Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs

Guidance for Industry

DRAFT GUIDANCE

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

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Generic Drugs

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Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The recommendations in this guidance relate exclusively to studies submitted in support of an abbreviated new drug application (ANDA).[2] This guidance provides recommendations for the design and conduct of studies evaluating the adhesive performance of a transdermal or topical delivery system (collectively referred to as TDS[3]). Depending on the objectives of a TDS product development program, applicants may choose to evaluate TDS adhesion in studies performed to evaluate TDS adhesion only or in studies performed with a combined purpose (e.g., for the simultaneous evaluation of adhesion and bioequivalence (BE) with pharmacokinetic (PK) endpoints).

In this guidance, the letter *T* (representing *Test*) will refer to proposed generic products that are the subject of an ANDA, and the letter *R* (representing *Reference*) will refer to a reference listed drug and/or reference standard product.

[1] This guidance has been prepared by the Office of Research and Standards in the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with CDER's Office of New Drugs and Office of Pharmaceutical Quality at the Food and Drug Administration.

[2] The recommendations for studies characterizing TDS adhesion in a new drug application or a supplemental new drug application may be different than those submitted in support of an ANDA and may involve the assessment of different ages and strengths of the TDS product, potentially dosed to different anatomical sites. Also, the design, conduct, and assessment of TDS adhesion in studies supporting a new drug application are inherently different because TDS adhesion in that context is not typically evaluated in relation to a reference product.

[3] The acronym *TDS* refers to both transdermal delivery systems and topical delivery systems and includes products that may described elsewhere or known as *patches*, *topical patches*, or *extended release films*.

FDA recommends that applicants consult this guidance in conjunction with any relevant product-specific guidances[4] and in conjunction with any relevant guidances for industry[5], when considering the design and conduct of studies that may be appropriate to support the BE of a proposed generic TDS product to its reference listed drug and/or reference standard product. FDA also recommends that applicants routinely refer to FDA's website[6], since additional guidances may become available that could assist in the development of a generic TDS product.

In general, FDA's guidance documents 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.

II. BACKGROUND

The amount of drug delivered into and through the patient's skin from a TDS is dependent, in part, on the surface area dosed. It is expected that the entire contact surface area of a TDS should remain consistently and uniformly adhered to the patient's skin throughout the duration of wear under the conditions of use included in the product labeling. When a TDS loses its adherence during wear, the amount of drug delivered to the patient may be reduced.

During the product's labeled wear period, a TDS is reasonably expected to encounter torsional strains arising from body movements, changes in environmental temperature or humidity such as the daily exposure to water (e.g., during routine showering), and contact with clothing, bedding or other surfaces. TDS products that do not maintain consistent and uniform adhesion with the skin during the labeled wear period can experience varying degrees of TDS detachment, including complete detachment, at different times during the product wear.

When the adhesion characteristics of a TDS are not sufficiently robust, as evaluated against its labeled conditions of use, the TDS may exhibit variability in the surface area that is in contact with the skin. For example, when a TDS is partially detached, there may be uncertainty about the resulting drug delivery profile and, hence, uncertainty about the rate and extent of drug absorption from the TDS. When the potential for complete detachment of the TDS increases, the risk of unintentional exposure of the drug product to an unintended recipient (e.g., a household member who may be a child) also increases.

[4] Generic drug product-specific guidances are available at the Product-Specific Guidances for Generic Drug Development web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[5] For example, a relevant guidance for industry is the draft guidance for industry: *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems Submitted in ANDAs*. When final, these guidances will represent the FDA's current thinking on these topics.

[6] For newly-posted draft guidances, or the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/regulatoryinformation/guidances/default.htm.

III. EVALUATION OF ADHESION

A. Study Design and Conduct

In general, the Agency recommends that applicants design their adhesion studies to support a comparative evaluation of the adhesion characteristics of the T and R TDS.

FDA recommends that applicants use a single-dose, randomized, two-treatment, two-period crossover study design where all subjects are dosed with the same strength of the T and R TDS. However, FDA may also consider the acceptability of a study using a single-period, two-treatment-per-subject design, with the site of application randomized, if applicants appropriately justify their parallel dosing study design. The population for the TDS adhesion study should typically be the same as the population enrolled, or recommended for enrollment, in the PK BE study for the product and should typically include healthy males and non-pregnant, non-lactating females unless product-specific considerations indicate otherwise.

Applicants should randomize subjects to receive either the T or R TDS product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.

Because alterations in the product design, the active or inactive ingredients, the backing membrane, or the manufacturing process can affect the adhesion properties of a TDS, the study should utilize the to-be-marketed TDS product.[7] Post-approval changes to the TDS may necessitate confirmation that product quality attributes related to adhesion remain consistent with the product quality attributes characterized for the TDS product that demonstrated acceptable adhesion.

Unless otherwise justified, when conducting an adhesion study, applicants should utilize the specific size/strength of the TDS that is recommended in the applicable product-specific guidance. A larger TDS may be more sensitive to detachment than a smaller one because the larger TDS may be subjected to greater conformational or torsional strains arising from potentially increased anatomical curvatures or from a greater magnitude of flexion across relatively greater anatomical distances across which the larger TDS may be adhered. It may also be possible for applicants to assess an adhesion score more precisely with a larger TDS than with a smaller one.

Applicants should not use an overlay or a cover for blinding because the overlay or cover may affect the product's performance.

Applicants should evaluate the adhesion of each TDS at multiple adhesion time points following application of the TDS to provide a sufficient temporal resolution to adequately compare the adhesion characteristics of the T and the R TDS throughout the duration of wear. For example, the adhesion of a TDS with a 7-day wear period should be assessed at least daily and at equally spaced time points (e.g., 24 hours (hrs), 48 hrs, 72 hrs, 96 hrs, 120 hrs, 144 hrs, and 168 hrs); the

[7] See 21 CFR 320.21(b).

adhesion of a TDS with 72-hour wear period should be assessed at least every 12 hours (e.g., at 12 hrs, 24 hrs, 36 hrs, 48 hrs, 60 hrs, and 72 hrs); the adhesion of a TDS with a wear period between 12 and 24 hours should be assessed at least every 4 hours; and the adhesion of a TDS with a wear period of less than 12 hours should be assessed at least hourly.

In addition, applicants should typically distribute these time points in a uniform manner, equally spaced throughout the entire labeled wear period because the mean adhesion score that is calculated from the individual assessments is intended to be representative of the entire wear period. For some TDS, adhesion during the earlier period of wear may be better than during the later period of wear; therefore, a greater number of adhesion assessments early in the TDS wear period may (1) disproportionately weight the calculation of the mean adhesion score by over-representing the adhesion assessments during the initial period when TDS adhesion might be relatively better and (2) inappropriately decrease the mean adhesion score in a manner that is not representative of the entire wear duration for that TDS.

For the comparative assessment of adhesion (i.e., for the noninferiority (NI) test described in section III.B of this guidance), applicants should use the following five-point adhesion scale, in which each score corresponds to a specified range of adhered surface area for the TDS:

0 = ≥ 90% adhered (i.e., the TDS has essentially no lift off the skin)

1 = ≥ 75% to < 90% adhered (e.g., only some edges of the TDS lift off the skin)

2 = ≥ 50% to < 75% adhered (i.e., less than half of the TDS lifts off the skin)

3 = > 0% to < 50% adhered (i.e., the TDS is not detached, but more than half of it lifts off the skin without falling off)

4 = 0% adhered (i.e., the TDS is detached and is completely off the skin)

When recording measurements of TDS adhesion, applicants may use appropriate methods (e.g., a trained visual assessment and/or dot matrix templates) and alternative scales (other than the five-point adhesion scale described above) to estimate the percentage of the entire TDS surface area that is adhered to the skin. If applicants use a scale different than the five-point adhesion scale described above to record TDS adhesion measurements, they should report each TDS adhesion measurement as both the score according to the selected scale as well as the corresponding score according to the five-point adhesion scale. For example, if the observer scores the TDS adhesion as a two on the five-point scale, and estimates that the product appears to be 60 percent adhered, a score of two and the estimate of 60 percent should both be reported for that time point. Information and/or analyses based upon scores from the alternative scale may be considered as supportive information, provided that the use of the alternative scale is justified and that information is submitted with the study to demonstrate that the scale has been adequately qualified. When recording measurements of TDS adhesion, applicants should also record photographic evidence showing the TDS as it is adhered to the skin (or completely detached and absent from the skin) and submit photographs for each time point when TDS adhesion is assessed.

With each consecutive TDS adhesion measurement at each time point, applicants should record the score based upon the actual measurement of TDS adhesion at that timepoint (not carrying forward a score from a previous time point), regardless of whether the score increases or decreases relative to the preceding score. TDS adhesion measurements should be made independently, with the observer blinded to the previous measurement.

However, when analyzing the results for the comparative assessment of adhesion (i.e., for the NI test described in section III.B of this guidance), the highest adhesion score using the five-point adhesion scale described above (i.e., the score representing the greatest degree of detachment for that TDS) assessed at any time point after the baseline or $time_0$ should be used for subsequent time points until a higher score is assessed. For a TDS that completely detaches, a score of *4* should be assigned for any remaining assessments scheduled for that TDS across the study duration.

Applicants should use the mean adhesion score, $\bar{X}$, as the primary endpoint for evaluating TDS adhesion. For a TDS, the mean adhesion score, $\bar{X}$, should be derived from its individual adhesion scores at each assessment time point, averaged across all the equally spaced time points (except the baseline time point, t_0). Let $\bar{x}$ denote the observed mean adhesion score for a TDS across n equally spaced time points after the baseline. It can be calculated as follows:

$$\bar{x} = \sum_{i=1}^{n} x_i / n$$

Here, is the observed mean adhesion score for a TDS across equally spaced time points after the baseline and x_i is the observed adhesion score at the i^{th} measurement for a TDS.

Despite the recommendation in this guidance to distribute time points in a uniform, equally spaced manner, if the data set contains scores from unequally spaced time points, a weighted average $\bar{X}_w$, with weights corresponding to interval length, may be calculated as follows:

$$\bar{x}_w = \sum_{i=1}^{n} w_i x_i = \frac{\sum_{i=1}^{n}(t_i - t_{i-1})x_i}{D}, \text{ where } w_i = \frac{(t_i - t_{i-1})}{D}$$

Here, $\bar{x}_w$ is the observed weighted mean adhesion score for a TDS across n unequally spaced time points after the baseline, x_i is the observed adhesion score at the i^{th} measurement, w_i is the corresponding weight for x_i, D is the total duration of wear, t_i is the i^{th} measurement time, and t_{i-1} is the preceding $(i\text{-}1)^{th}$ measurement time. Because of the potential round-off error of computer software, FDA recommends that applicants calculate the sum in the numerator first, $\sum_{i=1}^{n}(t_i - t_{i-1})x_i$, and then divide that sum by the total duration D.

For example, for a 24-hour-wear TDS, if an applicant measured adhesion at hours 2, 4, 8, 12, and 24 after the baseline, the total duration of wear would be 24 hours. The coefficient $(t_i - t_{i-1})$ corresponding to the i^{th} measurement x_i (i = 1, 2, 3, 4, 5) would be (2-0), (4-2), (8-4), (12-8), and

(24-12) respectively. The weighted mean $\bar{x}_w$ can be calculated by summing $\sum_{i=1}^{5}(t_i - t_{i-1})x_i$ first, then dividing the sum by the total duration *D* (i.e., in this example, 24 hours). The corresponding weights for all five measurements would be $\frac{1}{12}, \frac{1}{12}, \frac{1}{6}, \frac{1}{6}$, and $\frac{1}{2}$, which add up to 1.

In addition to the primary endpoint, FDA recommends that applicants perform the following descriptive analyses for the evaluation of TDS adhesion (using the five-point adhesion scale described above) to assess possible treatment group differences in potentially clinically meaningful values or events:

1. Proportion of subjects with an adhesion score ≥ 2 at any time point, compared between T and R

2. Proportion of subjects with their T mean adhesion score greater than the corresponding R mean adhesion score by 1 or more, compared to the proportion of subjects with their R mean adhesion score greater than the corresponding T mean adhesion score by 1 or more.

3. Time to an adhesion score ≥ 2 compared between T and R. If there are a sufficient number of events, a Kaplan Meier cumulative incidence curve can be plotted.

In addition, applicants should submit descriptive adhesion score data in a frequency table illustrating the number and the proportion of the T and the R TDS with each adhesion score at each evaluation time point and across all time points. An example of such a frequency table is shown below:

Frequency of Adhesion Scores for a Per-Protocol Population (Hypothetical Data)

Time Point	T Score (N=100) n (%)						R Score (N=100) n (%)					
	0	**1**	**2**	**3**	**4**	**Mean**	**0**	**1**	**2**	**3**	**4**	**Mean**
1	95 (95)	5 (5)	0 (0)	0 (0)	0 (0)	0.05	82 (82)	16 (16)	2 (2)	0 (0)	0 (0)	0.20
2	90 (90)	10 (10)	0 (0)	0 (0)	0 (0)	0.10	68 (68)	30 (30)	2 (2)	0 (0)	0 (0)	0.34
3	87 (87)	13 (13)	0 (0)	0 (0)	0 (0)	0.13	57 (57)	41 (41)	2 (2)	0 (0)	0 (0)	0.45
4	86 (86)	14 (14)	0 (0)	0 (0)	0 (0)	0.14	46 (46)	51 (51)	3 (3)	0 (0)	0 (0)	0.57
5	85 (85)	15 (15)	0 (0)	0 (0)	0 (0)	0.15	42 (42)	55 (55)	2 (2)	1 (1)	0 (0)	0.62
All	443 (88.6)	57 (11.4)	0 (0)	0 (0)	0 (0)	0.11	295 (59.0)	193 (38.6)	11 (2.2)	1 (0.2)	0 (0)	0.44

Applicants should note that both the T and the R TDS should be administered to study subjects in the manner described by the R product label, and TDS adhesion should be assessed throughout the maximum labeled duration of wear for the R product. In general, movement of study subjects should not be restricted during the study; instead, subjects should be allowed to freely conduct normal activities within the study unit and/or at home (e.g., to perform real-world activities like showering) that may reasonably be expected to occur during the labeled duration of use for the product. For products with a wear period of up to or greater than 24 hours, FDA recommends that subjects be permitted to bathe or shower routinely during the study, in a manner consistent with the labeled use of the product, and that the TDS should not be protected from direct exposure to water during such routine activities.

Generally, applicants should use only whole, intact T and R TDS for their assessment of comparative adhesion performance because altering the size or shape of the TDS may alter its adhesion characteristics.

Applicants should include provisions in their study protocol to ensure that deliberate actions with the intent to reapply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study. The study protocol should include provisions to ensure that TDS detachment is not inappropriately inhibited (e.g., by the constant pressure of a chair back on the TDS).

Subjects should not apply makeup, creams, lotions, powders, or other topical products to the skin area where the TDS will be placed because they could affect adhesive performance. Also, hair at the application site should be clipped (not shaved) before TDS application and/or the site should be prepared in a manner consistent with the labeled use of the TDS.

Applicants should describe the method of randomization in the study protocol and provide the randomization schedule as a SAS transport data set in XPT format. (Note that the randomization in this context refers to the sequence, not the treatment.) FDA recommends that an independent third party generate and hold the randomization code throughout the conduct of the study to minimize bias. However, applicants may generate the randomization code if they are not involved in the packaging and labeling of the study medication. Applicants should ensure that a sealed copy of the randomization scheme is retained at the study site, and this sealed copy should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity for each application site on each subject.

B. Considerations for Statistical Analysis

Applicants should prespecify the per-protocol (PP) population for the adhesion analysis, and define it per TDS for each subject. The PP population for the adhesion analysis should include all TDS except those that were intentionally removed early in the study (e.g., because of unacceptable irritation) or those that were on subjects who discontinued use of the TDS before the end of the labeled duration of wear for reasons unrelated to adhesion (e.g., because of a protocol violation). Applicants should include individual case reports describing any subjects who were excluded from the PP population, and the reasons for their exclusion, in their study report.

Applicants should compare the means of the per treatment group mean adhesion scores (i.e., the primary endpoint described above) for the T and R products. To calculate the mean adhesion score, applicants should carry forward the highest adhesion score at each time point after the baseline time point (t_0) for subsequent time points until a higher score is assessed. To demonstrate adequate product adhesion, applicants should show that the T product is statistically noninferior to the R product based upon evaluating the difference in the T and R overall mean adhesion scores, with an NI margin of 0.15 ($\delta = 0.15$). The NI margin of 0.15 applies to the difference of the mean adhesion scores between the T and R products based on the five-point adhesion scale previously described; the NI margin of 0.15 does not apply to the difference of the mean adhesion scores based on other adhesion scales or non-location-based data transformations (e.g., a logarithmic transformation) or the difference of median adhesion scores between T and R.

Applicants should test the following hypotheses at the significance level of 0.05:

$$H_0: \mu_T - \mu_R \geq \delta$$
$$H_1: \mu_T - \mu_R < \delta$$

Here, μ_T and μ_R are the population means for the mean adhesion score for the T and R products, respectively, and the alternative hypothesis H_1 represents the NI of the T product's adhesion relative to the R product's adhesion.

To demonstrate acceptable adhesion of the T product, applicants should design and conduct an adhesion study as described above and enroll a sufficient number of subjects to power the study at a level of 0.80 or higher. Because of the discrete nature of adhesion scales and other potential complications of the adhesion data, FDA recommends that applicants use a larger sample size than what might ordinarily be calculated (under standard assumptions) to ensure the validity of any large-sample (asymptotic) Gaussian assumptions, if used.

Incomplete data and data associated with noncompliance can compromise the validity of an NI study. FDA recommends good clinical study design and conduct to prevent patient dropout and noncompliance. Nonetheless, when these events occur, applicants should document the detailed reasons for these events. Although the FDA recommends using the PP population as the primary analysis population for NI studies, the Agency also has significant concerns with the possibility of informative dropout and noncompliance. If applicable, applicants should prespecify imputation methods in their protocol. FDA recommends that applicants conduct a prespecified sensitivity analysis to evaluate the potential impact of any unbalanced or informative dropout and noncompliance on the conclusion of the NI in adhesion.

IV. COMBINED EVALUATION OF ADHESION AND BIOEQUIVALENCE

If applicants elect to conduct a study evaluating both the adhesion performance and the PK BE of the T and R products in a single study, this study should be conducted in a population of sufficient size to adequately power the comparative evaluation of adhesion and to include a

subpopulation of subjects of sufficient size to adequately power the evaluation of BE with appropriately selected PK endpoints. Applicants should select the participants for the PK BE evaluation according to a randomization scheme prespecified in the protocol.

The study design and conduct recommendations described in section III.A of this guidance, for a study performed exclusively for the purpose of evaluating TDS adhesion, also apply to a combined study evaluating adhesion and BE with PK endpoints.

The simultaneous application of multiple T TDS or of multiple R TDS to a subject may be appropriate in a combined study of TDS adhesion and PK BE when doing so is safe and justified, for example, by the potential need for increased drug delivery to compensate for an insufficient analytical sensitivity to measure the relevant analyte(s) in the PK samples. In such cases, when multiple TDS are simultaneously applied to a subject, the adhesion performance of each and all TDS should be assessed.

Applicants should prespecify their inclusion criteria for the statistical analysis of PK endpoints and perform their primary PK analysis on the PP population. For the primary PK parameters, applicants should calculate the geometric mean ratios for the T/R treatments and the two-sided 90% confidence intervals.

Applicants should collect and analyze PK samples from all subjects in the PK subpopulation, regardless of the subjects' TDS adhesion scores, and report the sample concentrations for all time points as well as the PK results for all subjects in the PK study. All TDS units that are removed at the end of (or which detach during) the in vivo adhesion and/or PK BE study should be retained for analysis of residual drug content.[8]

Applicants should refer to the guidance for industry *Handling and Retention of BA and BE Testing Samples* for recommendations on the retention of study drug samples and on the maintenance of records of BE testing.

V. FORMAT OF DATA SUBMISSION

Applicants should submit study data in standardized format and refer to the FDA web page on Study Data for Submission to CDER[9] for more information about study data standards.

In addition, applicants should provide SAS transport data sets in XPT format with the define file. If imputation is applied, applicants should also submit analysis data after the imputation.

[8] See guidance for industry *Residual Drug in Transdermal and Related Drug Delivery Systems*.

[9] This web page is available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.