Assessment of Adhesion for Topical and Transdermal Systems Submitted in New Drug Applications

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DRAFT GUIDANCE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)

July 2021
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 clinical trials designed to assess the adhesion performance of transdermal and topical delivery systems (collectively referred to as TDS). Adhesion performance is defined in this guidance as whether the TDS fully adheres to the subject in the applied location for the duration of use of the TDS. Adhesion performance can affect both safety and effectiveness of TDS products because adhesion failures can result in reduced effectiveness caused by suboptimal dosing or potentially increased exposure when a new TDS needs to be applied sooner than the scheduled dose. Additionally, partial or full detachment of a TDS from a patient's skin may result in unintentional exposure of the active pharmaceutical ingredient to a partner, child, or other individual, potentially exposing them to the drug's toxicity. Adhesion performance may also inform the Dosage and Administration section of labeling.

The recommendations in this guidance relate to studies to be submitted in support of a new drug application (NDA) or supplemental new drug application (sNDA) for human prescription and nonprescription drug products under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355) and 21 CFR Part 314. Because biological products are often more complex and of a higher molecular weight, it is likely that these products would not be absorbed across the skin, requiring a different approach for administration, so they are outside the scope of this guidance.

Sponsors are encouraged to contact the appropriate clinical review division in advance of conducting these adhesion performance studies to discuss specific design and methodology issues.

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

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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

Transdermal delivery systems are designed to deliver an active pharmaceutical ingredient across the skin and into systemic circulation, whereas topical delivery systems are designed to deliver the active ingredient to local tissue.[2] The amount of drug delivered into and through the patient's skin from a TDS depends, in part, on the surface area in direct contact with the TDS. The TDS should remain consistently and uniformly adherent to the patient's skin throughout the duration of wear. During the product's wear period, a TDS is reasonably expected to encounter torsional strains arising from body movements, changes in environmental temperature or humidity such as daily exposure to water (e.g., during routine showering), and contact with clothing, bedding, or other surfaces. When a TDS loses its adhesion during wear, the amount of drug delivered to the patient may be reduced, potentially compromising effectiveness.

TDS development has evolved over the years, especially with respect to expected adhesion performance. TDS products developed today may use technologies that were not available when the first TDS products were approved. This guidance takes these developments into consideration. When final, this draft guidance will expand upon the recommendation for in vivo adhesion studies in section V., Special Topics, subsection A., Product Adhesion Considerations, in the draft guidance for industry *Transdermal and Topical Delivery Systems – Product Development and Quality Considerations* (November 2019).[3]

III. EVALUATING ADHESION

A. Selecting the Trial Drug Product and Conducting an Adhesion Trial

Sponsors should conduct an in vivo clinical adhesion trial as outlined in sections B and D of this guidance as part of an NDA or sNDA in certain circumstances. Examples include, but are not limited to, the following:

[2] Topically administered liquid and semisolid drug products (e.g., gels, creams, lotions, foams, ointments, or sprays) are not considered to be TDS and are not covered by this guidance, even though they can be formulated to provide local, or in some cases, transdermal delivery of the drug.

[3] See the draft guidances for industry *Transdermal and Topical Delivery Systems – Product Development and Quality Considerations* and *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* (October 2018). When final, these guidances will represent the FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- A new TDS submitted in an NDA

- An sNDA for an approved TDS proposing a different population, application site or sites, wear time, or higher strength from the approved conditions of use

- A postapproval change to a TDS, such as a reformulation, change in excipient, or change in critical process parameters that may affect adhesion unless there is strong scientific justification for why another trial is not needed[4]

Sponsors should use the following criteria to select the product for the adhesion trial:

- Use the proposed commercial product

  – Studying a placebo formulation is not appropriate because the active pharmaceutical ingredient can influence the adhesive properties of the finished product.

  – Altering the product design, the qualitative or quantitative composition, or the manufacturing process can affect the adhesion properties of a TDS.

- Use the largest proposed size of the proposed commercial TDS.

  – A larger TDS may be more sensitive to detachment than a smaller one because a larger TDS may be subjected to greater conformational and torsional strains arising from increased anatomical curvatures or a greater magnitude of flexion across a larger sized product.

B. Inpatient Clinical Wear Trial Design

Sponsors should conduct an inpatient clinical wear trial as outlined in this section and, when appropriate, an outpatient clinical trial using patient diary data (as outlined in section D). The inpatient clinical wear trial may be conducted as a dedicated trial or in conjunction with a planned pharmacokinetic trial. Sponsors should account for the following product application and wear techniques when designing and conducting the inpatient clinical wear trial:

- The use of overlays or taping of the edges of the system should be prohibited.

- The product should be applied to the proposed application site or sites.

  – In cases where multiple anatomical application sites are proposed for the product's use:

[4] Only in rare instances, such as the addition of a new manufacturing site, would a noninferiority adhesion study design similar to that outlined in the draft guidance for industry *Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs* apply.

- Sponsors should study the anatomical site or sites of greatest expected torsional strain and/or potential to be impacted by clothing or changing of clothes (e.g., for multiday wear products where clothing may stick to the edges and cause partial detachment). If a TDS is reformulated in response to previously noted issues with adhesion and multiple anatomical sites are permitted, sponsors should ensure that subjects apply the TDS to the sites that have been reported to have the most adhesion issues.

- If the product is proposed to be used at multiple anatomical sites, sponsors should make additional evaluations at more than one anatomical site.

- The application site should be prepared in a manner consistent with the proposed use of the TDS.

  - Subjects should not apply makeup, creams, lotions, powders, or other topical products to the skin area where the TDS is to be placed.

  - Hair at the application site should be clipped (not shaved) before TDS application. Shaving is not recommended because of the possibility of resulting skin abrasion.

- The subject's movements should not be restricted during the trial. Subjects should be allowed to freely conduct normal activities and wear normal attire within the trial unit or facility site.

- For products with a wear period of 24 hours or more, subjects should be permitted to bathe or shower routinely during the trial.

  - The TDS should not be protected (e.g., do not apply a water-resistant covering over the product) or wholly excluded from direct exposure to water (e.g., do not restrict bathing to only a sponge bath) during such routine activities.

  - Activities that are thought to potentially impact adhesion, including bathing or showering, should be recorded for each subject (i.e., activity, duration, and timing relative to TDS application).

- Deliberate actions with the intent to reapply or reattach a detached area of the TDS, to apply pressure to the TDS, or to inappropriately inhibit detachment (e.g., by the constant pressure of a chair back on the TDS) should be prohibited.

Sponsors should include the following adhesion assessment techniques:

- Adhesion should be evaluated at multiple, equally spaced time points following TDS application throughout the wear period. The adhesion of a TDS with a 7-day wear period should be assessed at least daily; the adhesion of a TDS with a 72-hour wear period should be assessed at least every 12 hours; and the adhesion of a TDS with a wear period of 24 hours or less should be assessed at least every 4 hours.

- Adhesion should be assessed in person by a trained observer, and measurements or assessments of adhesion should be based on an estimate of the percentage of the total surface area that is adhered to the skin.

  - With each consecutive measurement, observers should record the percentage based upon the actual measurement at each time point with the observer blinded to the previous recorded percentage finding.

  - For a product that fully detaches (i.e., 0 percent adhered), the time of detachment should be recorded, and 0 percent should be assigned for that and all remaining time points.

  - To assist in objectively estimating the percentage of adhesion, sponsors may use aids such as grids or dot matrices; however, provisions in the protocol should ensure tactile pressure is not applied to the TDS during the observations.

  - At each adhesion assessment time point, sponsors should also record photographic evidence showing the extent of TDS adhesion to the skin. This additional photographic information generally supports the visual observation of percentage of adhesion and is not intended to be used for automated or photometric analysis.

C. Data Assessment

Sponsors should conduct a statistical evaluation, as outlined below, in conjunction with other information (e.g., photographs, trends, narratives, and patient diaries), and the impact of the findings on effectiveness and safety should be considered as part of the benefit-risk framework.[5]

The statistical assessment should consider the following:

- The statistical analysis for adhesion should be performed for the prespecified per-protocol population. The adhesion analysis should include all TDS except those that were intentionally removed early in the trial (e.g., because of unacceptable irritation) or subjects who discontinued use of the TDS before the end of the proposed duration of wear for reasons unrelated to adhesion (e.g., because of a protocol violation or an adverse event). Sponsors should include individual case reports describing any subjects who were excluded from the per-protocol population, and the reasons for their exclusion, in the trial report.

- Let p denote the probability that a randomly selected TDS maintains at least π% of a TDS's total surface area adhesion during its entire wear period. In general, π should be at least 75.

[5] See Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA VI Implementation Plan (FY 2018-2022) available at https://www.fda.gov/media/112570/download. Also, see the appendix at the end of this document for guidance for formatting and submitting statistical information for NDA adhesion studies.

- p is estimated by the proportion of TDS in the wear trial that maintains a surface area adhesion of at least π% at every time point.

- A statistical assessment of the adhesion of a TDS should be evaluated via the following hypothesis test:

  - $H_0: p \leq p_0$ versus $H_1: p > p_0$
  - p_0 should be set at no less than 0.80
  - H_0 is rejected if the 95% lower confidence limit for p is greater than p_0

- Sponsors should specify how the 95% lower confidence limit is calculated and provide justification for the chosen method.

- Sponsors should enroll a sufficient number of subjects to ensure at least 80% power. FDA generally recommends using a larger sample size than that calculated under standard assumptions to ensure the intended power can be maintained to account for dropouts and noncompliance.

Depending on the proposed indication and drug safety profile, TDS assessments may warrant a higher threshold for either π or p_0 than outlined above. Sponsors should discuss the thresholds with the clinical division before conducting the trial.

D. Other Trial Design Considerations

Although the inpatient setting of a clinical wear trial informs the adhering capability of the TDS, the actual user experience may differ. Therefore, in addition to the clinical wear trial described above, if subsequent larger clinical trials are conducted (e.g., a phase 2 or phase 3 trial), sponsors should collect information on product adhesion. Sponsors should obtain this information by using patient diaries describing their user experience with product adhesion. This information is especially important when a novel transdermal or topical system is being studied, when the TDS contains a drug substance (e.g., an opioid) that has a higher risk associated with accidental exposure, or when the clinical wear trial may not adequately capture use in the intended population. The following information should be included in the diaries in these trials:

- Subjects should record the application site in their diaries.

- Subjects should record multiple, equally spaced timed assessments throughout the wear period.

- Subjects should estimate the percentage of surface area adhered and record the percentage in their diaries. Sponsors should provide clear instructions to subjects on how to determine the percentage of surface area. Alternative methodologies to collect the percentage surface area in diaries can be considered, but sponsors should first discuss the approach with the appropriate review division.

- Subjects should record how often (i.e., the date and time) they pressed the detached parts back on, smoothed the product out over the wear period, removed their TDS, or replaced their TDS.

- Subjects should record the time and date of any unscheduled TDS placement or replacement and the reason (e.g., "It was itching," "I preferred a different location on my body," "It fell off").

- If a subject removes the TDS for localized discomfort, the time should be recorded and the site photographed if possible by the subject or caregiver.

- Subjects should record in diaries those events associated with daily activities that may impact adhesion, such as the following:

  - Shower, bath, or water immersion (e.g., swimming)

  - Activities that caused sweating (e.g., strenuous exercise, mowing the lawn)

- Subjects should record localized issues encountered during wear (e.g., itching or burning, difficulty removing from the body, adhesive residue after TDS removal from site or sites). Sponsors should designate a specific electronic case report form (eCRF) module that collects this adverse-event information (i.e., type/appearance of local reaction, duration, intensity, additional local symptoms, outcome (resolved, ongoing, trial drug interrupted, patient continuing in trial, patient withdrawn from trial, etc.)).

APPENDIX: FORMAT OF DATA SUBMISSION

Sponsors should submit trial data in standardized format and refer to the FDA web page on Study Data for Submission to CDER and CBER[1] for more information about trial data standards. In addition, sponsors should provide SAS transport datasets in XPT format with the define file. If imputation is applied, sponsors should also submit analysis data after the imputation. The information should be submitted in Module 5 of the electronic common technical document.

For ease of evaluation, sponsors should submit an Excel, csv, or XPT file with each row representing the observations of the percentage of adhesion of a TDS on a subject for all subjects in the per-protocol population, including subject ID, application site, actual date and time of each evaluation, and percentage of adhesion at the time of each evaluation. Sponsors may omit application site information if a single application site is used in the trial. An example is shown in the table below.

Subject ID	Application site	Date and time of first evaluation	Percentage of adhesion of first evaluation	Date and time of second evaluation	Percentage of adhesion of second evaluation
XXX	Site 1	YYYY-MM-DD: hh:mm	XX%	YYYY-MM-DD: hh:mm	XX%

[1] The web page is available at https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber.