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Client Alert

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FDA Issues New Guidance Document on Minimizing Residual Drug in Transdermal and Related Products

The U.S. Food and Drug Administration (FDA) recently released a new guidance document that provides recommendations for manufacturers of transdermal drug delivery systems, transmucosal drug delivery systems, and topical patch products on minimizing the amount of drug substance that remains in the product at the end of the labeled use period.[1] In the guidance, entitled *Residual Drug in Transdermal and Related Drug Delivery Systems*, the FDA explains that, although some amount of surplus drug is typically necessary to maintain appropriate systemic drug levels in the patient, manufacturers should reduce the surplus to the minimum amount possible due to safety risks associated with residual drugs. The guidance is relatively short, but provides some high-level recommendations that focus on the scientific approaches that manufacturers can use to minimize residual drug levels.[2] The FDA's recommendations apply to investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplemental new drug applications (sNDAs) for transdermal products.

The guidance emphasizes the importance of using a "robust design and development approach," such as quality by design (or QbD).[3] The FDA refers readers to the International Conference on Harmonization (ICH) guidance on pharmaceutical development, which includes a detailed discussion of QbD. The ICH guidance defines QbD as a "systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."[4] The FDA guidance explains that QbD may generate helpful information, such as a quality target product profile, critical quality attributes, and a control strategy, thereby enabling continual improvement to the product throughout its lifecycle. Importantly, the FDA asserts that implementation of QbD will aid in developing products that deliver the optimum amount of drug across the skin while minimizing the amount of residual drug substance. The FDA also advises that choice of formulation, design, and system components can help optimize drug delivery and minimize residual drug. The FDA lists the following examples: 1) the use of penetration enhancers, 2) use of

1 For simplicity, we will refer to these product types collectively as "transdermal products."
2 FDA, *Guidance for Industry, Residual Drug in Transdermal and Related Drug Delivery Systems* (Aug. 2011), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220796.pdf (hereinafter Transdermal Guidance)
3 *Id.* at 2
4 FDA and ICH, *Guidance for Industry, Q8(R2) Pharmaceutical Development* (Nov. 2009), at 22

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self-depleting solvent systems, and 3) judicious choice of adhesive. According to the guidance, other factors include the type and concentration of excipients, drug load, adhesive thickness, and the composition and thickness of the product backing layer.

The FDA recommends that applicants for transdermal product approval include "sufficient scientific justification" in the application to support the amount of residual drug in the product.[5] The justification should include an evaluation of the safety risks involved and should demonstrate that a "scientific, risk-based approach has been taken to minimize the amount of residual drug."[6] The agency explains that the residual drug in new products (including generics) should not exceed that of similar FDA-approved products. According to the FDA, currently marketed transdermal products may retain anywhere from 10 to 95 percent of the initial total amount of drug as residual drug after the intended use period. Manufacturers will have to be aware of comparable products and their residual drug levels to ensure that they set appropriate residual drug level goals during the product development phase.

The guidance and its recommendations demonstrate that the FDA is concerned about the safety risks associated with residual drug levels in transdermal products (e.g., risks to patients who wear the product longer than indicated, risks to children who touch discarded products, and abuse risks), and the agency expects transdermal product applications to demonstrate that proper product development and scientific approaches have been used to minimize the amount of a residual drug. In light of this guidance, transdermal product applicants should be prepared to discuss these issues with the FDA during the product development phase to ensure that the scientific approach and the expected amount of residual drug in the product are satisfactory to the agency. This guidance will provide an appropriate road map for these discussions.

5 Transdermal Guidance, at 3
6 *Id.*