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

Guidance for Industry

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

November 2017
Generics

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This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist a person who plans to develop and submit an abbreviated new drug application (ANDA) (hereinafter potential ANDA applicant) to seek approval of a generic version of a solid oral opioid drug product that references an opioid drug product with abuse-deterrent properties described in its labeling. The guidance recommends studies, including comparative in vitro and pharmacokinetic (PK) studies, that the potential ANDA applicant should conduct and submit 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 widespread public health problem. One potentially important step toward the goal of creating safer opioid analgesics has been the development of opioid drug products with abuse deterrent properties. FDA considers development of these products a high public health priority.

[1] This guidance has been prepared by the Office of Generic Drugs, with the assistance of the Office Pharmaceutical Quality, in the Center for Drug Evaluation and Research at the Food and Drug Administration.

On April 1, 2015, FDA published in the *Federal Register* a notice of availability for its final guidance, *Abuse-Deterrent Opioids — Evaluation and Labeling* (80 FR 17765).[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 in that guidance as the intentional, nontherapeutic 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 the potential for some abuse of these products. Further, products with abuse-deterrent properties do not prevent addiction; opioid analgesics, even when taken as recommended, can result in addiction.

It is important that less costly generic versions of opioids that reference RLDs whose labeling describes abuse-deterrent properties are available to ensure 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 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/antagonist combinations, aversive agents, or a combination 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 such testing recommendations in future product-specific guidance. 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

For FDA to approve an ANDA, the Agency generally must find, among other things, that the generic drug[5] has the same active ingredient(s), conditions of use, dosage form, route of

[2] For the most recent version of any guidance referenced in this document, check the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[3] Smith SM, Dart RC, Katz NP, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. Pain 2013;154:2287-2296.
[4] Ibid.
[5] Throughout this guidance, we use the term *generic drug* to refer to a new drug product described in an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)).

administration, strength, and (with certain permissible differences) labeling as the RLD; it is bioequivalent to the RLD; the methods used in, and 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 the inactive ingredients and composition of the generic drug are not unsafe under the conditions of use prescribed, recommended, or suggested in the labeling.[6]

FDA considers a generic drug to be therapeutically equivalent to its RLD when certain conditions are met. *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated and that can be expected to have the same clinical effect and safety profile.[7] With certain limitations, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product/RLD.[8]

When a potential ANDA applicant develops a generic solid oral opioid drug product, the applicant should review the approved labeling for the RLD, particularly the information presented in the DRUG ABUSE AND DEPENDENCE section under 9.2 *Abuse*. If the summary in section 9.2 indicates that FDA has concluded that the product has properties that are expected to (or have been shown through postmarketing studies or trials to) deter abuse, in addition to other testing that may be needed to support the ANDA, the potential ANDA applicant should evaluate its proposed generic drug to show that it is no less abuse deterrent than the RLD with respect to **all** of the potential routes of abuse.[9] This will ensure the generic drug is no less abuse deterrent than the RLD with respect to all potential routes of abuse and minimize the risk of shifting abuse to other, potentially more dangerous, routes.

The data from in vitro and in vivo studies conducted to evaluate the abuse deterrence of a proposed generic product should be included in Module 3.2.P.2 and Module 5, respectively, of the Common Technical Document in an ANDA submission.[10]

FDA intends to consider the totality of the evidence when evaluating the abuse deterrence of a generic solid oral opioid drug product. That is, FDA intends to consider all of the evidence presented in the ANDA including, but not limited to, study type, methodological and design quality, number of studies of each type, sample sizes, relevance of the evidence, replication of results, and overall consistency of the evidence.

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[6] See section 505(j)(2)(A) and (j)(4) of the FD&C Act.
[7] See 21 CFR 314.3(b).
[8] *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), preface at vii.
[9] For questions related to evaluating an RLD's abuse deterrence, the potential ANDA applicant may seek the Agency's input through submission of controlled correspondence to the Office of Generic Drugs. See FDA's guidance for industry on *Controlled Correspondence Related to Generic Drug Development*.
[10] For additional information regarding the information that should be provided in an ANDA submission, refer to the draft guidance for industry, *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*.

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 "Test (T) product" and its respective RLD as "Reference (R) product." If the labeling for R product does not describe any abuse-deterrent properties, the testing recommendations in this guidance are not applicable. Where the labeling for R product describes properties expected to deter abuse, a comparative evaluation of the abuse deterrence of T product relative to R product for all potential routes of abuse should be conducted 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. A *tier* refers to manipulations of similar complexity, difficulty, and effort that may be used by an abuser to release the opioid drug substance. Each subsequent tier increases the complexity, difficulty, or effort of manipulation that may be used. Thus, this tier-based approach allows for hierarchical testing, evaluating abuse-deterrent properties under progressively more challenging conditions.

- **Performance-based evaluation of abuse deterrence.** The evaluation of the abuse deterrence of T product should be based on its performance relative to R product. The proposed generic drug need not have the same formulation design as R product. The evaluation of the abuse deterrence of T product for each potential route of abuse should be based on the potential ANDA applicant's best understanding of the abuse deterrence of R product for that route, the particular potential route of abuse being evaluated, and the use of specific measures meaningful to the evaluation of abuse by that route. For example, the measure that is expected to be the most meaningful for evaluation of abuse by injection is the percentage of opioid drug substance extracted from the product under various test conditions (see Appendices 1 and 3).

- **Most effective manipulation.** FDA recommends that a potential ANDA applicant identify the most effective manipulation conditions for T and R products before comparing them. Appendix 1 provides recommendations for physical manipulations that may be used to evaluate the abuse deterrence of solid oral opioid drug products and recommendations for selecting the most effective physical manipulation to use on the drug products tested in each relevant tier.

- **Sample selection after physical manipulation.** A potential ANDA applicant should select an appropriate sample before conducting comparative in vitro studies. At a minimum, the two extreme forms of a drug product (i.e., the intact and most effectively manipulated form) should be selected for evaluation in each relevant tier. Further recommendations regarding sample size are discussed in section VIII.

- **Comparing T and R products in extraction studies.** FDA recommends that a potential ANDA applicant conduct extraction studies to assess the particular

vulnerabilities of T and R products to inform the comparison of their abuse deterrence. Appendix 1 provides recommendations for extraction studies. For each solvent within a given tier, the potential ANDA applicant should first identify whether the most effectively manipulated R product has an observable reduction in drug extraction. If the drug extraction of R product is greater than or equal to 50 percent in 30 minutes in any solvent within the tier, R product is considered to have no abuse deterrence for purposes of that tier of testing, and no further testing to compare T and R products is recommended. Otherwise, the most effectively manipulated T product should be compared to the most effectively manipulated R product for each solvent within a tier. Then, the maximum percent extraction of opioid drug substance from T product should be compared with the maximum percent extraction of opioid drug substance from R product in each solvent.

- **Statistical comparison of T and R products.** Section VIII provides general recommendations for conducting statistical analyses.

The general principles outlined in this section are applicable to all generic solid oral opioid drug products within the scope of this guidance. This testing is in addition to other testing that may be needed to support ANDA approval. FDA may issue product-specific guidances, as appropriate, that provide more detailed recommendations for conducting in vitro testing, PK testing, or other studies or may issue guidances that provide more detailed recommendations for conducting testing to evaluate specific abuse-deterrent technologies.

Potential ANDA applicants may pose questions regarding evaluation of the abuse deterrence for a generic solid oral opioid drug product through FDA's pre-ANDA program. The goals of the pre-ANDA program are to clarify regulatory expectations for prospective applicants early in the development process, assist applicants in developing complete submissions, promote a more efficient and effective ANDA review process, and reduce the number of review cycles required to obtain ANDA approval, particularly for complex products. FDA considers abuse-deterrent opioids to be products that fall within the definition of "complex product."[11] The pre-ANDA program provides for, among other things, submission of controlled correspondence and requests for formal meetings between FDA and applicants on complex generic drug development issues.[12]

V. ROUTES OF ABUSE

If the summary in section 9.2 of the RLD labeling indicates that FDA has concluded that the RLD has properties that are expected to (or have been shown through postmarketing studies or trials to) deter abuse, in addition to other testing that may be needed to support an ANDA,

[11] *Complex product* is defined in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (commonly referred to as the GDUFA II Goals letter), which can be found at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf. Among other things, *complex product* generally includes "…products where complexity or uncertainty concerning the approval pathway or possible alternative approaches would benefit from early scientific engagement."

[12] See FDA's guidances for industry *Controlled Correspondence Related to Generic Drug Development* and *Formal Meetings Between FDA and Applicants of Complex Generic Drug Products under GDUFA*.

an ANDA applicant should evaluate the abuse deterrence of its proposed generic solid oral opioid drug product for all of the potential routes of abuse.

- **Ingestion (oral route)**—evaluate oral bioavailability of physically manipulated or chewed products, as described in section VII and Appendix 2.

- **Injection (parenteral route)**—evaluate the extractability and syringeability of intact and manipulated products, as described in Appendix 3.

- **Insufflation (nasal route)**—evaluate the nasal bioavailability and pharmacodynamic (PD) effects (i.e., human abuse potential) of manipulated and insufflated products, as described in section VII and Appendix 4.

- **Smoking (inhalation route)**—evaluate the ability to sublimate intact and manipulated products, as described in Appendix 5.

VI. COMPARATIVE IN VITRO STUDIES

FDA recommends that potential ANDA applicants follow a tier-based approach to efficiently compare the abuse deterrence of T product to R product in in vitro studies. Appendix 1 provides recommendations for physical manipulations that may be used to evaluate the abuse deterrence of solid oral opioid drug products and recommendations for selecting the most effective physical manipulation to use on the drug product tested in the tiers. In addition, Appendix 1 provides recommendations for extraction studies using different levels of solvents to assess the particular vulnerabilities of T and R products to inform the comparison of their abuse deterrence.

FDA recommends the following levels of solvents be used in different tiers of comparative in vitro extraction studies (Appendix 1):

- Level 1 solvent: deionized water

- Level 2 solvents: commercially available food-grade vinegar, 0.2% baking soda solution, 40% ethanol, and carbonated drink

- Level 3 solvents: 100% ethanol, 100% isopropyl alcohol, acetone, 0.1 N HCl, and 0.1 N NaOH

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

A potential ANDA applicant seeking approval of more than one strength of a generic solid oral opioid drug product should evaluate and compare T product against R product for each of the strengths in any in vitro study(ies). Alternatively, the potential ANDA applicant should provide supportive data to demonstrate compositional proportionality across different strengths of T and R products or other justification as may be appropriate for not conducting

studies to evaluate T product against R product for all strengths in the in vitro studies. When such justification is provided, a bracketing design covering the extremes of the ratios of opioid drug substance to excipients that contribute to the abuse deterrence should be applied to in vitro evaluation studies.[13]

VII. COMPARATIVE IN VIVO STUDIES

Comparative PK Studies

PK studies to evaluate the abuse deterrence of T product in comparison to R product should be conducted in cases in which no reliable in vitro testing methodologies exist or when in vitro testing methodology is overly sensitive or cannot adequately assess the abuse deterrence of T product relative to R product. For example, PK studies may be recommended to compare the abuse deterrence of T and R products for the nasal and oral routes because no reliable in vitro testing currently exists that can adequately assess abuse deterrence by those routes. The potential ANDA applicant may seek the Agency's input on the PK study design before conducting the study. FDA's recommendations for conducting comparative PK studies for various routes of abuse follow.

- **Nasal PK study**: If in vitro testing suggests that T product is no less resistant to physical manipulation than R product and both T and R products can be pulverized to a particle size range that is considered safe and tolerable for human insufflation studies, the Agency generally recommends that a nasal PK study be conducted using the same dose that was used in in vitro testing to evaluate the nasal abuse deterrence of the R product. A potential ANDA applicant should characterize the particle size distribution of physically manipulated T and R products used in the nasal PK study using an appropriate procedure. A nasal PK study should be conducted in recreational opioid users. The nasal PK study should incorporate naltrexone or other opioid antagonist to block the PD effects of the opioids except for the agonist/antagonist combination products. The recommended PK parameters for the opioid drug substance and any metabolites (if recommended for measurement in the product-specific guidance) include maximum concentration (C_{max}), time of maximum concentration (T_{max}), and area under the curve ($AUC_{(0-t)}$ and $AUC_{(0-\infty)}$). A potential ANDA applicant should also determine the partial AUCs (p-AUCs), e.g., in the case in which there is a clear relationship between the truncated partial area in the PK profiles at specific time points and a clinically relevant PD measure (e.g., likability or take-drug-again).

- **Oral PK study**: FDA recommends an oral PK study (e.g., chewed) be conducted on manipulated products if the summary in section 9.2 of the RLD labeling indicates that FDA has concluded that the product has properties that are expected to deter abuse by the oral route (e.g., Drug X is expected "to reduce . . . oral abuse when chewed.") or FDA otherwise recommends such a study in product-specific guidance. Such studies

[13] For additional information regarding bracketing design, refer to the guidance for industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*

should be designed to compare the PK profile of the orally administered T product to that of the R product when physically manipulated (e.g., cut, grated, or milled) or chewed. A potential ANDA applicant should ensure that a suitable level of physical manipulation(s) or chewing has been applied to both T and R products to achieve the maximum percent extraction of opioid drug substance for T product and the maximum percent extraction of opioid drug substance for R product. For an oral PK study of physically manipulated products, T and R products should be physically manipulated (e.g., cut, grated, or milled) into a particle size range that can discriminate between T product's and R product's ability to deter abuse. For an oral chewing PK study, patient-relevant chewing conditions (e.g., 10 minutes) should be identified.

Oral PK studies should compare the rate and extent of absorption of physically manipulated or chewed and ingested drug products in healthy volunteers. Oral PK studies should incorporate naltrexone or other opioid antagonist to block the PD effects of the opioids except for the agonist/antagonist combination products. The recommended PK parameters for the opioid drug substance and any metabolites (if recommended for measurement in the product-specific guidance) include C_{max}, T_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$. A potential ANDA applicant should also determine p-AUCs, e.g., in the case in which there is a clear relationship between the truncated partial area in the PK profiles at specific time points and a clinically relevant PD measure (e.g., likability or take-drug-again).

- **Agonist/antagonist combination**: For any agonist/antagonist combination product, both the agonist and the antagonist, along with their metabolites (if recommended for measurement in the product-specific guidance), should be measured in a PK study. Appropriate bioanalytical methods should be developed to measure the concentration of both the agonist and the antagonist in the PK study. The oral PK study should be conducted to demonstrate that minimal antagonist absorption occurs when fully intact agonist/antagonist combination products are orally administered. When an oral PK study on the physically manipulated or chewed agonist/antagonist combination product is recommended, the oral PK study should compare both agonist and antagonist levels from manipulated T and R products to confirm that the antagonist is sequestered within the formulation and released upon physical manipulation or chewing followed by oral ingestion. Appropriate methods should be used to manipulate both T and R products to obtain the maximum percent extraction of opioid drug substance for R product and the maximum percent extraction of opioid drug substance for T product, based on extraction studies (Appendix 1). In addition, if T and R products can be manipulated into fine particles (Appendix 4), the potential ANDA applicant generally should conduct a human insufflation PK study, administering physically manipulated T and R products in recreational opioid users, and measure both the agonist and the antagonist, along with their metabolites, if recommended in the product-specific guidance (Appendix 4).

- **Multiple strengths**: When PK studies are conducted to evaluate the abuse deterrence of T product in comparison to R product for approval of more than one strength of a

proposed generic solid oral opioid drug product, the strength(s) selected for the PK studies should be based on the strength(s) used to evaluate the R product's abuse deterrence. Clinical abuse potential studies conducted to evaluate the abuse deterrence for new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)) are generally conducted using an intermediate strength. If the labeling for the R product does not identify the strength(s) tested, FDA intends to provide recommendations in a product-specific guidance.

Other Studies

For generic drugs, comparative in vitro and PK studies generally 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 in which such studies may be needed to establish that a generic product can rely on the finding of safety and effectiveness for the RLD. For example, where R product contains a known aversive agent and T product contains a different aversive agent, FDA may recommend that the potential ANDA applicant conduct a PD study to compare human abuse potential (e.g., willingness to take the drug again) between T product and R product. Potential ANDA applicants are encouraged to seek the Agency's input on study design before conducting such studies.

VIII. STATISTICAL ANALYSIS

Potential ANDA applicants should use inferential analyses to evaluate the abuse deterrence of T product versus R product. A non-inferiority approach should be taken when comparing T product with R product to conclude that T product is no less abuse deterrent than R product. In the analyses recommended in this guidance, a hierarchical set of null hypotheses serves as a gatekeeper for subsequent null hypotheses, evaluating the abuse deterrence of T and R products under progressively more challenging conditions. A hierarchical inferential approach is used to maintain a fixed family-wise experiment Type 1 error rate. Typically, the acceptable Type I error probability (α) will be set at 5 percent.

Tiers, defined by the complexity, difficulty, and effort of manipulations, start with the mildest set of manipulations in Tier 1. Tier 1 serves as a serial gatekeeper for the subsequent tiers. All the null hypotheses within Tier 1 should be rejected prior to testing the null hypotheses in the next tiers, which are defined by a relevant parameter describing T or R product (e.g., the percent of opioid drug substance extracted from T or R product in extraction studies) under progressively more challenging conditions. In Tier 1, all the null hypotheses are evaluated at the Type I error level of α without adjusting for the number of hypotheses; this follows from the closed testing principle.

With tiers (sets) labeled T_1, T_2, T_3, etc., and arranged hierarchically (i.e., in strictly increasing order), T_j ($j > 1$) is tested only if *all* null hypotheses in the preceding tiers 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, etc. (Maurer et al.[14]).

Dmitrienko et al.[15] further generalized this hierarchical testing procedure. They proposed tree-structured gatekeeping tests that rely on a decision tree with multiple branches corresponding to multiple objectives within a tier. This approach could be used, for example, in evaluating extractability, where the effects of solvents at elevated temperature are of interest distinct from those at room temperature.

For example, to evaluate the extractability of opioid drug substance from T product and R product using this tier-based approach, a potential ANDA applicant should first find and use the most effective physical manipulation for R product and evaluate the percent extraction of opioid drug substance from R product in each solvent within the tier. If at 30 minutes the percent extraction of opioid drug substance from R product is statistically less than 50 percent (Type I error = 0.05) in all solvents for the extraction studies, the potential ANDA applicant should evaluate whether or not the maximum percent extraction of opioid drug substance from T product in each solvent is greater than or equal to maximum percent extraction of opioid drug substance from R plus 10 percent in the same solvent, 10 percent being an absolute margin (e.g., if the percent of opioid drug substance extracted from R product is 25 percent, the percent extracted from T product must be less than 35 percent).

When abuse deterrence is evaluated by comparing the percent of opioid drug substance extracted from a product, if the percent of opioid drug substance extracted from T product is statistically greater than or equal to the percent of opioid drug substance extracted from R plus 10 percent in any of the solvents within the tier, then T product is considered to be less abuse deterrent than R; thus, T product will not be tested further. In contrast, if the percent of opioid drug substance extracted from T product is statistically less than the percent of opioid drug substance extracted from R plus 10 percent in all the solvents within the tier, the abuse deterrence of T product is then evaluated in the next tier. The percent of opioid drug substance extracted from T product must be less than the percent of opioid drug substance extracted from R plus10 percent for each set of 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 in the appendices for more detail).

All inferential comparisons involve the mean of the measure of the abuse deterrence or a function of the mean (e.g., the mean of T product minus the mean of R product). The inferential tests used to evaluate the hypotheses are left to the discretion of the potential ANDA applicant. In general, FDA recommends conducting all in vitro tests using 6 units

[14] Maurer W, Hothorn LA, Lehmacher W. Multiple comparisons in drug clinical trials and preclinical assays: A-priori ordered hypotheses. Biometrie in der Chemisch-pharmazeutischen Industrie. 1995;6:3-18.

[15] Dmitrienko A, Wiens BL, Tamhane AC, Wang X. Tree-structured gatekeeping tests in clinical trials with hierarchically ordered multiple objectives. Stat Med. 2007;26(12):2465-2478.

(e.g., tablets or capsules) of each T and R product. The potential ANDA applicant may propose a different sample size if the applicant can provide justification that such sample size allows for accurate characterization of the mean. FDA recommends that the potential ANDA applicant develop an analysis plan that has contingencies for various scenarios (e.g., data that are not normally distributed and data that are left-censored (i.e., values below the limit of quantification)).

Tables 1 and 2 found in the appendices guide potential ANDA applicants through the recommended series of study conditions and statistical analyses for extractability and abuse by smoking (sublimation), respectively. As the first step in each tier, the potential ANDA applicant should identify the most effective physical manipulations and compare R product to a constant (in the case of extractability, see Appendix 1) or R product directly to T product (in the case of sublimation). If the percent of opioid drug substance extracted from R product is less than a constant in case of extractability, the testing should continue to the second step within that tier. If, at the end of the second step, it is possible to conclude that T product is no less abuse deterrent than R product, then testing of T product should move on to the next tier. This process continues for the remaining tiers within a table until:

- The percent extraction of opioid drug substance from R product is greater than or equal to the constant in the case of extractability, in which case R product is considered to have no abuse deterrence for the route of abuse being tested; or

- The percent extraction of opioid drug substance from T product is greater than or equal to that from R plus 10 percent.

In order to show that T product is no less abuse deterrent than R product, T product should be shown to be non-inferior to R product at each tier for which it is evaluated.

IX. ADDITIONAL STUDIES

There may be instances in which the testing recommended in this guidance cannot adequately capture the complete profile for T product because of factors including, but not limited to, inclusion of novel inactive ingredients, use of new technology, and formulation design. In such instances, 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 to 5, be conducted to evaluate the abuse deterrence of T product. As new technologies emerge, FDA intends to continue adapting its recommendations for developing and evaluating generic solid oral and other opioid drug products formulated to deter abuse to help ensure access to effective analgesics for patients who need them.

APPENDIX 1: PHYSICAL MANIPULATION AND EXTRACTABILITY

Physical Manipulation

The extent to which a solid oral opioid drug product can be physically manipulated is a function of several factors including, but not limited to, tampering skills, time, and tampering resources available. This appendix describes some of the ways in which solid oral opioid drug products can be physically manipulated using readily available household equipment. There are additional ways in which products could be physically manipulated (e.g., crushing, hammering). The Food and Drug Administration (FDA) recommends that potential abbreviated new drug application (ANDA) applicants use the physical manipulation(s) most likely to be used by abusers when they conduct studies to evaluate the abuse deterrence of a specific Test (T) product.

Some of the questions that the physical manipulation evaluation should address include:

- What is the degree of difficulty of the manipulation?
- How successful is each manipulation method in achieving its goal (e.g., compromising a tablet's integrity)?
- If the structure of the dosage form is compromised, what are the size and size distribution of the resulting particles?

Physical manipulation should be used to gain an understanding of the robustness of the abuse-deterrent properties. To identify the most effective physical manipulation, potential applicants should use a relevant endpoint, which may vary based on formulation design. For example, for a tablet dosage form designed to be crush resistant, such an endpoint could be the size of the fragment after cutting, grating, or milling. In this case, the potential applicant should provide particle size distribution data to justify the selection of the manipulation method. Particle size for physically manipulated products can be analyzed using techniques including, but not limited to, photograph with scale, image analysis, sieve analysis, and laser diffraction. In addition, if deemed useful, the extraction data in deionized water of manipulated dosage forms may be used to further justify the selection of the most effective physical manipulation that will result in high extraction levels.

Manipulation by cutting

As illustrated in Figure 1 below, progressive manipulation by cutting involves:

- Cutting without thermal pretreatment: 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, manipulation with thermal pretreatment (freezing or heating) is not needed.

- Cutting with thermal pretreatment: If a drug product cannot be cut at RT as described above, suitable thermal pretreatment should be developed and used.

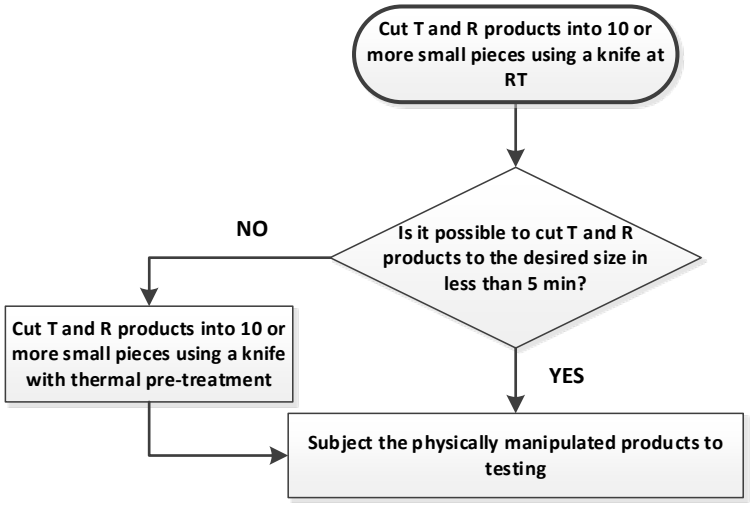


Figure 1: Physical Manipulation by Cutting for Solid Oral Opioid Drug Products

Manipulation by grating

As illustrated in Figure 2 below, progressive manipulation by grating involves:

- Grating without thermal pretreatment: If a drug product can be grated in less than 5 minutes at RT to a size less than 1 millimeter (mm) using a household grater, manipulation with thermal pretreatment (freezing or heating) is not needed.

- Grating with thermal pretreatment: If a drug product cannot be grated at RT as described above, suitable thermal pretreatment should be developed and used.

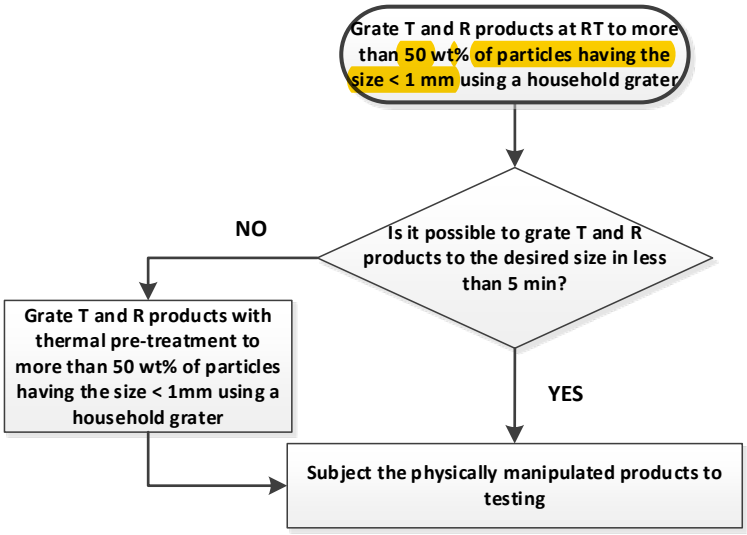


Figure 2: Physical Manipulation by Grating for Solid Oral Opioid Drug Products

Manipulation by milling

As illustrated in Figure 3 below, progressive manipulation by milling involves:

- Milling without thermal pretreatment: If a drug product can be milled in less than 5 minutes at RT to a size less than 1 mm using a household coffee grinder, manipulation with thermal pretreatment (freezing or heating) is not needed.

- Milling with thermal pretreatment: If a drug product cannot be milled at RT as described above, suitable thermal pretreatment should be developed and used.

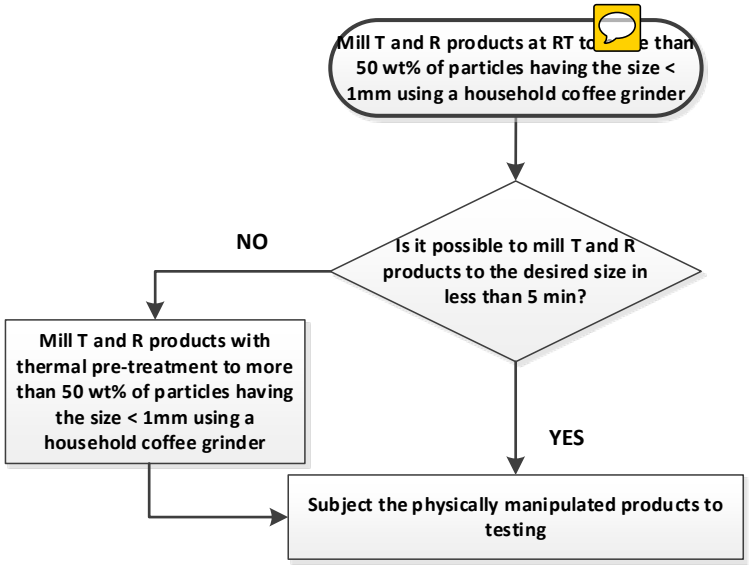


Figure 3: Physical Manipulation by Milling for Solid Oral Opioid Drug Products

Extractability

Evaluation of the extractability of physically manipulated opioid drug products

The potential ANDA applicant should conduct comparative extractability testing on T and Reference (R) products to assess the particular vulnerabilities of each product to inform the comparison of their abuse deterrence. Comparative extractability testing should be conducted on both the intact and most effectively physically manipulated (e.g., cut, grated, or milled) drug products. To conclude that T product is no less abuse deterrent than R product in terms of its extractability, the potential applicant should test the intact and physically manipulated T products and show they are no worse than the intact and manipulated R products, respectively.

Extractability of the opioid drug substance into large volumes of water or an organic solvent may be assessed at RT[16] or elevated temperature (ET).[17] The focus of the extraction studies is to assess the extractability of the opioid drug substance and measure the amount of opioid drug substance available in solutions, determined experimentally by measurement of the concentration and volume of the extraction media.

The percent of opioid drug substance extracted is determined as follows: (CONC*V/labeled strength of the R product) *100, where CONC is the concentration of opioid drug substance in the extraction medium and V is the volume of the extraction solution. If R product is an agonist/antagonist combination, both the percent of opioid drug substance extracted and the ratio of percent of agonist and antagonist extracted should be determined.

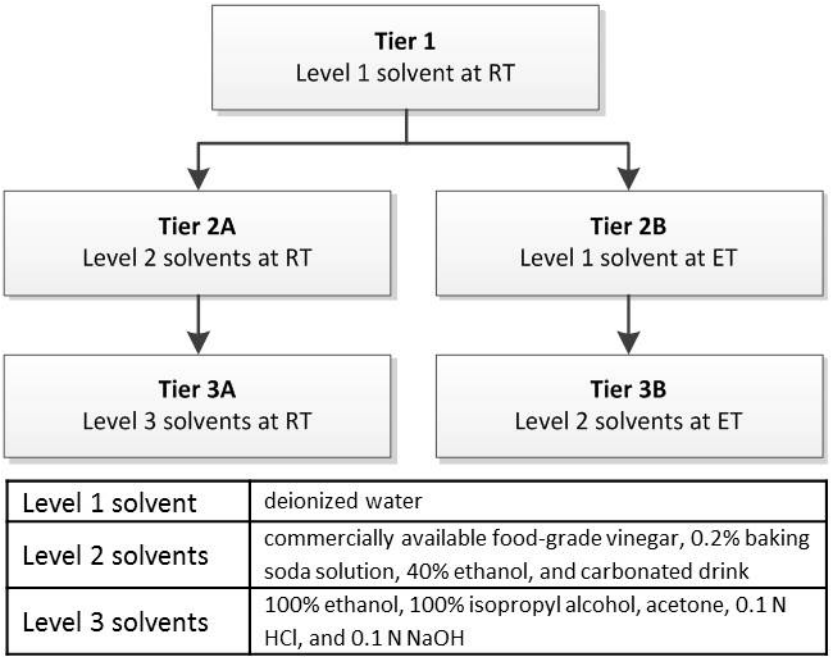
Study conditions

Extractability testing should be conducted for intact and physically manipulated product at RT and ET with relevant solvents using the tiered approach. Some of the ways in which solid oral opioid drug products can be physically manipulated are described above. At a minimum, the potential ANDA applicant should compare the intact T and R products and most effectively physically manipulated T and R products.

Because different solvents could be used to extract the opioid drug substance from the opioid drug product, all solvents within relevant tiers (see section VI) should be tested to assess extractability. For example, the following range of extraction conditions can be used: extraction volume of 240 milliliters (mL), RT or ET for the relevant extraction media, duration 30 minutes, with or without stirring.

The tier-based approach for evaluating extractability is illustrated in Figure 4. The parallel tier-based approach (e.g., Tier 1→ Tier 2A → Tier 3A and Tier 1 → Tier 2B → Tier 3B) to the comparative extractability studies is based on using different levels of solvents and increasing temperature within the recommended range of study conditions.

[16] U.S. Pharmacopoeia (USP) controlled room temperature (20°C to 25°C).
[17] Boiling temperature of the solvents used.



Level 1 solvent	deionized water
Level 2 solvents	commercially available food-grade vinegar, 0.2% baking soda solution, 40% ethanol, and carbonated drink
Level 3 solvents	100% ethanol, 100% isopropyl alcohol, acetone, 0.1 N HCl, and 0.1 N NaOH

Figure 4: Parallel Tiered Approach for Determining the Extractability of Opioid Drug Substance

If the percent of opioid drug substance extracted from T product is less than that extracted from R product plus an absolute 10 percent in Tier 1, the potential ANDA applicant should conduct the extractability study in both Tiers 2A and 2B. If the percent of opioid drug substance extracted from T product is less than that from R plus an absolute 10 percent in Tier 2A, the potential ANDA applicant should proceed with the extractability study in Tier 3A. If the percent of opioid drug substance extracted from T product is less than that from R plus an absolute 10 percent in Tier 2B, the potential ANDA applicant should proceed with the extractability study in Tier 3B. Figure 5 and Table 1 guide potential ANDA applicants through the recommended series of study conditions and statistical analyses for determining extractability.

Tier 1: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 1 solvent at RT

Evaluate R product. A potential ANDA applicant should identify the most effective physical manipulation for R product at RT. If the percent of opioid drug substance extracted from R product using 240 mL of solvent is greater than or equal to 50 percent at 30 minutes for the intact or physically manipulated R product, 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.

Compare T and R products. If the maximum percent of opioid drug substance extracted from R product in 240 mL of solvent is less than 50 percent in 30 minutes in the level 1 solvent, the potential ANDA applicant should compare the maximum percent of opioid drug substance extracted from the intact and most effectively physically manipulated T product to

the maximum percent extracted from the intact and most effectively physically manipulated R product, respectively. If the maximum percent of opioid drug substance extracted from T product is less than the maximum percent of opioid drug substance extracted from R product plus an absolute 10 percent (section VIII), the potential ANDA applicant should conduct testing at the next tier.

Tier 2A: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 2 solvents at RT

Evaluate R product. A potential ANDA applicant should identify the most effective physical manipulation for R product at RT. If the percent of opioid drug substance extracted from R using 240 mL of solvent is greater than or equal to 50 percent at 30 minutes in any of the level 2 solvents, 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.

Compare T and R products. If the maximum percent of opioid drug substance extracted from R product in 240 mL of solvent is less than 50 percent in 30 minutes in all level 2 solvents, the potential ANDA applicant should identify conditions (physical and thermal manipulation methods) that lead to the extraction of the maximum percent of opioid drug substance from intact and physically manipulated T products in all level 2 solvents at RT. The maximum percent of opioid drug substance extracted from T and R products in each solvent should be compared. Extractability of T and R products should be compared as described in section VIII and shown in Figure 5 and Table 1.

Tier 2B: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 1 solvents at ET

As shown in Table 2, the same steps described in Tier 1 (identify the study condition where extraction of opioid drug substance from T and R products is maximum, evaluate R product, and compare T and R products) should be used for testing T and R products in Tier 2B using level 1 solvents at ET.

Tier 3A: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 3 solvents at RT

As shown in Table 2, the same steps described in Tier 2A (identify the study condition where extraction of opioid drug substance from T and R products is maximum, evaluate R product, and compare T and R products) should be used for testing T and R products in Tier 3A using level 3 solvents at RT.

Tier 3B: Extraction of intact and manipulated (e.g., cut, grated, or milled) products in Level 2 solvents at ET

As shown in Table 2, the same steps described in Tier 2A (identify the study condition where extraction of opioid drug substance from T and R products is maximum in each solvent, evaluate R product, and compare T and R products) should be used for testing T and R products in Tier 3B using level 2 solvents at ET.

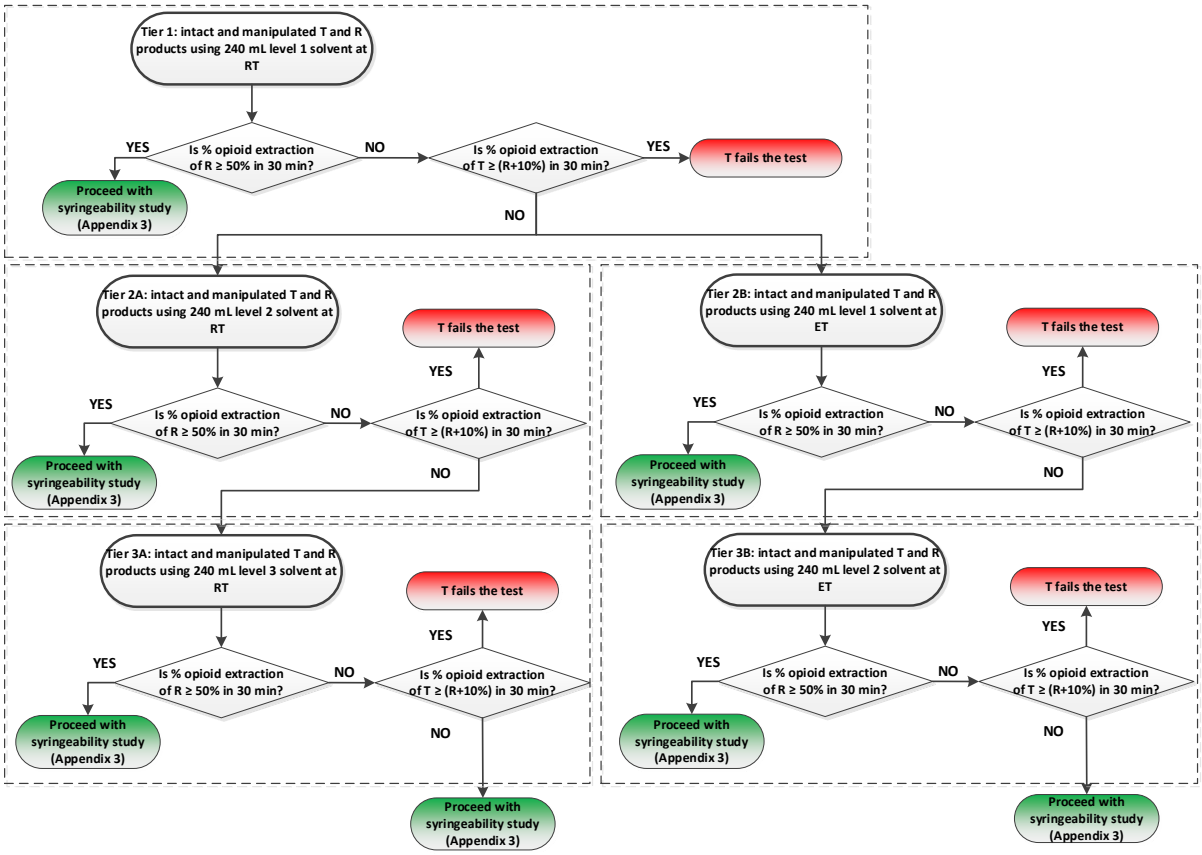


Figure 5: Decision Tree for Determining Extractability of Opioid Drug Substance (each dotted box represents one tier)

Table 1: Statistical Evaluation of Extractability

TIER	**Study Conditions** **240 mL all solvents within the tier** **Extraction Duration 30 min**		
Identify extraction study condition	**H_a: R < 50% in 30 min versus H_0: R ≥ 50% in 30 min**		
	If R < 50% in 30 min *Conclude that less than 50% of opioid drug substance can be extracted from R product* ⬇		**If R ≥ 50% in 30 min** *Conclude that equal or more than 50% of opioid drug substance can be extracted from R product; no further comparative testing*
Evaluate T vs R at study conditions identified in this tier	**H_a: T < R+10% in 30 min versus H_0: T ≥ R+10% in 30 min**		**STOP** no further testing
	If T < R+10% in 30 min *Conclude that T product is no worse than R product by an amount < 10%; T product passes the study under this tier* **CONTINUE** to the next tier or **STOP** no further testing, if this is the last tier ⬇	**If T ≥ R+10% in 30 min** *Conclude that T product is worse than R product by an amount ≥ 10%; T product fails the study under this tier* **STOP** no further testing	

Note: The measure used to evaluate extractability is **the % opioid drug substance extraction**, determined as follows: **(CONC*V/ labeled strength of R product) *100**, where CONC is the concentration of opioid drug substance in the solution, and V is the volume of the solution. 10% is applied as an absolute margin.

APPENDIX 2: ABUSE BY INGESTION (ORAL ROUTE)

Abuse by ingestion may involve orally ingesting physically manipulated (e.g., cut, grated, or milled) or chewed drug products. FDA recommends an oral PK study be conducted on physically manipulated or chewed products if the summary in section 9.2 of the RLD labeling indicates that FDA has concluded that the product has properties that are expected to deter abuse by the oral route (i.e., Drug X is expected "to reduce . . . oral abuse when chewed.") or FDA otherwise recommends such a study in product-specific guidance.

FDA recommends a potential ANDA applicant first conduct comparative extractability studies as described in Appendix 1 to assess the particular vulnerabilities of the T and R products to inform the comparison of their abuse deterrence. If the potential ANDA applicant conducts a PK study, the study should compare the rate and extent of absorption of orally administered T and R products that are physically manipulated or chewed. The strength(s) selected for the PK study should be based on the strength(s) used to evaluate the R product's abuse deterrence. If the upper 95 percent confidence bound of the T/R ratio for the rate and extent of oral absorption of the opioid drug substance is less than 125 percent, then T product passes the test. For agonist/antagonist combination products, T product passes the test if the lower 95 percent confidence bound of the T/R ratio for the rate and extent of oral absorption of the antagonist is greater than 80 percent. Section VII.A. outlines general recommendations for conducting oral PK studies. Alternatively, the potential ANDA applicant may rely on data from in vitro testing if such methods and data are adequate to compare the rate and extent of absorption of orally administered T and R products to evaluate whether T product is no less abuse deterrent than R product for the oral route.

APPENDIX 3: ABUSE BY INJECTION (PARENTERAL ROUTE)

Abuse by injection usually involves extraction of opioid drug substance from intact or physically manipulated (e.g., cut, grated, or milled) opioid drug products at RT and ET in small volumes of water followed by injection using a syringe. To evaluate abuse deterrence for the parenteral route, a potential ANDA applicant should measure the amount of opioid drug substance available for injection after evaluating whether or not the solvent used can be parenterally administered in humans or evaporated for reconstitution. The amount is determined by the opioid drug substance concentration in a solvent 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 ANDA applicant should note that comparative extractability and syringeability testing should be conducted with intact and physically manipulated (e.g., cut, grated, or milled) drug products. To evaluate whether T product is no less abuse deterrent than R product for the parenteral route of abuse, the intact and physically manipulated T products should be compared with intact and physically manipulated R products, respectively, under each applicable study condition, as described below.

The measure considered meaningful for evaluating the abuse deterrence relevant to abuse by injection is the percent of opioid drug substance extraction determined as follows: (CONC*V/labeled strength of the R product) *100, where CONC is the concentration of opioid drug substance in the sample 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 percent of opioid drug substance extraction of agonist to antagonist should be determined.

Study conditions

Syringeability testing should be conducted on the intact and manipulated T and R products in a small volume (10 mL) of each of the solvents in the relevant tier as described in Figure 6 if the maximum extraction of opioid drug substance from R product in 240 mL of solvent is equal or more than 50 percent in 30 minutes in a tier or T product successfully passes the large volume (240 mL) extraction study in all tiers (Figure 5). If the opioid drug substance can be extracted from R product in a large volume of solvent, the potential applicant should conduct comparative syringeability testing in a small volume of the same solvent. In general, FDA recommends conducting syringeability testing using a single unit of each T product and R product. If single-unit syringeability testing cannot accurately characterize the syringeability of R product, the potential ANDA applicant should conduct multiple-unit syringeability tests and justify that the number of tablets or capsules used in syringeability tests can sufficiently discriminate the comparative syringeability of T and R products. Appendix 1 describes some of the ways in which solid oral opioid drug products can be physically manipulated. For each manipulation likely to be used by abusers, T and R products should be statistically compared, as described in section VIII.

Following physical manipulation (e.g., cutting, grating, or milling), further testing of syringeability is recommended under the following range of study conditions: solvents used

in the tier, volume 10 mL, temperature RT or ET, duration 5 to 60 minutes, and needle gauge 21 or finer. The study conditions, including extraction time, syringing time, needle gauge number, and filtering of particles, should be specified in the ANDA.

Evaluate solvents. If the solvent cannot be parenterally administered in humans or evaporated for reconstitution, no comparative syringeability testing of T product to R product is needed using that solvent. If the solvent can be administered in humans or evaporated for reconstitution, the potential ANDA applicant should compare T and R products.

Compare T and R products. The potential ANDA applicant should test the intact and manipulated T product and compare the abuse deterrence of T product to intact and manipulated R product, respectively. Then, the maximum percent of opioid drug substance extracted from T product should be evaluated to determine whether it is greater than or equal to R plus an absolute 10 percent in 30 minutes.

Figure 6 illustrates the tier-based approach for evaluating the syringeability of opioids for abuse by injection, as described above.

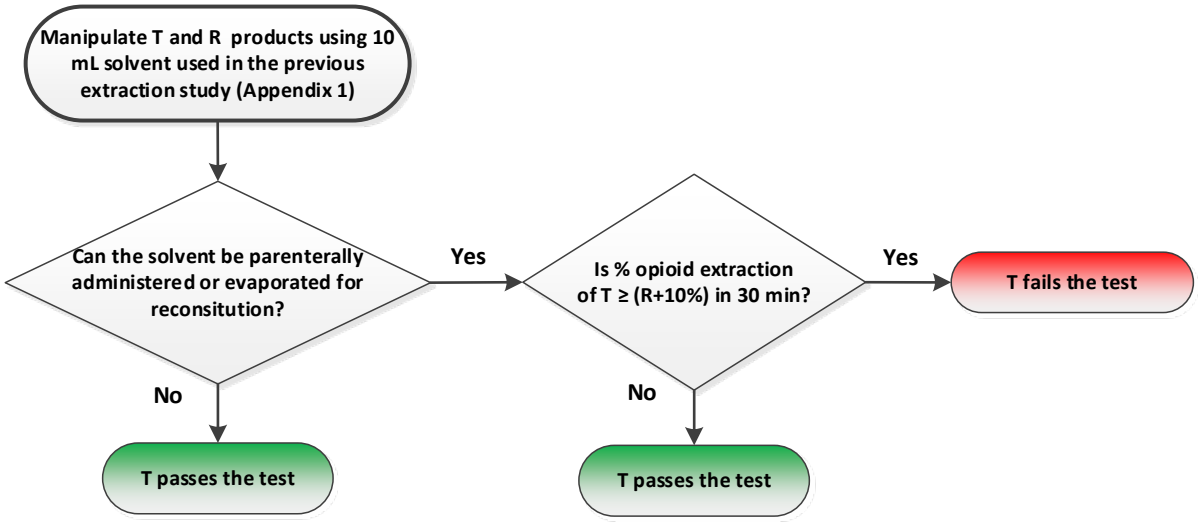


Figure 6: Decision Tree for Determining the Syringeability of Opioid to Evaluate Abuse-Deterrence Potential (abuse by injection)

APPENDIX 4: ABUSE BY INSUFFLATION (NASAL ROUTE)

Abuse by insufflation generally involves the snorting of manipulated solid oral opioid drug products. The known approaches to deterring insufflation include reducing bioavailability and reducing human abuse potential (e.g., likability or take-drug-again) of the abused product. Thus, to evaluate abuse deterrence for the nasal route of abuse, a potential ANDA applicant should test T product for reduced bioavailability and/or reduced human abuse potential.

The measure considered meaningful for in vitro evaluation of reduced bioavailability is the mass percent of fine particles (<500 micrometers (µm)) available for insufflation.

Reduced Bioavailability

Reducing the opioid drug substance available for insufflation may be accomplished by inclusion of excipients that impart hardness to the formulation and make it difficult to manipulate, retard the rate of release of the opioid drug substance from the manipulated product, or increase the size of the drug product, thereby increasing the amount of manipulated powder and proportionally decreasing the amount of opioid drug substance to be insufflated.

Consequently, the amount of opioid drug substance available following insufflation of manipulated T and R products is a function of several factors, including, but not limited to, the ease of manipulation of the drug product, the amount of manipulated product available for insufflation, the degree of effort needed for manipulation, and the rate of release of opioid drug substance from the manipulated product. Therefore, evaluation of a product's bioavailability includes measuring the size and amount of particles available for insufflation and measuring the rate and extent of absorption of manipulated T and R products following nasal administration.

The tier-based approach to the comparative studies for evaluating bioavailability of opioid drug substance when abused through the nasal route is based on the progressively more complex studies moving from in vitro studies in Tier 1 to a PK study in Tier 2. The potential ANDA applicant can propose alternative in vitro evaluation methods to assess the abuse deterrence of T products to avoid conducting a PK study if the methods provide reliable and predictive information on the PK behavior and performance of manipulated opioid drug products following insufflation.

Tier 1: Evaluation of manipulated T and R products

Identify study condition. Appendix 1 describes some of the ways in which solid oral opioid drug products can be physically manipulated. If T and R products cannot be pulverized into fine particles (<500 µm) after 5 minutes of manipulation (with or without thermal pretreatment), alternative approaches such as crushing, hammering, or grating after thermal pretreatment can be used to generate particles of size less than 500 µm.

Evaluate T product. If the mass percent of fine particles (<500 µm) of T product is less than or equal to 10 percent, then T product is deemed unsuitable for insufflation. No comparative testing of T product to R product is needed. Otherwise, the potential applicant should evaluate R product.

Evaluate R product. R product is manipulated under the same manipulation condition. If the mass percent of fine particles (<500 µm) of R product is less than or equal to 10 percent, then R product is deemed more resistant to physical manipulation than T product for insufflation. If the mass percent of fine particles (<500 µm) of R product is greater than 10 percent, testing should proceed to Tier 2.

If both T and R products can be manipulated into fine particles with the mass percent of fine particles (<500 µm) being greater than 10 percent, FDA generally recommends conducting a comparative PK study (Tier 2) to evaluate whether a proposed generic drug deters abuse by the nasal route. Any exceptions would be provided in product-specific guidance.

Tier 2: Evaluation of manipulated and insufflated T and R products in a PK study

Identify manipulation condition. Approaches to physical manipulation of T product should be identified to achieve a particle size range that is considered safe and tolerable for human insufflation PK studies (i.e., D_{10}>100 µm and D_{90}<1000 µm). To conduct a comparative nasal PK study, R product should be manipulated into the same particle size range using an equal or lesser amount of energy input. A potential ANDA applicant should characterize the particle size distribution of physically manipulated T and R products used in a nasal PK study using an appropriate procedure.

Compare T and R products. In section VII.A., FDA provides general recommendations for conducting nasal PK studies. The strength(s) selected for a PK study should be based on the strength(s) used to evaluate R product's abuse deterrence. If the upper 95 percent confidence bound of the T/R ratio for the rate and extent of absorption of the insufflated opioid drug substance is less than 125 percent, then T product passes the test. In addition, for agonist/antagonist combination products, T product passes the test if the lower 95 percent confidence bound of the T/R ratio for the rate and extent of absorption of the insufflated antagonist is greater than 80 percent. Otherwise, T product is considered to be less abuse deterrent than R product.

The tier-based approach to testing products for nasal bioavailability, as just described, is illustrated in Figure 7.

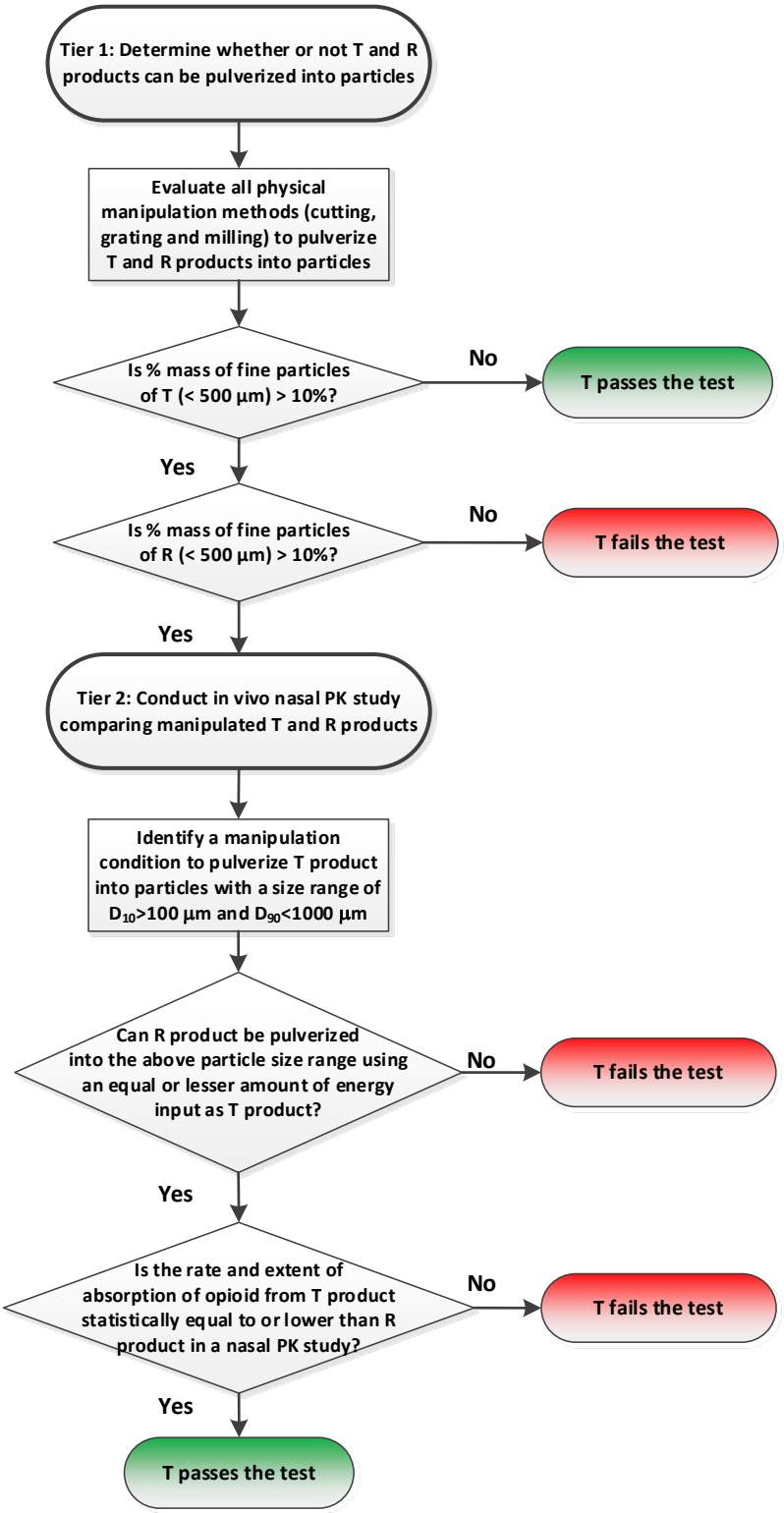


Figure 7: Decision Tree for Evaluation of Abuse Deterrence Potential (abuse by insufflation)

Reduced Human Abuse Potential

Abuse deterrence by the nasal route may also be accomplished by addition of excipients that produce an unpleasant effect if the dosage form is manipulated and insufflated. These excipients (e.g., sodium lauryl sulfate), referred to as aversive agents, are known to cause nasal mucosal irritation. In product-specific guidance, FDA may recommend a potential applicant evaluate human abuse potential (e.g., willingness to take the drug again) if R product contains a known aversive agent.

Evaluate R product. If R product does not contain a known aversive agent in its formulation, then no comparative human abuse potential testing of T and R products is needed. If R product contains a known aversive agent, the potential applicant should evaluate T product.

Evaluate T product. If T product contains a different aversive agent than R product, the potential applicant should conduct a comparative pharmacodynamics (PD) study to determine the human abuse potential (e.g., willingness to take the drug again) of T product in comparison to R product. If T product contains the same aversive agent as R product, the potential applicant should compare availability of the aversive agent at the local sites of aversion for manipulated T and R products.

Compare T and R products with same aversive agent. If T product contains the same aversive agent and the availability of the aversive agent in T product at the local sites of aversion is not less than that of R, T product is considered to have similar abuse deterrence as R product and no further testing is needed. The availability of an aversive agent at the local sites of aversion could be based on evidence including, but not limited to, qualitative (Q1) and quantitative (Q2) formulation sameness between T and R products, in vitro methods that demonstrate equivalent performance, and PK studies to measure systemic exposure of the aversive agent. The potential ANDA applicant may propose alternative studies if the applicant can provide justification that such study allows for accurate and sensitive comparison of availability of the aversive agent at the local sites of aversion between T and R products. If the above approaches cannot confirm that the availability of the aversive agent of T product is not less than that of R product at the local sites of aversion, the potential ANDA applicant should conduct a comparative PD study to determine the human abuse potential of T product in comparison to R product. The potential ANDA applicant should discuss the study design with the Agency before conducting the study.

The proposed testing for comparison of T and R products' human abuse potential is illustrated in Figure 8.

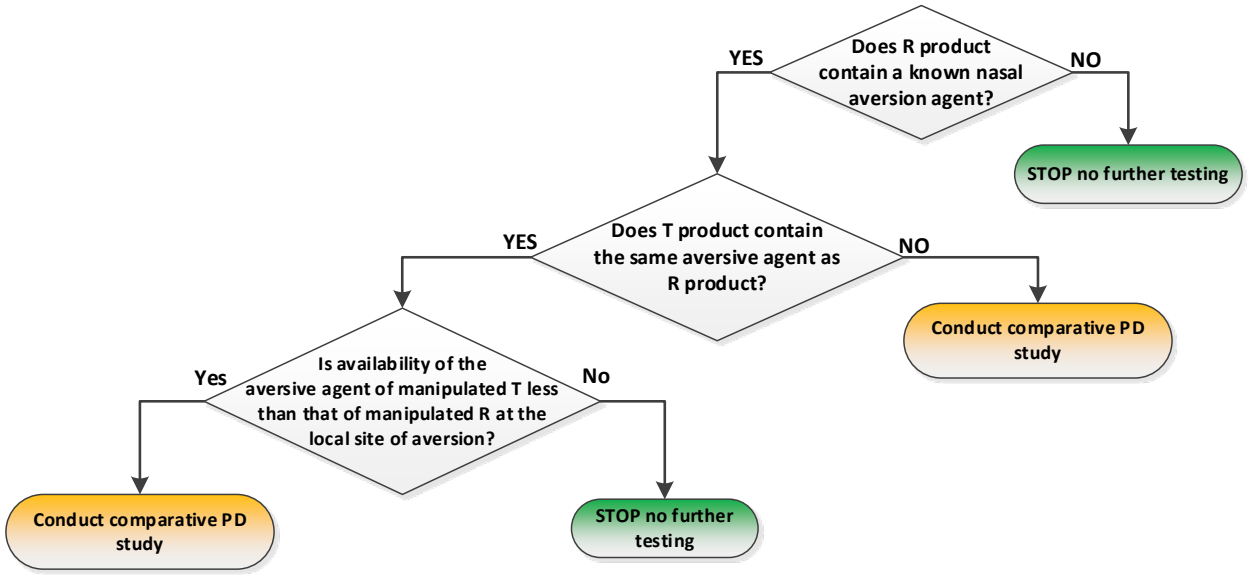


Figure 8: Evaluation of Reduced Human Abuse Potential (abuse by insufflation)

APPENDIX 5: ABUSE BY SMOKING (INHALATION ROUTE)

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

The measure used to evaluate abuse by smoking is the percent 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 percent of agonist and antagonist should be determined.

Study conditions

Appendix 1 describes some of the ways in which solid oral opioid drug products can be physically manipulated. The potential ANDA applicant should use a household coffee grinder or other household milling appliance. The smoking test should be conducted on intact and manipulated T and R products at three different temperatures. The selected temperatures should fall within the range of 200°C to 300°C for 2 to 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 manipulated product in Tier 1, to freebasing the opioid drug substance from the intact and manipulated product prior to sublimation of the free base in Tier 2 (Table 2).

Tier 1: Sublimation of intact and manipulated products

Identify study condition. Appendix 1 describes some of the ways in which solid oral opioid drug products can be physically manipulated. If T or R product cannot be manipulated to generate particles of less than 1 mm after attempted manipulation for 5 minutes, alternate approaches such as crushing or grating after thermal pretreatment can be used to generate particles of size less than 1 mm.

Evaluate T and R products. Determine the percent of opioid sublimation of intact and manipulated R product by heating at three different temperatures between 200°C and 300°C (selected temperatures should fall within the range of 200°C to 300°C) for 2 to 15 minutes. Using the same conditions and temperatures, determine the percent of opioid sublimation of intact and manipulated T product.

Compare T and R products. Statistically compare the abuse deterrence of T and R products. If the percent of opioid sublimation of T is greater than R, then T product is less abuse deterrent than R product. If the percent of opioid sublimation of T is less than or equal to R and the opioid drug product tested is not a salt, T product is no less abuse deterrent than R and no further comparative testing of T product to R product is needed. If the percent of opioid sublimation of T is less than or equal to R and the opioid drug product is a salt, the abuse deterrence of T product should be tested further in Tier 2.

Tier 2: Sublimation of precipitated opioid retrieved from intact and manipulated products

Identify study condition. Convert the opioid salt in intact and manipulated T and R products to precipitated free-base opioid with a household reagent (e.g., baking soda). Dry the resulting mixtures obtained from T and R products at three different temperatures (selected temperatures should fall within the range of 200°C to 300°C) for 2 to 15 minutes.

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

Compare T and R products. Statistically compare the abuse deterrence of T and R products. If the percent of opioid sublimation of T is greater than R, T product is less abuse deterrent than R product. If the percent of opioid sublimation of T is less than or equal to R, T product is no less abuse deterrent than R product.

Figure 9 and Table 2 illustrate the tier-based approach for evaluating the sublimation of opioid drug substance for abuse by smoking, as described above.

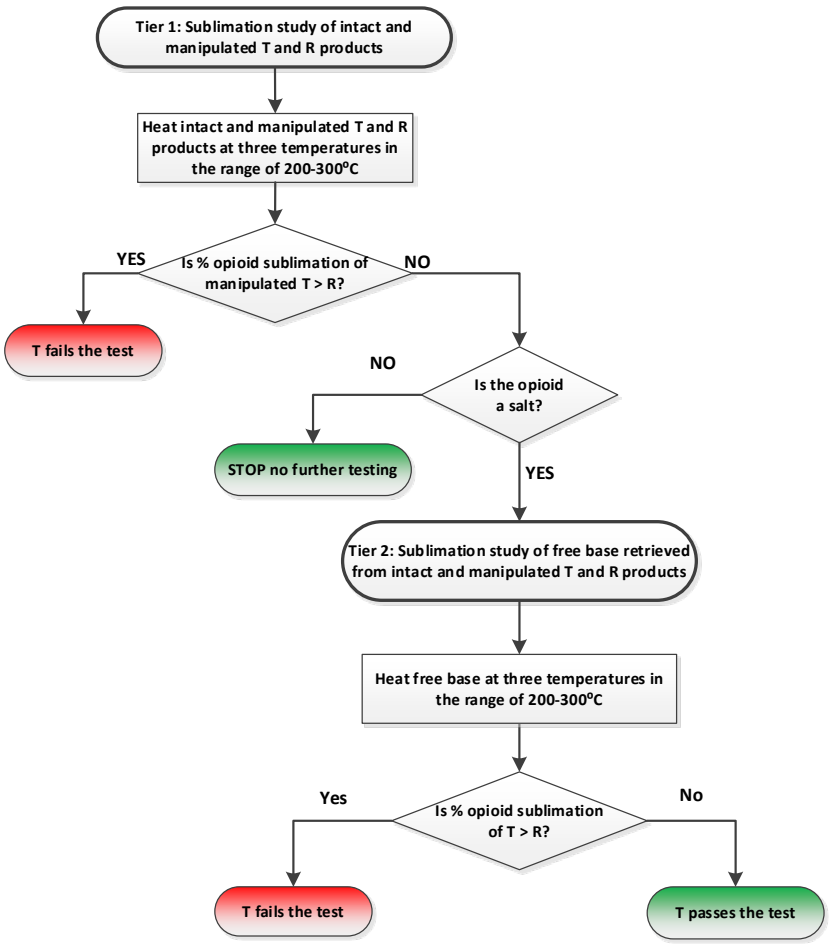


Figure 9: Decision Tree for Evaluation of Abuse Deterrence Potential (abuse by smoking)

Table 2. Statistical Evaluation of Sublimation (abuse by smoking)

TIER 1	**Study Condition** **Three Temperatures in the Range of 200-300°C / Duration of 2–15 minutes**		
Identify Study Condition	*Determine the % of opioid sublimation of the intact and manipulated R product.* *Using the same method, determine the % opioid sublimation of intact and manipulated T product.* ⬇		
Evaluate the R Sublimation versus the T Sublimation	**H_0: T > R versus H_a: T ≤ R**		
	If T ≤ R and **% opioid drug substance is a salt** *Conclude that % opioid sublimation of T product is less than or equal to R product; T product passes the study under Tier 1* **CONTINUE** to Tier 2 ⬇	**If T ≤ R and** **% opioid drug substance is NOT a salt** *Conclude that % opioid sublimation of T product is less than or equal to R product; T product passes the study under Tier 1* **STOP** no further testing	**If T > R** *Conclude that % opioid sublimation of T product is greater than R product* **STOP** no further testing

TIER 2	**Study Condition** **Three Temperatures in the Range of 200-300°C / Duration of 2–15 minutes**	
Identify Study Condition	*Convert the opioid salt in intact and manipulated T and R products to free base with a household reagent. Dry the resulting mixtures obtained from the T and R products at three temperatures in the range of 200-300°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 product is less than or equal to R product; T product passes the study under Tier 2* **STOP** no further testing	**If T > R** *Conclude that % opioid sublimation of T product is greater than R product; T product fails the study under Tier 2* **STOP** no further testing

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