
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)**

**August 2011
CMC**

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42 **II. BACKGROUND**

43
44 TDDS and TMDS are drug delivery systems designed to deliver at least one therapeutically
45 active ingredient (drug substance) across the skin or mucosa, respectively, for systemic effect.
46 The systems' design can range from drug-in-adhesive matrix systems to more complex systems
47 that require microelectronics. These include passive systems (e.g., drug in patches, gels, foams,
48 films, and spray-on films) and active systems (e.g., iontophoresis and sonophoresis). TDDS and
49 TMDS offer advantages over other dosage forms by delivering prolonged, systemic drug levels
50 to allow for simplified dosing regimens and overcome limitations in oral bioavailability or first-
51 pass metabolism. Topical patches, on the other hand, contain a therapeutically active drug
52 substance designed to provide a local effect.

53
54 Currently marketed TDDS, TMDS, and topical patches may retain 10-95 percent of the initial
55 total amount of drug as the residual drug after the intended use period. This raises a potential
56 safety issue not only to the patient, but also to others including family members, caregivers,
57 children, and pets. For example, adverse events due to a patient's failure to remove TDDS at the
58 end of the intended use period have been reported and are generally related to an increased or
59 prolonged pharmacological effect of the drug. Also, some children have died from inadvertent
60 exposure to discarded TDDS. Reported adverse events resulting from various quality problems
61 pertaining to TDDS have lead to product recalls, withdrawals, and public health advisories.²

62
63
64 **III. QUALITY BY DESIGN**

65
66 To reduce some of these risks, we recommend that a robust design and development approach be
67 used when developing and manufacturing TDDS, TMDS, and topical patches. One example of
68 such an approach is Quality by Design (QbD), as described in the International Conference on
69 Harmonization (ICH) guidance for industry [Q8\(R2\) Pharmaceutical Development](#).³

70
71 QbD is a scientific, risk-based, and proactive approach to pharmaceutical process and product
72 development that may or may not include the use of a design space. An application containing
73 QbD approaches—which may include information such as a quality target product profile
74 (QTPP), critical quality attributes (CQA), and a control strategy—can lead to a better
75 understanding of and continual improvement to the product throughout its lifecycle. A QbD
76 approach can facilitate the development of TDDS, TMDS, and topical patches designed to meet
77 patient requirements and post-use considerations. In particular, it can aid in developing a
78 product to deliver the optimum amount of drug across the skin while minimizing the amount of
79 drug load, thus resulting in the least possible amount of residual drug substance. QbD is
80 applicable to both new products and reformulation of existing products. Another benefit of a
81 QbD approach is that the higher level of understanding of the product and manufacturing process
82 may assist in evaluating the effects of variations in raw materials and the manufacturing process
83 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.

Contains Nonbinding Recommendations

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

87

88

89 **IV. MINIMIZING RESIDUAL DRUG**

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

99

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

107

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

⁴ See 21 CFR 314.50(d).