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# General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products 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## *DRAFT GUIDANCE*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)**

**March 2016  
Generics**

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# General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products Guidance for Industry

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**U.S. Department of Health and Human Services  
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1                   **General Principles for Evaluating the Abuse Deterrence of**  
2                   **Generic Solid Oral Opioid Drug Products**  
3                   **Guidance for Industry<sup>1</sup>**  
4

5  
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person  
8 and is not binding on FDA or the public. You can use an alternative approach if it satisfies the  
9 requirements of the applicable statutes and regulations. To discuss an alternative approach,  
10 contact the FDA staff responsible for this guidance as listed on the title page.  
11

12  
13 **I. INTRODUCTION**

14 This guidance is intended to assist a potential applicant who plans to develop, and submit an  
15 abbreviated new drug application (ANDA) to seek approval of, a generic version of a solid oral  
16 opioid drug product that has the potential for abuse and which references an opioid drug product  
17 with abuse-deterrent properties described in its labeling. The guidance recommends studies,  
18 including comparative in vitro studies, that should be conducted by the potential ANDA  
19 applicant and submitted to FDA in an ANDA to demonstrate that a generic solid oral opioid drug  
20 product is no less abuse-deterrent than its reference listed drug (RLD) with respect to all  
21 potential routes of abuse.

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

27 **II. BACKGROUND**

28 Prescription opioid analgesics are an important component of modern pain management.  
29 However, abuse and misuse of these drug products have created a serious and growing public  
30 health problem. One potentially important step toward the goal of creating safer opioid  
31 analgesics has been the development of opioid drug products that are formulated to deter abuse.  
32 FDA considers development of these products a high public health priority.

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<sup>1</sup> The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) prepared this guidance.

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33 On April 1, 2015, FDA published in the *Federal Register* a notice of availability for its final  
34 guidance, *Abuse-Deterrent Opioids – Evaluation and Labeling*.<sup>2</sup> For purposes of that guidance,  
35 “abuse-deterrent properties” are defined as those properties shown to meaningfully *deter* abuse,  
36 even if they do not fully *prevent* abuse. The term “abuse” is defined as the intentional, non-  
37 therapeutic use of a drug product or substance, even once, to achieve a desired psychological or  
38 physiological effect.<sup>3</sup> Abuse is not the same as “misuse,” which refers to the intentional  
39 therapeutic use of a drug product in an inappropriate way and specifically excludes the definition  
40 of abuse.<sup>4</sup> Because opioid drug products must in the end be able to deliver the opioid to the  
41 patient, there may always be some abuse of these products.

42 It is important that generic versions of opioids that reference RLDs whose labeling describes  
43 abuse-deterrent properties are available to ensure widespread access to safe and effective  
44 analgesics for patients who need them. However, it is also important that the availability of such  
45 generics does not exacerbate the public health problems associated with prescription opioid  
46 abuse. Where abuse-deterrent properties are described in the labeling of an RLD, marketing a  
47 generic version of the RLD that is less abuse-deterrent could lead opioid abusers to preferentially  
48 seek out and abuse such easier-to-abuse generics.

49 The *Abuse-Deterrent Opioids – Evaluation and Labeling* guidance describes seven categories of  
50 abuse-deterrent technologies — physical/chemical barriers, agonist/antagonist combinations,  
51 aversion, delivery system, new molecular entities (NMEs) and prodrugs, combinations, and  
52 novel approaches. This guidance focuses on the general principles for developing and evaluating  
53 the abuse deterrence of generic solid oral opioid drug products formulated to incorporate  
54 physical or chemical barriers, agonist/antagonists, aversive agents, or combinations of two or  
55 more of these technologies. It does not provide testing recommendations for generic versions of  
56 opioid drug products incorporating other technologies (i.e., delivery system, NME/prodrug, or  
57 novel approaches), but FDA may provide testing recommendations in future product-specific  
58 guidances. Further, FDA will continue to assess the state of science and, as novel technologies  
59 develop, will address them by issuing additional guidance, as appropriate.

### 60 **III. ABUSE DETERRENCE OF GENERIC SOLID ORAL OPIOID DRUG** 61 **PRODUCTS**

62 In order for FDA to approve an ANDA, the Agency must find, among other things, that the  
63 generic drug product has the same active ingredient(s), dosage form, route of administration,  
64 strength, and, with limited exceptions, labeling as the RLD, is bioequivalent to its RLD, that the  
65 methods used in, or the facilities and controls used for, the manufacture, processing, and packing  
66 of the drug are adequate to assure and preserve its identity, strength, quality, and purity, and that

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<sup>2</sup> 2015 guidance on *Abuse-Deterrent Opioid – Evaluation and Labeling*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>

<sup>3</sup> Smith, S M, Dart R C, Katz N P, et al., 2013, Classification and Definition of Misuse, Abuse, and Related Events in Clinical Trials: ACTION Systematic Review and Recommendations, *Pain*, 154:2287-2296.

<sup>4</sup> *Ibid.*

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67 the inactive ingredients and composition of the generic drug are not unsafe under the conditions  
68 of use prescribed, recommended, or suggested in the labeling.<sup>5</sup>

69 Bioequivalent drug products that meet the following criteria are “therapeutically equivalent” and  
70 can be substituted for each other: (1) they are approved as safe and effective; (2) they are  
71 pharmaceutical equivalents in that they: (a) contain identical amounts of the same active  
72 ingredient(s) with the same route of administration and dosage form, and (b) meet compendial or  
73 other applicable standards of strength, quality, purity, and identity; (3) they are adequately  
74 labeled; and (4) they are manufactured in compliance with current good manufacturing practices  
75 regulations.<sup>6</sup>

76 If the RLD’s labeling describes properties that are expected to deter misuse or abuse, the  
77 potential ANDA applicant should evaluate its proposed generic drug product in comparative in  
78 vitro studies and, in some cases, in relevant pharmacokinetic or other studies to show that it is no  
79 less abuse-deterrent than the RLD with respect to all potential routes of abuse. This will ensure  
80 the generic is no less abuse-deterrent than the RLD with respect to all potential routes of abuse  
81 and will minimize the risk of shifting abuse to other potentially more dangerous routes. FDA  
82 intends to consider the totality of the evidence when evaluating the abuse deterrence of a generic  
83 solid oral opioid drug product.

84 When a potential ANDA applicant is developing a generic solid oral opioid drug product, the  
85 potential applicant should review the labeling for the RLD, particularly the information presented  
86 in the DRUG ABUSE AND DEPENDENCE section under 9.2 Abuse, to determine if FDA has  
87 approved labeling that describes the product’s abuse-deterrent properties, including any  
88 information related to in vitro, pharmacokinetic, or clinical abuse potential studies the RLD’s  
89 applicant conducted. In addition to the RLD’s labeling, the potential applicant should also  
90 consider public literature on the abuse deterrence of the RLD and results of any testing the  
91 potential applicant conducted to assess the physical and chemical properties of the RLD to  
92 inform the appropriate testing of the proposed generic drug product. For questions related to  
93 evaluating an RLD’s abuse deterrence, the potential applicant may seek the Agency’s input  
94 through submission of controlled correspondence to the Office of Generic Drugs.<sup>7</sup>

#### 95 **IV. GENERAL PRINCIPLES FOR EVALUATING THE ABUSE DETERRENCE OF** 96 **GENERIC SOLID ORAL OPIOID DRUG PRODUCTS**

97 In this guidance, a proposed generic solid oral opioid drug product is referred to as “T product”  
98 and its respective RLD as “R product.” If the labeling for the R product does not describe any  
99 abuse-deterrent properties, the testing recommendations in this guidance are not applicable.  
100 Where the labeling for the R product describes abuse-deterrent properties, a comparative  
101 evaluation of the abuse deterrence of T product compared to R product should be conducted

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<sup>5</sup> See section 505(j)(2)(A) and (j)(4) of the Federal Food, Drug, and Cosmetic Act.

<sup>6</sup> See FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), Preface at vii.

<sup>7</sup> 2015 guidance on *Controlled Correspondence Related to Generic Drug Development*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM411478.pdf>

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102 according to the following general principles:

- 103 • **Tier-based approach to testing.** FDA recommends that potential ANDA applicants  
104 follow a tier-based approach to efficiently compare a T product to its R product and limit  
105 the number of tests required for evaluating the abuse deterrence of T product. This tier-  
106 based approach allows for hierarchical testing, starting with simple and gentle  
107 manipulations of the product in in vitro studies (Tier 1) and progressing to more  
108 destructive mechanical and chemical manipulations until R product’s abuse deterrence is  
109 defeated or compromised, or T product is shown to be less abuse-deterrent than R  
110 product.
  
- 111 • **Evaluation of Abuse Deterrence.** The evaluation of the abuse deterrence of the T  
112 product should be based on its performance relative to R product. The proposed generic  
113 product need not have the same formulation design as the R product. In order to  
114 adequately compare R and T products, a potential ANDA applicant should identify the R  
115 product’s abuse deterrence for all routes of abuse using the tier-based approach described  
116 in this guidance. If R product has not been found by the potential applicant to have any  
117 abuse deterrence for a particular route of abuse, the potential applicant should summarize  
118 the studies conducted and the results to support the applicant’s assessment that the RLD  
119 has no abuse deterrence with respect to that route and explain why there is no need to test  
120 its T product in comparative in vitro or other studies for that route. The evaluation of the  
121 abuse deterrence of T product should be based on the potential applicant’s best  
122 understanding of the abuse deterrence of R product, the potential routes of abuse, and  
123 specific measures meaningful to the evaluation of abuse by those routes. For example,  
124 the measure of abuse deterrence relevant to abuse by injection is the % of opioid that can  
125 be extracted from the product formulation and expelled from a syringe under the  
126 conditions specified in Appendix 2.
  
- 127 • **Use of control.** Manipulation of an opioid product is a function of several factors  
128 including, but not limited to, tampering skills, time, and tampering resources available.  
129 The abuse-deterrent properties of currently approved drug products are not absolute, and  
130 can eventually be compromised or defeated. Therefore, it is important to identify  
131 appropriate discriminatory study conditions to compare R and T products. For certain  
132 comparative studies (e.g., extractability studies), such discriminatory study conditions  
133 should be identified by including a control product (referred to in this guidance as “C  
134 product”) and comparing it to R product in order to identify the abuse deterrence of R  
135 product. Potential ANDA applicants should select an appropriate C product for their  
136 proposed T product. When available, C product should be a non-abuse-deterrent version  
137 of the opioid R product that contains the same active pharmaceutical ingredient (API) as  
138 the R product.<sup>8</sup>

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<sup>8</sup> If a marketed non-abuse-deterrent version containing the same API is not available, the potential ANDA applicant should submit controlled correspondence to the Office of Generic Drugs seeking input on selection of an appropriate alternative control.



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- 139       • **Identification of discriminatory study conditions.** The parameters for the  
140       discriminatory study conditions should lie within the range specified in this guidance for  
141       different routes of abuse (Appendices 2-5). In order to determine the abuse deterrence of  
142       T product by, for example, the injection route, a potential ANDA applicant should first  
143       identify the in vitro discriminatory study conditions under which the % extraction of  
144       opioid from R product is statistically less than the % extraction of opioid from C product,  
145       i.e., the conditions under which R product is statistically superior to C product<sup>9</sup>. The  
146       potential applicants should then compare the % extraction of opioid of T product to R  
147       product under the same discriminatory study conditions.
- 148       • **Comparison of R and T products.** Once the in vitro discriminatory study conditions  
149       have been identified, a potential ANDA applicant should perform the recommended  
150       statistical comparisons<sup>10</sup> for each of the different routes of abuse as recommended in  
151       Section VIII and as shown in Appendices 2-5.

152       The general principles outlined in this section are applicable to all generic solid oral opioid drug  
153       products within the scope of this guidance. FDA will continue considering whether to provide  
154       more detailed, product-specific recommendations for in vitro testing, pharmacokinetic, or other  
155       studies in cases where additional principles may be applicable to product-specific technologies  
156       used to deter abuse.

## 157       **V.        ROUTES OF ABUSE**

158       Solid oral opioid analgesics can be swallowed as intact dosage forms or swallowed after  
159       chewing, cutting, crushing, grating, milling, or extracting the opioid from the intact or  
160       mechanically manipulated form. In addition, the opioid products may be injected, insufflated, or  
161       smoked.

162       The Agency believes that the evaluation of the abuse deterrence of generic solid oral opioid drug  
163       products should take into consideration all potential routes of abuse, as recommended below:

164       **Injection (parenteral route)**—evaluate the extractability and syringeability of intact and  
165       mechanically manipulated products, as described in Appendix 2.

166       **Ingestion (oral route)**—evaluate the extractability, dissolution, and, where applicable, the rate  
167       and extent of a product’s absorption for intact and mechanically or chemically manipulated  
168       products, as described in Appendix 3.

169       **Insufflation (nasal route)**—evaluate the nasal availability and likability of mechanically  
170       manipulated and insufflated products, as described in Appendix 4.

171       **Smoking (inhalation route)**—evaluate the ability to sublimate intact and mechanically or

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<sup>9</sup> Study conditions that demonstrate that R product is statistically superior to the C product aid in validation of the discriminatory study conditions chosen.

<sup>10</sup> T product should be no worse than the R product when tested using discriminatory study conditions.



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172 chemically manipulated products, as described in Appendix 5.

173 **VI. COMPARATIVE IN VITRO STUDIES**

174 As discussed in Section IV, FDA recommends that potential ANDA applicants follow a tier-  
175 based approach to efficiently compare the abuse deterrence of T product to R product. In vitro  
176 testing should start with simple and gentle manipulations and progress to complex and more  
177 destructive manipulations. Appendix 1 provides recommendations for mechanical manipulations  
178 to evaluate the abuse deterrence of solid oral opioid products.

179 In addition to mechanical manipulation, chemical manipulation using different levels of solvents  
180 may be used in the comparative in vitro studies for extraction of opioid. Appendix 3 describes  
181 the solvents, by level, recommended for use in comparative in vitro testing for extraction of  
182 opioid for the purpose of oral abuse. This guidance recommends the following levels of solvents  
183 be used for chemical manipulation in comparative in vitro studies:

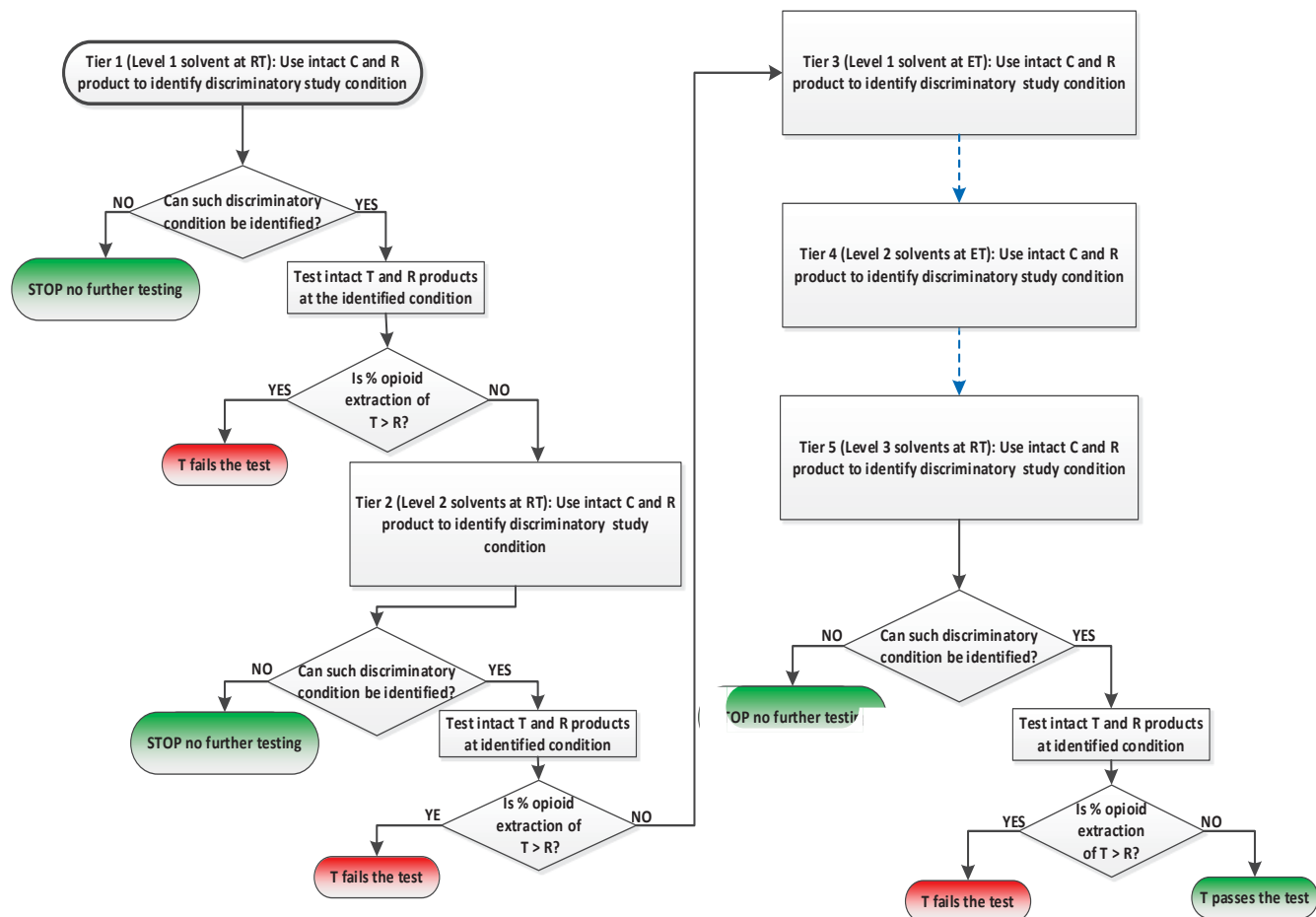
- 184 • Level 1 solvent: water
- 185
- 186 • Level 2 solvents: commercially available food-grade vinegar, 0.2% baking soda solution,  
187 40% ethanol, and carbonated drink
- 188 • Level 3 solvents: cooking oil, isopropyl alcohol, acetone, 0.1 N HCl, and 0.1 N NaOH

189 Potential applicants may use other solvents in addition to those described above and are  
190 encouraged to seek the Agency’s input on additional testing suitable for product-specific  
191 development.

192 Figure 1 provides an example of a tier-based approach to evaluating the extractability of opioid  
193 from an intact product for ingestion (see further discussion in Appendix 3) in the form of a  
194 decision tree.

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196  
197  
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Figure 1: Decision Tree for Evaluation of Extractability of Intact Product (Oral Route). RT – Room temperature, ET – Elevated temperature

## 199 VII. OTHER CONSIDERATIONS

### 200 A. Multiple Strengths

201 A potential ANDA applicant seeking approval of several strengths of a generic solid oral opioid  
202 drug product should evaluate and compare T product against the R product for each of the  
203 strengths. Alternatively, the potential applicant may provide supportive data to demonstrate  
204 compositional proportionality across different strengths of R and T products as justification for  
205 not conducting studies to evaluate T product against R product for all strengths. When such  
206 justification is provided, a bracketing design covering the extremes of the ratios of opioid to  
207 excipients that contribute to abuse deterrence should be applied to in vitro evaluation studies.<sup>11</sup>

<sup>11</sup> For additional information regarding bracketing design, refer to the guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*, December 2013.

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### 208 **B. Pharmacokinetic Studies**

209 Pharmacokinetic (PK) studies to evaluate the abuse deterrence of T product in comparison to R  
210 product should be conducted in cases where there are no reliable in vitro testing methodologies.  
211 Potential ANDA applicants may also propose to conduct PK studies in cases where available in  
212 vitro testing methodology is overly sensitive or cannot adequately assess the abuse deterrence of  
213 the T product relative to the R product. For instance, when evaluating the potential to abuse the  
214 proposed product by ingestion, if, after attempting the dissolution study recommended in  
215 Appendix 3, the potential applicant believes the testing is overly sensitive to characterize its  
216 generic drug product with respect to abuse deterrence, the product may be evaluated further in a  
217 PK study. In such cases, the potential applicant should seek the Agency's input on the PK study  
218 design before conducting the study.

219 As a general principle, PK studies should be conducted in healthy volunteers, incorporating a  
220 naltrexone blockade to block the pharmacodynamic effects of the opioids. The PK parameters  
221 for the opioid drug product and any active metabolites recommended for measurements include  
222 maximum concentration ( $C_{max}$ ), time to maximum concentration ( $T_{max}$ ), and area under the curve  
223 ( $AUC_{(0-t)}$  and  $AUC_{(0-\infty)}$ ). When applicable, partial AUCs (p-AUCs) should also be determined.  
224 For agonist/antagonist products, the PK parameters for both the agonist and the antagonist, along  
225 with their active metabolites (if any), should be determined. When comparing PK profiles of R  
226 and T products, a potential ANDA applicant should ensure that the same level of mechanical or  
227 chemical manipulation has been applied to both products prior to administration through the  
228 proposed route. Potential ANDA applicants should submit PK study protocols to the Agency for  
229 review.

230

### 231 **C. Other Studies**

232 Generally, comparative in vitro and PK studies provide sufficient evidence to demonstrate that T  
233 product is no less abuse-deterrent than R product. Other studies are generally not recommended,  
234 except in certain circumstances, such as comparing the abuse deterrence potential of an excipient  
235 that functions as an aversive agent, for example, where the aversive agent included in T product  
236 differs from the aversive agent, or differs in the amount of the aversive agent, included in R  
237 product (see discussion relating to Reduced Likability in Appendix 4). For example, in  
238 comparing the abuse deterrence potential of an excipient that functions as an aversive agent,  
239 FDA may recommend that applicants conduct pharmacodynamics studies with drug liking as a  
240 comparative endpoint between the R and the T product to permit FDA to evaluate formulation  
241 equivalence. Potential ANDA applicants are encouraged to seek the Agency's input on study  
242 design before conducting such studies.

## 243 **VIII. DATA ANALYSIS**

244 Inferential analyses should be used to evaluate the abuse deterrence of T product for each route  
245 of abuse by comparing R versus C, T versus C, and T versus R. In the analyses recommended in  
246 this guidance for each route of abuse, a tier-based approach with a hierarchical set of null  
247 hypotheses serves as a gatekeeper for subsequent null hypotheses, with the discriminatory study  
248 conditions moving from mild to progressively more destructive. A hierarchical inferential

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249 approach is used in order to maintain a family-wise experiment rate of  $\alpha = 0.05$ . Use of step-  
250 wise algorithms and statistical analyses are determinative only with regard to whether further  
251 testing of the T product is needed to evaluate its abuse deterrence.

252 Tiers are defined by the discriminatory study conditions, starting with the mildest set of  
253 conditions in Tier 1. Tier 1 serves as a serial gatekeeper for the subsequent tiers. One must  
254 reject all the null hypotheses within Tier 1 prior to testing the null hypotheses in the next tiers,  
255 which are defined by progressively more complex discriminatory study conditions. In Tier 1, all  
256 the null hypotheses are evaluated at the Type I error level of  $\alpha$ -level = 0.05 without adjusting for  
257 the number of hypotheses; this follows from the closed testing principle. All possible  
258 intersections among the null hypotheses must be elements within the tier of null hypotheses to be  
259 tested. Any null hypothesis is rejected if it is rejected at the Type I error level of  $\alpha = 0.05$ , and all  
260 possible intersections with this null hypothesis are also rejected at this  $\alpha$ -level.<sup>12</sup>

261 Maurer *et al.*<sup>13</sup> proposed a generalization of this principle to partially ordered sets of null  
262 hypotheses. With tiers (sets) labeled  $T_1, T_2, T_3, T_4$ , and  $T_5$  and arranged hierarchically, i.e., in  
263 strictly increasing order,  $T_j$  ( $j > 1$ ) is tested only if *all* null hypotheses in the tiers preceding it  
264 have been rejected by their within-tier  $\alpha$ -level tests. From the closed testing principle, it follows  
265 that this partially ordered procedure controls the  $\alpha$ -level for all null hypotheses in the tiers  $T_1, T_2,$   
266  $T_3, T_4$ , and  $T_5$ .

267 To evaluate abuse deterrence for each route of abuse using this tier-based approach, a potential  
268 ANDA applicant must first demonstrate that R product is statistically more abuse-deterrent than  
269 C product (Type I error = 0.05). Once this has been established, the following steps should be  
270 undertaken to demonstrate that T product is no worse than R product with respect to abuse  
271 deterrence for that particular route by an amount  $< \Delta$ :

272 i) The measure of the abuse deterrence (e.g., % extraction) for the R product should be  
273 statistically less than (superior to) the measure of the abuse deterrence for the C product (Type I  
274 error = 0.05),

275 ii) The value from T product should be no worse than the value from R product by an amount  $<$   
276  $\Delta$  (Type I error = 0.05),

277 iii) The acceptable  $\Delta$  for comparing T and R products is no more than 10% of the difference  
278 between R and C products for the % of opioid released.

279 For example, when abuse deterrence for resistance to extraction is measured by the % of opioid  
280 extracted from a product, if the % of opioid extracted from T is statistically greater than or equal  
281 to the  $R+\Delta$ , then T product is considered to be less abuse-deterrent than R; thus, T product will

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<sup>12</sup> Berger RL, 1982, Multiparameter Hypothesis Testing and Acceptance Sampling, *Technometrics*, 24:295-300.

<sup>13</sup> Maurer, W, L A Hothorn, and W Lehmacher, 1995, Multiple Comparisons in Drug Clinical Trials and Preclinical Assays: A-Priori Ordered Hypotheses, *Biometrie in der Chemisch-pharmazeutischen Industrie*, 6:3-18.

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282 not be tested further. In contrast, if the % of opioid extracted from T is statistically less than  
283  $R+\Delta$ , and T is statistically superior to C, the abuse deterrence of T is then evaluated in the next  
284 tier. A T product must be  $< R+\Delta$  and statistically superior to C, for each set of discriminatory  
285 study conditions for which it is evaluated in order to claim it is no less abuse-deterrent than the  
286 corresponding R product (see Tables 1 and 2 for more detail).

287 All inferential comparisons involve the mean of the measure of abuse deterrence or a function of  
288 the mean (for example, the mean of T minus the mean of R). The inferential tests used to  
289 evaluate the hypotheses are left to the discretion of the potential applicant. For the tests chosen,  
290 the potential applicant should provide justification of the proposed sample size selected to  
291 accurately characterize the mean. FDA recommends that the potential applicant develop an  
292 analysis plan that has contingencies for various scenarios, for example, data that are not normally  
293 distributed and data that are left-censored (values below the limit of quantification).

294 Tables 1 through 4 found in the appendices guide applicants through the recommended series of  
295 discriminatory study conditions for each of the potential routes of abuse, injection (extractability  
296 and syringeability), ingestion (extractability), ingestion (dissolution), and smoking (sublimation),  
297 respectively, as described here. The first step in each tier identifies the discriminatory study  
298 conditions for that tier by comparing R product to C product (in the case of extractability and  
299 syringeability), R product to a constant (in the case of dissolution), or R product directly to T  
300 product (in the case of sublimation). If R product is superior to C product or less than a constant  
301 (in case of dissolution), the testing should continue to the second step within that tier. The  
302 second step uses the discriminatory study conditions defined in the first step to evaluate T  
303 product in relation to R product, and, where C product is used, to evaluate T product in relation  
304 to C product. If, at the end of the second step, it is possible to conclude that T product is no less  
305 abuse-deterrent than R product and superior to C product, then testing of T product should move  
306 on to the next tier. This process continues for the remaining tiers within a table until:

- 307 (1) R product fails superiority to C product (or the constant, in the case of dissolution), in  
308 which case R is considered to have no abuse deterrence for the route of abuse or method  
309 of manipulation being tested; or  
310 (2) T product fails superiority to C product or non-inferiority to R product.

311 T product must be found non-inferior to the R product, and superior to C product, at each set of  
312 discriminatory study conditions for which it is evaluated in order to claim it is no less abuse-  
313 deterrent than the corresponding R product.

## 314 **IX. ADDITIONAL STUDIES**

315 There may be instances in which the tier-based approach to evaluation of abuse deterrence for  
316 various routes of abuse cannot adequately capture the complete profile for T product due to  
317 factors including, but not limited to, inclusion of novel inactive ingredients, use of new  
318 technology, and formulation design. In such instances, based on the performance profile of T  
319 product, FDA may, as permitted under section 505(j) of the FD&C Act, request that additional  
320 studies, aside from the ones described in Appendices 2-5, be conducted to evaluate the failure  
321 mode(s) of the T product. As new technologies emerge, FDA will continue adapting its

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322 recommendations for developing and evaluating generic solid oral and other opioid drug  
323 products formulated to deter abuse in order to ensure access to effective analgesics for patients  
324 who need them.

325

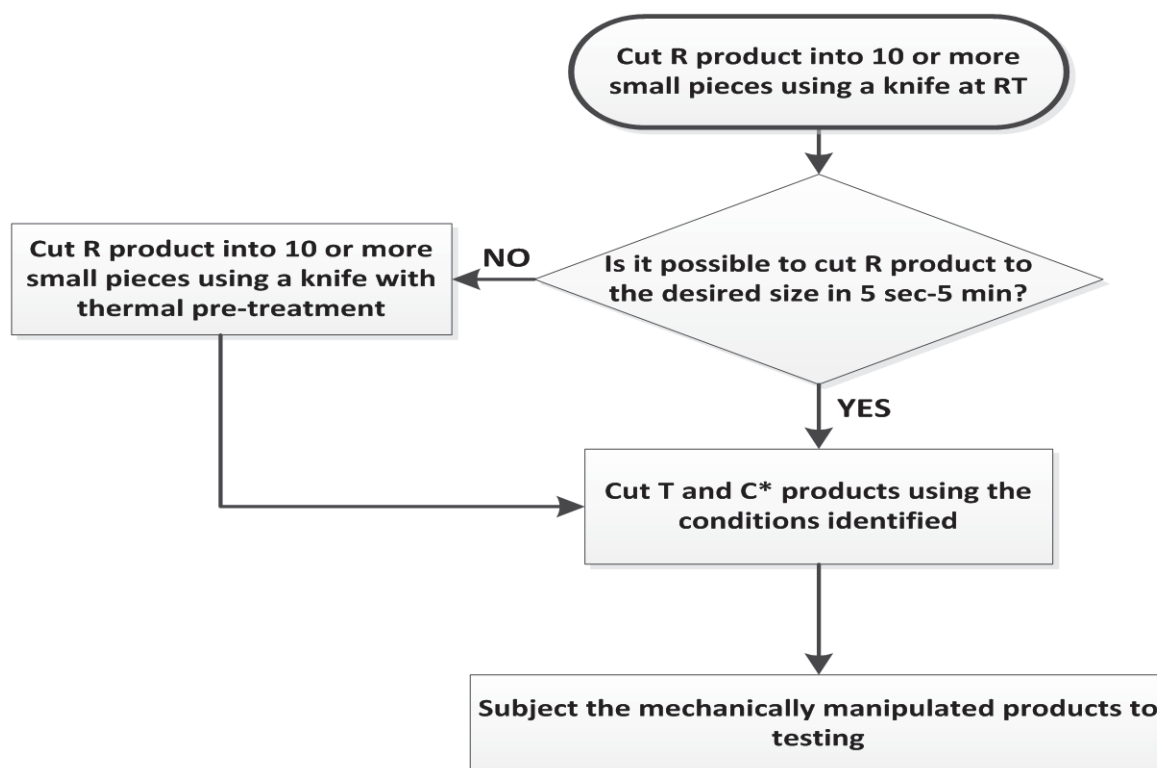
326 **APPENDIX 1: MECHANICAL MANIPULATION**

327 Appendix 1 describes some of the ways in which solid oral opioid products can be mechanically  
328 manipulated using readily available household equipment. There are additional ways in which  
329 products could be mechanically manipulated (e.g., crushing, hammering). FDA recommends  
330 that a potential ANDA applicant use the mechanical manipulation(s) most likely to be used by  
331 abusers when conducting studies to evaluate the abuse deterrence of a specific T product.  
332 Particle size for the mechanically manipulated products can be analyzed using techniques  
333 including, but not limited to, photograph with scale, image analysis, sieve analysis, and laser  
334 diffraction.

335 **1. Cutting**

336 As illustrated in figure 2 below:

- 337
- 338 • Cutting without thermal pre-treatment: If a drug product can be cut in less than  
339 5 minutes at room temperature (RT) into 10 or more small pieces using a knife,  
no thermal pre-treatment is needed.
  - 340 • Cutting with thermal pre-treatment: If a drug product cannot be cut at room  
341 temperature, thermal pre-treatment should be used (e.g., freezing at -20°C or  
342 heating).



343

344 Figure 2: Mechanical Manipulation by Cutting for Solid Oral Opioid Drug Products



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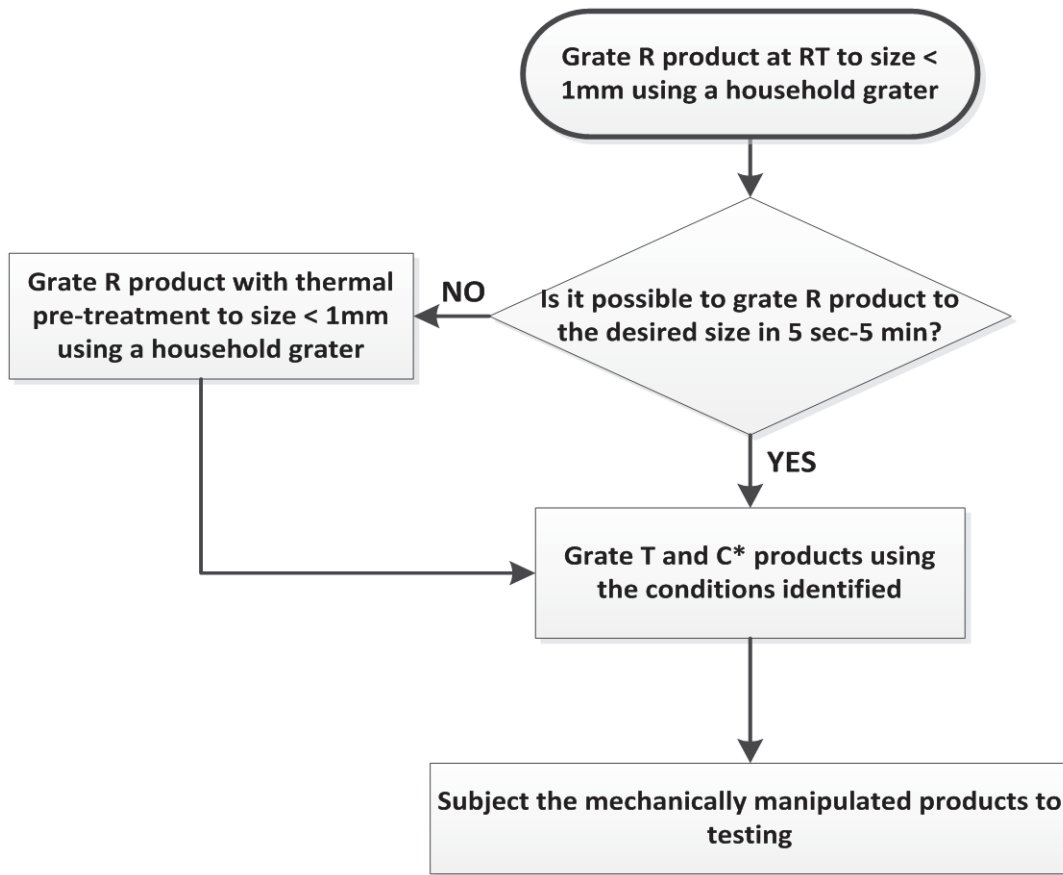
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345 **2. Grating**

346 As illustrated in figure 3 below:

- 347
- 348 • Grating without thermal pre-treatment: If a drug product can be grated within  
349 5 seconds to 5 minutes at RT to a size less than 1mm using a household grater,  
no thermal pre-treatment is needed.
  - 350 • Grating with thermal pre-treatment: If a drug product cannot be grated at RT,  
351 thermal pre-treatment should be used (e.g., freezing at -20°C or heating).

352



353

354 Figure 3: Mechanical Manipulation by Grating for Solid Oral Opioid Drug Products

355

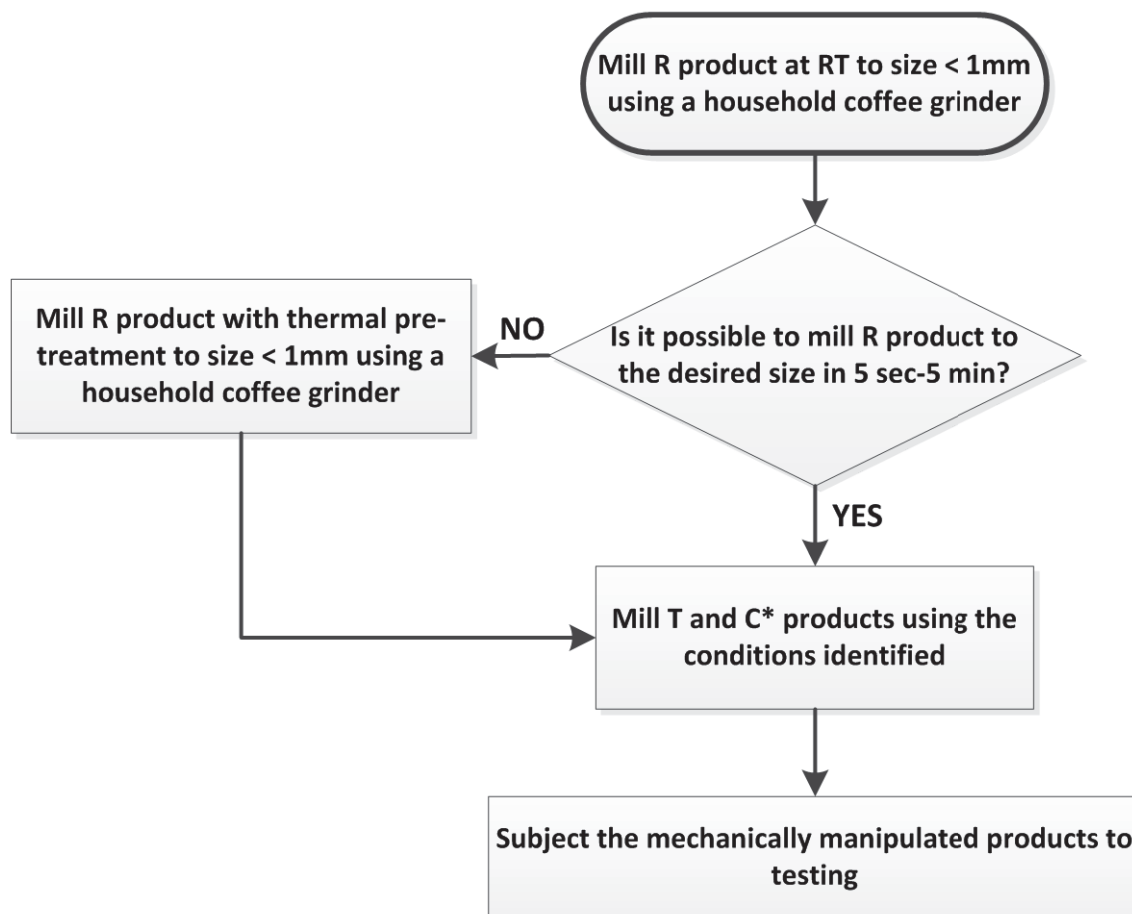
356 **3. Milling**

357 As illustrated in figure 4 below:

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- 358
- 359
- 360
- If a drug product can be milled in 5 seconds to 5 minutes at RT to a size less than 1 mm using a household coffee grinder, no thermal pre-treatment is needed.
- 361
- If a drug product cannot be milled at RT, thermal pre-treatment should be used (e.g., freezing at -20°C or heating).
- 362
- 363



364

365 \*Refer to different routes of abuse for products to be tested

366 Figure 4: Mechanical Manipulation by Milling for Solid Oral Opioid Drug Products

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### 368 **APPENDIX 2: ABUSE BY INJECTION (PARENTERAL ROUTE)**

369 Abuse by injection usually involves extraction of intact or mechanically manipulated (e.g., cut,  
370 grated, milled) opioid drug products at room temperature (RT)<sup>14</sup> or elevated temperature (ET)<sup>15</sup>  
371 in small volumes of water followed by injection using a syringe. To evaluate the abuse  
372 deterrence for the parenteral route, a potential ANDA applicant should measure the amount of  
373 opioid available for injection. The amount is determined by the opioid concentration in the  
374 extraction medium such as water (extractability), the volume that can be drawn into a syringe,  
375 and the volume that can be expelled from the syringe's needle (syringeability).

376 The potential applicant should note that the comparative extractability and syringeability testing  
377 should be conducted for intact and mechanically manipulated (cut, where applicable, grated and  
378 milled) drug products in a parallel manner. In order to conclude that T product is no less abuse-  
379 deterrent than R product for the parenteral route of abuse, the intact and mechanically  
380 manipulated T products should be tested and shown to be no less abuse-deterrent than the intact  
381 and manipulated R products, respectively, under each applicable discriminatory study condition.

382 The measure considered meaningful for evaluating the abuse deterrence relevant to abuse by  
383 injection is the % of opioid extraction determined as follows:  $(\text{CONC} \times \text{V} / \text{labeled strength of the}$   
384  $\text{R product}) \times 100$ , where CONC is the concentration of opioid in the solution that can be expelled  
385 from the syringe needle, and V is the volume of the solution expelled. If R product is an  
386 agonist/antagonist combination, the ratio of the % of opioid extraction of agonist to antagonist  
387 should be determined.

#### 388 Discriminatory Study Conditions:

389 The extractability and syringeability testing should be conducted on intact, cut (where  
390 applicable), grated, and milled products at RT or ET using the tiered approach. Approaches to  
391 mechanical manipulation of products to be tested are described in Appendix 1. For each  
392 manipulation likely to be used by abusers, R, T, and C products should be compared, as  
393 described in Section VIII.

394 Following grating and milling (and cutting, where applicable), further testing of extractability  
395 and syringeability is recommended under the following range of discriminatory study conditions  
396 (Table 1): solvent water, volume 1-10 mL, temperature RT or ET, duration 5-60 minutes, and  
397 needle gauge 18-28. The same extractability and syringeability conditions are recommended for  
398 intact products.

399 The tier-based approach to the comparative extractability and syringeability studies (Table 1) is  
400 based on increasing the temperature, starting with extraction in water at RT in Tier 1 to  
401 extraction in water at ET in Tier 2.

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<sup>14</sup> U.S. Pharmacopoeia (USP) controlled room temperature (20° – 25°C)

<sup>15</sup> 2015 final guidance on *Abuse-Deterrent Opioid – Evaluation and Labeling*

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#### 402 **Tier 1: Extraction of intact, grated, and milled product in water at RT**

403 Identify discriminatory study condition. C and R products are used to identify the discriminatory  
404 study condition within the Agency-specified range at RT (Table 1). Under that discriminatory  
405 study condition, R product should be statistically superior to C product (refer to Section VIII).

406 Evaluate the R product. If a discriminatory study condition cannot be identified for intact R  
407 product, intact R product is considered to have no abuse deterrence under this tier of testing.  
408 Therefore, no comparative testing of T product to R product is needed. In addition, if a  
409 discriminatory study condition cannot be identified for grated or milled<sup>16</sup> R product, R is  
410 considered to have no abuse deterrence under this tier of testing for grated and milled product.<sup>17</sup>  
411 Therefore, no further comparative testing of the T product to the R product is needed.

412 Compare R and T products. If the discriminatory study condition can be identified for intact,  
413 grated, or milled R product, the potential applicant should test the respective intact, grated, or  
414 milled R and T products under the identified conditions and compare the abuse deterrence of T  
415 and R as follows (Table 1):

416 i) The % opioid extraction value from T product should be statistically less than (superior to) the  
417 % opioid extraction value from C product (Type I error = 0.05)

418 ii) The % opioid extraction value from T product should be no worse than the % opioid  
419 extraction value from R product by an amount  $< \Delta$  (Type I error = 0.05)

420 iii) The acceptable  $\Delta$  for comparing T and R products is no more than 10% of the difference  
421 between R and C products for the % of opioid released.

#### 422 **Tier 2: Extraction of intact, grated, and milled product in water at ET**

423  
424 Identify discriminatory study condition. C and R products are used to identify the discriminatory  
425 study condition within the Agency-specified range at ET. Under that discriminatory study  
426 condition, the R product should be statistically superior to the C product (refer to Section VIII).  
427

428 Evaluate the R product. If the discriminatory study condition cannot be identified for intact R,  
429 intact R is considered to have no abuse deterrence under this tier of testing. Therefore, no  
430 comparative testing of the T product to the R product is needed. In addition, if the  
431 discriminatory study condition cannot be identified for grated<sup>15</sup> or milled<sup>16</sup> R product, R is  
432 considered to have no abuse deterrence under this tier of testing.<sup>17</sup> Therefore, no further  
433 comparative testing of T product to R product is needed.

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<sup>16</sup> If R product cannot be either grated or milled under the conditions specified in Appendix 1, cut the R, T, and C products to 10 or more small pieces in 5 sec-5 min.

<sup>17</sup> Although grating and milling procedures are conducted using different household equipment, e.g., cheese or nutmeg grater and coffee grinder, respectively, all these devices are readily accessible household equipment, and therefore represent a similar level of mechanical manipulation complexity for this route.

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434 Compare R and T products. If the discriminatory study condition can be identified for intact,  
 435 grated, or milled R product, the potential applicant should test the respective intact, grated, or  
 436 milled R and T products under the identified conditions and compare the abuse deterrence of T  
 437 and R products, as indicated in Section VIII.

438 Table 1 illustrates the tier-based approach for evaluating the extractability and syringeability of  
 439 an opioid for abuse by injection, as described above.

440 Table 1: Evaluation of Extractability and Syringeability (Abuse by Injection)

<b>TIER 1</b>		<b>Study Conditions</b> 1 – 10mL Level 1 Solvent (water) at Room Temperature Extraction Duration 5 – 60 min with Needle Gauge 18 – 28	
Identify Discriminatory Extraction Study Condition and $\Delta < 10\%$	$H_0: R \geq C$ versus $H_a: R < C$		
	<p><b>If <math>R &lt; C</math></b> Conclude that R is superior to C</p> <p align="center">↓</p>	<p><b>If <math>R \geq C</math></b> Conclude that R is not superior to C; no further comparative testing</p>	
Evaluate T vs C and T vs R at Discriminatory Study Conditions Identified in Tier 1	$H_0: T \geq C$ versus $H_a: T < C$ and $H_0: T - R \geq \Delta$ versus $H_a: T - R < \Delta$		
	<p><b>If <math>T &lt; C</math> and <math>T - R &lt; \Delta</math></b> Conclude that T is superior to C &amp; no worse than R by an amount <math>&lt; \Delta</math>; T passes the study under Tier 1</p> <p align="center"><b>CONTINUE</b> to Tier 2</p> <p align="center">↓</p>	<p><b>If <math>T \geq C</math> and/or <math>T - R \geq \Delta</math></b> Conclude that T is not superior to C and/or is worse than R by an amount <math>\geq \Delta</math>; T fails the study under Tier 1</p> <p align="center"><b>STOP</b> no further testing</p>	<b>STOP</b> no further testing
<b>TIER 2</b>		<b>Study Conditions</b> 1 – 10mL Level 1 Solvent (water) at Elevated Temperature Extraction Duration 5 – 60 min with Needle Gauge 18 – 28	
Identify Discriminatory Extraction Study Condition and $\Delta < 10\%$	$H_0: R \geq C$ versus $H_a: R < C$		
	<p><b>If <math>R &lt; C</math></b> Conclude that R is superior to C</p> <p align="center">↓</p>	<p><b>If <math>R \geq C</math></b> Conclude that R is not superior to C; no further comparative testing</p>	
Evaluate T vs C and T vs R at Discriminatory Study Conditions Identified in Tier 2	$H_0: T \geq C$ versus $H_a: T < C$ and $H_0: T - R \geq \Delta$ versus $H_a: T - R < \Delta$		
	<p><b>If <math>T &lt; C</math> and <math>T - R &lt; \Delta</math></b> Conclude that T is superior to C &amp; no worse than R by an amount <math>&lt; \Delta</math>; T passes the study under Tier 2</p> <p align="center"><b>STOP</b> no further testing</p>	<p><b>If <math>T \geq C</math> and/or <math>T - R \geq \Delta</math></b> Conclude that T is not superior to C and/or is worse than R by an amount <math>\geq \Delta</math>; T fails the study under Tier 2</p> <p align="center"><b>STOP</b> no further testing</p>	<b>STOP</b> no further testing

441 The measure used to evaluate abuse by injection is **the % opioid extraction** determined as follows: **(CONC\*V/ labeled strength of the R**  
 442 **product) \*100**, where CONC is the concentration of opioid in the solution that can be expelled from the syringe needle and V is the volume of  
 443 the solution expelled.  
 444

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447 **APPENDIX 3: ABUSE BY INGESTION (ORAL ROUTE)**

448 Abuse by ingestion may involve orally ingesting an opioid solution obtained through extraction  
449 of opioid from intact or mechanically manipulated (e.g., cut, grated, milled) drug product or  
450 ingestion of chewed or mechanically manipulated drug product itself. To evaluate the abuse  
451 deterrence for the oral route of abuse, a potential ANDA applicant should test their T products in  
452 the recommended in vitro mechanical manipulation studies and dissolution studies, including  
453 extractability and dissolution of intact, cut, grated, and milled product within the recommended  
454 range of discriminatory study conditions.

455 The sections below provide recommendations for evaluating extractability and dissolution of T  
456 products referencing R products that have been found through comparison to C product to have  
457 abuse deterrence for the oral route of abuse. If, after attempting the recommended in vitro  
458 testing, the potential applicant believes that the testing is overly sensitive to characterize the  
459 abuse deterrence for the oral route of abuse for its generic drug product, the product may be  
460 evaluated further in a pharmacokinetic (PK) study comparing the rate and extent of absorption of  
461 the mechanically manipulated and ingested products or the chewed and ingested products.

462 **Evaluation of the extractability of opioid to determine abuse deterrence for oral route of**  
463 **abuse**

464 The potential applicant should note that the comparative extractability testing should be  
465 conducted for intact and mechanically manipulated (cut, grated, and milled) drug products in a  
466 parallel manner. In order to conclude that T product is no less abuse-deterrent than R product for  
467 the oral route of abuse, the intact and mechanically manipulated T products should be tested and  
468 shown to be no worse than the intact and manipulated R products, respectively.

469 Extractability of opioid into a solution may be assessed at RT<sup>18</sup> or ET for water<sup>19</sup> and for an  
470 organic solvent (50 °C) in relatively large volumes of different solvents. The focus of the studies  
471 for this route of abuse is to assess the extractability of the opioid and measure the amount of  
472 opioid available for oral administration, determined experimentally by measurement of the  
473 concentration and volume of the extraction media.

474 The measure considered meaningful for this route of abuse is the % of opioid extraction  
475 determined as follows:  $(\text{CONC} \times \text{V} / \text{labeled strength of the R product}) \times 100$ , where CONC is the  
476 concentration of opioid in the extraction medium and V is the volume of the extraction solution.  
477 If R product is an agonist/antagonist combination, the ratio of % extraction of agonist and  
478 antagonist should be determined.

479

480 Discriminatory study conditions:

---

<sup>18</sup> U.S. Pharmacopoeia (USP) controlled room temperature (20° – 25°C)

<sup>19</sup> 2015 final guidance on *Abuse-Deterrent Opioid – Evaluation and Labeling*

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481 The extractability testing should be conducted for intact, grated, and milled product at RT and  
482 ET with relevant solvents using the tiered approach. Approaches to mechanical manipulation of  
483 products to be tested are described in Appendix 1. For each manipulation likely to be used by  
484 abusers, R, T, and C products should be compared, as explained in Section VIII.

485 Because different solvents could be used to assess the extractability of opioids for the purpose of  
486 subsequent oral ingestion, all three levels of solvents (see Section VI) should be used for the  
487 recommended studies for this route of abuse. In addition, the following range of extraction  
488 conditions is recommended: extraction volume: 100-300 mL, RT or ET for the relevant  
489 extraction media, duration 5-60 minutes, stirring speed 50 rpm.

490 The tier-based approach to the comparative extractability studies (Table 2) is based on using  
491 different level solvents and increasing temperature within the recommended range of study  
492 conditions.

#### 493 **Tier 1: Extraction of intact, cut, grated, or milled product in water at RT**

494 Identify discriminatory study condition. C and R products are used to identify the discriminatory  
495 study condition within the recommended range at RT. Under that discriminatory study  
496 condition, R product should be statistically superior to C product (Section VIII).

497 Evaluate R product. If the discriminatory study condition cannot be identified for intact R, intact  
498 R is considered to have no abuse deterrence under this tier of testing. Therefore no comparative  
499 testing of T product to R product is needed. In addition, if the discriminatory study condition  
500 cannot be identified for cut, grated, or milled R product, R product is considered to have no  
501 abuse deterrence under this tier of testing for cut, grated, and milled product.<sup>20</sup> Therefore, no  
502 comparative testing of R product to T product is needed.

503  
504 Compare R and T products. If the discriminatory study condition can be identified for intact,  
505 cut, grated, and milled R product, the potential applicant should test the respective intact, cut,  
506 grated, and milled R and T products under the identified conditions and compare the abuse  
507 deterrence of T and R products as follows (Table 2):

- 508 i) The % of opioid extraction value from T product should be statistically less than (superior  
509 to) the % opioid extraction value from the C product (Type I error = 0.05)  
510 ii) The % of opioid extraction value from T product should be no worse than the % opioid  
511 extraction value from R product by an amount  $< \Delta$  (Type I error = 0.05)  
512 iii) The acceptable  $\Delta$  for comparing T and R products is no more than 10% of the difference  
513 between R and C products for the % of opioid released

---

<sup>20</sup> Although cutting, grating, and milling procedures are conducted using different household equipment, i.e., knife, cheese or nutmeg grater, and coffee grinder, respectively, all are readily accessible household equipment, and therefore represent a similar level of manipulation complexity for the purposes of evaluation of the extractability of opioid for oral abuse.



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#### 514 **Tier 2: Extraction of intact, cut, grated, or milled product in Level 2 solvents at RT**

515  
516 *Identify study condition.* C and R products are used to identify the discriminatory study  
517 condition within the recommended range in all Level 2 solvents at RT. Under that  
518 discriminatory study condition, R product should be statistically superior to C product (see  
519 Section VIII).

520 *Evaluate R product.* If the discriminatory study condition cannot be identified for intact R  
521 product in any one of the Level 2 solvents, intact R product is considered to have no abuse  
522 deterrence under this tier of testing. Therefore, no comparative testing of T product to R product  
523 is needed. In addition, if the discriminatory study condition cannot be identified for cut, grated,  
524 or milled R product in any one of the Level 2 solvents, R product is considered to have no abuse  
525 deterrence under this tier of testing for cut, grated, and milled product.<sup>21</sup> Therefore, no  
526 comparative testing of T product to R product is needed.

527 *Compare R and T products.* If the discriminatory study condition can be identified for intact,  
528 cut, grated, and milled R product in all Level 2 solvents, the potential applicant should test the  
529 respective intact, cut, grated, and milled R and T products under the identified conditions and  
530 compare the abuse deterrence of T and R products, as described in Section VIII and shown in  
531 Table 2.

#### 532 **Tier 3: Extraction of intact, cut, grated, or milled product in water at ET**

533  
534 As shown in Table 2, the same steps as in Tiers 1 and 2 (identify discriminatory study condition,  
535 evaluate R product, and compare R and T products) should be used for testing R and T products  
536 in Tier 3.

#### 538 **Tier 4: Extraction of intact, cut, grated, or milled product in Level 2 solvents at ET**

539  
540 As shown in Table 2, the same steps as in Tiers 1, 2, and 3 (identify discriminatory study  
541 condition, evaluate R product, and compare R and T products) should be used for testing R and T  
542 products in Tier 4.

#### 544 **Tier 5: Extraction of intact, cut, grated, or milled product in Level 3 solvents at RT**

545  
546 As shown in Table 2, the same steps as in Tiers 1, 2, 3, and 4 (identify discriminatory study  
547 condition, evaluate R product, and compare R and T products) should be used for testing R and T  
548 products in Tier 5.

549  
550 Table 2 illustrates the tier-based approach for evaluating the extractability of opioids for abuse by  
551 ingestion, as described above.

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557 Table 2: Evaluation of Extractability (Abuse by Ingestion)

<b>TIER 1</b>		<b>Study Condition</b>	
		100-300 ml Level 1 Solvent (water) at Room Temperature / Extraction Stirring Speed 50 rpm and Extraction Duration 5-60 minutes	
Identify Discriminatory Extraction Study Condition and $\Delta < 10\%$	$H_0: R \geq C$ versus $H_1: R < C$ <b>If <math>R &lt; C</math></b> Conclude that R is superior to C ↓		<b>If <math>R \geq C</math></b> Conclude that R is not superior to C; no further comparative testing
Evaluate T vs R and T vs C at Identified Discriminatory Study Condition Identified in Tier 1	$H_0: T \geq C$ versus $H_1: T < C$ and $H_0: T - R \geq \Delta$ versus $H_1: T - R < \Delta$ <b>If <math>T &lt; C</math> and <math>T - R &lt; \Delta</math></b> Conclude that T is superior to C & no worse than R by an amount $< \Delta$ ; T passes the study under Tier 1 CONTINUE to Tier 2 ↓		<b>If <math>T \geq C</math> and/or <math>T - R \geq \Delta</math></b> Conclude that T is not superior to C and/or is worse than R by an amount $\geq \Delta$ ; T fails the study under Tier 1 STOP no further testing
<b>TIER 2</b>		<b>Study Condition</b>	
		100-300 ml Level 2 Solvents (food-grade vinegar, 0.2% baking soda solution, 40% ethanol, carbonated drink) at Room Temperature / Extraction Stirring Speed 50 rpm with Extraction Duration 5-60 minutes	
Identify Discriminatory Extraction Study Condition and $\Delta < 10\%$	$H_0: R \geq C$ versus $H_1: R < C$ <b>If <math>R &lt; C</math></b> Conclude that R is superior to C if R passes ALL Level 2 solvents ↓		<b>If <math>R \geq C</math></b> Conclude that R does not have abuse deterrent characteristics for extraction using progressively destructive conditions if R fails at least one Level 2 solvent; no further comparative testing
Evaluate T vs R and T vs C at Identified Discriminatory Study Condition Identified in Tier 2	$H_0: T \geq C$ versus $H_1: T < C$ and $H_0: T - R \geq \Delta$ versus $H_1: T - R < \Delta$ <b>If <math>T &lt; C</math> and <math>T - R &lt; \Delta</math></b> Conclude that T is superior to C & no worse than R by the amount of $\Delta$ ; T passes the study under Tier 2 for all Level 2 solvents CONTINUE to Tier 3 ↓		<b>If <math>T \geq C</math> and/or <math>T - R \geq \Delta</math></b> Conclude that T is not superior to C and/or is worse than R by an amount $\geq \Delta$ , if it fails at least one Level 2 solvent. In that case, T fails the study under Tier 2 STOP no further testing
<b>TIER 3</b>		<b>Study Condition</b>	
		100-300 ml Water Level 1 Solvent at Elevated Temperature / Extraction Stirring Speed 50 rpm and Extraction Duration 5-60 minutes	
Identify Discriminatory Extraction Study Condition and $\Delta < 10\%$	$H_0: R \geq C$ versus $H_1: R < C$ <b>If <math>R &lt; C</math></b> Conclude that R is superior to C ↓		<b>If <math>R \geq C</math></b> Conclude that R is not superior to C; no further comparative testing
Evaluate T vs R and T vs C at Identified Discriminatory Study Condition Identified in Tier 3	$H_0: T \geq C$ versus $H_1: T < C$ and $H_0: T - R \geq \Delta$ versus $H_1: T - R < \Delta$ <b>If <math>T &lt; C</math> and <math>T - R &lt; \Delta</math></b> Conclude that T is superior to C & no worse than R by an amount $< \Delta$ ; T passes the study under Tier 3 CONTINUE to Tier 4 ↓		<b>If <math>T \geq C</math> and/or <math>T - R \geq \Delta</math></b> Conclude that T is not superior to C and/or is worse than R by an amount $\geq \Delta$ ; T fails the study under Tier 3 STOP no further testing

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580 Table 2: Evaluation of Extractability (Abuse by Ingestion)

<b>TIER 4</b>		
<b>Study Condition</b> 100-300 ml Level 2 Solvents (food-grade vinegar, 0.2% baking soda solution, 40% ethanol, carbonated drink) at Elevated Temperature / Extraction Stirring Speed 50 rpm and Extraction Duration 5-60 min.		
$H_0: R \geq C$ versus $H_1: R < C$		
Identify Discriminatory Extraction Study Condition and $\Delta < 10\%$	<b>If <math>R &lt; C</math></b> Conclude that R is superior to C <i>if R passes ALL Level 2 solvents</i>	<b>If <math>R \geq C</math></b> Conclude that R does not have abuse deterrent characteristics for extraction using progressively destructive conditions <i>if R fails at least one Level 2 solvent; no further comparative testing</i>
↓		
Evaluate T vs R and T vs C at Identified Discriminatory Study Condition Identified in Tier 4	$H_0: T \geq C$ versus $H_1: T < C$ and $H_0: T - R \geq \Delta$ versus $H_1: T - R < \Delta$  <b>If <math>T &lt; C</math> and <math>T - R &lt; \Delta</math></b> Conclude that T is superior to C & no worse than R by an amount $< \Delta$ ; T passes the study under Tier 4 for all Level 4 solvents  <b>CONTINUE</b> to Tier 5	<b>If <math>T \geq C</math> and/or <math>T - R \geq \Delta</math></b> Conclude that T is not superior to C and/or is worse than R by an amount $\geq \Delta$ , if it fails at least one Level 4 solvent; T fails the study under Tier 4  <b>STOP</b> no further testing
↓		
<b>TIER 5</b>		
<b>Study Condition</b> 100-300 ml Level 3 Solvents (cooking oil, isopropyl alcohol, acetone, 0.1 N HCl, 0.1 N NaOH) at Room Temperature / Extraction Stirring Speed 50 rpm with Extraction Duration 5-60 minutes		
$H_0: R \geq C$ versus $H_1: R < C$		
Identify Discriminatory Extraction Study Condition and $\Delta < 10\%$	<b>If <math>R &lt; C</math></b> Conclude that R is superior to C <i>if R passes ALL Level 3 solvents</i>	<b>If <math>R \geq C</math></b> Conclude that R does not have abuse deterrent characteristics for extraction using progressively destructive conditions <i>if R fails at least one Level 3 solvent; no further comparative testing</i>
↓		
Evaluate T vs R and T vs C at Identified Discriminatory Study Condition Identified in Tier 5	$H_0: T \geq C$ versus $H_1: T < C$ and $H_0: T - R \geq \Delta$ versus $H_1: T - R < \Delta$  <b>If <math>T &lt; C</math> and <math>T - R &lt; \Delta</math></b> Conclude that T is superior to C & no worse than R by an amount $< \Delta$ ; T passes the study under Tier 5 for all Level 5 solvents  <b>STOP</b> no further testing	<b>If <math>T \geq C</math> and/or <math>T - R \geq \Delta</math></b> Conclude that T is not superior to C and/or is worse than R by an amount $\geq \Delta$ , if it fails at least one Level 5 solvent; T fails the study under Tier 5  <b>STOP</b> no further testing

581 The measure used to evaluate abuse by ingestion is the % opioid extraction, determined as follows: **(CONC\*V/ labeled strength of the R**  
 582 **product) \*100**, where CONC is the concentration of opioid in the solution that can be expelled from the syringe needle, and V is the volume of  
 583 the solution expelled.  
 584

### 585 Evaluation of the dissolution of opioid to determine abuse deterrence upon oral ingestion

586 Abuse by the oral route may also take the form of ingestion of a solid oral opioid drug product  
 587 itself (vs. the extracted opioid substance) after it has been mechanically manipulated, for  
 588 example, by cutting, grating, or milling. In order to simulate the release of the opioid from a  
 589 mechanically manipulated drug product in the gastrointestinal tract, a potential ANDA applicant  
 590 should conduct the comparative testing recommended below to determine the effect of  
 591 mechanical manipulation (e.g., cutting, grating, or milling) on the dissolution of the manipulated  
 592 product in 0.1 N hydrochloric acid (HCl).  
 593

594 The focus of the dissolution studies for this route of abuse is to assess the rate and extent of  
 595 dissolution of T product when compared to R product following the product's cutting, grating,  
 596 and milling. The recommended range of dissolution conditions are as follows: USP apparatus II  
 597 at 50 rpm, temperature 37°C, duration of 30-120 minutes, and volume 500 mL of 0.1N HCl.  
 598  
 599

600 The measure considered meaningful for this route of abuse % of opioid released upon  
 601 dissolution, determined as (CONC\*V/labeled strength of the R product) \*100, where CONC is  
 602 the concentration of opioid in the dissolution medium and V is the volume of the dissolution  
 603 medium. If R product is an agonist/antagonist combination, the ratio of % dissolution of agonist  
 604 to antagonist should be determined.

605 The tier-based approach for the comparative dissolution studies is based on progressive product  
 606 manipulation - cutting, then grating, then milling.

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#### 607 **Tier 1: Evaluation of dissolution for cut product**

608  
609 Identify discriminatory study condition. Approaches to mechanical manipulation of products to  
610 be tested are described in Appendix 1.

611 Evaluate R product. If % of opioid dissolution of cut  $R_M$  (M - manipulated) product is  $\geq 80\%$  in  
612 30 minutes, then R product is considered to have no abuse deterrence under this tier of testing.  
613 Therefore, no additional comparative testing of T to R products is needed. If % dissolution of  
614 cut  $R_M < 80\%$  in 30 minutes, the potential applicant should then characterize the % of opioid  
615 dissolution in 30 minutes of the intact  $R_I$  (I = intact) product.

616 Compare R and T products. Once the difference in dissolution between cut and intact ( $R_M - R_I$ )  
617 R product has been determined, the potential applicant should determine the difference between  
618 cut and intact T ( $T_M - T_I$ ) and compare it to ( $R_M - R_I$ ). If the change of dissolution of ( $T_M - T_I$ )  
619  $< (R_M - R_I)$ , the abuse deterrence of T product should be tested further under Tier 2 conditions.  
620 If the dissolution change of ( $T_M - T_I$ )  $\geq (R_M - R_I)$ , then T is less abuse-deterrent than R.

#### 621 **Tier 2: Evaluation of dissolution for grated product**

622 Identify discriminatory study condition. Approaches to mechanical manipulation of products to  
623 be tested are described in Appendix 1.

624 Evaluate R product. If % of opioid dissolution of grated  $R_M$  is  $\geq 80\%$  in 30 minutes, then R  
625 product is considered to have no abuse deterrence under this tier of testing. Therefore, no  
626 additional comparative testing of T product to R product is needed. If % dissolution of grated  
627  $R_M < 80\%$  in 30 minutes, the potential applicant should then characterize the % of opioid  
628 dissolution in 30 minutes of  $R_I$ .

629 Compare R and T products. Once the difference in dissolution between grated and intact ( $R_M -$   
630  $R_I$ ) R product has been determined, the potential applicant should determine the difference  
631 between the grated and intact ( $T_M - T_I$ ) T product and compare it to ( $R_M - R_I$ ). If the dissolution  
632 change of ( $T_M - T_I$ )  $< (R_M - R_I)$ , the abuse deterrence of T product should be tested further under  
633 Tier 3 conditions. If the dissolution change of ( $T_M - T_I$ )  $\geq (R_M - R_I)$ , then T product is less  
634 abuse-deterrent than R.

#### 635 **Tier 3: Evaluation of dissolution for milled product**

636 Identify discriminatory study condition. Approaches to mechanical manipulation of products to  
637 be tested are described in Appendix 1.

638 Evaluate R product. If % of opioid dissolution of milled R product is  $\geq 80\%$  in 30 minutes, then  
639 R product is considered to have no abuse deterrence under this tier of testing. Therefore, no  
640 additional comparative testing of T product to R product is needed. If % dissolution of  $R_M < 80\%$   
641 in 30 minutes, the potential applicant should then characterize the % of opioid dissolution in 30  
642 minutes of  $R_I$ .

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643 Compare R and T products. Once the difference in dissolution between milled and intact ( $R_M -$   
644  $R_I$ ) R product has been determined, the potential applicant should determine the difference for  
645 the milled and intact ( $T_M - T_I$ ) T product and compare it to ( $R_M - R_I$ ). If the dissolution change  
646 of  $(T_M - T_I) < (R_M - R_I)$ , then T product is no less abuse-deterrent than R. If the dissolution  
647 change of  $(T_M - T_I) \geq (R_M - R_I)$ , then T product is less abuse-deterrent than R.

648 In addition to the comparative testing of change in dissolution, the potential applicant should also  
649 provide comparative data of  $R_M$  and  $T_M$  for R and T products, respectively, and time-release  
650 profiles of opioid to the time point where 80% of the opioid has been released from the drug  
651 product for R and T products at the conditions tested. This information will be used as  
652 supportive evidence for comparing the abuse deterrence of R and T products.

653  
654 Table 3 illustrates the tier-based approach for evaluating the dissolution of opioids for abuse by  
655 ingestion, as described above.

656  
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658 Table 3: Evaluation of Dissolution (Abuse by Ingestion)

<b>TIER 1</b>		
<b>Cut Product Study Condition</b>		
Dissolution Conditions: USP apparatus II at 50 rpm at Temperature 37°C for Duration of 30–120 minutes in Volume 500 mL of 0.1N HCl		
H <sub>0</sub> : R <sub>M</sub> ≥ 80% versus H <sub>1</sub> : R <sub>M</sub> < 80%		
Evaluate the R Product Dissolution	If R <sub>M</sub> < 80% Conclude that the 30 minute % dissolution of R <sub>M</sub> is less than 80% ↓	If R <sub>M</sub> ≥ 80% Conclude that the % dissolution of R <sub>M</sub> in 30 minutes is greater than or equal to 80%; no further comparative testing
	Characterize the 30 minute % dissolution of R <sub>i</sub> ↓	
Evaluate the R Dissolution Change versus the T Dissolution Change	H <sub>0</sub> : (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) ≥ 0 versus H <sub>1</sub> : (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) < 0 If (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) < 0 Conclude that the % dissolution change in T is less than the % dissolution change in R; T passes the study under Tier 1  <b>CONTINUE</b> to Tier 2 ↓	If (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) ≥ 0 Conclude that the % dissolution change in T is equal to or greater than % dissolution change in R; T fails the study under Tier 1  <b>STOP</b> no further testing
<b>TIER 2</b>		
<b>Grated Product Study Condition</b>		
Dissolution Conditions: USP apparatus II at 50 rpm at Temperature 37°C for Duration of 30–120 minutes in Volume 500 mL of 0.1N HCl		
H <sub>0</sub> : R <sub>M</sub> ≥ 80% versus H <sub>1</sub> : R <sub>M</sub> < 80%		
Evaluate the R Product Dissolution	If R <sub>M</sub> < 80% Conclude that the 30 minute % dissolution of R <sub>M</sub> is less than 80% ↓	If R <sub>M</sub> ≥ 80% Conclude that the % dissolution of R <sub>M</sub> in 30 minutes is greater than or equal to 80%; no further comparative testing
	Characterize the 30 minute % dissolution of R <sub>i</sub> ↓	
Evaluate the R Dissolution Change versus the T Dissolution Change	H <sub>0</sub> : (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) ≥ 0 versus H <sub>1</sub> : (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) < 0 If (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) < 0 Conclude that the % dissolution change in T is less than the % dissolution change in R; T passes the study under Tier 1  <b>CONTINUE</b> to Tier 2 ↓	If (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) ≥ 0 Conclude that the % dissolution change in T is equal to or greater than % dissolution change in R; T fails the study under Tier 1  <b>STOP</b> no further testing
<b>TIER 3</b>		
<b>Milled Product Study Condition</b>		
Dissolution Conditions: USP apparatus II at 50 rpm at Temperature 37°C for Duration of 30–120 minutes in Volume 500 mL of 0.1N HCl		
H <sub>0</sub> : R <sub>M</sub> ≥ 80% versus H <sub>1</sub> : R <sub>M</sub> < 80%		
Evaluate the R Product Dissolution	If R <sub>M</sub> < 80% Conclude that the 30 minute % dissolution of R <sub>M</sub> is less than 80% ↓	If R <sub>M</sub> ≥ 80% Conclude that the % dissolution of R <sub>M</sub> in 30 minutes is greater than or equal to 80%; no further comparative testing
	Characterize the 30 minute % dissolution of R <sub>i</sub> ↓	
Evaluate the R Dissolution Change versus the T Dissolution Change	H <sub>0</sub> : (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) ≥ 0 versus H <sub>1</sub> : (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) < 0 If (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) < 0 Conclude that the % dissolution change in T is less than the % dissolution change in R; T passes the study under Tier 1  <b>STOP</b> no further testing	If (T <sub>M</sub> - T <sub>i</sub> ) - (R <sub>M</sub> - R <sub>i</sub> ) ≥ 0 Conclude that the % dissolution change in T is equal to or greater than % dissolution change in R; T fails the study under Tier 1  <b>STOP</b> no further testing

659 The measure used to evaluate abuse by ingestion is the % of opioid released upon dissolution, determined as follows: (CONC\*V/ labeled  
 660 strength of the R product) \*100, where CONC is the concentration of opioid in the dissolution medium, and V is the volume of the dissolution  
 661 medium.  
 662

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665 **APPENDIX 4: ABUSE BY INSUFFLATION (NASAL ROUTE)**

666 Abuse by insufflation generally involves snorting of milled solid oral opioid drug products. The  
667 known approaches to deterring insufflation include reduced availability and reduced likability of  
668 the abused product. To evaluate abuse deterrence for the nasal route of abuse, a potential ANDA  
669 applicant should test the T product for both reduced availability and reduced likability.

670 The measure considered meaningful for evaluation of reduced availability is the % mass of fine  
671 particles (<500 µm) available for insufflation.

672 **Reduced Availability**

673 Reduction in opioid availability may be accomplished by inclusion of excipients that impart  
674 hardness to the formulation and make it difficult to mill, retard the rate of release of the opioid  
675 from the milled product, and/or increase the size of the drug product, thereby increasing the  
676 amount of milled powder and proportionally decreasing the amount of opioid to be insufflated.

677 Consequently, the amount of opioid available following insufflation of milled R and T products  
678 is a function of several factors, including but not limited to the ease of milling of the drug  
679 product, the amount of milled product available for insufflation, the degree of effort needed for  
680 manipulation, and the rate of release of opioid from the milled product. Therefore, evaluation of  
681 a product's availability includes measuring the size and amount of particles available for  
682 insufflation and measuring the rate and extent of absorption of milled T and R products  
683 following nasal administration. The potential applicant can propose alternative in vitro  
684 evaluation methods to assess the abuse deterrence of T products if the methods provide reliable  
685 and predictive information on the pharmacokinetic behavior and performance of milled opioid  
686 products following insufflation.

687 The tier-based approach to the comparative studies for evaluating reduced availability of opioid  
688 when abused through the nasal route is based on the progressively more complex studies moving  
689 from in vitro study in Tier 1 to PK study in Tier 2.

690 Discriminatory study conditions:

691 Approaches to mechanical manipulation (milling) of products to be tested are described in  
692 Appendix 1. If the % mass of fine particles of T or R products is not <500 µm after milling for 5  
693 minutes (with and without thermal pre-treatment), alternative approaches such as crushing,  
694 hammering, or grating after thermal pre-treatment can be used to generate particles of size < 500  
695 µm.

696 **Tier 1: Evaluation of milled T and R products**

697

698 Identify discriminatory study condition. As above.

699 Evaluate R product. If the % mass of fine particles (<500 µm) of R <10%, then R is deemed



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700 unsuitable for insufflation. No comparative testing of T product to R product is needed.

701 Compare R and T products. T product is milled under the same milling condition. If the % mass  
702 of fine particles (<500 µm) of T <10%, then T is deemed unsuitable for insufflation. No further  
703 comparative testing of T and R products is needed. If the % mass of fine particles (<500 µm) of  
704 T ≥10%, testing should proceed to Tier 2.

705 Testing should proceed to Tier 2 if R product has been demonstrated to have abuse deterrence for  
706 the nasal route of abuse by PK or human abuse potential studies of the R product and T product  
707 can be milled into fine particles with % mass of fine particles (<500 µm) ≥10%.

#### **Tier 2: Evaluation of milled and insufflated R and T products in a pharmacokinetic study**

709 Identify milling condition. As above.

710 Evaluate R product. If information is available, for example, from a previously conducted PK  
711 study in which R product delivered through the nasal route demonstrated superiority to a  
712 comparator product in terms of C<sub>max</sub> and AUC (see Section III), the potential applicant may  
713 consider testing T product in a comparative PK study.

714 Compare R and T products. If the rate and extent of absorption of the opioid from insufflated R  
715 is not statistically significantly different from that of insufflated T, then T product passes the test.  
716 Otherwise, T product is considered to be less abuse-deterrent than R product.

717 The tier-based approach to testing products for nasal availability, as just described, is illustrated  
718 in Figure 5.

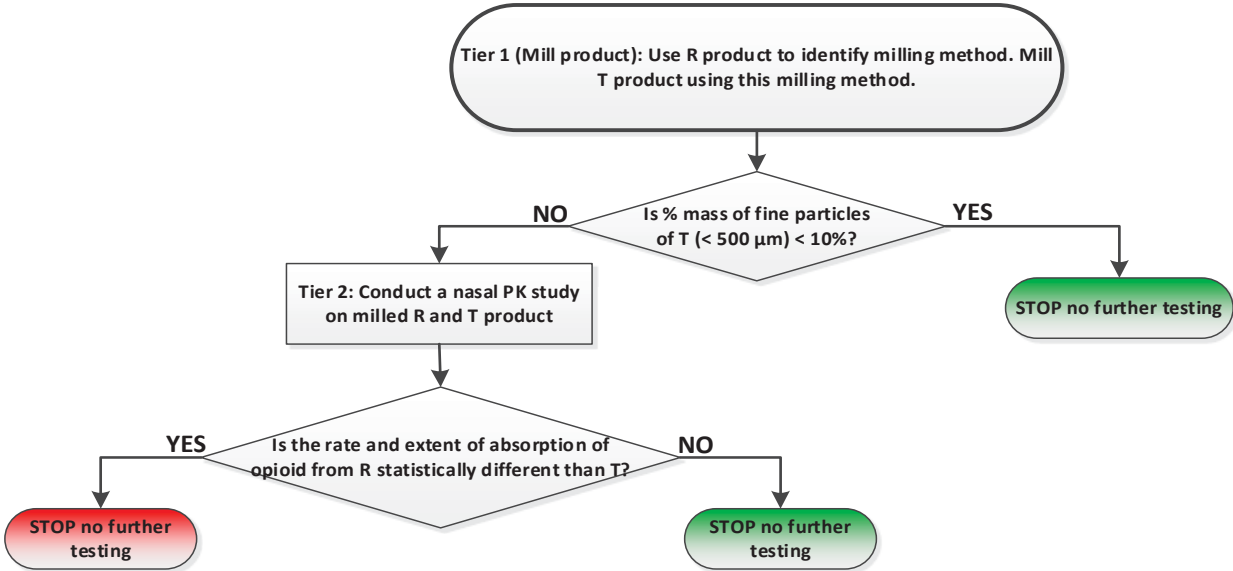
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724 Figure 5: Decision Tree for Evaluation of Abuse Deterrence Potential (Abuse by

725 Insufflation).

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### 726 **Reduced Likability**

727 Reduced likability may be accomplished by addition of excipients that produce an unpleasant  
728 effect (e.g., nasal mucosal irritation) if the dosage form is milled and insufflated.

729 Consequently, testing for demonstration of reduced likability should be conducted when R  
730 product contains an excipient that functions as an aversive agent to produce an unpleasant effect  
731 upon mechanical manipulation and insufflation of the drug product. This testing should focus on  
732 determination of the type and quantity of aversive substances in T product in comparison to R  
733 product.

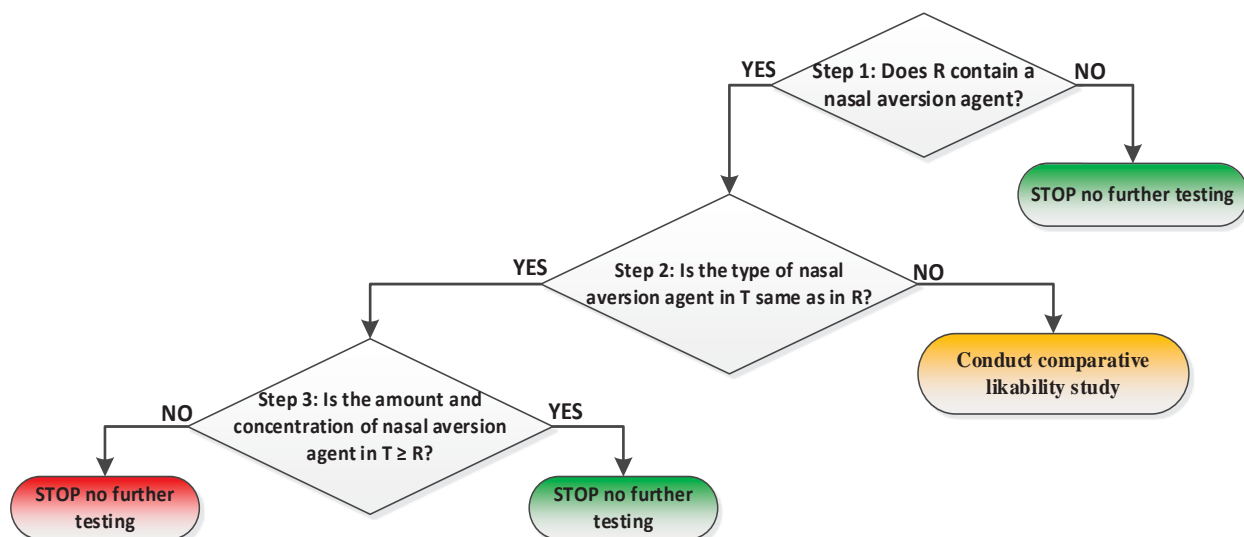
734 Identify discriminatory study condition. Identification of discriminatory study conditions is not  
735 relevant for this type of comparative studies; therefore it is not described in this section.

736 Evaluate R product. If R product does not contain an aversive agent in its formulation, then no  
737 comparative testing of R and T products is needed. If R product contains an aversive agent,  
738 sponsors should evaluate T product.

739  
740 Evaluate T product. If T product contains the same aversive agent as R product, the aversive  
741 agent in T product should be quantified. If the amount and concentration of aversive agent in T  
742  $\geq$  R, then T product is considered to have similar abuse deterrence and no additional testing is  
743 needed. If the amount or concentration of aversive agent in T  $<$  R, then T product is considered  
744 to be less abuse-deterrent than R product.

745  
746 Compare R and T products. If T product contains a different aversive agent than R product, a  
747 comparative likability (abuse potential) study may need to be conducted to determine the abuse  
748 deterrence of T product in comparison to R product. The potential applicant should submit the  
749 study protocol to the Agency for comments before conducting the study.

750 The proposed testing for comparison of T and R products' likability is illustrated in Figure 6.



751  
752 Figure 6: Evaluation of Reduced Likability (Abuse by Insufflation)

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753 **APPENDIX 5: ABUSE BY SMOKING (INHALATION ROUTE)**

754 Abuse by smoking involves the sublimation of an opioid salt or free-basing of the salt with  
755 sublimation following ignition. To evaluate the abuse deterrence for the inhalation route, a  
756 potential ANDA applicant should determine the amount of sublimated opioid salt or free base for  
757 intact and following manipulation of the drug product.

758 The measure used to evaluate abuse by smoking is the % of opioid sublimation calculated as:  
759 (sublimed amount/labeled strength of the R product)\* 100, where the sublimated amount is the  
760 amount of drug available for smoking following ignition of the product. If R product is an  
761 agonist/antagonist combination product, the ratio of % sublimation of agonist and antagonist  
762 should be determined.

763 Study conditions:

764 Approaches to mechanical manipulation (milling) of products to be tested are described in  
765 Appendix 1. The potential applicant should use a household coffee grinder or other household  
766 milling appliance. The smoking test should be conducted on intact and milled product at 233°C  
767 (the ignition temperature of paper). For this comparative study, intact and milled R and T  
768 products should be compared at 233°C for 2-15 minutes.

769 The tier-based approach to comparative sublimation is based on using different methods to  
770 prepare the product for smoking, starting with direct sublimation of the intact and milled product  
771 in Tier 1, to free-basing the opioid from the intact and milled product prior to sublimation of the  
772 free base in Tier 2 (Table 4).

773 **Tier 1: Sublimation of intact and milled products**

774 Identify study condition. Approaches to mechanical manipulation (milling) of products to be  
775 tested are described in Appendix 1. If T or R product cannot be milled to generate particles of <  
776 1 mm after attempted milling for 5 minutes (with and without thermal pre-treatment), alternate  
777 approaches such as crushing or grating after thermal pre-treatment can be used to generate  
778 particles of size < 1 mm.

779 Evaluate R and T products. Determine the % of opioid sublimation of intact and milled R  
780 product. Using the same method, determine the % opioid sublimation of intact and milled T  
781 product.

782 Compare R and T products. Statistically compare the abuse deterrence of T versus R products.  
783 If the % of opioid sublimation of T > R, then T product is less abuse-deterrent than R product. If  
784 the % opioid sublimation of T ≤ R and the opioid product tested is not a salt, no further  
785 comparative testing of T product to R product is needed. If the % of opioid sublimation of T ≤ R  
786 and the opioid product is a salt, the abuse deterrence of T should be tested further in Tier 2.

787 **Tier 2: Sublimation of free base retrieved from intact and milled products**

788 Identify study condition. Convert the opioid salt in intact and milled R and T products to free

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789 base with a household reagent (e.g., baking soda). Dry the resulting mixtures obtained from R  
790 and T products at 233°C for 2-15 minutes.

791  
792 Evaluate R and T products. Determine the % of opioid sublimation of the R product after  
793 conversion to a free base. Using the same method, determine the % opioid sublimation of T  
794 product.

795 Compare R and T products. Statistically compare the abuse deterrence of T versus R products.  
796 If the % of opioid sublimation of  $T \leq R$ , T product is no less abuse-deterrent than the R product.  
797 If the % of opioid sublimation of  $T > R$ , T product is less abuse-deterrent than the R product.

798 Table 4 illustrates the tier-based approach for evaluating the sublimation of opioids for abuse by  
799 smoking, as described above.

800  
801 Table 4. Evaluation of Sublimation (Abuse by Smoking)

<b>TIER 1</b>		<b>Study Condition</b>	
		<b>Temperature 233°C / Duration of 2–15 minutes</b>	
Identify Study Condition	Determine the % of opioid sublimation of the intact and milled R product. Using the same method, determine the % opioid sublimation of intact and milled T product ↓		
Evaluate the R Sublimation versus the T Sublimation	<b>H<sub>0</sub>: T &gt; R versus H<sub>a</sub>: T ≤ R</b>		
	<b>If <math>T \leq R</math> and % opioid is a salt</b> Conclude that % opioid sublimation of T is less than R; T passes the study under Tier 1  <b>CONTINUE</b> to Tier 2  ↓	<b>If <math>T \leq R</math> and % opioid is NOT a salt</b> Conclude that % opioid sublimation of T is less than R; T passes the study under Tier 1  <b>STOP</b> no further testing	<b>If <math>T &gt; R</math></b> Conclude that % opioid sublimation of T is greater than or equal to R  <b>STOP</b> no further testing
<b>TIER 2</b>		<b>Condition</b>	
		<b>Temperature 233°C / Duration of 2–15 minutes</b>	
Identify Study Condition	Convert the opioid salt in intact and milled R and T products to free base with a household reagent. Dry the resulting mixtures obtained from the R and T products at 233°C for 2 – 15 minutes.		
Evaluate the R Sublimation versus the T Sublimation	<b>H<sub>0</sub>: T &gt; R versus H<sub>a</sub>: T ≤ R</b>		
	<b>If <math>T \leq R</math></b> Conclude that % opioid sublimation of T is less than R; T passes the study under Tier 2  <b>STOP</b> no further testing	<b>If <math>T &gt; R</math></b> Conclude that % opioid sublimation of T is greater than or equal to R; T fails the study under Tier 2  <b>STOP</b> no further testing	

802  
803  
804 The measure used to evaluate abuse by smoking is the **% of opioid sublimation**, determined as follows: **(sublimed amount/ labeled strength of the R product)\* 100**, where the sublimed amount is the amount of drug available for smoking following ignition of product.