Guidance for Industry

Residual Drug in Transdermal and Related Drug Delivery Systems

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

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CMC

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I. INTRODUCTION

This guidance provides recommendations to developers and manufacturers of transdermal drug delivery systems (TDDS), transmucosal drug delivery systems (TMDS), and topical patch products regarding use of an appropriate scientific approach during product design and development—as well as during manufacturing and product lifecycle management—to ensure that the amount of residual drug substance at the end of the labeled use period is minimized.

Existing TDDS, TMDS, and topical patches contain a larger amount of the drug substance than what is intended to be delivered to the patient. This excess amount of drug substance is needed to facilitate delivery of the intended amount of the drug to the patient and remains as residual drug in the used system. The amount of residual drug substance in TDDS, TMDS, and topical patches has a significant potential to impact the products' quality, efficacy, and safety (including abuse potential). Consequently, it is necessary to ensure that an appropriate scientific approach is used to design and develop these products. The approach should ensure that the amount of residual drug substance is minimized consistent with the current state of technology. This guidance is applicable to investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplemental new drug applications (sNDAs) for TDDS, TMDS, and topical patch products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

II. BACKGROUND

TDDS and TMDS are drug delivery systems designed to deliver at least one therapeutically active ingredient (drug substance) across the skin or mucosa, respectively, for systemic effect. The systems' design can range from drug-in-adhesive matrix systems to more complex systems that require microelectronics. These include passive systems (e.g., drug in patches, gels, foams, films, and spray-on films) and active systems (e.g., iontophoresis and sonophoresis). TDDS and TMDS offer advantages over other dosage forms by delivering prolonged, systemic drug levels to allow for simplified dosing regimens and overcome limitations in oral bioavailability or first-pass metabolism. Topical patches, on the other hand, contain a therapeutically active drug substance designed to provide a local effect.

Currently marketed TDDS, TMDS, and topical patches may retain 10-95 percent of the initial total amount of drug as the residual drug after the intended use period. This raises a potential safety issue not only to the patient, but also to others including family members, caregivers, children, and pets. For example, adverse events due to a patient's failure to remove TDDS at the end of the intended use period have been reported and are generally related to an increased or prolonged pharmacological effect of the drug. Also, some children have died from inadvertent exposure to discarded TDDS. Reported adverse events resulting from various quality problems pertaining to TDDS have lead to product recalls, withdrawals, and public health advisories.[2]

III. QUALITY BY DESIGN

To reduce some of these risks, we recommend that a robust design and development approach be used when developing and manufacturing TDDS, TMDS, and topical patches. One example of such an approach is Quality by Design (QbD), as described in the International Conference on Harmonization (ICH) guidance for industry *Q8(R2) Pharmaceutical Development*.[3]

QbD is a scientific, risk-based, and proactive approach to pharmaceutical process and product development that may or may not include the use of a design space. An application containing QbD approaches—which may include information such as a quality target product profile (QTPP), critical quality attributes (CQA), and a control strategy—can lead to a better understanding of and continual improvement to the product throughout its lifecycle. A QbD approach can facilitate the development of TDDS, TMDS, and topical patches designed to meet patient requirements and post-use considerations. In particular, it can aid in developing a product to deliver the optimum amount of drug across the skin while minimizing the amount of drug load, thus resulting in the least possible amount of residual drug substance. QbD is applicable to both new products and reformulation of existing products. Another benefit of a QbD approach is that the higher level of understanding of the product and manufacturing process may assist in evaluating the effects of variations in raw materials and the manufacturing process on drug product quality. This includes, but is not limited to, drug product quality attributes and

[2] See www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/default.htm.

[3] CDER updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

product performance characteristics such as drug permeation/flux rate, adhesion, application site reaction, and safety/quality issues (e.g., residual drug substance, cold flow, and seal breakage of the liquid reservoir systems).

IV. MINIMIZING RESIDUAL DRUG

We recognize that a surplus of drug substance is typically required in TDDS, TMDS, and topical patches to achieve and maintain the desired release rate of the drug substance throughout its usage period and for TDDS and TMDS to maintain the appropriate systemic drug levels. The choice of formulation, design, and system components may provide potential pathways to optimize drug delivery and minimize residual drug. Examples include, but are not limited to, the following: the use of penetration enhancers, use of self-depleting solvent systems, and judicious choice of adhesive. Other factors may include the type and concentration of excipients, drug load, adhesive thickness, and the composition and thickness of the backing layer.

We recommend that sufficient scientific justification to support the amount of residual drug in TDDS, TMDS, or topical patches be included in an application.[4] The justification should include an evaluation of the safety risks involved with the formulation and system design, as well as support the amount of drug load in the TDDS, TMDS, or topical patch based on the proposed QTPP and formulation studies. Most important, the justification for applications of products with known safety issues—such as those with fentanyl-containing liquid reservoir systems—should demonstrate that the safety risk factors have been adequately mitigated.

In all cases, the level of information in the justification should be sufficient to demonstrate product and process understanding and ensure that a scientific, risk-based approach has been taken to minimize the amount of residual drug in a system after use to the lowest possible level. It is expected that the amount of residual drug in a newly developed system (including new generic drug products) will not exceed that of similar FDA-approved products. This discussion of the product and process development and justification for the final formulation and system design can be provided in the 3.2.P.2 (Pharmaceutical Development) section of a common technical document (CTD) formatted application.

[4] See 21 CFR 314.50(d).