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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## *DRAFT GUIDANCE*

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

**October 2018  
Generic Drugs**

# 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)**

**October 2018  
Generic Drugs**

*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*Draft — Not for Implementation*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>**  
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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7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  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.  
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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  
20 exclusively to studies submitted in support of an abbreviated new drug application (ANDA).<sup>3</sup>  
21

22 In this guidance, the letter *T* (representing *Test*) will refer to proposed generic products that are  
23 the subject of an ANDA, and the letter *R* (representing *Reference*) will refer to the reference  
24 listed drug and/or reference standard product.  
25

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

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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 product.

<sup>4</sup> 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>.

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33 bioequivalence of a proposed generic TDS drug product to its reference listed drug and/or  
34 reference standard product.

35  
36 In general, FDA's guidance documents do not establish legally enforceable responsibilities.  
37 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only  
38 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
39 the word *should* in Agency guidances means that something is suggested or recommended, but  
40 not required.

41  
42

### **II. BACKGROUND**

44

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

56  
57

### **III. GENERAL CONSIDERATIONS**

58  
59

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

69

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

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

87

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

91

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

93

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

95

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

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

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

108

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

114

- 115 • For 21 consecutive days, TDS units should be worn, removed, and replaced by a new  
116 TDS unit, for repeated durations to the same skin site as the initial application; each  
117 duration should be representative of the labeled wear period. For example, a TDS with a  
118 3-day wear period may be removed every 3 days, assessed for I/S, and replaced to the  
119 same skin site every 3 days, for a total of 21 days.
- 120 • Applicants should evaluate the subject's irritation response at the time of each TDS  
121 change by individually assessing the subject's "dermal response" and "other effects"  
122 scores (both of which are described below) by using a separate scoring scale.
- 123

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- 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.**

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<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 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

159

160

161

### Scale 2. Other Effects

162

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

163

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

168

169 When no “other effects” are observed, score zero should be applied to an observed “other  
170 effects.”

171

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

178

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



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182 evaluating the adhesion of the TDS is described in the draft guidance for industry *Assessing*  
183 *Adhesion With Transdermal and Topical Delivery Systems for ANDAs*.<sup>5</sup>

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

190  
191 If a TDS completely detaches, the subject should replace the new TDS within 24 hours and  
192 continue in the study. The subject should note the date and time of detachment as soon as it  
193 occurs, and applicants should maintain the source document generated by the subject (e.g.,  
194 subject diaries). If a TDS completely detaches for more than 24 hours during the 21-day  
195 induction phase, applicants should exclude the subject from both the irritation and sensitization  
196 analyses for that product unless the subject intentionally removed the TDS because of excessive  
197 irritation. If a TDS completely detaches for more than 24 hours during the 48-hour challenge  
198 phase, applicants should exclude the subject from the sensitization analysis.

199  
200 For I/S studies, applicants should enroll an adequate number of subjects to ensure that at least  
201 200 evaluable subjects are included in their per protocol (PP) population; however, for irritation-  
202 only studies, the number of evaluable subjects in the PP population can vary. Subjects should not  
203 apply makeup, creams, lotions, powders, alcohol, or other topical products to the skin area where  
204 the TDS will be placed because these products could affect the adhesive performance or irritation  
205 potential of the TDS. Also, the subject's hair at the application site should be clipped (not  
206 shaved) before TDS application. In addition, applicants should advise subjects to avoid exposing  
207 the TDS application site to external sources of direct heat, such as heating pads, electric blankets,  
208 heat lamps, saunas, hot tubs, heated water beds, and/or prolonged direct sunlight.

209  
210 The following lists specify some inclusion and exclusion criteria that applicants can use to select  
211 test subjects; however, these lists are not exhaustive, and applicants can use other criteria as  
212 desired to select subjects. Applicants should describe, as part of the protocol, the rationale for  
213 inclusion and/or exclusion criteria that are in addition to or different from those identified below.

214  
215 • Inclusion criteria:

- 216  
217 - Healthy male and female (nonpregnant, nonlactating) subjects between 18 and 65  
218 years of age (inclusive)  
219  
220 - Females of childbearing potential must be prepared to either abstain from sexual  
221 intercourse or use a reliable barrier method of contraception (e.g., condom with  
222 spermicide, diaphragm, IUD, contraceptive sponge) for at least 14 days before and  
223 throughout the duration of study or have used a hormonal method of contraception for

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<sup>5</sup> 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>

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

226

227 • Exclusion criteria:

228

229 – Subject is pregnant or lactating

230

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

234

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

240

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

244

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

250

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

253

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

258

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

265

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

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

271  
272 Applicants should randomize their assignment of the T and R products to skin sites, describe  
273 their method of randomization in the protocol, and provide the randomization schedule as an  
274 SAS transport data set in XPT format.

275  
276 A trained observer should score the TDS’s adherence and the subject’s skin reactions at each  
277 TDS removal, and applicants should try to ensure that the same scorer is used for all  
278 observations. If the same scorer is not used in all observations, the applicants should provide the  
279 evidence to ensure the scoring is consistent across different scorers. Because of likely differences  
280 in the appearance of the TDS between the T product and the R product, blinding of the observer  
281 may not be possible, especially for monitoring TDS adhesion, which requires direct observation  
282 of the TDS. However, applicants should try to blind the evaluation of I/S when possible.

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

289  
290 Applicants should submit descriptive irritation score data in a frequency table illustrating the  
291 number and proportion of each TDS unit with each combination of the dermal response  
292 numerical score and the “other effects” letter score at each evaluation time point. If a TDS is  
293 moved or removed because of excessive irritation, the irritation score(s) observed at the original  
294 application site at the time of removal should be considered as the irritation score(s) for the  
295 remaining time points. This approach is referred to as the last observation carried forward  
296 (LOCF) from the original application site. The frequency table should reflect the irritation scores  
297 after the LOCF. The table below provides an example of a frequency table.

298  
299 **Frequency of Irritation Scores for a Per-Protocol Population (Hypothetical Data)**

Day: TDS	<b>“Dermal Response” and “Other Effects” Scores</b>															
	<b>0</b>		<b>0A *</b>		<b>1**</b>		<b>1A</b>		<b>2</b>		<b>2A</b>		<b>3</b>		<b>4</b>	
	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

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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.

### 300 **B. Considerations for Statistical Analyses**

301

#### 302 *1. Irritation Analysis*

303

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

310

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

321

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

323

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

325

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

326

327 Here,  $\mu_T$  and  $\mu_R$  are the population means for the MIS for the T and R products, respectively, and  
328 the alternative hypothesis  $H_1$  represents the NI of the T product’s irritation relative to the R  
329 product’s irritation.

330

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

334

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

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339 Incomplete data and data associated with noncompliance can seriously affect the validity of an  
340 NI study. Therefore, FDA recommends good study design and conduct to prevent patient  
341 dropout and noncompliance. If either occur, applicants should document, in detail, the reasons  
342 for the dropout and/or noncompliance. Although the FDA recommends using the PP population  
343 as the primary analysis population for NI studies, the Agency also has significant concerns with  
344 the possibility of informative dropout and non-compliance. Applicants should prespecify, in their  
345 protocol, the imputation methods used (if applicable). FDA recommends that applicants conduct  
346 a prespecified sensitivity analysis to evaluate the potential impact of any unbalanced or  
347 informative dropout and noncompliance on the conclusion of NI.  
348

349 For the irritation evaluation, FDA also considers other clinically relevant data, including the  
350 number of TDS unit applications that reach a maximum irritation score and the number of  
351 subjects who discontinue product application because of excessive irritation. The same MIS  
352 could be reached with a small number of high scores (e.g., 3 or higher), which may be of greater  
353 clinical concern, or with a larger number of low scores (e.g., 1), which may be of lesser clinical  
354 concern. Thus, it is difficult to determine the clinical meaningfulness of a given MIS or a given  
355 difference between products with respect to their MIS.  
356

357 Therefore, in addition to MIS, FDA recommends the applicant evaluate the proportion of  
358 subjects with excessive irritation for each product. The proportion of subjects with excessive  
359 irritation should be no higher for the T product than for the R product, and irritation should not  
360 occur earlier in the application period for the T product than for the R product. The T product  
361 should be noninferior to the R product with respect to the MIS, and the T product should show  
362 no meaningful difference, compared to the R product, with respect to the degree of irritation.  
363

### 364 2. *Sensitization Analysis*

365  
366 Applicants should define, in the protocol, the PP population for the sensitization analysis per  
367 TDS instead of per subject.  
368

369 The PP population for the sensitization analysis should include all TDS units worn (without any  
370 period of detachment longer than 24 hours) for the full 21-day induction phase and the entire 48-  
371 hour challenge phase. Each subject should return for at least one of the scheduled evaluations at  
372 48 and 72 hours after removal of the challenge TDS. If a TDS unit is removed before the end of  
373 the 48-hour challenge phase because of excessive irritation, the application site should be  
374 evaluated at 24 hours, 48 hours, and 72 hours after TDS removal and be included in the  
375 sensitization analysis using the LOCF from the original application site.  
376

377 For each TDS unit, each PP subject with a combined score of 2 or greater at 48 or 72 hours after  
378 TDS removal during the challenge phase should be individually evaluated for potential  
379 sensitization. Applicants should consider a subject *potentially sensitized* if all the following  
380 criteria are met:  
381

- 382 a. The subject has at least one evaluation timepoint occurring at more than 24 hours (e.g., at  
383 48 or 72 hours) after the removal of the challenge phase TDS.

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

386 c. The above two criteria were met during both the challenge phase and the re-challenge  
387 phase, if the subject completed a re-challenge phase.  
388

389 Skin reactions that resolve before 48 hours are generally considered to be caused by irritation  
390 instead of sensitization. For any potential sensitization reaction observed during the challenge or  
391 re-challenge phase, applicants should provide a justification to support that the rate of  
392 sensitization of the T product is comparable to that observed with the use of the R product.  
393

394 Applicants should report the respective numbers of subjects considered to be potentially  
395 sensitized to the T and/or R products.  
396

397 Applicants should provide descriptive statistics comparing both the number and the proportion of  
398 subjects potentially sensitized to each TDS unit and both the number and the proportion of  
399 subjects sensitized to each TDS unit.  
400

401 Applicants should provide a frequency table showing the number of applications of each TDS  
402 unit during the challenge phase, with each specific combined “dermal response” numerical score  
403 and “other effects” letter score at each evaluation time point.  
404

405 For all subjects with at least one combined irritation score of 2 or more at 48 or 72 hours after  
406 TDS removal in the challenge phase, applicants should provide a table showing the actual scores  
407 for each subject at each evaluation time point during the induction and challenge phases.  
408

409 For TDS products that are known to be skin sensitizers (e.g., methylphenidate TDS), a  
410 sensitization evaluation may be unnecessary if justifications are provided (e.g., related to  
411 components and the composition of TDS products) to show that the T product is not likely to be  
412 more sensitizing than the R product.  
413

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

414  
415  
416 If safety concerns preclude the usual comparative studies, which include the use of the T and R  
417 products, the I/S potential of the active ingredient can be assumed to be reasonably equivalent  
418 between the T and R products, and the evaluation of skin I/S by the T product can be evaluated  
419 by testing a vehicle TDS versus a positive control TDS that produces mild irritation (e.g.,  $\leq 0.1\%$   
420 sodium lauryl sulfate). The vehicle TDS should contain all of the inactive ingredients in the T  
421 product and be identical to the T product in every manner except for the absence of the active  
422 ingredient. If the inactive ingredients in the vehicle TDS are different than those contained in the  
423 T product or are in different amounts than in the T product, then the applicant should clearly  
424 describe the differences and provide data to show that the differences will not affect the safety of  
425 the T product or the applicant’s interpretation of the study results.  
426

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

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

431

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

432

433  
434 If a safety concern prevents the simultaneous application of two whole TDS on the same subject  
435 during the 21-day combined I/S study, a matrix TDS can be cut to a smaller size. In such  
436 situations, the T and R products should both have designs that can be safely cut to a smaller size.  
437 Applicants should not manufacture a separate batch of product to use a smaller TDS in this  
438 study. When using a cut TDS, the general recommendations provided in sections III.A and III.B  
439 in this guidance apply.

440

441

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

442

443  
444 Applicants should include, in their analysis, all subjects who receive at least one dose of TDS.  
445 This analysis should include a comparison of all TDS units (e.g., the T product and the R  
446 product) with respect to any application site adverse events. Applicants should report all adverse  
447 events, including systemic ones, whether or not applicants consider them to be related to the T  
448 product or the R product.

449

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

456

457

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

458

459  
460 Applicants should refer to the Study Data for Submission to CDER web page<sup>6</sup> for information  
461 about data standards.

462

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

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<sup>6</sup> This web page is available at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.