop a new approach to design and statistically analyze comparative clinical studies evaluating generic TDS product adhesion. FDA accomplished this goal and successfully resolved several issues that facilitated the approval of well-adhering, high-quality generic TDS.
2. The second initiative was an in vitro test system that had the potential to correlate with and be predictive of in vivo heat effects with TDS products. This test system can be used efficiently during product development to ensure that the heat effects observed with a generic TDS are no worse than those observed for the corresponding RLD/RS TDS product. This research yielded promising indications that an In Vitro Permeation Test (IVPT) using excised human skin mounted in diffusion cells can show in vitro-in vivo correlations (IVIVC) for heat effects with nicotine and fentanyl TDS⁴. These findings were consistent with a similar IVIVC developed for estradiol TDS⁵, and research with several other TDS products is ongoing.
3. The third initiative involved FDA's use of computational (in silico) modeling approaches to help to develop appropriate BE standards for TDS products that had no generics available prior to GDUFA. For example, it is known that there is a close relationship between the concentration of methylphenidate in the systemic circulation and its therapeutic effect. The Office of Generic Drugs' (OGD's) model-based approach evaluated potential variations in pharmacokinetic (PK) profiles with hypothetical methylphenidate TDS products that may be developed as prospective generics. A population PK model was linked to a published model⁶ of pharmacodynamic (PD) response for this drug, to simulate the impact on therapeutic efficacy of potential differences in the shape of the PK profiles between the RLD methylphenidate TDS and hypothetical generics. In particular, the research evaluated the potential for differences in therapeutic performance in situations where the PK profiles of a prospective generic methylphenidate TDS were evaluated using traditional PK endpoints of maximum concentration (C_{max}) and area under the concentration-time curve (AUC). The in silico modeling helped to identify more sensitive PK endpoints that are based upon a comparison of partial AUC (pAUC) between 2 and 9 hours, to ensure that any generic methylphenidate TDS would be as safe and effective as the RLD product for its indicated populations of children and adolescents. The results of this computational modeling research was aligned with insights from experts across the FDA, and exemplifies the manner in which OGD integrates multidisciplinary approaches to develop scientifically well-

⁴ Shin S, Yu, M, Thomas S, Hammell DC, Ghosh P, Raney SG, Hassan HE, Stinchcomb AL. Level A In Vitro In Vivo Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems with Transient Heat Exposure, Evaluated using Multiple Approaches. Poster presentation at the 2017 Gordon Research Conference on the Barrier Function of Mammalian Skin, 2017, New Hampshire, USA.

⁵ Yang Y, Manda P, Pavurala N, Khan MA, Krishnaiah YSR. Development and validation of in vitro-in vivo correlation (IVIVC) for estradiol transdermal drug delivery systems. *Journal of Controlled Release*. 2015;210: 58–66.

⁶ Kimko H, Gibiansky E, Gibiansky L, Starr HL, Berwaerts J, Massarella J, Wiegand F. Population pharmacodynamic modeling of various extended-release formulations of methylphenidate in children with attention deficit hyperactivity disorder via meta-analysis. *J Pharmacokinet Pharmacodyn*. 2012;39(2):161-76.

supported and clinically meaningful BE standards, in this case for generic methylphenidate TDS products.

4. The fourth initiative, led by the Office of Pharmaceutical Quality (OPQ) and supported in part by GDUFA, was focused on developing a meaningful and reproducible approach to evaluate the strength of a TDS product, so that a single, standardized method could be used efficiently during product development. This research is currently underway using standardized protocols for PK and residual drug approaches in the same study. FDA is evaluating multiple TDS products and corresponding parenteral formulations in crossover studies to evaluate whether a generally applicable method can be identified for determining the strength of a TDS.

The work associated with these four innovative approaches is discussed in more detail below, using specific projects that are exemplary of the research for transdermal drug products performed under GDUFA.

Research and Collaborations

Below are some of the research initiatives that have supported the development of science-based regulatory standards. These initiatives strategically advance specific areas of pharmaceutical science for transdermal products, that collectively establish a scientific basis for appropriate regulatory standards. These regulatory standards, in turn, ensure that the quality and performance of generic TDS products are appropriate and efficient, so that the therapeutic equivalence of generic and RLD/RS products is comparably robust, and so that inappropriate barriers to the development of generic TDS are reduced, thereby facilitating patient access to these high quality generic products.

1. Development of new statistical methods for assessing adhesion with TDS and topical delivery systems for ANDAs

The amount of drug delivered into and through the skin from a TDS is proportional to the surface area dosed. When a TDS loses adherence and detaches from the skin, the surface area of contact to the skin, and potentially the amount of drug delivered, is reduced. The entire contact surface area of the TDS should remain consistently and uniformly adhered to the skin throughout the duration of wear under the conditions of use included in the product labeling.

The adhesion of some RLD/RS TDS products over the duration of wear is almost perfect. However, for other RLD/RS TDS products, there may be a gradual partial loss of adhesion over the duration of wear. These RLD/RS TDS would still be therapeutically effective, although there is the potential for greater variability in the rate and extent of drug delivery from individual doses of the TDS product when the adhesion performance of the TDS is more variable.

The in vivo adhesive performance of an FDA-approved generic TDS product is required to be non-inferior (NI) compared to that of the RLD/RS TDS. The traditional statistical approach recommended in earlier FDA product-specific guidances (PSGs) to evaluate NI for generic TDS had a low statistical power in situations where the adhesion of the RLD/RS TDS was almost perfect. This had the consequence of making it more difficult for comparably well-adhering generic TDS to demonstrate NI, and negatively impacted the availability of high-quality generic TDS.

Exhaustive research within the FDA, including collaboration among clinicians, statisticians, and other scientists resulted in a new approach to address this issue. The new statistical approach replaced the traditional ratio-of-means (ROM) NI test with a difference-of-means (DOM) NI test, which was still based upon mean adhesion scores. The DOM NI test is robust in power to the direction of adhesion scores (unlike the traditional ROM NI test). This new approach to evaluating NI dramatically improved the statistical power for well-adhering TDS products, and dramatically reduced the subject population size needed for in vivo studies to demonstrate NI.

This work, as well as related initiatives to optimize and harmonize regulatory recommendations for all TDS products, directly supported the development of a draft guidance for industry on in vivo adhesion studies⁷, as well as revisions to 18 product-specific guidances for the development of generic TDS products (see “Outcomes” section below). These enhancements in regulatory standards have also directly supported the approval of multiple well-adhering generic TDS that were not previously approvable, but which are now available to patients.

2. Development of IVPT models for the evaluation of comparative heat effects with generic and reference transdermal delivery systems

The FDA sought to characterize potential differences in heat effects because prospective generic TDS products, which may be bioequivalent to their corresponding RLDs under labeled use conditions, may yet have the potential to deliver drug(s) at a higher rate when exposed to elevated temperatures during use.

The GDUFA-funded research initiatives evaluated methods to compare TDS heat effects in vitro, using IVPT studies, and in vivo, using systemic PK studies in human subjects. FDA’s research sought to develop predictive in vitro methodologies to evaluate the effects of an elevated temperature on the increase in the rate and extent of drug delivery from TDS, topical patches, and transdermal gel products. This research also helped to develop appropriate and relevant study conditions under which to evaluate TDS heat effects by comparing in vivo results in human subjects and in vitro results using excised human skin in diffusion cells.

Related research sought to elucidate the factors that influence how heat affects the release of a drug from a TDS, as well as the subsequent permeation of a drug through the skin. The potential influencing factors considered included the thickness or thermal resistance of the TDS, the physicochemical properties of the drug and/or the TDS formulation, and the directionality of heat gradients, which are different when the heat is environmental (external) as opposed to when the heat arises from an elevated core body temperature (internal). An understanding of these factors supported the development of computational models that could simulate the effect of heat on TDS drug delivery under a variety of different conditions, based upon studies conducted under only one or a few conditions.

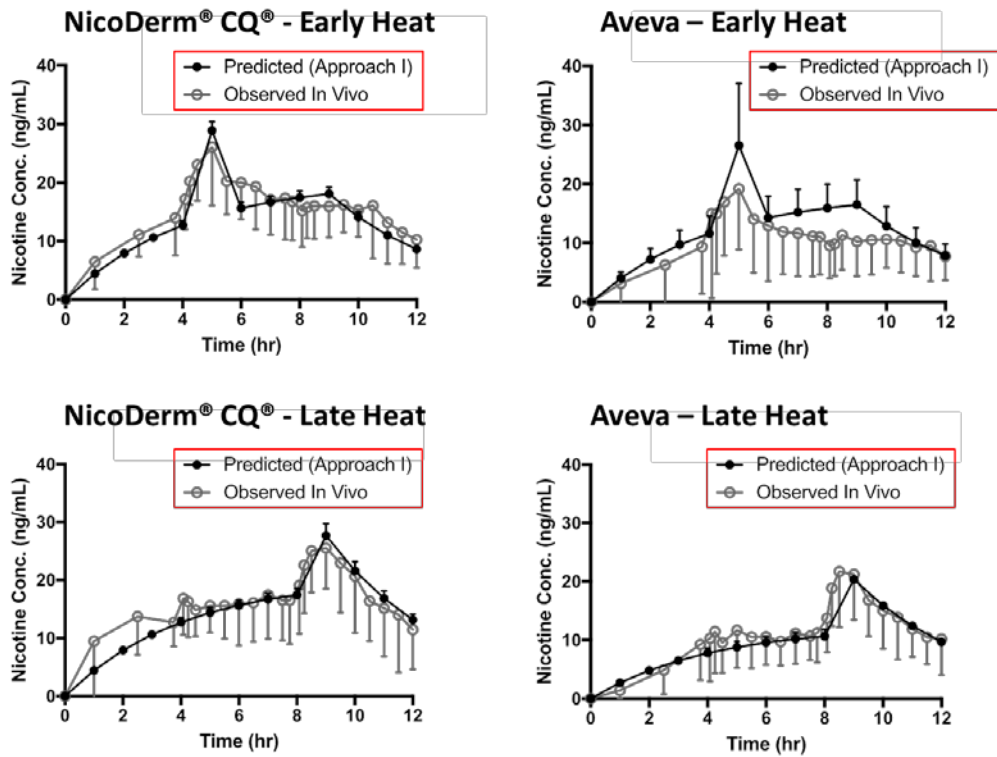
FDA awarded the collaborative research projects described above to two institutions as cooperative research agreements to develop efficient, predictive in vitro methods for the comparative assessment of TDS heat effects between a prospective generic TDS product and its corresponding RLD/RS product. This research included studies performed in vitro, using the IVPT model with excised human skin mounted in diffusion cells, and in vivo with parallel PK

⁷ Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs Draft Guidance for Industry available online at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf>.

studies that measured the plasma/serum concentrations of the drugs in human subjects using a harmonized study design. The two cooperative agreements and research projects were:

- Heat Effect on Generic Transdermal Drug Delivery Systems (PI: Professor Audra Stinchcomb; University of Maryland, Baltimore)-1U01FD004955
- Tiered Testing Strategy for Assessing Thermal Effects on Transdermal Products (PI: Professor Kevin Li; University of Cincinnati)-1U01FD004942

The University of Maryland award included the IVPT studies and parallel in vivo plasma/serum PK studies in human subjects, with both types of studies evaluating the same set of drug products for each of multiple drugs (nicotine, fentanyl, lidocaine, oxybutynin, etc.). Recent results with the first set of products studied in vitro and in vivo led to the development of IVIVCs (Figure 2) for two pharmaceutically equivalent nicotine TDS.



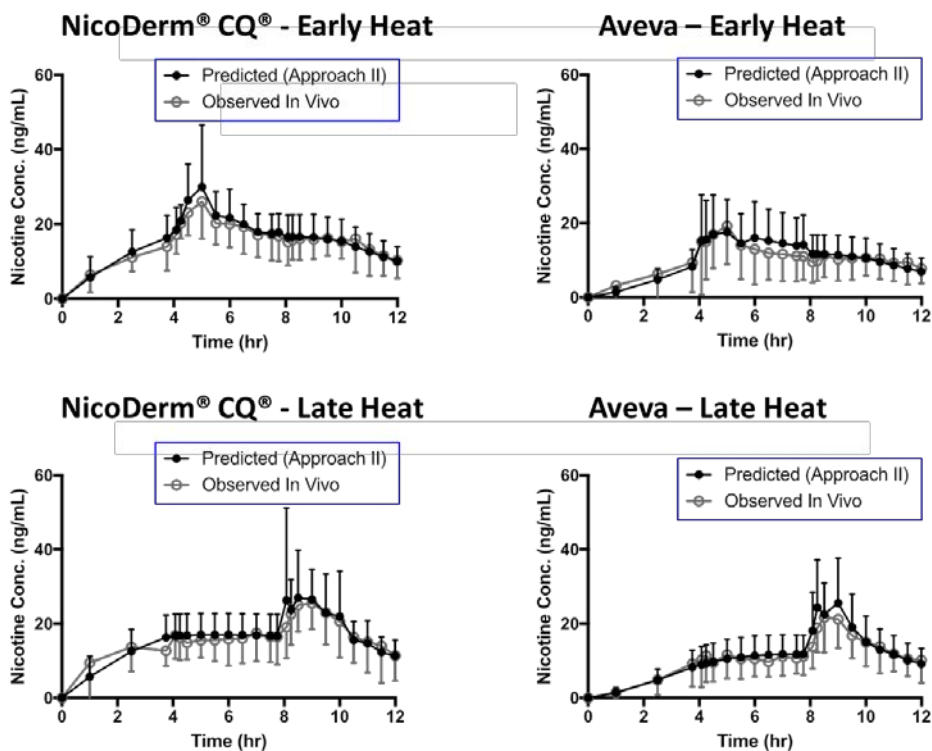


Figure 2: Predicted vs. observed nicotine in vivo PK profiles using two different IVIVC approaches. Different approaches to developing a Level A IVIVC were evaluated for their utility in predicting in vivo serum concentrations for two nicotine TDS. The in vitro (IVPT) results were able to correlate with 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 IVIVC approaches. Adapted from Shin S, Yu M, Thomas S, Hammell DC, Ghosh P, Raney SG, Hassan HE, Stinchcomb AL. Level A In Vitro In Vivo Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems with Transient Heat Exposure, Evaluated using Multiple Approaches; Poster presentation at the 2017 Gordon Research Conference on the Barrier Function of Mammalian Skin, 2017, New Hampshire, USA, and 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.

The University of Cincinnati award provided a cross-laboratory comparison for the IVPT studies, evaluating the same set of nicotine, fentanyl, and buprenorphine TDS products that were evaluated independently at the University of Maryland. The studies at the University of Cincinnati evaluated the same products using a variation in the IVPT diffusion cell apparatus and method of heat application relative to the University of Maryland, and included an in vivo study in human subjects designed to elucidate certain fundamental mechanistic aspects of heat transfer and tolerability. The latter study helped to identify appropriate temperatures to use when evaluating heat effects for transdermal products. An additional aspect of the University of Cincinnati award was the development of computational modeling and simulation tools that may help to correlate in vitro and in vivo results, and which could potentially simulate in vivo heat effects for a TDS under conditions beyond those tested in vitro. An FDA co-authored publication describes an evaluation of the IVIVC between temperatures and temperature gradients produced in vitro and in vivo under different scenarios using different IVPT apparatus and mechanisms to study the effects of heat on TDS, and discusses the fundamental biophysical

study design factors that must be considered to appropriately model different in vivo heat exposure scenarios in vitro with different types of TDS⁸.

3. Development of computational (in silico) modeling approaches to support the evaluation of BE for TDS products

Potential differences in formulation and product design between an RLD and a prospective generic TDS could influence the comparability of the PK profiles. In some cases, differences in the precise shape of the PK profile may be clinically meaningful, particularly for drugs where the PD response is very sensitive to differences in the PK. Appropriate BE evaluation criteria must be used in such situations to ensure that a generic TDS product is therapeutically equivalent to the RLD product.

Methylphenidate is one example of a drug that exhibits a well-defined PK-PD relationship. The FDA used a model-based approach to evaluate potential variations in PK profiles of hypothetical methylphenidate TDS products. This evaluation supported the development of appropriate BE standards for methylphenidate TDS. Specifically, a population PK model was developed that was linked to a published PD model⁹ to simulate how variations in PK profiles might influence the efficacy of a methylphenidate TDS product. This computational modeling and simulation approach evaluated the sensitivity with which different BE criteria could detect clinically meaningful PK differences from hypothetical methylphenidate TDS products. Furthermore, the results of simulated in vivo BE studies suggested that a partial AUC between two and nine hours following TDS administration (pAUC_{2-9h}) was the most sensitive metric for detecting clinically relevant PK differences.

This work supported a revision of the PSG for methylphenidate TDS¹⁰, which now recommends the inclusion of pAUC_{2-9h}, in addition to conventional metrics like C_{max} and AUC, among the PK endpoints supporting an evaluation of BE.

4. Development of an appropriate method to determine the strength of a TDS

The research collaborations led by OPQ (through research funding to the National Institute for Pharmaceutical Technology and Education (NIPTe)) and supported in part by GDUFA (through research funding to the University of Maryland, Baltimore and other resources) evaluated methodologies used to characterize the strength of a TDS. The strength of a TDS is usually expressed in terms of the nominal rate of drug delivery (e.g., milligrams of drug per hour), unlike solid oral dosage forms, where the strength reflects the amount of drug in the product. The most commonly used techniques to determine this rate are 1) PK studies that quantify the amount of drug delivered into the systemic circulation and 2) an analysis of the residual (remaining) amount of drug in the TDS after the wear duration, from which the amount of drug delivered during TDS wear can be imputed. These methods rely upon assumptions/estimates to derive the nominal drug delivery rate. Substantial variability can exist in the calculated strength derived by either method, as well as differences in what the measure of strength reflects in each

⁸ Zhang Q, Murawsky M, LaCount T, Hao J, Kasting GB, Newman B, Ghosh P, Raney, SG, Li SK. Characterization of Temperature Profiles in Skin and Transdermal Delivery System When Exposed to Temperature Gradients In Vivo and In Vitro. *Pharm Res.* 2017;34:1491–1504. DOI 10.1007/s11095-017-2171-x

⁹ Kimko H, Gibiansky E, Gibiansky L, Starr HL, Berwaerts J, Massarella J, et al. Population pharmacodynamic modeling of various extended-release formulations of methylphenidate in children with attention deficit hyperactivity disorder via meta-analysis. *J Pharmacokinetic Pharmacodyn.* 2012;39(2):161-76.

¹⁰ Draft Guidance on Methylphenidate for TDS products available online at:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf>.

case. Since a generic TDS must be the same strength as the reference TDS in order to establish pharmaceutical equivalence, it is important to be able to accurately characterize the strength of a TDS product. Issues with the manner in which the nominal strength was established for the RLD product can potentially complicate generic product approvals.

This research initiative used PK and residual drug data from multiple TDS products to evaluate different methods to evaluate the strength of TDS products. These research projects aimed to develop appropriate and relevant study conditions under which to evaluate the strength of a TDS. A second goal was to standardize the mathematical calculations used for the evaluation of strength, whether using the PK or the residual drug approach.

The FDA awarded research agreements to develop efficient methods for the evaluation of strength for TDS products. This research included studies performed in vivo using TDS products and parenteral formulations that measured the plasma/serum concentrations of the drugs in human subjects. The two projects were:

- Heat Effect on Generic Transdermal Drug Delivery Systems (PI: Professor Audra Stinchcomb; University of Maryland, Baltimore)-1U01FD004955 (expansion of scope)
- Manufacturing Sector Research Initiative (NIPTE: Professor Audra Stinchcomb, University of Maryland; Professor Nicole Brogden, University of Iowa; Professor Karunya Kandimalla, University of Minnesota; and Professor Kenneth Morris, Long Island University)-5U01FD004275

The University of Maryland was awarded an expansion of scope for a separate project originally designed to evaluate the influence of heat on the rate and extent of drug delivery from a TDS. The FDA expanded the research project to initiate the efforts to determine the most appropriate method for evaluating the drug delivery rate (and thereby, the strength) of a TDS, because the factors that complicate determining strength for a TDS fundamentally impact the potential methods by which to evaluate and calculate the rate of drug delivery.

The NIPTE award includes an in vivo evaluation of multiple TDS products (fentanyl, scopolamine and lidocaine) and the corresponding parenteral formulations using standardized protocols for determining the strength of each TDS using both PK and residual drug approaches. This research is on-going.

Key Outcomes

During GDUFA, the FDA revised 18 PSGs for TDS products as part of an initiative to establish modern, efficient, and harmonized regulatory standards for all TDS products. The FDA also published a detailed general guidance⁷ describing significant enhancements for the design and conduct of studies comparing the adhesive performance of generic TDS products compared to the RLD. These revised regulatory standards contributed to the approval of multiple well-adhering generic TDS products. A noteworthy generic TDS approved was the first generic scopolamine TDS, for which the RLD/RS scopolamine TDS had originally been approved four decades ago, but had gone all these years without a generic.

These advances in pharmaceutical science for transdermal products under GDUFA enabled the FDA to be responsive to numerous product development communications with prospective generic product applicants through general guidance and PSGs, controlled correspondences, and pre-ANDA meeting

communications. The evidence and insights gained from the GDUFA science and research projects directly supported the review and approval of multiple generic TDS products.

Future Directions

Much has been accomplished since the implementation of the GDUFA science and research initiatives. Yet, there is an ongoing need to continue and complete these massive research enterprises, in part to understand the general applicability of the newly-developed TDS characterization tools to a wide variety of TDS products. Further research is also needed so that additional tools and techniques can be developed, which may include new methods to control advanced manufacturing processes for TDS products and transdermal gels, studies to better understand how different transdermal gel (pump) packaging and TDS designs and/or formulations may need to be controlled, and techniques to ensure the stable performance of a transdermal product throughout its shelf life.

Ongoing research is laying the foundations for future work. For example, research funded by the Critical Path Initiative, in collaboration with support from GDUFA funding, is utilizing X-ray diffraction, differential scanning calorimetry, microscopy and near infrared hyperspectral imaging to characterize crystallization phenomena in rotigotine TDS. The ongoing development of computational modeling approaches will likely facilitate more efficient product development and regulatory decision-making for transdermal products. In silico models could help to predict the influence of tapes or overlays on TDS drug delivery, the impact of varying degrees of TDS detachment on the resulting PK profile for a given product, the influence of differences in adhesion characteristics between products on BE, or the extrapolation of single-dose PK data to simulated multi-dose PK profiles. Other ongoing research involving data mining is focused on statistical innovations to optimize the power and efficiency of in vivo studies. For example, FDA's OGD and the Office of Translational Sciences, Office of Biostatistics are collaborating on research to evaluate potential enhancements to the designs and statistical evaluation of TDS irritation and sensitization studies, in a manner analogous to what was developed for TDS adhesion studies.

The goal of this and other ongoing GDUFA science and research is to develop generally applicable BE approaches and supplemental regulatory standards for all types of transdermal products. These approaches and standards may involve rational combinations of in vitro, in silico (modeling), and/or in vivo evidence that collectively support an efficient and compelling demonstration of BE, as well as of all the supplemental quality and performance requirements for a generic transdermal product. The methods and tools that result from this ongoing research would become valuable resources for the pharmaceutical and regulatory community to efficiently advance transdermal drug development, provide increased certainty in regulatory decision making, and ultimately, enhance patient access to high-quality generic transdermal products.

Outcomes

General Guidances

1. Draft Guidance for Industry: Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs (June 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf>

Product-Specific Guidances

1. Posting of Draft product-specific guidance on Buprenorphine Film, extended release (Apr 2014; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384107.pdf>
2. Revision of Draft product-specific guidance on Clonidine Film, extended release (Nov 2009; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM191775.pdf>
3. Revision of Draft product-specific guidance on Estradiol Film, extended release (for products referencing New Drug Application (NDA) 019081 as the RLD) (Nov 2010; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234961.pdf>
4. Revision of Draft product-specific guidance on Estradiol Film, extended release (for products referencing NDA 020538 as the RLD) (Nov 2010; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234963.pdf>
5. Posting of Draft product-specific guidance on Estradiol Film, extended release (for products referencing NDA 203752 as the RLD) (Apr 2014; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384116.pdf>
6. Revision of Draft product-specific guidance on Estradiol Film, extended release (for products referencing NDAs 020375 or 021674 as the RLD) (Nov 2010; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234962.pdf>
7. Revision of Draft product-specific guidance on Ethinyl Estradiol; Norelgestromin Film, extended release (May 2009; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM162407.pdf>
8. Posting of Draft product-specific guidance on Fentanyl Film, extended release (May 2009; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM162427.pdf>
9. Revision of Draft product-specific guidance on Granisetron Film, extended release (Mar 2012; revised Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296900.pdf>
10. Revision of Draft product-specific guidance on Methylphenidate Film, extended release (Jul 2010; revised Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220196.pdf>

11. Posting of Draft product-specific guidance on Nicotine Film, extended release (Nov 2013; revised Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM373700.pdf>

12. Revision of Draft product-specific guidance on Nitroglycerin Film, extended release (Dec 2009; revised Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194647.pdf>

13. Posting of Draft product-specific guidance on Oxybutynin Film, extended release (Jun 2015; revised Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM452848.pdf>

14. Revision of Draft product-specific guidance on Rivastigmine Film, extended release (Feb 2010; revised Jun 2010; Nov 2010; Nov 2013; Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201278.pdf>

15. Revision of Draft product-specific guidance on Rotigotine Film, extended release (Jun 2012; revised Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM308070.pdf>

16. Revision of Draft product-specific guidance on Scopolamine Film, extended release (Aug 2009; revised Dec 2009; Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM179189.pdf>

17. Revision of Draft product-specific guidance on Selegiline Film, extended release (Aug 2009; revised Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM179190.pdf>

18. Posting of Draft product-specific guidance on Testosterone Film, extended release (Dec 2014; revised Apr 2016; Oct 2016)

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428222.pdf>

Publications

- Abdallah IA, Hammell DC, Hassan HE, Stinchcomb AL. Norelgestromin/Ethinyl Estradiol Intravenous Infusion Formulation Optimization, Stability and Compatibility Testing: A Case Study to Overcome Polysorbate 80 Interference in Chromatographic Analysis. *Journal of Pharmaceutical and Biomedical Analysis*. 2016;125:145–153.
- Abdallah IA, Hammell DC, Stinchcomb AL, Hassan HE. A Fully Validated LC–MS/MS Method for Simultaneous Determination of Nicotine and its Metabolite Cotinine in Human Serum and its

Application to a Pharmacokinetic Study after Using Nicotine Transdermal Delivery Systems with Standard Heat Application in Adult Smokers. *Journal of Chromatography B*. 2016;1020:67–77.

- Hao J, Ghosh P, Li SK, Newman B, Kasting GB, Raney SG. Heat Effects on Drug Delivery Across Human Skin. *Expert Opinion on Drug Delivery*. 2016;13(5):755-768.
- Shin, SH, Ghosh, P, Newman B, Hammell DC, Raney SG, Hassan HE, & Stinchcomb AL. On the Road to Development of an *In Vitro* Permeation Test (IVPT) Model to Compare Heat Effects on Transdermal Delivery Systems: Exploratory Studies with Nicotine and Fentanyl. *Pharmaceutical Research*, 2017;1-14.
- Strasinger C, Raney SG, Tran DC, Ghosh P, Newman B, Bashaw ED, Ghosh T, Shukla CG. Navigating Sticky Areas in Transdermal Product Development. *Journal of Controlled Release*. 2016;233:1–9.
- Zhang Q, Murawsky M, LaCount T, Hao J, Kasting GB, Newman B, Ghosh P, Raney SG, Li SK. Characterization of Temperature Profiles in Skin and Transdermal Delivery System When Exposed to Temperature Gradients *In Vivo* and *In Vitro*. *Pharmaceutical Research*. 2017;7:1491-1504.

Presentations

- Shin SH. Evaluation of Level A *In Vitro In Vivo* Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems (TDS) with Transient Heat Exposure by Using Multiple Approaches Oral presentation at the 2017 Gordon Research Seminar on the Barrier Function of Mammalian Skin, August 2017, New Hampshire.
- Shin SH. *In Vitro* and *In Vivo* Evaluation of Three Fentanyl Transdermal Delivery Systems In Conjunction With Transient Heat Exposure. Invited oral presentation at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting Dermatopharmaceutics Focus Group Town Hall, November 2016, Denver, CO.
- Stinchcomb AL. Bioavailability and Bioequivalence of Products Applied to the Skin. Invited Oral Presentation at the Third Bioequivalence Summit: Ensure Regulatory Compliance When Demonstrating the Bioequivalence of New Dosage Forms, Delivery Methods and Biosimilars, September 2016, Boston MA
- Stinchcomb AL. IVIVC in Transdermal Drug Delivery: Streamlining the Drug Approval Process. Invited Oral Presentation at Transdermal and Intradermal Drug Delivery Systems 2016: Advanced Design, Development and Delivery of Skin-Mediated Therapies and Vaccines, September, 2016.

Posters

- Abdallah IA, Ghosh P, Newman B, Raney SG, Stinchcomb A, Hassan H. LC–MS/MS Determination of Nicotine and Its Metabolite Cotinine In Human Plasma. American Association of Pharmaceutical Scientists Annual Meeting, November 2014, San Diego, CA.
- Abdallah I, Hammell D, Hassan H, Stinchcomb AL. Preformulation Analysis and Product Stability of Norelgestromin/Ethinyl Estradiol Intravenous Infusion. The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, October 2015, Orlando, FL.
- La Count TD, Li SK, Kasting GB. Computational Model For Estimating The Effect of Heat on Dermal Clearance in Skin Transport. The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, October 2015, Orlando, FL.

- Murawsky MK, Zhang Q, La Count T, Hao J, Newman B, Ghosh P, Raney SG, Lionberger R, Kasting G, Li S. Skin Temperature Under Transdermal Patch With Heat Application. The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, November 2014, San Diego, CA.
- Patel N, Cristea S, Rose R, Salem F, Abduljalil K, Johnson T, Jamei M, Raney SG, Zhang X, Lin H-P, Newman B, Chow E, Ghosh P, Fan J, Fang L, Polak S. Mechanistic Modelling of Dermal Drug Absorption Using the Simcyp Multi-Phase Multi-Layer MechDermA Model: Case Study of a Transdermal Patch Formulation of Weak Base Drug Timolol. Barrier Function of Mammalian Skin Gordon Research Conference, August 2015, Waterville Valley, NH.
- Shin SH, Ghosh P, Newman B, Raney SG, Hassan HE, Stinchcomb AL. Influence of heat on reference and generic transdermal drug delivery systems. The American Association of Pharmaceutical Scientists Annual Meeting, November 2014, San Diego, CA.
- Shin S, Ghosh P, Raney SG, Hammell DC, Hassan HE, Stinchcomb AL. Effect of Heat on Nicotine and Fentanyl Transdermal Delivery Evaluated In Vitro Using Different Skin/Membranes. Fifteenth International Conference on Perspectives in Percutaneous Penetration, March 2016, La Grande Motte, France.
- Shin SH, Raney SG, Ghosh P, Newman B, Hassan HE, Stinchcomb AL. In Vitro/In Vivo Correlation (IVIVC) Of Bioavailability from Nicotine Transdermal Drug Delivery Systems under the Influence of Heat. The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, October 2015, Orlando, FL.
- Shin S, Thomas SH, Abdallah I, Raney SG, Ghosh P, Hammell DC, Hassan HE, Stinchcomb AL. Evaluation Of Bioavailability And In Vitro/In Vivo Correlation Of Nicotine Transdermal Drug Delivery Systems Under The Influence Of Heat. Barrier Function of Mammalian Skin Gordon Research Conference, August 2015, Waterville Valley, NH.
- Shin S, Yu M, Hammell DC, Hassan HE, Stinchcomb AL. In Vitro and In Vivo Evaluation of Three Fentanyl Transdermal Delivery Systems in Conjunction with Transient Heat Exposure. Poster presentation at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition, November 2016, Denver, CO.
- Shin SH, Yu M, Thomas S, Hammell DC, Hassan HE, Stinchcomb AL. Level A In Vitro/In Vivo Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems with Transient Heat Exposure, Evaluated using Multiple Approaches. GSK AAPS Student Chapter Conference, June 2017, Philadelphia, PA.
- Shukla S, Ghosh P, Raney SG, Hassan HE, Bunge A, Stinchcomb AL. Evaluation of Two Lidocaine Topical Patch 5% Products by Cutaneous Pharmacokinetic Methods: In Vitro Tape Stripping and In Vitro Permeation Testing. The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, November 2016, Denver, CO.
- Thomas S, Ghosh P, Newman B, Raney SG, Hammell DC, Hassan HE, Stinchcomb AL. A Pharmacokinetic Study of the Effect of a Standardized Exposure to Heat on Nicotine Transdermal Delivery in Adult Smokers. The American Association of Pharmaceutical Scientists Annual Meeting, October 2015, October 2015, Orlando, FL.
- Thomas S, Ghosh P, Raney SG, Hammell DC, Hassan HE, Stinchcomb AL. Effect of Controlled Heat Application on Topical Diclofenac Formulations Evaluated by In Vitro Permeation Tests (IVPT) Using Porcine And Human Skin. The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, November 2016, Denver, CO.

- Thomas S, Ghosh P, Raney S. G., Hammell DC, Hassan HE, Stinchcomb AL. 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. Gordon Research Conference on the Barrier Function of Mammalian Skin. August 2017, Waterville Valley, NH.
- Yu M, Shin SH, Hammell DC, Hassan HE, Stinchcomb AL. Pharmacokinetics of Fentanyl After Using Reference and Generic Transdermal Fentanyl Patches With and Without Standardized Heat Application In Healthy Human Volunteers. The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, November 2016, Denver, CO.
- Zhang Q, Murawsky MK, La Count T, Hao J, Raney SG, Ghosh P, Kasting G, Li S. Evaluation of Heat Effects on Transdermal Delivery Systems Using an In Vitro Permeation Test (IVPT) Strategy. The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, November 2016, Denver, CO.