Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs

Draft Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Kris Andre at 240-402-7959.

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

June 2016
Generic Drugs

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Draft Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance provides recommendations for the design and conduct of studies evaluating the adhesive performance of a Transdermal Delivery System (TDS) or a topical patch submitted in support of an Abbreviated New Drug Application (ANDA). The recommendations in this guidance relate exclusively to TDS adhesion studies submitted in support of an ANDA[2]. For the purposes of this guidance, the term "T" (representing Test) will be used to refer to proposed generic products that are the subject of an ANDA, and the term "R" (representing Reference) will be used to refer to the Reference Listed Drug (RLD) product.

Depending on the objectives of a TDS drug product development program, applicants may choose to evaluate TDS adhesion in clinical studies performed exclusively for the purpose of evaluating TDS adhesion, or in clinical studies performed with a combined purpose; for example, simultaneous evaluation of adhesion and bioequivalence (BE) with pharmacokinetic (PK) endpoints. This guidance describes the recommended approach to the adhesion study design and, therefore, will supersede the recommendations related to adhesion studies provided in individual product-specific guidances published prior to the date of publication of this guidance.

This guidance, once finalized, is intended to provide updated recommendations for the design and conduct of adhesion studies submitted in support of an ANDA for a topical patch or a TDS. While the recommendations in this guidance apply to both topical patches and TDS, the single term "TDS" will be used exclusively hereafter in reference to both TDS and topical patches. The

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

[2] The expectations for studies characterizing TDS adhesion in a New Drug Application (NDA) or a supplemental NDA may be different than for 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 an NDA are inherently different because TDS adhesion in that context is not typically evaluated in relation to a reference product.

use of the term "TDS" should not be construed to exclude topical patches. FDA recommends that applicants consult this guidance in conjunction with any relevant product-specific guidance documents[3] when considering other studies (e.g. irritation, sensitization) that may be necessary to support the BE of a proposed generic TDS drug product to its RLD.

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.

II. BACKGROUND

The amount of drug delivered into and through the 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 skin throughout the duration of wear under the conditions of use included in the product label. Under circumstances in which a TDS loses its adherence during wear, the amount of drug delivered to the patient may be reduced.

During the course of the product's labeled wear period, a TDS is reasonably expected to encounter torsional strains arising from anatomical 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 under the range of conditions experienced during the labeled wear period for the TDS can result in varying degrees of TDS detachment, including complete detachment, at different times during the course of 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. In such situations where 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. In addition, as the potential for complete detachment of the TDS increases, so does the risk of unintentional exposure of the drug product to an unintended recipient (e.g., a household member who may potentially be a child).

Generic TDS products are developed after the development of an RLD product and may be able to utilize technologies that may not have been available at the time when the RLD was developed. Applicants submitting an ANDA for a TDS product (including supplemental ANDAs relating to reformulations of an approved generic TDS product) are expected to demonstrate that reasonable efforts were made to optimize the adhesive characteristics of the TDS. This optimization is expected to balance properties such as adhesiveness, cohesiveness and stability, to ensure a consistent and uniform adhesion of its entire surface area to the skin for the entire duration of wear.

[3] U.S. FDA Product-Specific Recommendations for Generic Drug Development available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Applicants should consider adhesion as part of the Quality Target Product Profile (QTPP)[4] and develop a comprehensive strategy for assessing the adhesive attributes of the TDS. For example, the characterization of the adhesive properties of a TDS should demonstrate that any conditions of labeled use for the R product relevant to TDS adhesion are substantiated for the T product (e.g., demonstrating that incidental exposure of the TDS to water, such as while bathing or showering, is acceptable). Applicants should also ensure that the TDS can be removed from the packaging and peeled off the release liner without difficulty. In addition, the TDS is expected not to cause undue irritation when worn, and not to damage the skin when the TDS is removed after the duration of wear.

III. ADHESION SCORING SYSTEM

To evaluate adhesion in a study, the Agency recommends assessing the adhesion of T and R TDS products at a series of time points throughout the study to determine whether the entire surface area of the TDS remains adhered for the duration of wear under labeled conditions of use. The number of adhesion measurements performed throughout the study will depend on the duration of the labeled conditions of use for each TDS and should be pre-specified in the study protocol.

For each assessment, applicants should use a 5-point numerical scale in which each score corresponds to a specified range of adhered surface area of the TDS, as follows:

0 = ≥ 90% adhered (essentially no lift off the skin)
1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to < 75% adhered (less than half of the TDS lifting off the skin)
3 = > 0% to < 50% adhered (not detached, but more than half of the TDS lifting off the skin without falling off)
4 = 0% adhered (TDS detached; completely off the skin).

With each consecutive assessment, the highest adhesion score (representing the greatest degree of TDS detachment) assessed at any time point 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 all remaining assessments scheduled for that TDS across the study duration.

IV. ADHESION STUDY

A. STUDY DESIGN

In general, the Agency recommends that the adhesion study is designed to support a comparative evaluation of the adhesion characteristics of the T and R TDS.

[4] U.S. FDA Guidance for Industry: Q8(R2) Pharmaceutical Development (November 2009; Revision 2) available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073507.pdf

The recommended study design is a single-dose, randomized, two-treatment, two-period crossover study where all subjects are dosed with the same strength of T and R TDS. A study using a single-period, two-treatment-per-subject design with the site of application randomized may be considered if the parallel dosing is appropriately justified. The study population for the TDS adhesion study should typically be the same as enrolled or as recommended for enrollment in the PK BE study for the product, and should typically include healthy males and non-pregnant females in the general population, unless product-specific considerations associated with the labeled conditions of use of the selected size and strength of the TDS indicate otherwise.

Subjects should be randomized to receive either T or R TDS product in a given study period, and where possible, the TDS administered in the second study period should be applied to the same anatomical site on the contralateral side of the body. Because alterations in the product design, the active or inactive ingredients, or the manufacturing process can affect the adhesion properties of a TDS, the study must utilize the to-be-marketed TDS product[5]. Post-approval changes in the scale of manufacture and/or other process variables may necessitate confirmation that product quality attributes related to adhesion remain consistent with those characterized for the TDS product that demonstrated acceptable adhesion.

The choice of TDS strength and, of particular relevance to assessing adhesion, the size of the TDS, should be justified as appropriate for the use in the proposed study population and be pre-specified in the study protocol. The size of a TDS to be studied should be selected based upon a consideration of the potential failure modes for adhesion. Where possible, the largest size TDS (which often corresponds to the highest strength) should be employed in the study because the larger size TDS may be more sensitive to detachment as a result of the greater conformational or torsional strains induced by potentially increased anatomical curvatures or a greater magnitude of flexion across relatively greater anatomical distances. In addition, a more accurate adhesion score assessment (see Section III) could be made with a larger TDS than with a smaller one. However, in certain cases, the smallest size (corresponding to the lowest strength) TDS may be more susceptible to some failure modes for adhesion to skin than a larger size of that TDS. When selecting a size of TDS for study in generic development programs, applicants should provide adequate justification for the choice of the TDS size to be evaluated in the proposed adhesion study.

Blinding of the T and R products is recommended whenever possible. However, blinding may not be possible in instances where the appearance of T or R TDS reveals the identity of the products. The use of an overlay or a cover is not justified for the purpose of blinding because an overlay may affect the product's performance.

Adhesion of each TDS should be evaluated at multiple adhesion time points following TDS application to provide a sufficient temporal resolution for the adhesion characteristics of the T and the R TDS to be adequately compared throughout the duration of wear. For example, 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 hr, 48 hr, 72hr, 96 hr, 120 hr, 144 hr, and 168 hr); adhesion of TDS with 72-hour wear period should be assessed at least every 12 hours (e.g., 12 hr, 24 hr, 36 hr, 48

[5] *See* 21 CFR 320.21(b)

hr, 60 hr, and 72 hr); adhesion of TDS with a wear period between 12 and 24 hours should be assessed at least every 4 hours; adhesion of a TDS with a 9-hour wear period should be assessed at least hourly.

In addition, the time points should typically be distributed in a uniform manner, equally spaced throughout the entire labeled wear period since 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. A greater number of adhesion assessments early in the TDS wear period may 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 may inappropriately decrease the mean adhesion score in a manner that is not representative of the entire wear duration for that TDS.

The submission of photographic documentation is recommended. Photographic evidence can help to identify qualitative issues related to the assessment of TDS adhesion.

The recommended *primary endpoint* for evaluating adhesion of TDS is the mean adhesion score $\bar{X}$ derived for a TDS from individual adhesion scores at each assessment time point averaged across all the equally spaced time points (except the baseline or time$_0$).

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

where $\bar{x}$ is the observed mean adhesion score for a TDS across n equally-spaced time points after the baseline and x_i is the observed adhesion score at the i^{th} measurement.

If scores from unequally spaced time points are available, a weighted average $\bar{X}_w$, with weights corresponding to interval length, may be calculated as follows:

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

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, T denotes the total duration of wear, t_i denotes the i^{th} measurement time, and t_{i-1} denotes the preceding $(i\text{-}1)^{th}$ measurement time. For example, for a 24-hour-wear patch, if adhesion was measured at hours 2, 4, 8, 12, and 24 after the baseline, the total duration of wear is 24 hours, the weight (w_1) for the first measurement x_1 is $\frac{2-0}{24} = \frac{1}{12}$, and the corresponding weights for all five measurements are $\frac{1}{12}, \frac{1}{12}, \frac{1}{6}, \frac{1}{6}$, and $\frac{1}{2}$, which sum up to 1.

In addition to the primary endpoint, the following *secondary endpoints* are recommended for evaluation of adhesion (descriptive statistics only) to assess the potential treatment group difference in clinically meaningful extreme 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 a T mean adhesion score greater than the corresponding R mean adhesion score by 1 or more, compared to the proportion of subjects with an 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 can be plotted.

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

Table 1: Frequency of Adhesion scores for Per Protocol Population (Example)

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

B. STUDY CONDUCT

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 daily activities and to simulate real-world conditions relevant to the labeled conditions of use for the product. For products with a wear period of equal to or greater than 24 hours, it is recommended that subjects be permitted to bathe or shower routinely during the study if doing so is consistent with the labeled use of the product, and the TDS should not be protected from direct exposure to water during such routine activities.

Only whole, intact T and R TDS should be used for the assessment of comparative adhesion because altering the size or shape of the TDS may alter its adhesion characteristics.

Provisions should be included in the study protocol to ensure that interventions like re-application of a detached area of the TDS, re-pressing of the TDS, or any reinforcement of 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) and should include appropriate provisions to prevent re-adhesion to the skin of a TDS that is partially or completely detached.

Subjects should not apply make-up, creams, lotions, powders, or other topical products to the skin area where the TDS will be placed, as this could affect adhesive performance. Hair at the application site should be clipped (not shaved) prior to TDS application.

The method of randomization should be described in the protocol and the randomization schedule provided as a SAS transport data set in .xpt format. The FDA recommends that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and 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.

C. CONSIDERATIONS FOR STATISTICAL ANALYSIS

The Per-Protocol (PP) population for the adhesion analysis should be pre-specified and defined per TDS for each subject. The PP population for adhesion analysis should include all TDS except those intentionally removed early, for example, due to unacceptable irritation, or those on subjects who were discontinued prior to the end of the labeled duration of wear for reasons unrelated to adhesion (e.g., due to a protocol violation). Individual case reports describing subjects who were excluded from the PP population, and the reasons for their exclusion, should be included in the study report.

The means of the per treatment group mean adhesion score (primary endpoint as described above) for the T and R products should be compared. For the calculation of the mean adhesion score, the highest adhesion score at each time point should be carried forward for subsequent time points until a higher score is assessed. To demonstrate adequate product adhesion, the T product should be shown to be statistically non-inferior compared to the R product based upon evaluating the difference in the T and R overall mean adhesion scores, with a non-inferiority (NI) margin of 0.15 ($\delta = 0.15$). The NI margin of 0.15 is for the difference of the mean adhesion scores between T and R based on the 5-point adhesion scale as previously described, not for the difference of the mean adhesion scores based on other adhesion scales (e.g. a 100-point adhesion scale) or non-location-based data transformations (e.g. logarithmic transformation), nor for the difference of median adhesion scores between T and R.

The following hypotheses should be tested at the significance level of 0.05:

$$H_0: \mu_T - \mu_R > \delta$$
$$H_1: \mu_T - \mu_R \leq \delta$$

where μ_T and μ_R are the population means for the mean adhesion score for T and R respectively and the alternative hypothesis H_1 represents the NI of T adhesion relative to R 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. Due to the discrete nature of adhesion scales, a larger sample size than what might be ordinarily calculated (under standard assumptions) is recommended in order to ensure the validity of any large-sample Gaussian assumptions.

A statistical analysis plan (SAP), describing the planned analysis in detail, should be submitted to the Agency as soon as possible, and certainly prior to the un-blinding of the data.

Incomplete data and non-compliance data can seriously affect the validity of an NI study. Good clinical study design and conduct are recommended to prevent patient drop out and non-compliance. When they happen, dropout and non-compliance reasons should be documented in detail. Although the PP population is often suggested as the primary analysis population for NI studies, there are also significant concerns with the possibility of informative dropout and non-compliance. Imputation methods (if applicable) need to be pre-specified in the protocol. Sensitivity analyses are recommended to test the robustness of the primary analysis results in the intent-to-treat population and by relaxing the assumed missing data mechanism of the primary analysis. Difference in conclusions between primary and sensitivity analyses will need close examination.

V. STUDIES EVALUATING ADHESION AND BIOEQUIVALENCE WITH PHARMACOKINETIC ENDPOINTS

Applicants may elect to conduct a study evaluating both the adhesion performance and PK BE of the T and R products in a single study. If pursued, such a 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. The participants for PK BE evaluation should be selected according to a randomization scheme pre-specified in the protocol.

The study design and conduct recommendations described above (for a study performed exclusively for the purpose of evaluating TDS adhesion) also apply to the combined study evaluating adhesion and BE with PK endpoints. When conducting such a combined study, the TDS strength selected should be justified based on the BE (PK) evaluation (for which an appropriate strength of the TDS may be indicated in a product specific recommendation) as well as upon consideration of the potential differences in adhesion failure modes among different strengths.

Simultaneous application of multiple T TDS or of multiple R TDS to a subject may be acceptable in a combined study of TDS adhesion and PK BE, when doing so is safe and justified, for example, by the potential need for an increased drug delivery to compensate for an insufficient analytical sensitivity to measure the relevant analyte(s) in the PK samples.

The inclusion criteria for the statistical analysis of PK endpoints should be pre-specified. The primary PK analysis should be performed on the PP population, which includes all subjects who meet the inclusion criteria for statistical analysis in the PK study. For the primary PK parameters, the geometric mean ratios for T/R treatment and 2-sided 90% confidence intervals (CIs) should be calculated.

PK samples should be collected and analyzed from all subjects in the PK subpopulation, regardless of their adhesion score, and the sample concentrations for all time points as well as the PK results for all subjects in the PK study should be reported. All TDS units that are removed at the end of (or which detach during) the adhesion study should be retained for analysis of residual drug content (see Guidance for Industry: Residual Drug in Transdermal and Related Drug Delivery Systems[6]).

Applicants should refer to Guidance for Industry *Handling and Retention of BA and BE Testing Samples*[7] for recommendations on the retention of study drug samples and maintenance of records of BE testing.

VI. RECOMMENDATIONS ON THE FORMAT OF DATA SUBMISSION

The study data should be submitted in standardized format. Please refer study data standards published at www.FDA.gov.[8]

For the adhesion study analysis, a separate line listing should be provided for each individual test article (i.e., T TDS, R TDS, T overlay, R overlay, etc.) per subject, per adhesion assessment time point (if data exist), using the following headings, if applicable:

1. Subject identifier
2. Study center (if applicable)
3. Age
4. Gender
5. Race
6. Treatment: test article (i.e., T TDS, R TDS, T overlay, R overlay, etc.)
7. Period (i.e., TDS was applied during Period 1 or Period 2) if applicable

[6] U.S. FDA Guidance for Industry: Residual Drug in Transdermal and Related Drug Delivery Systems (August 2011) available at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM220796.pdf

[7] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072869.pdf

[8] Study Data Standards for Submission to CDER available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

8. Application sequence number: number of particular test article application (i.e., 1=first, 2=second)
9. Location of dose administration: individual test article application site
10. Application date/time
11. Number of days/hours since TDS application
12. Adhesion assessment /scoring date/time
13. Initials of adhesion evaluator
14. TDS complete detachment (yes or no)
15. Date and time of complete detachment
16. Treatment discontinued (yes or no)
17. Date and time of treatment discontinuation
18. Reasons for treatment discontinuation
19. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
20. Included in PP population for adhesion analysis (yes/no)
21. Reason for exclusion from PP population for adhesion analysis

SAS transport data sets in the .xpt format should be provided with the define file. If imputation is applied, analysis data after imputation should be submitted. All computer programs used for the primary analysis and sensitivity analysis should be submitted as well.