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# 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## ***DRAFT GUIDANCE***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)**

**April 2023  
Generic Drugs  
Revision 1**

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

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

**April 2023  
Generic Drugs  
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*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

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1           **Assessing the Irritation and Sensitization Potential of Generic**  
2           **Transdermal and Topical Delivery Systems for ANDAs**  
3           **Guidance for Industry<sup>1</sup>**  
4  
5

6  
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
11 for this guidance listed on the title page.  
12

13  
14  
15 **I. INTRODUCTION**  
16

17 This guidance provides recommendations for the design and conduct of studies to evaluate the in  
18 vivo skin irritation and sensitization (I/S) potential of a proposed transdermal or topical delivery  
19 system (collectively referred to as TDS<sup>2</sup>). The recommendations in this guidance relate to  
20 studies submitted in support of an abbreviated new drug application (ANDA).<sup>3</sup> This guidance  
21 revises the draft guidance for industry *Assessing the Irritation and Sensitization Potential of*  
22 *Transdermal and Topical Delivery Systems for ANDAs* (October 2018). This revision provides  
23 the following updates to the original draft guidance:  
24

- 25       (1) Clarifies recommendations for the design and conduct of studies to evaluate the in vivo  
26       skin I/S potential of a proposed TDS.  
27  
28       (2) Clarifies when an in vivo study to assess the sensitization potential of a TDS product may  
29       not be needed.  
30

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<sup>1</sup> 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.

<sup>2</sup> 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*.

<sup>3</sup> 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>.

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31 (3) Provides guidance to applicants intending to utilize alternative scoring scales or  
32 alternative approaches to compare I/S between the test and reference TDS.  
33

34 In this guidance, the letter *T* (representing *Test*) will refer to proposed generic products that are  
35 the subject of an ANDA, and the letter *R* (representing *Reference*) will refer to the reference  
36 listed drug (RLD) and/or reference standard product.  
37

38 FDA recommends that applicants consult this guidance in conjunction with any relevant product-  
39 specific guidances (PSGs)<sup>4</sup> and in conjunction with any relevant guidances for industry<sup>5</sup> when  
40 considering the design and conduct of studies that may be appropriate to support the  
41 bioequivalence of a proposed generic TDS product to its RLD. FDA also recommends that  
42 applicants routinely refer to FDA’s website, since additional guidances may become available  
43 that could assist in the development of a generic TDS product.  
44

45 FDA encourages an applicant who seeks to use an alternative approach to FDA’s  
46 recommendations in the relevant PSG for the design and conduct of studies evaluating the in  
47 vivo I/S potential of a TDS between T and R products to contact the Agency to discuss the  
48 proposed alternative approach to evaluate the I/S potential for that drug product.<sup>6</sup>  
49

50 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
51 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
52 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
53 the word *should* in Agency guidances means that something is suggested or recommended, but  
54 not required.  
55

## 56 57 **II. BACKGROUND** 58

59 The components and composition of a TDS formulation, including the nature of the drug  
60 substance and/or the degree to which the TDS materials occlude the transmission of water vapor  
61 from the skin, in conjunction with other factors such as the environmental humidity or the  
62 condition of the skin, may have the potential to irritate the skin or lead to a sensitization

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<sup>4</sup> 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>.

<sup>5</sup> 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.

<sup>6</sup> 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.

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63 reaction.<sup>7</sup> Such reactions can be unpleasant to the patient and may affect patient compliance,  
64 skin permeability, and/or adhesion of the TDS to the skin. The collective consequence of these  
65 potential effects could create uncertainty about the resulting drug delivery profile and uncertainty  
66 about the rate and extent of drug absorption from the TDS. Therefore, when appropriate,  
67 applicants should perform a comparative assessment of the T and R TDS products using an  
68 appropriately designed skin I/S study with human subjects to demonstrate that the potential for a  
69 skin irritation or sensitization reaction with the T TDS is no worse than the reaction observed  
70 with the R TDS (see General Considerations below for information about when such a study may  
71 be appropriate).

72  
73

### **III. GENERAL CONSIDERATIONS**

74  
75

76 Skin I/S studies are designed to compare the similarity between the T and R TDS products for  
77 the potential to cause irritation and/or sensitization reactions. A TDS may elicit these reactions  
78 in only some of the patients using the product, but even if the frequency of this occurrence were  
79 low, the adverse reactions could affect thousands of individuals. To evaluate this I/S potential,  
80 applicants should compare the T and R TDS products in at least 200 evaluable subjects (see  
81 section IV.A.), and the study should be conducted under provocative conditions (repeated  
82 removal and reapplication of the TDS on the same skin site) to maximize the potential for the  
83 occurrence of an irritation and/or sensitization reaction in the subject population during the  
84 study.

85

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

92

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

102

103 In addition to I/S reactions that may arise from the corrosive or immunomodulatory nature of  
104 formulation components or from the pharmacodynamic response of the skin to the occlusion by  
105 the TDS, the skin may also become irritated in response to the physical insults that can occur

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<sup>7</sup> 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.

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106 during the removal of a TDS. For example, if the adhesive properties of the TDS are such that it  
107 strips away substantial portions of the stratum corneum during removal, the damage to the skin  
108 barrier may lead to irritation at the site of TDS removal, which may also increase the potential  
109 for a sensitization reaction.

110

111

### **IV. COMBINED EVALUATIONS OF SKIN IRRITATION AND SENSITIZATION**

113

#### **A. Study Design and Conduct**

115

116 In general, the Agency recommends that applicants conduct an evaluator-blinded, randomized  
117 study to support their comparative evaluation of the skin I/S characteristics of the T and R  
118 products. The study population should typically include healthy males and nonpregnant,  
119 nonlactating females, unless product-specific considerations consistent with the RLD's labeled  
120 conditions of use for certain TDS products indicate otherwise.<sup>8</sup> In the study protocol, the choice  
121 of TDS strength intended to be used should be prespecified and should be justified, as  
122 appropriate, based upon the use of the TDS in the proposed study population.

123

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

128

129 (1) A 21-day induction phase, followed by a 14- to 17-day rest period

130 (2) A challenge phase<sup>9</sup>

131

132 During the induction phase, applicants should simultaneously apply all TDS units (i.e., every  
133 whole or partial<sup>10</sup> T product and every whole or partial R product) to each subject. T and R  
134 products should be applied at contralateral locations of the same anatomical site (e.g., T product  
135 on the left buttock and R product on the right buttock); applicants should select the anatomical  
136 site based on the recommendations for dosing in the RLD labeling.

137

- 138 • For 21 consecutive days, TDS units should be worn, removed, and replaced by a new  
139 TDS unit, for repeated durations to the same skin site as the initial application; each  
140 duration should be representative of the RLD's labeled wear period, unless otherwise  
141 noted within the relevant PSG. For example, a TDS with a 3-day wear period may be  
142 removed every 3 days, assessed for I/S, and replaced to the same skin site every 3 days,  
143 for a total of 21 days.

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<sup>8</sup> 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.

<sup>9</sup> 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.

<sup>10</sup> *Partial* refers to a matrix TDS that is cut into smaller sizes.

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144

145 • Applicants should evaluate the subject’s irritation response at the time of each TDS  
146 change by individually assessing the subject’s “dermal response” and “other effects”  
147 scores (both of which are described below) by using a separate scoring scale.  
148

149

150 • For subjects who experience excessive irritation,<sup>11</sup> the TDS may be moved to a new site  
151 to complete the 21-day induction phase and to continue with the sensitization part of the  
152 study. Applicants should predefine in their protocol what criteria would trigger the  
153 movement of a TDS to a new site (due to skin reactions that are determined to represent  
154 excessive irritation). For example, the criteria may specify that TDS may be moved to a  
155 new site if the combined score is equal to or greater than 3.

156 During the challenge phase, applicants should simultaneously apply all TDS units (i.e., every  
157 whole or partial T product and every whole or partial R product) to each subject. T and R  
158 products should be applied at contralateral locations of the same anatomical site (e.g., T product  
159 on the left buttock and R product on the right buttock); applicants should select the anatomical  
160 site based on the recommendations for dosing in the RLD labeling.  
161

162

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

165

166 • Applicants should assess the subject’s skin reactions at 30 minutes, 24 hours, 48 hours,  
167 and 72 hours after removal of the TDS.

168

169 • Applicants should record any skin reactions observed with a narrative description of the  
170 subject’s “dermal response” and “other effects” scores (both of which are described  
171 below) by using a separate scoring scale for each.

172

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

177

178 • For all subjects who exhibit a potential sensitization reaction, applicants should conduct a  
179 rechallenge test 4 to 8 weeks following the original challenge and conducted in the same  
180 manner as described above for the challenge phase.

181

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

---

<sup>11</sup> This score may vary for different TDS products or different scenarios.



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### 184 Scale 1. Dermal Response.

185

<b>Skin Appearance</b>	<b>Score</b>
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

186

### 187 Scale 2. Other Effects.

188

<b>Observation</b>	<b>Score (Numerical Equivalent)</b>
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)

189

190 When one or more “other effects” are observed, applicants should report each score as a dermal  
191 response number, a letter combination score, and as a numerical total (i.e., numerical “dermal  
192 response” score + numeric equivalent for the “other effects” lettered score). For example, the  
193 dermal response of 6 with glazing with fissure (F (3)) will equal to the score of 9. When no  
194 “other effects” are observed, score zero should be applied to an observed “other effects.”

195

196 Applicants intending to utilize an alternative scale other than these two scales should request a  
197 meeting with FDA to discuss the alternative scale and the proposed statistical analysis plan  
198 before conducting the study (i.e., submit a pre-ANDA meeting request).<sup>12</sup> If applicants use a  
199 scale other than these two scales (e.g., a single numerical scale that captures the progressive  
200 changes in skin reactions) to score the skin reactions observed, they should report each score  
201 according to their selected alternate scale as well as the score according to these two scales.

202

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

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<sup>12</sup> See footnote 7.

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207 or an overlay, skin irritation of the tape or overlay area should be reported separately from the  
208 skin irritation associated with the TDS application area.

209  
210 Applicants should evaluate adhesion of the TDS to the skin at each time point before TDS  
211 removal throughout the entire study period to monitor the adequacy of skin contact, which is  
212 necessary for a suitably provocative induction of I/S. Accordingly, even where tape or an  
213 overlay is used, adhesion should be evaluated based on the surface area of the TDS (not  
214 including any tape or overlay) to ensure that the TDS is adhering well throughout the induction  
215 phase and challenge phase. FDA’s recommendations for evaluating the adhesion of the TDS are  
216 described in the draft guidance for industry *Assessing Adhesion With Transdermal and Topical*  
217 *Delivery Systems for ANDAs* (April 2023).<sup>13</sup>

218  
219 If a TDS completely detaches, the subject should replace the new TDS within 24 hours and  
220 continue in the study. The subject should note the date and time of detachment as soon as it  
221 occurs, and applicants should maintain the source document generated by the subject (e.g.,  
222 subject diaries). If a TDS completely detaches for more than 24 hours during the 21-day  
223 induction phase, applicants should exclude the subject from both the irritation and sensitization  
224 analyses for that product unless the subject intentionally removed the TDS because of excessive  
225 irritation. If a TDS completely detaches for more than 24 hours during the 48-hour challenge  
226 phase, applicants should exclude the subject from the sensitization analysis unless the subject  
227 intentionally removed the TDS because of excessive irritation.

228  
229 For I/S studies, applicants should enroll an adequate number of subjects to ensure that at least  
230 200 evaluable subjects are included in their per protocol (PP) population; however, for irritation-  
231 only studies, the number of evaluable subjects in the PP population can vary (see details in  
232 Section B.1. for sample size determination for the conduct of irritation-only studies). Subjects  
233 should not apply makeup, creams, lotions, powders, alcohol, or other topical products to the skin  
234 area where the TDS will be placed because these products could affect the adhesive performance  
235 or irritation potential of the TDS. Also, the subject’s hair at the application site should be  
236 clipped (not shaved) before TDS application. In addition, applicants should advise subjects to  
237 avoid exposing the TDS application site to external sources of direct heat, such as heating pads,  
238 electric blankets, heat lamps, saunas, hot tubs, heated water beds, and/or prolonged direct  
239 sunlight.

240  
241 The following lists specify some inclusion and exclusion criteria that applicants can use to select  
242 test subjects; however, these lists are not exhaustive, and applicants can use other criteria to  
243 select subjects, as appropriate. Applicants should describe, as part of the protocol, the rationale  
244 for inclusion and/or exclusion criteria that are in addition to or different from those identified  
245 below.

246

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<sup>13</sup> When final, this guidance will represent the FDA’s current thinking on this topic.

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- 247       • Inclusion criteria:  
248  
249       – Healthy<sup>14</sup> male and female (nonpregnant, nonlactating) subjects between 18 and 65  
250       years of age (inclusive).  
251  
252       – Females of childbearing potential must be prepared to either abstain from sexual  
253       intercourse or use a reliable barrier method of contraception (e.g., female condom,  
254       diaphragm, intrauterine system, contraceptive sponge, or have their partner use a  
255       barrier method (condom with spermicide)) for at least 14 days before and throughout  
256       the duration of study or have used a hormonal method of contraception for at least 30  
257       days before the study and will continue to use the same type of hormonal  
258       contraceptive during the study.  
259
- 260       • Exclusion criteria:  
261  
262       – Subject is pregnant or lactating  
263  
264       – Medical history of significant dermatologic diseases or conditions, such as atopy,  
265       psoriasis, vitiligo, or conditions known to alter skin appearance or physiologic  
266       response (e.g., diabetes or porphyria)  
267  
268       – Medical history of a condition that would significantly influence the immune  
269       response (e.g., primary or acquired immunodeficiencies such as HIV or AIDS;  
270       allergic diseases such as anaphylaxis, asthma, or generalized drug reaction;  
271       neoplasms such as lymphoma or leukemia; rheumatoid arthritis; or systemic lupus  
272       erythematosus)  
273  
274       – Medical history of significant dermatologic cancers (e.g., melanoma or squamous cell  
275       carcinoma), except basal cell carcinomas that were superficial and did not involve the  
276       TDS application sites  
277  
278       – Within 3 weeks of the start of study treatment, use of medications or treatments that  
279       would either: (1) significantly influence or exaggerate responses to the T or R product  
280       or (2) alter the inflammatory or immune response to the T or R product (e.g.,  
281       cyclosporine, tacrolimus, systemic or topical corticosteroids, cytotoxic drugs, immune  
282       globulin, Bacillus Calmette-Guerin immunotherapy, monoclonal antibodies, or  
283       radiation therapy)  
284  
285       – Within 72 hours of the start of study treatment, use of antihistamines or use of topical  
286       drugs at the TDS site  
287  
288       – Subject has an obvious difference in skin color between arms or the presence of a  
289       skin condition, excessive hair at the application sites, scar tissue, tattoos, open sores, a

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<sup>14</sup> 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.

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290 recent sunburn, or body piercing that would interfere with the placement of the test  
291 articles, the skin assessment, or the subject's reactions to the TDS

292  
293 Applicants should provide a list of the prescription and over-the-counter drug products that will  
294 be contraindicated for subjects during the study, such as medications or treatments that would  
295 significantly influence or exaggerate the subject's responses to the T or R product or that would  
296 alter the subject's inflammatory or immune response to the product (e.g., antihistamines,  
297 systemic or topical corticosteroids, cyclosporine, tacrolimus, cytotoxic drugs, immune globulin,  
298 Bacillus Calmette-Guerin immunotherapy, monoclonal antibodies, or radiation therapy).

299  
300 In general, a subject's body movement should not be restricted during the study. For products  
301 with a wear period of up to or greater than 24 hours, the Agency recommends that subjects be  
302 permitted to bathe or shower routinely during the study, in a manner consistent with the labeled  
303 use of the RLD, and that the TDS should not be protected from direct exposure to water during  
304 such routine activities.

305  
306 Applicants should randomize their assignment of the T and R products to skin sites, describe  
307 their method of randomization in the protocol, and provide the randomization schedule as a SAS  
308 transport data set in XPT format.

309  
310 A trained observer should score the TDS's adherence and the subject's skin reactions at each  
311 TDS removal, and applicants should try to ensure that the same scorer is used for all  
312 observations. If the same scorer is not used for all observations, applicants should provide  
313 evidence to ensure that the scoring is consistent across different scorers. Because of likely  
314 differences in the appearance of the TDS between the T product and the R product, blinding of  
315 the observer may not be possible, especially for monitoring TDS adhesion, which requires direct  
316 observation of the TDS. However, applicants should try to blind the evaluation of I/S when  
317 possible.

318  
319 FDA's recommended primary endpoint for evaluating irritation is the mean irritation score  
320 (MIS). At each assessment time point for each subject and for each product, applicants should  
321 calculate a combined irritation score by adding the "dermal response" score and the numeric  
322 equivalent for "other effects" letter score. For each subject and each product, applicants should  
323 calculate the MIS as the sum of the combined irritation scores over the assessment time points  
324 divided by the total number of assessments.

325  
326 Applicants should submit descriptive irritation score data in a frequency table illustrating the  
327 number and proportion of each TDS unit with each combination of the dermal response  
328 numerical score and the "other effects" letter score at each evaluation time point. If a TDS is  
329 moved or removed because of excessive irritation, the last irritation score(s) observed at the  
330 original application site prior to removal is considered a reasonable representation of the degree  
331 of irritation with the TDS at that site for the remaining time points. This approach is referred to  
332 as the last observation carried forward (LOCF) from the original application site. The frequency  
333 table should reflect the irritation scores after the LOCF. The table below provides an example of  
334 a frequency table.

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335  
336 **Frequency of Irritation Scores for a Per-Protocol Population (Hypothetical Data) (N=153**  
337 **patches for T, and N=152 patches for R).**  
338

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.

339 **B. Considerations for Statistical Analyses**

340  
341 *1. Irritation Analysis*

342  
343 For an irritation analysis, applicants should define, in the protocol, their per-protocol (PP)  
344 population per TDS instead of per subject. The PP population should include all TDS units  
345 applied sequentially to the same anatomical site for the entire 21-day induction phase without  
346 any period of detachment longer than 24 hours. If a TDS is moved or removed because of  
347 excessive irritation, it should be included in the PP population, using the LOCF from the original  
348 application site.

349  
350 Applicants should compare the overall mean of the per-subject MIS (i.e., the primary endpoint  
351 described above) for the T and R products. To demonstrate the noninferiority (NI) of the T  
352 product compared to the R product with respect to the MIS, the T product should be shown to be  
353 statistically noninferior to the R product based on evaluating the difference in the T and R  
354 products’ overall mean MIS, with an NI margin of 0.20 ( $\delta = 0.20$ ). The NI margin of 0.20  
355 represents the difference of the mean MIS between the T and R products based on the irritation  
356 scales as previously described; this NI margin may not be appropriate to use for either the  
357 difference of the mean MIS based on other irritation scales or data transformations (e.g., a

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358 logarithmic transformation or the addition of a constant to all irritation scores) or the difference  
359 of the median MIS between the T and R products.

360

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

362

$$363 H_0: \mu_T - \mu_R \geq \delta$$

$$364 H_1: \mu_T - \mu_R < \delta$$

365

366 Here,  $\mu_T$  and  $\mu_R$  are the population means for the MIS for the T and R products, respectively, and  
367 the alternative hypothesis  $H_1$  represents the NI of the T product's irritation relative to the R  
368 product's irritation. These hypotheses can also be written as follows:

369

$$370 H_0: \mu_D \geq \delta$$

$$371 H_1: \mu_D < \delta$$

372

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

377

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

384

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

388

389 Incomplete data and data associated with noncompliance can seriously affect the validity of an  
390 NI study. Therefore, FDA recommends good study design and conduct to prevent patient  
391 dropout and noncompliance. If either occur, applicants should document, in detail, the reasons  
392 for the dropout and/or noncompliance. Although the FDA recommends using the PP population  
393 as the primary analysis population for NI studies, the Agency also has significant concerns with  
394 the possibility of informative dropout and non-compliance. If methods other than LOCF will be  
395 used to impute data for a TDS that is moved or removed due to excessive irritation, applicants  
396 should prespecify these imputation methods in their protocol. FDA recommends that applicants  
397 conduct a prespecified sensitivity analysis to evaluate the potential impact of any unbalanced or  
398 informative dropout and noncompliance on the conclusion of NI.

399

400 For the irritation evaluation, FDA also considers other clinically relevant data, including the  
401 number of TDS unit applications that reach a maximum irritation score and the number of  
402 subjects who discontinue product application because of excessive irritation. The same MIS

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403 could be reached with a small number of high scores (e.g., 3 or higher), which may be of greater  
404 clinical concern, or with a larger number of low scores (e.g., 1), which may be of lesser clinical  
405 concern. Thus, it is difficult to determine the clinical meaningfulness of a given MIS or a given  
406 difference between products with respect to their MIS.

407  
408 Therefore, in addition to MIS, FDA recommends the applicant evaluate the proportion of  
409 subjects with excessive irritation for each product. The proportion of subjects with excessive  
410 irritation should be no higher for the T product than for the R product, and irritation should not  
411 occur earlier in the application period for the T product than for the R product. The T product  
412 should be noninferior to the R product with respect to the MIS, and the T product should show  
413 no meaningful difference, compared to the R product, with respect to the degree of irritation.

414

### 415 2. *Sensitization Analysis*

416

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

419

420 The PP population for the sensitization analysis should include all TDS units worn (without any  
421 period of detachment longer than 24 hours) for the full 21-day induction phase and the entire 48-  
422 hour challenge phase. Each subject should return for at least one of the scheduled evaluations at  
423 48 and 72 hours after removal of the challenge TDS. If a TDS unit is removed before the end of  
424 the 48-hour challenge phase because of excessive irritation, the application site should be  
425 evaluated at 24 hours, 48 hours, and 72 hours after TDS removal and be included in the  
426 sensitization analysis using the LOCF from the original application site.

427

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

432

433 • The subject has at least one evaluation timepoint occurring at more than 24 hours (e.g., at  
434 48 or 72 hours) after the removal of the challenge phase TDS.

435

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

438

439 • If the subject completed a rechallenge phase, the above two criteria were met during both  
440 the challenge phase and the rechallenge phase.

441

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

446

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

449  
450 Applicants should provide descriptive statistics comparing both the number and the proportion of  
451 subjects potentially sensitized to each TDS unit and both the number and the proportion of  
452 subjects sensitized to each TDS unit.

453  
454 Applicants should provide a frequency table showing the number of applications of each TDS  
455 unit during the challenge phase, with each specific combined “dermal response” numerical score  
456 and “other effects” letter score at each evaluation time point.

457  
458 For all subjects with at least one combined irritation score of 2 or more at 48 or 72 hours after  
459 TDS removal in the challenge phase, applicants should provide a table showing the actual scores  
460 for each subject at each evaluation time point during the induction and challenge phases.

461  
462 In some circumstances, an *in vivo* sensitization evaluation of a TDS product may be unnecessary  
463 if adequate justification is provided or FDA has determined that conducting a sensitization  
464 assessment is unnecessary or unethical (e.g., where the active ingredient is known to be a skin  
465 sensitizer or based on information/data related to the components and composition of TDS  
466 product) to show that the T product is not likely to be more sensitizing than the R product.

### 467 468 **C. Vehicle TDS and Positive Control TDS**

469  
470 If safety concerns preclude the usual comparative studies, which include the use of the T and R  
471 products, the evaluation of skin I/S by the T product can be evaluated by testing a vehicle TDS  
472 versus a positive control TDS that produces mild irritation (e.g., less than or equal to 0.1 percent  
473 sodium lauryl sulfate). The vehicle TDS should contain all the inactive ingredients in the T  
474 product and be identical to the T product in every manner except for the absence of the active  
475 ingredient. If the inactive ingredients in the vehicle TDS are different than those contained in the  
476 T product or are in different amounts than in the T product, then the applicant should clearly  
477 describe the differences and provide data to show that the differences will not affect the safety of  
478 the T product or the applicant’s interpretation of the study results.

479  
480 For a skin I/S study that compares the vehicle TDS to a positive control TDS, applicants should  
481 utilize essentially the same approach as is recommended for the comparison of T and R products  
482 in sections IV.A. and B. of this guidance, except that the vehicle TDS should serve as the T  
483 product and the positive control TDS should serve as the R product.

484  
485 Applicants should ensure that the positive control is consistently able to elicit and maintain an  
486 irritation response during the induction phase. A positive control that is either unable to  
487 consistently elicit an irritation response, or unable to maintain that response, may confound the  
488 interpretation of study results and undermine the validity of the study.

489  
490 It is not recommended to include multiple candidate positive control TDS products in the I/S  
491 study and post-hoc select one as the positive control TDS to compare with the vehicle TDS in the



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

494

### **D. Partial (Cut) TDS**

496

497 If a safety concern prevents the simultaneous application of two whole TDS on the same subject  
498 during the 21-day combined I/S study, a matrix TDS can be cut to a smaller size.<sup>15</sup> In such  
499 situations, the T and R products should both have designs that can be safely cut to a smaller size.  
500 Applicants should not manufacture a separate batch of product to use a smaller TDS in this  
501 study. When using a cut TDS, the general recommendations provided in sections IV.A and IV.B  
502 in this guidance apply.

503

504

## **V. OVERALL ASSESSMENT OF ADVERSE EVENT DATA**

506

507 Applicants should include, in their analysis, all subjects who receive at least one dose of TDS.  
508 This analysis should include a comparison of all TDS units (e.g., the T product and the R  
509 product) with respect to any application site adverse events. Applicants should report all adverse  
510 events, including systemic adverse events. For any application site related adverse events,  
511 applicants should report whether or not the adverse event is related to the T product or the R  
512 product.

513

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

520

521

## **VI. FORMAT OF DATA SUBMISSIONS**

523

524 Applicants should refer to the Study Data for Submission to CDER web page<sup>16</sup> for information  
525 about data standards.

526

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

---

<sup>15</sup> The recommended cut size for a matrix TDS is product specific and included in the relevant PSG.

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