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DRAFT GUIDANCE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[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

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

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

II. BACKGROUND

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

[1] 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.

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

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

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

III. ABUSE DETERRENCE OF GENERIC SOLID ORAL OPIOID DRUG PRODUCTS

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

[2] 2015 guidance on *Abuse-Deterrent Opioid – Evaluation and Labeling*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf

[3] Smith, S M, Dart R C, Katz N P, et al., 2013, Classification and Definition of Misuse, Abuse, and Related Events in Clinical Trials: ACTTION Systematic Review and Recommendations, Pain, 154:2287-2296.

[4] Ibid.

the inactive ingredients and composition of the generic drug are not unsafe under the conditions of use prescribed, recommended, or suggested in the labeling.[5]

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

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

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

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

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

[5] See section 505(j)(2)(A) and (j)(4) of the Federal Food, Drug, and Cosmetic Act.
[6] See FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), Preface at vii.
[7] 2015 guidance on *Controlled Correspondence Related to Generic Drug Development*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM411478.pdf

according to the following general principles:

- **Tier-based approach to testing.** FDA recommends that potential ANDA applicants follow a tier-based approach to efficiently compare a T product to its R product and limit the number of tests required for evaluating the abuse deterrence of T product. This tier-based approach allows for hierarchical testing, starting with simple and gentle manipulations of the product in in vitro studies (Tier 1) and progressing to more destructive mechanical and chemical manipulations until R product's abuse deterrence is defeated or compromised, or T product is shown to be less abuse-deterrent than R product.

- **Evaluation of Abuse Deterrence.** The evaluation of the abuse deterrence of the T product should be based on its performance relative to R product. The proposed generic product need not have the same formulation design as the R product. In order to adequately compare R and T products, a potential ANDA applicant should identify the R product's abuse deterrence for all routes of abuse using the tier-based approach described in this guidance. If R product has not been found by the potential applicant to have any abuse deterrence for a particular route of abuse, the potential applicant should summarize the studies conducted and the results to support the applicant's assessment that the RLD has no abuse deterrence with respect to that route and explain why there is no need to test its T product in comparative in vitro or other studies for that route. The evaluation of the abuse deterrence of T product should be based on the potential applicant's best understanding of the abuse deterrence of R product, the potential routes of abuse, and specific measures meaningful to the evaluation of abuse by those routes. For example, the measure of abuse deterrence relevant to abuse by injection is the % of opioid that can be extracted from the product formulation and expelled from a syringe under the conditions specified in Appendix 2.

- **Use of control.** Manipulation of an opioid product is a function of several factors including, but not limited to, tampering skills, time, and tampering resources available. The abuse-deterrent properties of currently approved drug products are not absolute, and can eventually be compromised or defeated. Therefore, it is important to identify appropriate discriminatory study conditions to compare R and T products. For certain comparative studies (e.g., extractability studies), such discriminatory study conditions should be identified by including a control product (referred to in this guidance as "C product") and comparing it to R product in order to identify the abuse deterrence of R product. Potential ANDA applicants should select an appropriate C product for their proposed T product. When available, C product should be a non-abuse-deterrent version of the opioid R product that contains the same active pharmaceutical ingredient (API) as the R product.[8]

[8] 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.

- **Identification of discriminatory study conditions.** The parameters for the discriminatory study conditions should lie within the range specified in this guidance for different routes of abuse (Appendices 2-5). In order to determine the abuse deterrence of T product by, for example, the injection route, a potential ANDA applicant should first identify the in vitro discriminatory study conditions under which the % extraction of opioid from R product is statistically less than the % extraction of opioid from C product, i.e., the conditions under which R product is statistically superior to C product[9]. The potential applicants should then compare the % extraction of opioid of T product to R product under the same discriminatory study conditions.

- **Comparison of R and T products.** Once the in vitro discriminatory study conditions have been identified, a potential ANDA applicant should perform the recommended statistical comparisons[10] for each of the different routes of abuse as recommended in Section VIII and as shown in Appendices 2-5.

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

V. ROUTES OF ABUSE

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

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

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

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

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

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

[9] Study conditions that demonstrate that R product is statistically superior to the C product aid in validation of the discriminatory study conditions chosen.

[10] T product should be no worse than the R product when tested using discriminatory study conditions.

chemically manipulated products, as described in Appendix 5.

VI. COMPARATIVE IN VITRO STUDIES

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

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

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

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

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

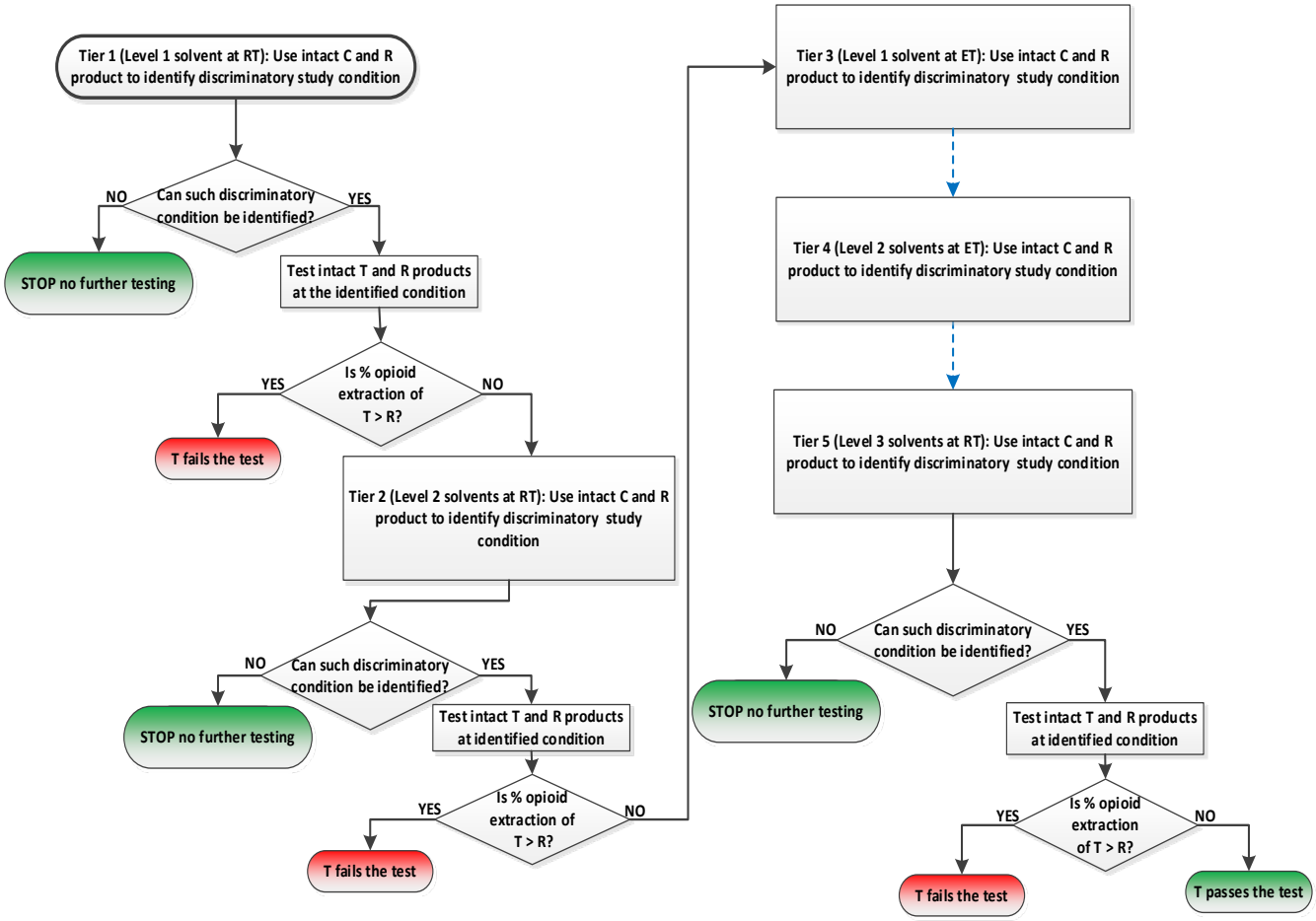


Figure 1: Decision Tree for Evaluation of Extractability of Intact Product (Oral Route). RT – Room temperature, ET – Elevated temperature

VII. OTHER CONSIDERATIONS

A. Multiple Strengths

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

[11] 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.

B. Pharmacokinetic Studies

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

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

C. Other Studies

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

VIII. DATA ANALYSIS

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

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

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

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

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

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

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

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

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

[12] Berger RL, 1982, Multiparameter Hypothesis Testing and Acceptance Sampling, Technometrics, 24:295-300.
[13] 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.

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

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

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

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

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

IX. ADDITIONAL STUDIES

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

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

APPENDIX 1: MECHANICAL MANIPULATION

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

1. Cutting

As illustrated in figure 2 below:

- Cutting without thermal pre-treatment: If a drug product can be cut in less than 5 minutes at room temperature (RT) into 10 or more small pieces using a knife, no thermal pre-treatment is needed.

- Cutting with thermal pre-treatment: If a drug product cannot be cut at room temperature, thermal pre-treatment should be used (e.g., freezing at -20°C or heating).

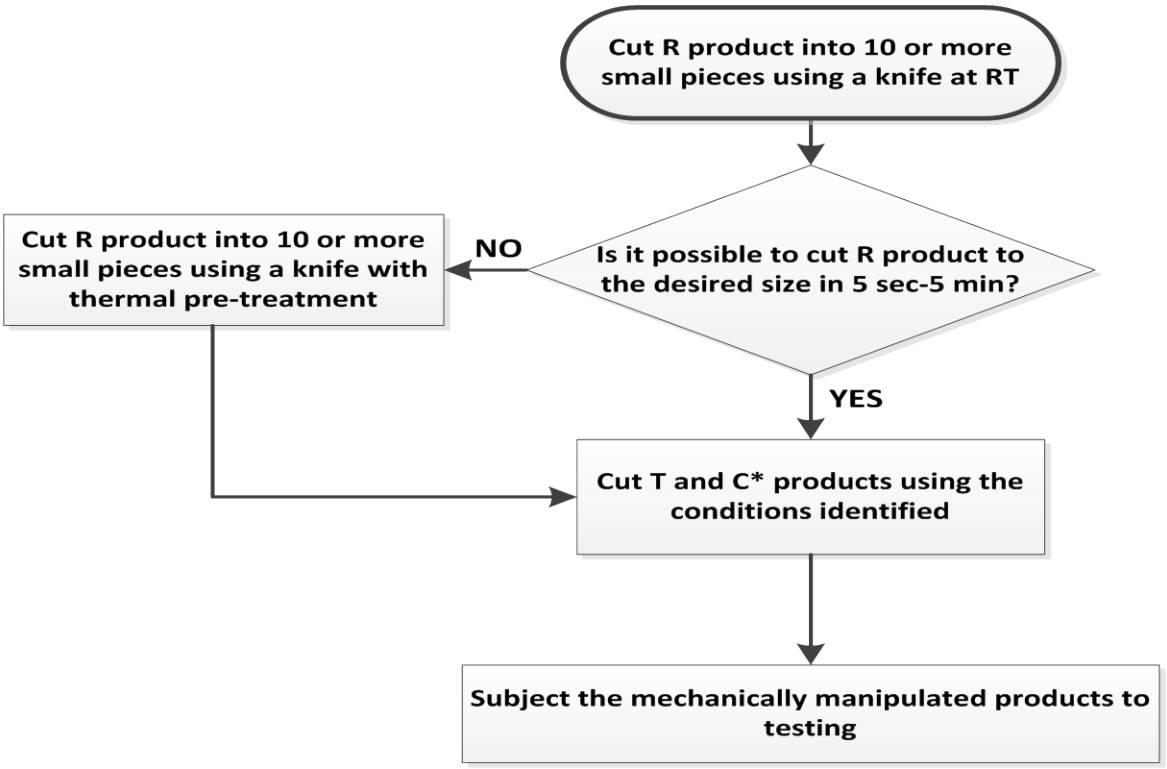


Figure 2: Mechanical Manipulation by Cutting for Solid Oral Opioid Drug Products

2. Grating

As illustrated in figure 3 below:

- Grating without thermal pre-treatment: If a drug product can be grated within 5 seconds to 5 minutes at RT to a size less than 1mm using a household grater, no thermal pre-treatment is needed.

- Grating with thermal pre-treatment: If a drug product cannot be grated at RT, thermal pre-treatment should be used (e.g., freezing at -20°C or heating).

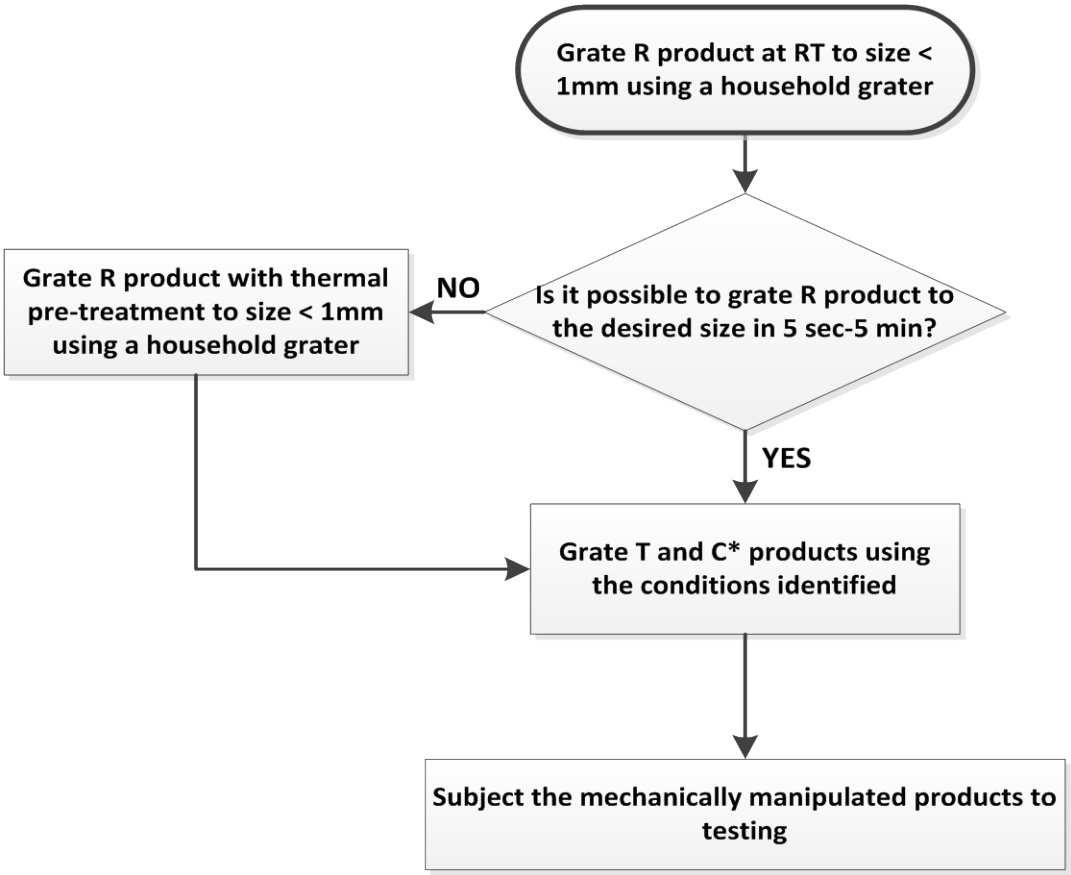


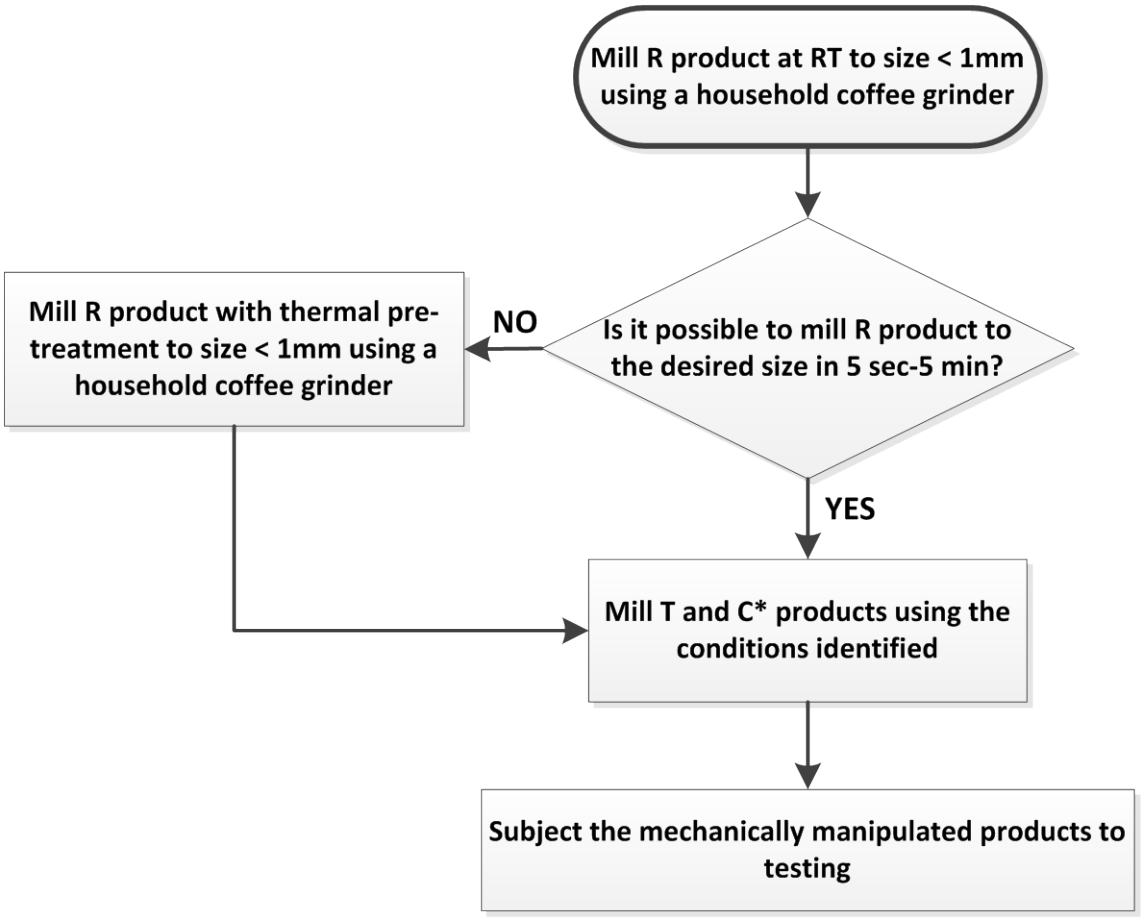
Figure 3: Mechanical Manipulation by Grating for Solid Oral Opioid Drug Products

3. Milling

As illustrated in figure 4 below:

- 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.

- If a drug product cannot be milled at RT, thermal pre-treatment should be used (e.g., freezing at -20°C or heating).



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

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

APPENDIX 2: ABUSE BY INJECTION (PARENTERAL ROUTE)

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

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

The measure considered meaningful for evaluating the abuse deterrence relevant to abuse by injection is the % of opioid extraction determined as follows: (CONC*V/labeled strength of the R 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 the solution expelled. If R product is an agonist/antagonist combination, the ratio of the % of opioid extraction of agonist to antagonist should be determined.

<u>Discriminatory Study Conditions</u>:

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

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

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

[14] U.S. Pharmacopoeia (USP) controlled room temperature (20° – 25°C)
[15] 2015 final guidance on *Abuse-Deterrent Opioid – Evaluation and Labeling*

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

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

Evaluate the R product. If a discriminatory study condition cannot be identified for intact R product, intact R product is considered to have no abuse deterrence under this tier of testing. Therefore, no comparative testing of T product to R product is needed. In addition, if a discriminatory study condition cannot be identified for grated or milled[16] R product, R is considered to have no abuse deterrence under this tier of testing for grated and milled product.[17] Therefore, no further comparative testing of the T product to the R product is needed.

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

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

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

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

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

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

Evaluate the R product. If the discriminatory study condition cannot be identified for intact R, intact R is considered to have no abuse deterrence under this tier of testing. Therefore, no comparative testing of the T product to the R product is needed. In addition, if the discriminatory study condition cannot be identified for grated[15] or milled[16] R product, R is considered to have no abuse deterrence under this tier of testing.[17] Therefore, no further comparative testing of T product to R product is needed.

[16] 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.

[17] 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.

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

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

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

TIER 1	**Study Conditions** **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: $R < C$**		
	If $R < C$ *Conclude that R is superior to C* ↓		**If $R \geq C$** *Conclude that R is not superior to C; no further comparative testing*
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: $T - R < \Delta$**		
	If $T < C$ and $T - R < \Delta$ *Conclude that T is superior to C & no worse than R by an amount < Δ; T passes the study under Tier 1* **CONTINUE** to Tier 2 ↓	**If $T \geq C$ and/or $T - R \geq \Delta$** *Conclude that T is not superior to C and/or is worse than R by an amount ≥ Δ; T fails the study under Tier 1* **STOP** no further testing	**STOP** no further testing
TIER 2	**Study Conditions** **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: $R < C$**		
	If $R < C$ *Conclude that R is superior to C* ↓		**If $R \geq C$** *Conclude that R is not superior to C; no further comparative testing*
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: $T - R < \Delta$**		
	If $T < C$ and $T - R < \Delta$ *Conclude that T is superior to C & no worse than R by an amount < Δ; T passes the study under Tier 2* **STOP** no further testing	**If $T \geq C$ and/or $T - R \geq \Delta$** *Conclude that T is not superior to C and/or is worse than R by an amount ≥ Δ; T fails the study under Tier 2* **STOP** no further testing	**STOP** no further testing

The measure used to evaluate abuse by injection is **the % opioid extraction** determined as follows**: (CONC*V/ labeled strength of the R 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 the solution expelled.

APPENDIX 3: ABUSE BY INGESTION (ORAL ROUTE)

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

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

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

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

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

The measure considered meaningful for this route of abuse is the % of opioid extraction determined as follows: (CONC*V/labeled strength of the R product) *100, where CONC is the concentration of opioid in the extraction medium and V is the volume of the extraction solution. If R product is an agonist/antagonist combination, the ratio of % extraction of agonist and antagonist should be determined.

<u>Discriminatory study conditions</u>:

[18] U.S. Pharmacopoeia (USP) controlled room temperature (20° – 25°C)

[19] 2015 final guidance on *Abuse-Deterrent Opioid – Evaluation and Labeling*

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

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

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

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

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

Evaluate R product. If the discriminatory study condition cannot be identified for intact R, intact R is considered to have no abuse deterrence under this tier of testing. Therefore no comparative testing of T product to R product is needed. In addition, if the discriminatory study condition cannot be identified for cut, grated, or milled R product, R product is considered to have no abuse deterrence under this tier of testing for cut, grated, and milled product.[20] Therefore, no comparative testing of R product to T product is needed.

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

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

[20] 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.

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

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

Evaluate R product. If the discriminatory study condition cannot be identified for intact R product in any one of the Level 2 solvents, intact R product is considered to have no abuse deterrence under this tier of testing. Therefore, no comparative testing of T product to R product is needed. In addition, if the discriminatory study condition cannot be identified for cut, grated, or milled R product in any one of the Level 2 solvents, R product is considered to have no abuse deterrence under this tier of testing for cut, grated, and milled product.[21] Therefore, no comparative testing of T product to R product is needed.

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

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

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

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

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

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

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

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

Table 2: Evaluation of Extractability (Abuse by Ingestion)

TIER 1	**Study Condition** **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 **Δ < 10%**	**H_0: R ≥ C versus H_a: R < C**		
	If R < C *Conclude that R is superior C* ↓		**If R ≥ C** *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 ≥ C versus H_a: T < C and H_0: T − R ≥ Δ versus H_a: T − R < Δ**		
	If T < C and T − R < Δ *Conclude that T is superior to C & no worse than R by an amount < Δ; T passes the study under Tier 1* **CONTINUE** to Tier 2 ↓	**If T ≥ C and/or T − R ≥ Δ** *Conclude that T is not superior to C and/or is worse than R by an amount ≥ Δ; T fails the study under Tier 1* **STOP** no further testing	**STOP** no further testing
TIER 2	**Study Condition** **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 **Δ < 10%**	**H_0: R ≥ C versus H_a: R < C**		
	If R < C *Conclude that R is superior to C* *if R passes ALL Level 2 solvents* ↓		**If R ≥ C** *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 ≥ C versus H_a: T < C and H_0: T − R ≥ Δ versus H_a: T − R < Δ**		
	If T < C and T − R < Δ *Conclude that T is superior to C & no worse than R by the amount of Δ; T passes the study under Tier 2 for all Level 2 solvents* **CONTINUE** to Tier 3 ↓	**If T ≥ C and/or T − R ≥ Δ** *Conclude that T is not superior to C and/or is worse than R by an amount ≥ Δ, if it fails at least one Level 2 solvent. In that case, T fails the study under Tier 2* **STOP** no further testing	**STOP** no further testing
TIER 3	**Study Condition** **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 **Δ < 10%**	**H_0: R ≥ C versus H_a: R < C**		
	If R < C *Conclude that R is superior to C* ↓		**If R ≥ C** *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 ≥ C versus H_a: T < C and H_0: T − R ≥ Δ versus H_a: T − R < Δ**		
	If T < C and T − R < Δ *Conclude that T is superior to C & no worse than R by an amount < Δ; T passes the study under Tier 3* **CONTINUE** to Tier 4 ↓	**If T ≥ C and/or T − R ≥ Δ** *Conclude that T is not superior to C and/or is worse than R by an amount ≥ Δ; T fails the study under Tier 3* **STOP** no further testing	**STOP** no further testing

Table 2: Evaluation of Extractability (Abuse by Ingestion)

TIER 4	**Study Condition** **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.**		
Identify Discriminatory Extraction Study Condition and **Δ < 10%**	**H_0: R ≥ C versus H_a: R < C**		
	If R < C *Conclude that R is superior to C* *if R passes ALL Level 2 solvents* ↓		**If R ≥ C** *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 4	**H_0: T ≥ C versus H_a: T < C and H_0: T − R ≥ Δ versus H_a: T − R < Δ**		
	If T < C and T − R < Δ *Conclude that T is superior to C & no worse than R by an amount < Δ; T passes the study under Tier 4 for all Level 4 solvents* **CONTINUE** to Tier 5 ↓	**If T ≥ C and/or T − R ≥ Δ** *Conclude that T is not superior to C and/or is worse than R by an amount ≥ Δ, if it fails at least one Level 4 solvent; T fails the study under Tier 4* **STOP** no further testing	**STOP** no further testing
TIER 5	**Study Condition** **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**		
Identify Discriminatory Extraction Study Condition and **Δ < 10%**	**H_0: R ≥ C versus H_a: R < C**		
	If R < C *Conclude that R is superior to C* *if R passes ALL Level 3 solvents* ↓		**If R ≥ C** *Conclude that R does not have abuse deterrent characteristics for extraction using progressively destructive conditions* *if R fails at least one Level 3 solvent;* *no further comparative testing*
Evaluate T vs R and T vs C at Identified Discriminatory Study Condition Identified in Tier 5	**H_0: T ≥ C versus H_a: T < C and H_0: T − R ≥ Δ versus H_a: T − R < Δ**		
	If T < C **and T − R < Δ** *Conclude that T is superior to C & no worse than R by an amount < Δ; T passes the study under Tier 5 for all Level 5 solvents* **STOP** no further testing	**If T ≥ C** **and/or T − R ≥ Δ** *Conclude that T is not superior to C and/or is worse than R by an amount ≥ Δ, if it fails at least one Level 5 solvent; T fails the study under Tier 5* **STOP** no further testing	**STOP** no further testing

The measure used to evaluate abuse by ingestion is **the % opioid extraction**, determined as follows: **(CONC*V/ labeled strength of the R 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 the solution expelled.

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

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

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

The measure considered meaningful for this route of abuse % of opioid released upon dissolution, determined as (CONC*V/labeled 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 medium. If R product is an agonist/antagonist combination, the ratio of % dissolution of agonist to antagonist should be determined.

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

Tier 1: Evaluation of dissolution for cut product

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

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

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

Tier 2: Evaluation of dissolution for grated product

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

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

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

Tier 3: Evaluation of dissolution for milled product

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

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

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

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

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

Table 3: Evaluation of Dissolution (Abuse by Ingestion)

TIER 1	**Cut Product Study Condition** **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**		
Evaluate the R Product Dissolution	**H_0: $R_M \geq 80\%$ versus H_a: $R_M < 80\%$**		
	If $R_M < 80\%$ *Conclude that the 30 minute % dissolution of R_M is less than 80%* ↓ *Characterize the 30 minute % dissolution of R_I*		**If $R_M \geq 80\%$** *Conclude that the % dissolution of R_M in 30 minutes is greater than or equal to 80%; no further comparative testing*
Evaluate the R Dissolution Change versus the T Dissolution Change	**H_0: $(T_M - T_I) - (R_M - R_I) \geq 0$ versus H_a: $(T_M - T_I) - (R_M - R_I) < 0$**		
	If $(T_M - T_I) - (R_M - R_I) < 0$ *Conclude that the % dissolution change in T is less than the % dissolution change in R; T passes the study under Tier 1* **CONTINUE** to Tier 2 ↓	**If $(T_M - T_I) - (R_M - R_I) \geq 0$** *Conclude that the % dissolution change in T is equal to or greater than % dissolution change in R; T fails the study under Tier 1* **STOP** no further testing	**STOP** no further testing
TIER 2	**Grated Product Study Condition** **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**		
Evaluate the R Product Dissolution	**H_0: $R_M \geq 80\%$ versus H_a: $R_M < 80\%$**		
	If $R_M < 80\%$ *Conclude that the 30 minute % dissolution of R_M is less than 80%* ↓ *Characterize the 30 minute % dissolution of R_I*		**If $R_M \geq 80\%$** *Conclude that the % dissolution of R_M in 30 minutes is greater than or equal to 80%; no further comparative testing*
Evaluate the R Dissolution Change versus the T Dissolution Change	**H_0: $(T_M - T_I) - (R_M - R_I) \geq 0$ versus H_a: $(T_M - T_I) - (R_M - R_I) < 0$**		
	If $(T_M - T_I) - (R_M - R_I) < 0$ *Conclude that the % dissolution change in T is less than the % dissolution change in R; T passes the study under Tier 1* **CONTINUE** to Tier 2 ↓	**If $(T_M - T_I) - (R_M - R_I) \geq 0$** *Conclude that the % dissolution change in T is equal to or greater than % dissolution change in R; T fails the study under Tier 1* **STOP** no further testing	**STOP** no further testing
TIER 3	**Milled Product Study Condition** **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**		
Evaluate the R Product Dissolution	**H_0: $R_M \geq 80\%$ versus H_a: $R_M < 80\%$**		
	If $R_M < 80\%$ *Conclude that the 30 minute % dissolution of R_M is less than 80%* ↓ *Characterize the 30 minute % dissolution of R_I*		**If $R_M \geq 80\%$** *Conclude that the % dissolution of R_M in 30 minutes is greater than or equal to 80%; no further comparative testing*
Evaluate the R Dissolution Change versus the T Dissolution Change	**H_0: $(T_M - T_I) - (R_M - R_I) \geq 0$ versus H_a: $(T_M - T_I) - (R_M - R_I) < 0$**		
	If $(T_M - T_I) - (R_M - R_I) < 0$ *Conclude that the % dissolution change in T is less than the % dissolution change in R; T passes the study under Tier 1* **STOP** no further testing	**If $(T_M - T_I) - (R_M - R_I) \geq 0$** *Conclude that the % dissolution change in T is equal to or greater than % dissolution change in R; T fails the study under Tier 1* **STOP** no further testing	**STOP** no further testing

The measure used to evaluate abuse by ingestion is the **% of opioid released upon dissolution**, determined as follows: **(CONC*V/ labeled 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 medium.

APPENDIX 4: ABUSE BY INSUFFLATION (NASAL ROUTE)

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

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

Reduced Availability

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

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

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

<u>Discriminatory study conditions</u>:

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

Tier 1: Evaluation of milled T and R products

<u>*Identify discriminatory study condition*</u>. As above.

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

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

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

Testing should proceed to Tier 2 if R product has been demonstrated to have abuse deterrence for the nasal route of abuse by PK or human abuse potential studies of the R product and T product 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

Identify milling condition. As above.

Evaluate R product. If information is available, for example, from a previously conducted PK study in which R product delivered through the nasal route demonstrated superiority to a comparator product in terms of C_{max} and AUC (see Section III), the potential applicant may consider testing T product in a comparative PK study.

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

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

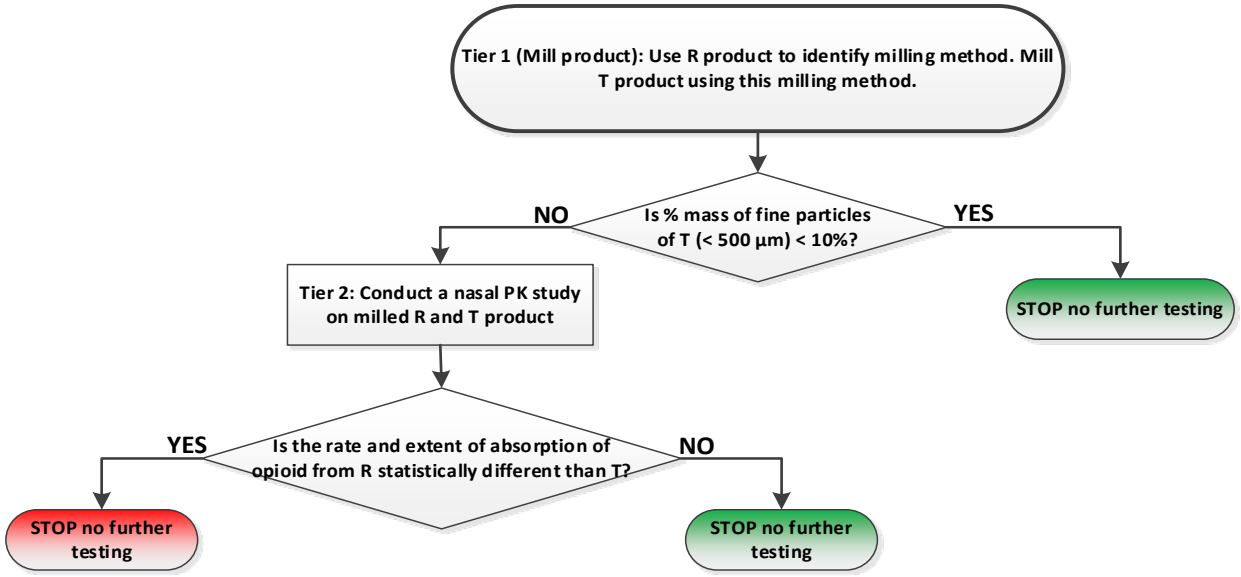


Figure 5: Decision Tree for Evaluation of Abuse Deterrence Potential (Abuse by Insufflation).

Reduced Likability

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

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

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

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

Evaluate T product. If T product contains the same aversive agent as R product, the aversive agent in T product should be quantified. If the amount and concentration of aversive agent in T ≥ R, then T product is considered to have similar abuse deterrence and no additional testing is needed. If the amount or concentration of aversive agent in T < R, then T product is considered to be less abuse-deterrent than R product.

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

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

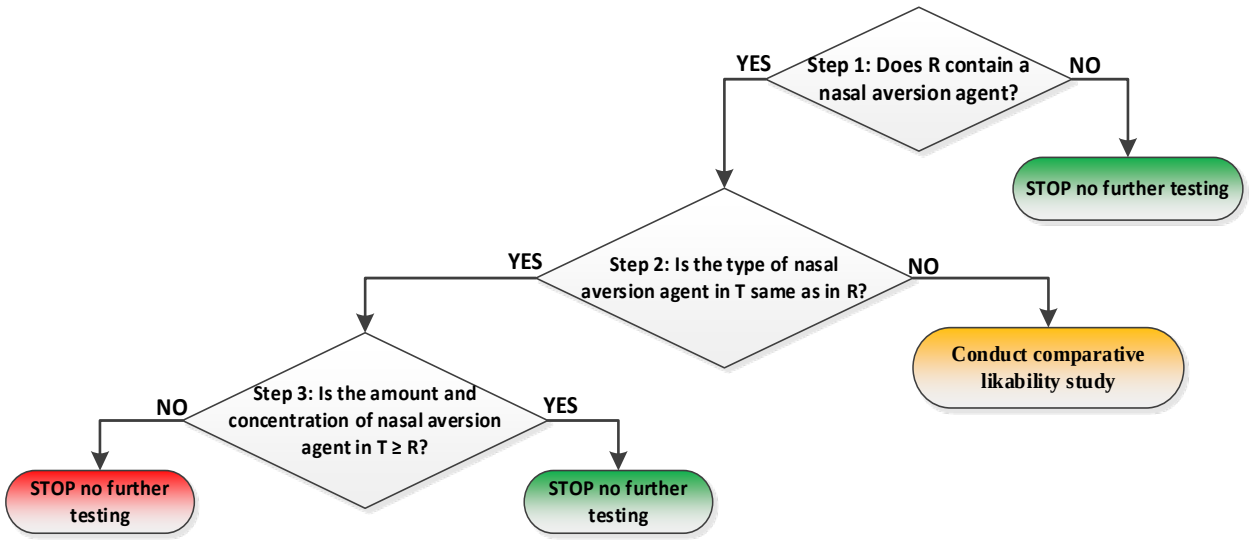


Figure 6: Evaluation of Reduced Likability (Abuse by Insufflation)

APPENDIX 5: ABUSE BY SMOKING (INHALATION ROUTE)

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

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

Study conditions:

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

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

Tier 1: Sublimation of intact and milled products

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

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

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

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

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

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

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

Compare R and T products. Statistically compare the abuse deterrence of T versus R products. If the % of opioid sublimation of T ≤ R, T product is no less abuse-deterrent than the R product. If the % of opioid sublimation of T > R, T product is less abuse-deterrent than the R product.

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

Table 4. Evaluation of Sublimation (Abuse by Smoking)

TIER 1	**Study Condition** **Temperature 233°C / Duration of 2–15 minutes**		
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	**H_0: T > R versus H_a: T ≤ R**		
	If T ≤ R and **% opioid is a salt** *Conclude that % opioid sublimation of T is less than R; T passes the study under Tier 1* **CONTINUE** to Tier 2 ↓	**If T ≤ R and** **% opioid is NOT a salt** *Conclude that % opioid sublimation of T is less than R; T passes the study under Tier 1* **STOP** no further testing	**If T > R** *Conclude that % opioid sublimation of T is greater than or equal to R* **STOP** no further testing
TIER 2	**Condition** **Temperature 233°C / Duration of 2–15 minutes**		
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	**H_0: T > R versus H_a: T ≤ R**		
	If T ≤ R *Conclude that % opioid sublimation of T is less than R; T passes the study under Tier 2* **STOP** no further testing	**If T > R** *Conclude that % opioid sublimation of T is greater than or equal to R; T fails the study under Tier 2* **STOP** no further testing	

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.