Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs

Guidance for Industry

DRAFT GUIDANCE

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

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Generic Drugs

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Assessing the Irritation and Sensitization Potential of Generic 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for the design and conduct of studies to evaluate the in vivo skin irritation and sensitization (I/S) potential of a proposed transdermal or topical delivery system (collectively referred to as TDS[2]). The recommendations in this guidance relate exclusively to studies submitted in support of an abbreviated new drug application (ANDA).[3]

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 the reference listed drug and/or reference standard product.

The recommendations relating to the design and conduct of I/S studies described in this guidance replace the recommendations related to I/S studies provided in product-specific guidances[4] published before this guidance. Nonetheless, FDA recommends that applicants consult this guidance in conjunction with any relevant product-specific guidances that contain product-specific recommendations (1) for their I/S study (such as the strength of the TDS, the duration of wear for the specific TDS, and the frequency of scoring observations) or (2) for other in vivo studies (such as adhesion or pharmacokinetics) that may be necessary to establish the

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

[2] 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*.

[3] The recommendations for studies characterizing the TDS irritation or sensitization potential in a new drug application or a supplemental new drug application may be different than those submitted in support of an ANDA. The design, conduct, and assessment of TDS irritation and sensitization in studies supporting a new drug application are inherently different because TDS irritation/sensitization in that context is not typically evaluated in relation to a reference product.

[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.

bioequivalence of a proposed generic TDS drug product to its reference listed drug and/or reference standard 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 components and composition of a TDS formulation, including the nature of the drug substance and/or the degree to which the TDS materials occlude the transmission of water vapor from the skin, in conjunction with other factors such as the environmental humidity or the condition of the skin, may have the potential to irritate the skin or lead to a sensitization reaction. Such reactions can be unpleasant to the patient and may affect patient compliance, skin permeability, and/or adhesion of the TDS to the skin. The collective consequence of these potential effects could create uncertainty about the resulting drug delivery profile and uncertainty about the rate and extent of drug absorption from the TDS. Therefore, applicants should perform a comparative assessment of the T and R TDS products using an appropriately designed skin I/S study with human subjects to demonstrate that the potential for a skin irritation or sensitization reaction with the T TDS is no worse than the reaction observed with the R TDS.

III. GENERAL CONSIDERATIONS

Skin I/S studies are designed to compare the potential for the T and R TDS products to cause irritation and/or sensitization reactions. A TDS may illicit these reactions in only some of the patients using the product, but even if the frequency of this occurrence was low, the adverse reactions could affect thousands of individuals among the millions who use the product. To evaluate this I/S potential, applicants should compare the T and R TDS products in a relatively small population (hundreds of subjects), and the study should be conducted under relatively provocative conditions (repeated removal and reapplication of the TDS on the same skin site) to maximize the potential for the occurrence of an irritation and/or sensitization reaction in the subject population during the study.

Changes in environmental temperature or humidity, including the daily exposure of the TDS to heat and water during routine showering, may transiently affect the rate at which components of the TDS formulation are released and permeate through skin. Such changes may also affect entrapped moisture in and/or under the TDS, which could alter skin hydration and impact the bioavailability of formulation components, which may, in turn, change I/S reactions. Therefore, when designing their I/S studies, applicants should consider any conditions of labeled use for the R product that may impact the I/S potential of a TDS product (e.g., incidental exposure of the TDS to water, such as while bathing or showering, particularly for a TDS with a duration of wear longer than 24 hours).

In addition to I/S reactions that may arise from the corrosive or immunomodulatory nature of formulation components or from the pharmacodynamic response of the skin to the occlusion by the TDS, the skin may also become irritated in response to the physical insults that can occur during the removal of a TDS. If the adhesive properties of the TDS are such that it strips away substantial portions of the stratum corneum during removal, the damage to the skin barrier may lead to irritation at the site of TDS removal, which may also increase the potential for a sensitization reaction.

This draft guidance provides recommendations for the design and conduct of studies to evaluate the in vivo skin I/S potential of a proposed TDS. The recommendations in this draft guidance relate exclusively to studies submitted in support of an ANDA.

IV. COMBINED EVALUATIONS OF SKIN IRRITATION AND SENSITIZATION

A. Study Design and Conduct

In general, the Agency recommends that applicants conduct a multi-center, evaluator-blinded, randomized study to support their comparative evaluation of the skin irritation and sensitization characteristics of the T and R products. The study population should typically include healthy males and nonpregnant, nonlactating females, unless product-specific considerations consistent with the labeled conditions of use for certain TDS products indicate otherwise. In the study protocol, the choice of TDS strength intended to be used should be pre-specified and should be justified, as appropriate, based upon the use of the TDS in the proposed study population.

The Agency recommends that applicants evaluate skin irritation and sensitization in a single study as long as a sufficient number of subjects are included to evaluate sensitization. The recommended study consists of the following two phases, which are each described in turn:

1. A 21-day induction phase, followed by a 14- to 17-day rest period
2. A challenge phase

During the induction phase, applicants should simultaneously apply all TDS units (i.e., every whole or partial T product and every whole or partial R product) to each subject. T and R products should be applied at contralateral locations of the same anatomical site (e.g., T product on the left buttock and R product on the right buttock); applicants should select the anatomical site based on the recommendations for dosing in the R product labeling.

- For 21 consecutive days, TDS units should be worn, removed, and replaced by a new TDS unit, for repeated durations to the same skin site as the initial application; each duration should be representative of the labeled wear period. For example, a TDS with a 3-day wear period may be removed every 3 days, assessed for I/S, and replaced to the same skin site every 3 days, for a total of 21 days.

- Applicants should evaluate the subject's irritation response at the time of each TDS change by individually assessing the subject's "dermal response" and "other effects" scores (both of which are described below) by using a separate scoring scale.

- For subjects who experience excessive irritation (applicants should predefine "excessive irritation" in their protocol), the TDS may be moved to a new site to complete the 21-day induction phase and to continue with the sensitization part of the study.

During the challenge phase, applicants should simultaneously apply all TDS units (i.e., every whole or partial T product and every whole or partial R product) to each subject. T and R products should be applied at contralateral locations of the same anatomical site (e.g., T product on the left buttock and R product on the right buttock); applicants should select the anatomical site based on the recommendations for dosing in the R product labeling.

- The TDS units should be applied for a 48-hour duration at a naïve skin site (i.e., a site onto which a TDS was not applied during the induction phase) and then removed.

- Applicants should assess the subject's skin reactions at 30 minutes, 24 hours, 48 hours, and 72 hours after removal of the TDS.

- Applicants should record any skin reactions observed with a narrative description of the subject's "dermal response" or "other effects" scores (both of which are described below) by using a separate scoring scale.

- Applicants should document the opinion of the investigator about whether the skin reaction(s) are indicative of a contact sensitization. Applicants should prespecify, in their study protocol how the investigators will be instructed to determine whether or not there is a contact sensitization.

- For all subjects who exhibit a potential sensitization reaction, applicants should conduct a re-challenge test 4 to 8 weeks following the original challenge and conducted in the same manner as described above.

During both the induction phase and challenge phase, applicants should score the subjects' skin responses according to the two scales shown below.

Scale 1. Dermal Response.

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema that is barely perceptible	1
Definite erythema that is readily visible and minimal edema or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the application site	7

Scale 2. Other Effects

Observation	Score (Numerical Equivalent)
Slightly glazed appearance	A (0)
Markedly glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the TDS site	G (3)
Small petechial erosions and/or scabs	H (3)

When one or more "other effects" are observed, applicants should report each score as a dermal response number, a letter combination score, and as a numerical total (i.e., numerical "dermal response" score + numeric equivalent for the "other effects" lettered score). For example, the dermal response of 6 with glazing with fissure (F (3)) will equal to the score of 9.

When no "other effects" are observed, score zero should be applied to an observed "other effects."

However, if applicants use a scale other than these two scales (e.g., a single numerical scale that captures the progressive change in skin reactions) to score the skin reactions observed, they should report each score according to their selected alternate scale as well as the score according to these two scales. In addition, applicants should request a meeting with FDA to discuss their alternative scale and their proposed statistical analysis plan before conducting the study, if possible.

Applicants should evaluate adhesion of the TDS to the skin at each time point before TDS removal throughout the entire study period to monitor the adequacy of skin contact, which is necessary for a suitably provocative induction of I/S. FDA's recommended scoring system for

evaluating the adhesion of the TDS is described in the draft guidance for industry *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs*.[5]

If applicants believe that use of tape or overlay may be needed to maintain maximum contact of the TDS with the skin throughout the relevant duration of an I/S study, then the use of tape or an overlay may be appropriate. Applicants should prespecify, in their study protocol, their criteria for using tape or an overlay to reinforce any TDS that is lifting. If a TDS is reinforced with tape or an overlay, skin irritation of the tape or overlay area should be reported separately from the skin irritation associated with the TDS application area.

If a TDS completely detaches, the subject should replace the new TDS within 24 hours and continue in the study. The subject should note the date and time of detachment as soon as it occurs, and applicants should maintain the source document generated by the subject (e.g., subject diaries). If a TDS completely detaches for more than 24 hours during the 21-day induction phase, applicants should exclude the subject from both the irritation and sensitization analyses for that product unless the subject intentionally removed the TDS because of excessive irritation. If a TDS completely detaches for more than 24 hours during the 48-hour challenge phase, applicants should exclude the subject from the sensitization analysis.

For I/S studies, applicants should enroll an adequate number of subjects to ensure that at least 200 evaluable subjects are included in their per protocol (PP) population; however, for irritation-only studies, the number of evaluable subjects in the PP population can vary. Subjects should not apply makeup, creams, lotions, powders, alcohol, or other topical products to the skin area where the TDS will be placed because these products could affect the adhesive performance or irritation potential of the TDS. Also, the subject's hair at the application site should be clipped (not shaved) before TDS application. In addition, applicants should advise subjects to avoid exposing the TDS application site to external sources of direct heat, such as heating pads, electric blankets, heat lamps, saunas, hot tubs, heated water beds, and/or prolonged direct sunlight.

The following lists specify some inclusion and exclusion criteria that applicants can use to select test subjects; however, these lists are not exhaustive, and applicants can use other criteria as desired to select subjects. Applicants should describe, as part of the protocol, the rationale for inclusion and/or exclusion criteria that are in addition to or different from those identified below.

- Inclusion criteria:

  - Healthy male and female (nonpregnant, nonlactating) subjects between 18 and 65 years of age (inclusive)

  - Females of childbearing potential must be prepared to either abstain from sexual intercourse or use a reliable barrier method of contraception (e.g., condom with spermicide, diaphragm, IUD, contraceptive sponge) for at least 14 days before and throughout the duration of study or have used a hormonal method of contraception for

[5] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

at least 30 days before the study and will continue to use the same type of hormonal contraceptive during the study

- Exclusion criteria:

  - Subject is pregnant or lactating

  - Medical history of significant dermatologic diseases or conditions, such as atopy, psoriasis, vitiligo, or conditions known to alter skin appearance or physiologic response (e.g., diabetes or porphyria)

  - Medical history of a condition that would significantly influence the immune response (e.g., primary or acquired immunodeficiencies such as HIV or AIDS; allergic diseases such as anaphylaxis, asthma, or generalized drug reaction; neoplasms such as lymphoma or leukemia; rheumatoid arthritis; or systemic lupus erythematosus)

  - Medical history of significant dermatologic cancers (e.g., melanoma or squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the TDS application sites

  - Within 3 weeks of the start of study treatment, use of medications or treatments that would either (1) significantly influence or exaggerate responses to the T or R product or (2) alter the inflammatory or immune response to the T or R product (e.g., cyclosporine, tacrolimus, systemic or topical corticosteroids, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin, monoclonal antibodies, or radiation therapy)

  - Within 72 hours of the start of study treatment, use of antihistamines or use of topical drugs at the TDS site

  - Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application sites, scar tissue, tattoos, open sores, a recent sunburn, or body piercing that would interfere with the placement of the test articles, the skin assessment, or the subject's reactions to the TDS

Applicants should provide a listing of the prescription and over-the-counter drug products that will be contraindicated for subjects during the study, such as medications or treatments that would significantly influence or exaggerate the subject's responses to the T or R product or that would alter the subject's inflammatory or immune response to the product (e.g., antihistamines, systemic or topical corticosteroids, cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin, monoclonal antibodies, or radiation therapy).

In general, a subject's body movement should not be restricted during the study. For products with a wear period of equal to or greater than 24 hours, the Agency recommends that (1) subjects be permitted to bathe or shower routinely during the study if doing so is consistent with the

labeled use of the product and (2) the TDS should not be protected from direct exposure to water during such routine activities.

Applicants should randomize their assignment of the T and R products to skin sites, describe their method of randomization in the protocol, and provide the randomization schedule as an SAS transport data set in XPT format.

A trained observer should score the TDS's adherence and the subject's skin reactions at each TDS removal, and applicants should try to ensure that the same scorer is used for all observations. If the same scorer is not used in all observations, the applicants should provide the evidence to ensure the scoring is consistent across different scorers. Because of likely differences in the appearance of the TDS between the T product and the R product, blinding of the observer may not be possible, especially for monitoring TDS adhesion, which requires direct observation of the TDS. However, applicants should try to blind the evaluation of I/S when possible.

FDA's recommended primary endpoint for evaluating irritation is the mean irritation score (MIS). At each assessment time point for each subject and for each product, applicants should calculate a combined irritation score by adding the "dermal response" score and the numeric equivalent for "other effects" letter score. For each subject and each product, applicants should calculate the MIS as the sum of the combined irritation scores over the assessment time points divided by the total number of assessments.

Applicants should submit descriptive irritation score data in a frequency table illustrating the number and proportion of each TDS unit with each combination of the dermal response numerical score and the "other effects" letter score at each evaluation time point. If a TDS is moved or removed because of excessive irritation, the irritation score(s) observed at the original application site at the time of removal should be considered as the irritation score(s) for the remaining time points. This approach is referred to as the last observation carried forward (LOCF) from the original application site. The frequency table should reflect the irritation scores after the LOCF. The table below provides an example of a frequency table.

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

Day: TDS	**"Dermal Response" and "Other Effects" Scores**															
	0		**0A ***		**1****		**1A**		**2**		**2A**		**3**		**4**	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
3:T	151	98.7	0	0.0	2	1.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3:R	151	99.3	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
7:T	149	97.4	0	0.0	4	2.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
7:R	145	95.4	0	0.0	7	4.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
10:T	140	91.5	0	0.0	10	6.5	1	0.7	1	0.7	0	0.0	1	0.7	0	0.0
10:R	141	92.8	0	0.0	9	5.9	0	0.0	2	1.3	0	0.0	0	0.0	0	0.0
14:T	142	92.8	0	0.0	7	4.6	2	1.3	1	0.7	0	0.0	1	0.7	0	0.0
14:R	139	91.5	0	0.0	11	7.2	0	0.0	1	0.7	0	0.0	1	0.7	0	0.0

17:T	120	78.4	1	0.7	23	15.0	2	1.3	3	2.0	0	0.0	4	2.6	0	0.0
17:R	129	84.9	0	0.0	16	10.5	0	0.0	3	2.0	1	0.7	2	1.3	1	0.7
21:T	112	73.2	5	3.3	25	16.3	4	2.6	3	2.0	0	0.0	4	2.6	0	0.0
21:R	121	79.6	2	1.3	20	13.2	3	2.0	3	2.0	0	0.0	2	1.3	1	0.7

* The combination *0A* means that the "dermal response" score is 0 and the "other effects" score is A.

** The number *1* means that the "dermal response" score is 1 and the "other effects" is not present.

B. Considerations for Statistical Analyses

1. Irritation Analysis

For an irritation analysis, applicants should define, in the protocol, their per-protocol (PP) population per TDS instead of per subject. The PP population should include all TDS units applied sequentially to the same anatomical site for the entire 21-day induction phase without any period of detachment longer than 24 hours. If a TDS is moved or removed because of excessive irritation, it should be included in the PP population, using the LOCF from the original application site.

Applicants should compare the overall mean of the per-subject MIS (i.e., the primary endpoint described above) for the T and R products. To demonstrate the noninferiority (NI) of the T product compared to the R product with respect to the MIS, the T product should be shown to be statistically non-inferior to the R product based on evaluating the difference in the T and R products' overall mean MIS, with an NI margin of 0.20 ($\delta = 0.20$). The NI margin of 0.20 represents the difference of the mean MIS between the T and R products based on the irritation scales as previously described; this NI margin may not be appropriate to use for either the difference of the mean MIS based on other irritation scales or data transformations (e.g., a logarithmic transformation or the addition of a constant to all irritation scores) or the difference of the median MIS between the T and R products.

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 MIS for the T and R products, respectively, and the alternative hypothesis H_1 represents the NI of the T product's irritation relative to the R product's irritation.

To demonstrate an acceptable irritation response for the T product, applicants should design and conduct an irritation study as described in section III.A of this guidance and enroll a sufficient number of subjects to power the study at a level of 0.80 or higher.

Applicants should finalize their statistical analysis plan, describing all aspects of the planned analysis in detail, before the data are unblinded; the statistical analysis plan should be provided to the Agency when the ANDA is submitted.

Incomplete data and data associated with noncompliance can seriously affect the validity of an NI study. Therefore, FDA recommends good study design and conduct to prevent patient dropout and noncompliance. If either occur, applicants should document, in detail, the reasons for the dropout and/or noncompliance. 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 non-compliance. Applicants should prespecify, in their protocol, the imputation methods used (if applicable). 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 NI.

For the irritation evaluation, FDA also considers other clinically relevant data, including the number of TDS unit applications that reach a maximum irritation score and the number of subjects who discontinue product application because of excessive irritation. The same MIS could be reached with a small number of high scores (e.g., 3 or higher), which may be of greater clinical concern, or with a larger number of low scores (e.g., 1), which may be of lesser clinical concern. Thus, it is difficult to determine the clinical meaningfulness of a given MIS or a given difference between products with respect to their MIS.

Therefore, in addition to MIS, FDA recommends the applicant evaluate the proportion of subjects with excessive irritation for each product. The proportion of subjects with excessive irritation should be no higher for the T product than for the R product, and irritation should not occur earlier in the application period for the T product than for the R product. The T product should be noninferior to the R product with respect to the MIS, and the T product should show no meaningful difference, compared to the R product, with respect to the degree of irritation.

2. Sensitization Analysis

Applicants should define, in the protocol, the PP population for the sensitization analysis per TDS instead of per subject.

The PP population for the sensitization analysis should include all TDS units worn (without any period of detachment longer than 24 hours) for the full 21-day induction phase and the entire 48-hour challenge phase. Each subject should return for at least one of the scheduled evaluations at 48 and 72 hours after removal of the challenge TDS. If a TDS unit is removed before the end of the 48-hour challenge phase because of excessive irritation, the application site should be evaluated at 24 hours, 48 hours, and 72 hours after TDS removal and be included in the sensitization analysis using the LOCF from the original application site.

For each TDS unit, each PP subject with a combined score of 2 or greater at 48 or 72 hours after TDS removal during the challenge phase should be individually evaluated for potential sensitization. Applicants should consider a subject *potentially sensitized* if all the following criteria are met:

a. The subject has at least one evaluation timepoint occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the challenge phase TDS.

b. The subject has a combined irritation score of at least 2 at their last evaluation during the challenge phase.

c. The above two criteria were met during both the challenge phase and the re-challenge phase, if the subject completed a re-challenge phase.

Skin reactions that resolve before 48 hours are generally considered to be caused by irritation instead of sensitization. For any potential sensitization reaction observed during the challenge or re-challenge phase, applicants should provide a justification to support that the rate of sensitization of the T product is comparable to that observed with the use of the R product.

Applicants should report the respective numbers of subjects considered to be potentially sensitized to the T and/or R products.

Applicants should provide descriptive statistics comparing both the number and the proportion of subjects potentially sensitized to each TDS unit and both the number and the proportion of subjects sensitized to each TDS unit.

Applicants should provide a frequency table showing the number of applications of each TDS unit during the challenge phase, with each specific combined "dermal response" numerical score and "other effects" letter score at each evaluation time point.

For all subjects with at least one combined irritation score of 2 or more at 48 or 72 hours after TDS removal in the challenge phase, applicants should provide a table showing the actual scores for each subject at each evaluation time point during the induction and challenge phases.

For TDS products that are known to be skin sensitizers (e.g., methylphenidate TDS), a sensitization evaluation may be unnecessary if justifications are provided (e.g., related to components and the composition of TDS products) to show that the T product is not likely to be more sensitizing than the R product.

C. Vehicle TDS and Positive Control TDS

If safety concerns preclude the usual comparative studies, which include the use of the T and R products, the I/S potential of the active ingredient can be assumed to be reasonably equivalent between the T and R products, and the evaluation of skin I/S by the T product can be evaluated by testing a vehicle TDS versus a positive control TDS that produces mild irritation (e.g., $\leq 0.1\%$ sodium lauryl sulfate). The vehicle TDS should contain all of the inactive ingredients in the T product and be identical to the T product in every manner except for the absence of the active ingredient. If the inactive ingredients in the vehicle TDS are different than those contained in the T product or are in different amounts than in the T product, then the applicant should clearly describe the differences and provide data to show that the differences will not affect the safety of the T product or the applicant's interpretation of the study results.

For a skin I/S study that compares the vehicle TDS to a positive control TDS, applicants should utilize essentially the same approach as is recommended for the comparison of T and R products

in sections III.A. and B of this guidance, except that the vehicle TDS should serve as the T product and the positive control TDS should serve as the R product.

D. Partial (Cut) TDS

If a safety concern prevents the simultaneous application of two whole TDS on the same subject during the 21-day combined I/S study, a matrix TDS can be cut to a smaller size. In such situations, the T and R products should both have designs that can be safely cut to a smaller size. Applicants should not manufacture a separate batch of product to use a smaller TDS in this study. When using a cut TDS, the general recommendations provided in sections III.A and III.B in this guidance apply.

V. OVERALL ASSESSMENT OF ADVERSE EVENT DATA

Applicants should include, in their analysis, all subjects who receive at least one dose of TDS. This analysis should include a comparison of all TDS units (e.g., the T product and the R product) with respect to any application site adverse events. Applicants should report all adverse events, including systemic ones, whether or not applicants consider them to be related to the T product or the R product.

Applicants should document, in their study report, all application site reactions (including subject complaints such as dryness, itching, burning, pain, or soreness) separate from the "dermal response" and "other effects" scores. In addition, applicants should include details about any application site to which the complaint applies. The study report should also include a frequency table listing application site reactions and comparing the severity of application site reactions between the T product and the R product.

VI. FORMAT OF DATA SUBMISSIONS

Applicants should refer to the Study Data for Submission to CDER web page[6] for information about data standards.

Applicants should provide SAS transport data sets in XPT format with the define file. If applicants apply imputation, they should submit both raw data and the analysis data after the imputation.

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