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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Melissa Mannion at 301-796-2747.

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
Revision 1

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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relate to studies submitted in support of an abbreviated new drug application (ANDA).[3] This guidance revises the draft guidance for industry *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (October 2018). This revision provides the following updates to the original draft guidance:

(1) Clarifies recommendations for the design and conduct of studies to evaluate the in vivo skin I/S potential of a proposed TDS.

(2) Clarifies when an in vivo study to assess the sensitization potential of a TDS product may not be needed.

[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 be 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 listed drug. For a new drug application, please refer to the guidance for industry *Contact Dermatitis From Topical Drug Products for Cutaneous Application: Human Safety Assessment* (March 2020). We update guidances periodically. 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.

(3) Provides guidance to applicants intending to utilize alternative scoring scales or alternative approaches to compare I/S between the test and reference TDS.

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 (RLD) and/or reference standard product.

FDA recommends that applicants consult this guidance in conjunction with any relevant product-specific guidances (PSGs)[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 bioequivalence of a proposed generic TDS product to its RLD. FDA also recommends that applicants routinely refer to FDA's website, since additional guidances may become available that could assist in the development of a generic TDS product.

FDA encourages an applicant who seeks to use an alternative approach to FDA's recommendations in the relevant PSG for the design and conduct of studies evaluating the in vivo I/S potential of a TDS between T and R products to contact the Agency to discuss the proposed alternative approach to evaluate the I/S potential for that drug product.[6]

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

[4] Generic drug product-specific guidances are available at the Product-Specific Guidances for Generic Drug Development web page, available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

[5] For example, relevant guidances include the draft guidances for industry *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* (April 2023) and *Transdermal and Topical Delivery Systems — Product Development and Quality Considerations* (November 2019). When final, these guidances will represent the FDA's current thinking on these topics.

[6] See Manual of Policies and Procedures (MAPP) 5220.8 *Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings* https://www.fda.gov/media/130874/download. See also the guidances for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020) and *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022) for additional information on how to obtain Agency feedback on the development of a specific drug product.

reaction.[7] 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, when appropriate, 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 (see General Considerations below for information about when such a study may be appropriate).

III. GENERAL CONSIDERATIONS

Skin I/S studies are designed to compare the similarity between the T and R TDS products for the potential to cause irritation and/or sensitization reactions. A TDS may elicit these reactions in only some of the patients using the product, but even if the frequency of this occurrence were low, the adverse reactions could affect thousands of individuals. To evaluate this I/S potential, applicants should compare the T and R TDS products in at least 200 evaluable subjects (see section IV.A.), and the study should be conducted under 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.

In some circumstances, an in vivo study to assess the sensitization potential of a TDS product submitted in an ANDA may not be necessary if adequate justification is provided or FDA has determined that conducting a sensitization assessment is unnecessary or unethical (e.g., where the active ingredient is known to be a skin sensitizer or based on information/data related to the components and composition of TDS products) to show that the T product is not likely to be more sensitizing than the R product.

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 RLD 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 that is up to or greater 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

[7] Skin sensitization reaction refers to an allergic skin reaction (i.e., allergic contact dermatitis) to a substance resulting from previous exposure, and is usually characterized by redness, swelling, and itching.

during the removal of a TDS. For example, 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.

IV. COMBINED EVALUATIONS OF SKIN IRRITATION AND SENSITIZATION

A. Study Design and Conduct

In general, the Agency recommends that applicants conduct an evaluator-blinded, randomized study to support their comparative evaluation of the skin I/S 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 RLD's labeled conditions of use for certain TDS products indicate otherwise.[8] In the study protocol, the choice of TDS strength intended to be used should be prespecified 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 if a sufficient number of subjects are included to evaluate sensitization, as described herein. 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[9]

During the induction phase, applicants should simultaneously apply all TDS units (i.e., every whole or partial[10] 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 RLD 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 RLD's labeled wear period, unless otherwise noted within the relevant PSG. 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.

[8] For product-specific considerations, refer to the relevant sections in current RLD labeling, including BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections, and the recommended inclusion and exclusion criteria of the relevant PSG.

[9] The challenge phase of the recommended study provides data to evaluate whether sensitization to the drug product has occurred after introducing the drug product in the induction phase.

[10] *Partial* refers to a matrix TDS that is cut into smaller sizes.

- 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,[11] 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. Applicants should predefine in their protocol what criteria would trigger the movement of a TDS to a new site (due to skin reactions that are determined to represent excessive irritation). For example, the criteria may specify that TDS may be moved to a new site if the combined score is equal to or greater than 3.

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 RLD 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" and "other effects" scores (both of which are described below) by using a separate scoring scale for each.

- 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 rechallenge test 4 to 8 weeks following the original challenge and conducted in the same manner as described above for the challenge phase.

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

[11] This score may vary for different TDS products or different scenarios.

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 or 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)
No other effects or only a 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."

Applicants intending to utilize an alternative scale other than these two scales should request a meeting with FDA to discuss the alternative scale and the proposed statistical analysis plan before conducting the study (i.e., submit a pre-ANDA meeting request).[12] If applicants use a scale other than these two scales (e.g., a single numerical scale that captures the progressive changes 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.

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

[12] See footnote 7.

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.

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. Accordingly, even where tape or an overlay is used, adhesion should be evaluated based on the surface area of the TDS (not including any tape or overlay) to ensure that the TDS is adhering well throughout the induction phase and challenge phase. FDA's recommendations for evaluating the adhesion of the TDS are described in the draft guidance for industry *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* (April 2023).[13]

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 unless the subject intentionally removed the TDS because of excessive irritation.

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 (see details in Section B.1. for sample size determination for the conduct of irritation-only studies). 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 to select subjects, as appropriate. 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.

[13] When final, this guidance will represent the FDA's current thinking on this topic.

- Inclusion criteria:

  - Healthy[14] 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., female condom, diaphragm, intrauterine system, contraceptive sponge, or have their partner use a barrier method (condom with spermicide)) for at least 14 days before and throughout the duration of study or have used a hormonal method of contraception for 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 immunotherapy, 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

[14] Healthy subjects are in general non-smoking adults 18 years of age or older without existing medical conditions or required medications that exert physiological effects.

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 list 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 immunotherapy, 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 up to or greater than 24 hours, the Agency recommends that subjects be permitted to bathe or shower routinely during the study, in a manner consistent with the labeled use of the RLD, and that 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 a 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 for all observations, applicants should provide evidence to ensure that 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 last irritation score(s) observed at the original application site prior to removal is considered a reasonable representation of the degree of irritation with the TDS at that site 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) (N=153 patches for T, and N=152 patches for R).

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" score is 0.

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 noninferior 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. These hypotheses can also be written as follows:

$$H_0: \mu_D \geq \delta$$
$$H_1: \mu_D < \delta$$

where μ_D is equal to the difference of the population mean for the MIS for the T and R products: $\mu_D = \mu_T - \mu_R$. When there is no missing data, in a matched pairs study, μ_D is the same as the population mean for the difference D_j between the paired T per-subject MIS ($\bar{X}_{jT}$) and R per-subject MIS ($\bar{X}_{jR}$) for individual subject j $\left(D_j = \bar{X}_{jT} - \bar{X}_{jR}, E\left(D_j\right) = \mu_D\right)$.

To demonstrate an acceptable irritation response for the T product, applicants should design and conduct an irritation study as described in section IV.A of this guidance. If an irritation-only study is designed, applicants should enroll a sufficient number of subjects to power the study at a level of 0.80 or higher. Because of the discrete nature of irritation scales and other potential complications of the irritation data, FDA recommends that applicants use a large enough sample size to ensure the validity of any large-sample (asymptotic) Gaussian assumptions, if used.

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. If methods other than LOCF will be used to impute data for a TDS that is moved or removed due to excessive irritation, applicants should prespecify these 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 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:

- 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.
- The subject has a combined irritation score of at least 2 at their last evaluation during the challenge phase.
- If the subject completed a rechallenge phase, the above two criteria were met during both the challenge phase and the rechallenge 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 rechallenge 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.

In some circumstances, an in vivo sensitization evaluation of a TDS product may be unnecessary if adequate justification is provided or FDA has determined that conducting a sensitization assessment is unnecessary or unethical (e.g., where the active ingredient is known to be a skin sensitizer or based on information/data related to the components and composition of TDS product) 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 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., less than or equal to 0.1 percent sodium lauryl sulfate). The vehicle TDS should contain all 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 IV.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.

Applicants should ensure that the positive control is consistently able to elicit and maintain an irritation response during the induction phase. A positive control that is either unable to consistently elicit an irritation response, or unable to maintain that response, may confound the interpretation of study results and undermine the validity of the study.

It is not recommended to include multiple candidate positive control TDS products in the I/S study and post-hoc select one as the positive control TDS to compare with the vehicle TDS in the

statistical analysis. Rather, it is recommended to pre-select one appropriate positive control to use as the positive control TDS prior to the I/S study.

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.[15] 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 IV.A and IV.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 adverse events. For any application site related adverse events, applicants should report whether or not the adverse event is 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[16] 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.

[15] The recommended cut size for a matrix TDS is product specific and included in the relevant PSG.

[16] Available at https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/study-data-submission-cder.