# Assessing Adhesion With 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

# Assessing Adhesion With 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)

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# Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs Guidance for Industry<sup>1</sup>

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

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## I. INTRODUCTION

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16 The recommendations in this guidance relate exclusively to studies submitted in support of an abbreviated new drug application (ANDA).<sup>2</sup> This guidance provides recommendations for the 17 design and conduct of studies evaluating the adhesive performance of a transdermal or topical 18 19 delivery system (collectively referred to as TDS<sup>3</sup>). Depending on the objectives of a TDS 20 product development program, applicants may choose to evaluate TDS adhesion in studies 21 performed to evaluate TDS adhesion only or in studies performed with a combined purpose (e.g., 22 for the simultaneous evaluation of adhesion and bioequivalence (BE) with pharmacokinetic (PK) 23 endpoints). 24

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 a reference listed

the subject of an ANDA, and the letter *R* (drug and/or reference standard product.

28

<sup>&</sup>lt;sup>1</sup> This guidance has been prepared by the Office of Research and Standards in the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with CDER's Office of New Drugs and Office of Pharmaceutical Quality at the Food and Drug Administration.

<sup>&</sup>lt;sup>2</sup> The recommendations for studies characterizing TDS adhesion in a new drug application or a supplemental new drug application may be different than those submitted in support of an ANDA and may involve the assessment of different ages and strengths of the TDS product, potentially dosed to different anatomical sites. Also, the design, conduct, and assessment of TDS adhesion in studies supporting a new drug application are inherently different because TDS adhesion in that context is not typically evaluated in relation to a reference product.

<sup>&</sup>lt;sup>3</sup> The acronym *TDS* refers to both transdermal delivery systems and topical delivery systems and includes products that may described elsewhere or known as *patches*, *topical patches*, or *extended release films*.

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29 FDA recommends that applicants consult this guidance in conjunction with any relevant product-

30 specific guidances<sup>4</sup> and in conjunction with any relevant guidances for industry<sup>5</sup>, when

31 considering the design and conduct of studies that may be appropriate to support the BE of a

32 proposed generic TDS product to its reference listed drug and/or reference standard product.

FDA also recommends that applicants routinely refer to FDA's website<sup>6</sup>, since additional
 guidances may become available that could assist in the development of a generic TDS product.

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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

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.

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# 41

# II. BACKGROUND

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45 The amount of drug delivered into and through the patient's skin from a TDS is dependent, in 46 part, on the surface area dosed. It is expected that the entire contact surface area of a TDS should 47 remain consistently and uniformly adhered to the patient's skin throughout the duration of wear 48 under the conditions of use included in the product labeling. When a TDS loses its adherence

49 during wear, the amount of drug delivered to the patient may be reduced.

50

51 During the product's labeled wear period, a TDS is reasonably expected to encounter torsional

52 strains arising from body movements, changes in environmental temperature or humidity such as

53 the daily exposure to water (e.g., during routine showering), and contact with clothing, bedding

54 or other surfaces. TDS products that do not maintain consistent and uniform adhesion with the

skin during the labeled wear period can experience varying degrees of TDS detachment,
 including complete detachment, at different times during the product wear.

57

When the adhesion characteristics of a TDS are not sufficiently robust, as evaluated against its
labeled conditions of use, the TDS may exhibit variability in the surface area that is in contact

60 with the skin. For example, when a TDS is partially detached, there may be uncertainty about the

61 resulting drug delivery profile and, hence, uncertainty about the rate and extent of drug

absorption from the TDS. When the potential for complete detachment of the TDS increases, the

risk of unintentional exposure of the drug product to an unintended recipient (e.g., a household

64 member who may be a child) also increases.

65 66

 $\underline{http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.}$ 

<sup>&</sup>lt;sup>4</sup> Generic drug product-specific guidances are available at the Product-Specific Guidances for Generic Drug Development web page at

<sup>&</sup>lt;sup>5</sup> For example, a relevant guidance for industry is the draft guidance for industry: *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems Submitted in ANDAs*. When final, these guidances will represent the FDA's current thinking on these topics.

<sup>&</sup>lt;sup>6</sup> For newly-posted draft guidances, or the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/regulatoryinformation/guidances/default.htm.

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# 67 III. EVALUATION OF ADHESION

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# A. Study Design and Conduct

In general, the Agency recommends that applicants design their adhesion studies to support a
 comparative evaluation of the adhesion characteristics of the T and R TDS.

73

FDA recommends that applicants use a single-dose, randomized, two-treatment, two-period

75 crossover study design where all subjects are dosed with the same strength of the T and R TDS.

However, FDA may also consider the acceptability of a study using a single-period, two treatment-per-subject design, with the site of application randomized, if applicants appropriately

77 ideathent-per-subject design, with the site of application randomized, if applicants appropriately 78 justify their parallel dosing study design. The population for the TDS adhesion study should

79 typically be the same as the population enrolled, or recommended for enrollment, in the PK BE

study for the product and should typically include healthy males and non-pregnant, non-lactating

81 females unless product-specific considerations indicate otherwise.

82

Applicants should randomize subjects to receive either the T or R TDS product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.

86

87 Because alterations in the product design, the active or inactive ingredients, the backing

88 membrane, or the manufacturing process can affect the adhesion properties of a TDS, the study

89 should utilize the to-be-marketed TDS product.<sup>7</sup> Post-approval changes to the TDS may

90 necessitate confirmation that product quality attributes related to adhesion remain consistent with

91 the product quality attributes characterized for the TDS product that demonstrated acceptable

- 92 adhesion.
- 93

94 Unless otherwise justified, when conducting an adhesion study, applicants should utilize the

95 specific size/strength of the TDS that is recommended in the applicable product-specific

96 guidance. A larger TDS may be more sensitive to detachment than a smaller one because the

97 larger TDS may be subjected to greater conformational or torsional strains arising from

98 potentially increased anatomical curvatures or from a greater magnitude of flexion across

relatively greater anatomical distances across which the larger TDS may be adhered. It may also

100 be possible for applicants to assess an adhesion score more precisely with a larger TDS than with

- 101 a smaller one.
- 102

Applicants should not use an overlay or a cover for blinding because the overlay or cover mayaffect the product's performance.

105

106 Applicants should evaluate the adhesion of each TDS at multiple adhesion time points following

107 application of the TDS to provide a sufficient temporal resolution to adequately compare the

adhesion characteristics of the T and the R TDS throughout the duration of wear. For example,

the adhesion of a TDS with a 7-day wear period should be assessed at least daily and at equally

spaced time points (e.g., 24 hours (hrs), 48 hrs, 72 hrs, 96 hrs, 120 hrs, 144 hrs, and 168 hrs); the

<sup>&</sup>lt;sup>7</sup> See 21 CFR 320.21(b).

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adhesion of a TDS with 72-hour wear period should be assessed at least every 12 hours (e.g., at 111 112 12 hrs, 24 hrs, 36 hrs, 48 hrs, 60 hrs, and 72 hrs); the adhesion of a TDS with a wear period between 12 and 24 hours should be assessed at least every 4 hours; and the adhesion of a TDS 113 114 with a wear period of less than 12 hours should be assessed at least hourly. 115 116 In addition, applicants should typically distribute these time points in a uniform manner, equally 117 spaced throughout the entire labeled wear period because the mean adhesion score that is 118 calculated from the individual assessments is intended to be representative of the entire wear 119 period. For some TDS, adhesion during the earlier period of wear may be better than during the 120 later period of wear; therefore, a greater number of adhesion assessments early in the TDS wear 121 period may (1) disproportionately weight the calculation of the mean adhesion score by over-122 representing the adhesion assessments during the initial period when TDS adhesion might be 123 relatively better and (2) inappropriately decrease the mean adhesion score in a manner that is not 124 representative of the entire wear duration for that TDS. 125 126 For the comparative assessment of adhesion (i.e., for the noninferiority (NI) test described in 127 section III.B of this guidance), applicants should use the following five-point adhesion scale, in 128 which each score corresponds to a specified range of adhered surface area for the TDS: 129 130  $0 = \ge 90\%$  adhered (i.e., the TDS has essentially no lift off the skin) 131 132 1 = 275% to < 90% adhered (e.g., only some edges of the TDS lift off the skin) 133 134 2 = 50% to < 75% adhered (i.e., less than half of the TDS lifts off the skin) 135 3 = >0% to < 50% adhered (i.e., the TDS is not detached, but more than half of it lifts off the 136 137 skin without falling off) 138 139 4 = 0% adhered (i.e., the TDS is detached and is completely off the skin) 140 141 When recording measurements of TDS adhesion, applicants may use appropriate methods (e.g., a 142 trained visual assessment and/or dot matrix templates) and alternative scales (other than the five-143 point adhesion scale described above) to estimate the percentage of the entire TDS surface area 144 that is adhered to the skin. If applicants use a scale different than the five-point adhesion scale 145 described above to record TDS adhesion measurements, they should report each TDS adhesion 146 measurement as both the score according to the selected scale as well as the corresponding score 147 according to the five-point adhesion scale. For example, if the observer scores the TDS adhesion 148 as a two on the five-point scale, and estimates that the product appears to be 60 percent adhered, 149 a score of two and the estimate of 60 percent should both be reported for that time point. 150 Information and/or analyses based upon scores from the alternative scale may be considered as 151 supportive information, provided that the use of the alternative scale is justified and that 152 information is submitted with the study to demonstrate that the scale has been adequately 153 qualified. When recording measurements of TDS adhesion, applicants should also record 154 photographic evidence showing the TDS as it is adhered to the skin (or completely detached and 155 absent from the skin) and submit photographs for each time point when TDS adhesion is 156 assessed.

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158 With each consecutive TDS adhesion measurement at each time point, applicants should record

159 the score based upon the actual measurement of TDS adhesion at that timepoint (not carrying

160 forward a score from a previous time point), regardless of whether the score increases or

decreases relative to the preceding score. TDS adhesion measurements should be made

162 independently, with the observer blinded to the previous measurement.

163

164 However, when analyzing the results for the comparative assessment of adhesion (i.e., for the NI

test described in section III.B of this guidance), the highest adhesion score using the five-point

adhesion scale described above (i.e., the score representing the greatest degree of detachment for that TDS) assessed at any time point after the baseline or time<sub>0</sub> should be used for subsequent

168 time points until a higher score is assessed. For a TDS that completely detaches, a score of 4

169 should be assigned for any remaining assessments scheduled for that TDS across the study

- 170 duration.
- 171

172 Applicants should use the mean adhesion score,  $\overline{X}$ , as the primary endpoint for evaluating TDS

adhesion. For a TDS, the mean adhesion score,  $\bar{X}$ , should be derived from its individual adhesion

scores at each assessment time point, averaged across all the equally spaced time points (except

the baseline time point,  $t_0$ ). Let  $\bar{x}$  denote the observed mean adhesion score for a TDS across *n* equally spaced time points after the baseline. It can be calculated as follows:

177

$$ar{x} = \sum_{i=1}^n x_i/n$$

179

178

180 Here, is the observed mean adhesion score for a TDS across equally spaced time points after the 181 baseline and  $x_i$  is the observed adhesion score at the *i*<sup>th</sup> measurement for a TDS.

182

183 Despite the recommendation in this guidance to distribute time points in a uniform, equally 184 spaced manner, if the data set contains scores from unequally spaced time points, a weighted 185 average  $\bar{X}_w$ , with weights corresponding to interval length, may be calculated as follows:

- 186
- 187

$$\bar{x}_w = \sum_{i=1}^n w_i x_i = \frac{\sum_{i=1}^n (t_i - t_{i-1}) x_i}{D}$$
, where  $w_i = \frac{(t_i - t_{i-1})}{D}$ 

188 189

Here,  $\bar{x}_w$  is the observed weighted mean adhesion score for a TDS across *n* unequally spaced time points after the baseline,  $x_i$  is the observed adhesion score at the *i*<sup>th</sup> measurement,  $w_i$  is the corresponding weight for  $x_i$ , *D* is the total duration of wear,  $t_i$  is the *i*<sup>th</sup> measurement time, and  $t_{i-1}$  is the preceding  $(i-1)^{th}$  measurement time. Because of the potential round-off error of computer software, FDA recommends that applicants calculate the sum in the numerator first,  $\sum_{i=1}^{n} (t_i - t_{i-1}) x_i$ , and then divide that sum by the total duration *D*.

- 197 For example, for a 24-hour-wear TDS, if an applicant measured adhesion at hours 2, 4, 8, 12, and
- 198 24 after the baseline, the total duration of wear would be 24 hours. The coefficient  $(t_i t_{i-1})$
- 199 corresponding to the  $i^{\text{th}}$  measurement  $x_i$  (i = 1, 2, 3, 4, 5) would be (2-0), (4-2), (8-4), (12-8), and

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200 201 202 203	(24-12) respectively. The weighted mean $\bar{x}_w$ can be calculated by summing $\sum_{i=1}^{5} (t_i - t_{i-1}) x_i$ first, then dividing the sum by the total duration $D$ (i.e., in this example, 24 hours). The corresponding weights for all five measurements would be $\frac{1}{12}, \frac{1}{12}, \frac{1}{6}, \frac{1}{6}$ , and $\frac{1}{2}$ , which add up to 1.
204	In addition to the primary endpoint, FDA recommends that applicants perform the following
205	descriptive analyses for the evaluation of TDS adhesion (using the five-point adhesion scale
206	described above) to assess possible treatment group differences in potentially clinically
207	meaningful values or events:
208	
209	1. Proportion of subjects with an adhesion score $\geq 2$ at any time point, compared between T
210	and R
211	
212	2. Proportion of subjects with their T mean adhesion score greater than the corresponding R
213	mean adhesion score by 1 or more, compared to the proportion of subjects with their R
214	mean adhesion score greater than the corresponding T mean adhesion score by 1 or more.
215	
216	3. Time to an adhesion score $\geq 2$ compared between T and R. If there are a sufficient
217	number of events, a Kaplan Meier cumulative incidence curve can be plotted.
218	
219	In addition, applicants should submit descriptive adhesion score data in a frequency table
220	illustrating the number and the proportion of the T and the R TDS with each adhesion score at
221	each evaluation time point and across all time points. An example of such a frequency table is
222	shown below:
223	

224

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

Time Point	T Score (N=100) n (%)					R Score (N=100) n (%)						
	0	1	2	3	4	Mean	0	1	2	3	4	Mean
1	95 (95)	5 (5)	0 (0)	0 (0)	0 (0)	0.05	82 (82)	16 (16)	2 (2)	0 (0)	0 (0)	0.20
2	90 (90)	10 (10)	0 (0)	0 (0)	0 (0)	0.10	68 (68)	30 (30)	2 (2)	0 (0)	0 (0)	0.34
3	87 (87)	13 (13)	0 (0)	0 (0)	0 (0)	0.13	57 (57)	41 (41)	2 (2)	0 (0)	0 (0)	0.45
4	86 (86)	14 (14)	0 (0)	0 (0)	0 (0)	0.14	46 (46)	51 (51)	3 (3)	0 (0)	0 (0)	0.57
5	85 (85)	15 (15)	0 (0)	0 (0)	0 (0)	0.15	42 (42)	55 (55)	2 (2)	1 (1)	0 (0)	0.62
All	443 (88.6)	57 (11.4)	0 (0)	0 (0)	0 (0)	0.11	295 (59.0)	193 (38.6)	11 (2.2)	1 (0.2)	0 (0)	0.44

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Applicants should note that both the T and the R TDS should be administered to study subjects 226 227 in the manner described by the R product label, and TDS adhesion should be assessed throughout 228 the maximum labeled duration of wear for the R product. In general, movement of study subjects 229 should not be restricted during the study; instead, subjects should be allowed to freely conduct 230 normal activities within the study unit and/or at home (e.g., to perform real-world activities like 231 showering) that may reasonably be expected to occur during the labeled duration of use for the 232 product. For products with a wear period of up to or greater than 24 hours, FDA recommends 233 that subjects be permitted to bathe or shower routinely during the study, in a manner consistent 234 with the labeled use of the product, and that the TDS should not be protected from direct 235 exposure to water during such routine activities. 236 237 Generally, applicants should use only whole, intact T and R TDS for their assessment of 238 comparative adhesion performance because altering the size or shape of the TDS may alter its 239 adhesion characteristics. 240 241 Applicants should include provisions in their study protocol to ensure that deliberate actions with 242 the intent to reapply a detached area of the TDS, to apply pressure to the TDS, or to reinforce 243 TDS adhesion with the skin (e.g., overlays) are avoided throughout the study. The study protocol 244 should include provisions to ensure that TDS detachment is not inappropriately inhibited (e.g., 245 by the constant pressure of a chair back on the TDS). 246 247 Subjects should not apply makeup, creams, lotions, powders, or other topical products to the skin 248 area where the TDS will be placed because they could affect adhesive performance. Also, hair at 249 the application site should be clipped (not shaved) before TDS application and/or the site should 250 be prepared in a manner consistent with the labeled use of the TDS. 251 252 Applicants should describe the method of randomization in the study protocol and provide the 253 randomization schedule as a SAS transport data set in XPT format. (Note that the randomization 254 in this context refers to the sequence, not the treatment.) FDA recommends that an independent 255 third party generate and hold the randomization code throughout the conduct of the study to 256 minimize bias. However, applicants may generate the randomization code if they are not 257 involved in the packaging and labeling of the study medication. Applicants should ensure that a 258 sealed copy of the randomization scheme is retained at the study site, and this sealed copy should 259 be available to FDA investigators at the time of site inspection to allow for verification of the 260 treatment identity for each application site on each subject.

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## **B.** Considerations for Statistical Analysis

264 Applicants should prespecify the per-protocol (PP) population for the adhesion analysis, and 265 define it per TDS for each subject. The PP population for the adhesion analysis should include 266 all TDS except those that were intentionally removed early in the study (e.g., because of unacceptable irritation) or those that were on subjects who discontinued use of the TDS before 267 268 the end of the labeled duration of wear for reasons unrelated to adhesion (e.g., because of a 269 protocol violation). Applicants should include individual case reports describing any subjects 270 who were excluded from the PP population, and the reasons for their exclusion, in their study 271 report.

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272 273 Applicants should compare the means of the per treatment group mean adhesion scores (i.e., the 274 primary endpoint described above) for the T and R products. To calculate the mean adhesion 275 score, applicants should carry forward the highest adhesion score at each time point after the 276 baseline time point  $(t_0)$  for subsequent time points until a higher score is assessed. To 277 demonstrate adequate product adhesion, applicants should show that the T product is statistically 278 noninferior to the R product based upon evaluating the difference in the T and R overall mean 279 adhesion scores, with an NI margin of 0.15 ( $\delta = 0.15$ ). The NI margin of 0.15 applies to the 280 difference of the mean adhesion scores between the T and R products based on the five-point 281 adhesion scale previously described; the NI margin of 0.15 does not apply to the difference of 282 the mean adhesion scores based on other adhesion scales or non-location-based data 283 transformations (e.g., a logarithmic transformation) or the difference of median adhesion scores 284 between T and R. 285 Applicants should test the following hypotheses at the significance level of 0.05: 286 287  $H_0: \mu_T - \mu_R \ge \delta$  $H_1: \mu_T - \mu_R < \delta$ 288 289 290 291 Here,  $\mu_T$  and  $\mu_R$  are the population means for the mean adhesion score for the T and R products, 292 respectively, and the alternative hypothesis  $H_1$  represents the NI of the T product's adhesion relative to the R product's adhesion. 293 294 295 To demonstrate acceptable adhesion of the T product, applicants should design and conduct an 296 adhesion study as described above and enroll a sufficient number of subjects to power the study 297 at a level of 0.80 or higher. Because of the discrete nature of adhesion scales and other potential 298 complications of the adhesion data, FDA recommends that applicants use a larger sample size 299 than what might ordinarily be calculated (under standard assumptions) to ensure the validity of 300 any large-sample (asymptotic) Gaussian assumptions, if used. 301 302 Incomplete data and data associated with noncompliance can compromise the validity of an NI study. FDA recommends good clinical study design and conduct to prevent patient dropout and 303 304 noncompliance. Nonetheless, when these events occur, applicants should document the detailed 305 reasons for these events. Although the FDA recommends using the PP population as the primary 306 analysis population for NI studies, the Agency also has significant concerns with the possibility 307 of informative dropout and noncompliance. If applicable, applicants should prespecify 308 imputation methods in their protocol. FDA recommends that applicants conduct a prespecified 309 sensitivity analysis to evaluate the potential impact of any unbalanced or informative dropout 310 and noncompliance on the conclusion of the NI in adhesion. 311

- 312
- 313 IV. COMBINED EVALUATION OF ADHESION AND BIOEQUIVALENCE
- 314

315 If applicants elect to conduct a study evaluating both the adhesion performance and the PK BE of

- the T and R products in a single study, this study should be conducted in a population of
- 317 sufficient size to adequately power the comparative evaluation of adhesion and to include a

- Draft Not for Implementation 318 subpopulation of subjects of sufficient size to adequately power the evaluation of BE with 319 appropriately selected PK endpoints. Applicants should select the participants for the PK BE 320 evaluation according to a randomization scheme prespecified in the protocol. 321 322 The study design and conduct recommendations described in section III.A of this guidance, for a 323 study performed exclusively for the purpose of evaluating TDS adhesion, also apply to a 324 combined study evaluating adhesion and BE with PK endpoints. 325 326 The simultaneous application of multiple T TDS or of multiple R TDS to a subject may be 327 appropriate in a combined study of TDS adhesion and PK BE when doing so is safe and justified, 328 for example, by the potential need for increased drug delivery to compensate for an insufficient 329 analytical sensitivity to measure the relevant analyte(s) in the PK samples. In such cases, when 330 multiple TDS are simultaneously applied to a subject, the adhesion performance of each and all 331 TDS should be assessed. 332 333 Applicants should prespecify their inclusion criteria for the statistical analysis of PK endpoints 334 and perform their primary PK analysis on the PP population. For the primary PK parameters, 335 applicants should calculate the geometric mean ratios for the T/R treatments and the two-sided 336 90% confidence intervals. 337 338 Applicants should collect and analyze PK samples from all subjects in the PK subpopulation, 339 regardless of the subjects' TDS adhesion scores, and report the sample concentrations for all 340 time points as well as the PK results for all subjects in the PK study. All TDS units that are 341 removed at the end of (or which detach during) the in vivo adhesion and/or PK BE study should 342 be retained for analysis of residual drug content.<sup>8</sup> 343 344 Applicants should refer to the guidance for industry Handling and Retention of BA and BE 345 Testing Samples for recommendations on the retention of study drug samples and on the 346 maintenance of records of BE testing. 347 348 349 V. FORMAT OF DATA SUBMISSION 350 351 Applicants should submit study data in standardized format and refer to the FDA web page on Study Data for Submission to CDER<sup>9</sup> for more information about study data standards. 352 353 354 In addition, applicants should provide SAS transport data sets in XPT format with the define file.
- 355 If imputation is applied, applicants should also submit analysis data after the imputation.

<sup>&</sup>lt;sup>8</sup> See guidance for industry Residual Drug in Transdermal and Related Drug Delivery Systems.

<sup>&</sup>lt;sup>9</sup> This web page is available at

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/u cm248635.htm.