Guidance for Industry

Abuse-Deterrent Opioids — Evaluation and Labeling

DRAFT GUIDANCE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)

January 2013
Clinical Medical

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Guidance for Industry[1]
Abuse-Deterrent Opioids — Evaluation and Labeling

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors who wish to develop formulations of opioid drug products with potentially abuse-deterrent properties (abuse-deterrent formulations). Specifically, the guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies will be evaluated, and what labeling claims may be approved based on the results of those studies.

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Therefore, FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. FDA welcomes comments and suggestions on this guidance, and encourages additional scientific and clinical research that will advance the development and assessment of abuse-deterrent technologies.

This guidance document is not intended to set forth FDA's views on the approvability of opioid drug products in general, whether formulated to deter abuse or otherwise, nor its views on abuse-deterrent formulations of other classes of drug products with potential for abuse. This guidance also does not address the manufacture, quality assurance, or stability evaluation of products designed to have abuse-deterrent properties.

FDA's guidance documents, including this guidance, 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

[1] This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Regulatory Policy, the Office of Surveillance and Epidemiology, the Office of Biostatistics, and the Controlled Substance Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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. Abuse and misuse of these products, however, have created a serious and growing public health problem. FDA has worked to address this problem while ensuring that patients in pain have appropriate access to opioid analgesics.

One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

Opioid analgesics are often manipulated for purposes of abuse. Most abuse-deterrent technologies developed to date are designed to make product manipulation more difficult or to make abuse of the manipulated product less attractive or rewarding. However, these technologies have not yet proven successful at deterring the most common form of abuse – swallowing a number of intact pills or tablets to achieve a feeling of euphoria. Because opioid analgesics must be able to deliver the opioid to patients for the management of pain, the extent to which an abuse-deterrent product is able to reduce abuse will never be absolute. Therefore, the extent of abuse deterrence can only be understood when studied relative to a comparator. The following sections describe the categories of abuse-deterrent formulations, discuss premarketing studies of the product's potentially abuse-deterrent properties, discuss the postmarketing studies that should be used to assess the real-world impact of a potentially abuse-deterrent formulation, and discuss possible labeling claims for abuse-deterrent formulations.

III. OPIOID ABUSE-DETERRENT FORMULATIONS

Opioid analgesics can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent formulations should target known or expected routes of abuse for the opioid drug substance for that formulation. As a general framework, abuse-deterrent formulations can be categorized as follows:

1. *Physical/Chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding. Chemical barriers can resist extraction of the opioid using common solvents like water, alcohol, or other organic solvents. Physical and chemical barriers can change the physical form of an oral drug rendering it less amenable to abuse.
2. *Agonist/Antagonist combinations* – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product may be formulated such that the substance that acts as an antagonist is not clinically active when

the product is swallowed but becomes active if the product is crushed and injected or snorted.

3. *Aversion* – Substances can be combined to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or a higher dosage than directed is used.
4. *Delivery System* (including depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, a sustained-release depot injectable formulation that is administered intramuscularly or a subcutaneous implant can be more difficult to manipulate.
5. *Prodrug* – A prodrug that lacks opioid activity until transformed in the gastrointestinal tract can be unattractive for intravenous injection or intranasal routes of abuse.
6. *Combination* – Two or more of the above methods can be combined to deter abuse.

IV. PREMARKETING STUDIES

First and foremost, studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the use of appropriate positive controls and comparator drugs, appropriate outcome measures, appropriate data analyses to permit a meaningful statistical analysis, and the selection of appropriate subjects for the study.

The evaluation of an abuse-deterrent formulation should take into consideration the most common routes of abuse for the opioid. For example, studies evaluating abuse by the intranasal route would not be particularly relevant if the drug is not known to be abused by that route. Overall, the oral route is the most common route of abuse of prescription opioids, followed by snorting and injection.

FDA is committed to retaining a flexible, adaptive approach to evaluating potentially abuse-deterrent opioid drug products. In some cases, data from all three categories or "tiers" of studies noted below may not be necessary. In most cases, however, in order to obtain a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential, data from each of the following three categories of premarketing studies are appropriate:

1. Laboratory-based in vitro manipulation and extraction studies (Category 1)
2. Pharmacokinetic studies (Category 2)
3. Clinical abuse potential studies (Category 3)

The results of Category 1 studies influence the design of Category 2 pharmacokinetic studies, and the results of Category 2 studies influence the need for Category 3 studies of human abuse potential and the designs and goals of these studies.

Category 4 studies analyze postmarketing data to assess the impact of an abuse-deterrent formulation on actual abuse. These studies are addressed in Section V of this guidance.

A. Laboratory Manipulation and Extraction Studies (Category 1)

The goal of the laboratory-based studies, Category 1, should be to evaluate the ease with which the potentially abuse-deterrent properties of a formulation can be defeated or compromised. These studies are critical to the understanding of formulation characteristics and performance.[2] Methodologically, these studies should be designed with knowledge of the physicochemical properties of the formulation and the methods available to abusers, and should be conducted on the to-be-marketed formulation. Sponsors should consider both the mechanisms by which abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the product as well as the ways that patients may alter the formulation (unintentionally or intentionally) that change the rate or amount of drug released (for example, dose dumping may occur when taking the product with alcohol or when the product is cut, chewed, or crushed). Testing should provide information sufficient to fully characterize the product's abuse-deterrent properties, including the degree of effort required to bypass or defeat those properties.

The in vitro studies should assess various simple and sophisticated mechanical and chemical ways a drug can be manipulated, such as: (1) defeating or compromising the controlled release of an opioid from extended-release formulations for purposes of abuse by different routes of administration; (2) preparing an immediate-release formulation for alternative routes of administration; or (3) separating the opioid antagonist, if present, from the opioid agonist, thus compromising the product's abuse-deterrent properties.

The test product should be compared to appropriate comparator products for ease of mechanical manipulation. The ability to crush, cut, grate, or grind the product formulation using readily available items such as spoons, cutters, and coffee grinders should be assessed. Particular attention should be given to particle size distribution following each mode of physical manipulation, as particle size may influence the rate of opioid extraction from manipulated product. The effect of heat and cold on mechanical manipulation should also be studied.

Extractability and solubility studies should be designed to determine whether any of the formulation components might be differentially solubilized and extracted, allowing an abuser to bypass the drug's abuse-deterrent properties. After establishing how a product could be manipulated, chemical extraction of the opioid from the intact and the manipulated product should be assessed and compared to opioid extraction from the selected intact and similarly manipulated comparator products. The ease of extracting the opioid from the intact and manipulated product should be determined using a variety of solvents that are commonly available (e.g., water, vinegar, ethanol, isopropanol, acetone, mineral spirits) and those which have potentially relevant solvent characteristics (e.g., pH, polarity, protic vs. aprotic). The

[2] This topic has been discussed at meetings of the Anesthetic & Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee (*NDA 022272, OxyContin*, May 5, 2008, and September 24, 2009). Additional information on these meetings is available on FDA's web site at the following location: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM187082.pdf.

effects of time, temperature, pH, and agitation on solvent extraction should also be determined. For combination products containing more than one drug substance, extractability and solubility studies should be designed to determine whether any of the drugs present in the combination might be differentially solubilized and extracted. The in vitro drug-release characteristics of the intact and manipulated product should also be compared using a discriminatory and robust dissolution method.

In addition to the general evaluation of the effects of physical and chemical manipulation on the product, there are important route-specific data that should be generated, as follows:

- For a product with potential for snorting, the particle size distribution should be established.
- For a product with potential for smoking, the vaporization temperature and degradation temperature of the opioid in salt and base form should be determined.
- For a product with potential for intravenous injection, the opioid concentration in a small injection volume and the viscosity (syringeability and injectability) of the injection fluid should be determined.

The following examples illustrate the kinds of outcomes that in vitro studies should evaluate:

1. Limitations to manipulation of the product by crushing, grinding or melting, or by changing the intact formulation through other methods that would limit insufflation of the manipulated product, and/or that would limit dissolution of the manipulated product and incorporation into a solvent that could then be injected by intravenous or subcutaneous routes.

2. Limitations to the extraction of the opioid of the product that would, therefore, reduce the likelihood of the product being injected by intravenous or subcutaneous routes and/or make the manipulated product difficult to draw up into a syringe.

3. A formulation that results in noxious effects either upon insufflation or injection when the product is manipulated for administration by those routes, or when the product is administered by oral ingestion and the noxious component is released into systemic circulation.

4. A formulation that, upon manipulation, would result in the release of pharmacologic antagonists to the opioid, thereby creating a substance that would either decrease the product's pharmacologic effects (e.g., euphoria) or result in a mild to moderate degree of drug withdrawal when the manipulated substance is injected or administered by another route of abuse.

5. A formulation that limits the user's ability to manipulate it for abuse due to a specific feature of the product, such as an injectable, intramuscular depot formulation or implant.

6. A prodrug that cannot be manipulated in vitro to release the abusable opioid and, therefore, the opioid can only be released by metabolism that occurs in the gastrointestinal track or the systemic circulation after ingestion.

B. Pharmacokinetic Studies (Category 2)

The goal of the clinical pharmacokinetic studies, Category 2, should be to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration. If food and alcohol alter the pharmacokinetic parameters of the formulation, data should be provided to characterize those effects.[3]

Relevant pharmacokinetic parameters for the opioid drug and any psychoactive metabolites that should be measured in these studies include:

- maximum concentration (C_{max}),
- time to maximum concentration (T_{max}),
- area under the curve ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$),
- relevant partial AUC, such as $AUC_{0\text{-}30}$ minutes or $AUC_{0\text{-}2}$ hours, and
- terminal elimination half-life ($T_{1/2}$).

The rate of rise of drug concentration should be assessed when possible, because it is thought to contribute to differential abuse potential among drugs, formulations, and routes of administration.[4] To support these analyses, it is important to have specimen collection and analysis time points sufficient to cover the onset, peak, and offset of the effects of both immediate-release (IR) and extended-release (ER) formulations, in both the intact and manipulated products. ER formulations typically have a slower onset and lower peak concentration compared to IR formulations. Pharmacokinetic parameters also differ between different routes of administration of a drug substance, such as oral versus intranasal routes.

If food significantly increases systemic exposure of the intact formulation, the underlying mechanism for the food effect should be established by assessing whether the effect is based on

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[3] See FDA draft guidance for industry, *Assessment of Abuse Potential of Drugs*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

[4] References suggesting that drugs associated with a rapid onset of action are associated with greater abuse potential include:

Abreu, M.E., G.E. Bigelow, L. Fleisher, S.L. Walsh, 2001, Effect of Intravenous Injection Speed on Responses to Cocaine and Hydromorphone in Humans, *Psychopharmacology*, 154:76-84.

de Wit, H., B. Bodker, J. Ambre, 1992, Rate of Increase of Plasma Drug Level Influences Subjective Responses in Humans, *Psychopharmacology*, 107:352-358.

de Wit, H., S. Didish, J. Ambre, 1993, Subjective and Behavioral Effects of Diazepam Depend on Its Rate of Onset, *Psychopharmacology*, 112: 324-330.

the drug substance or the formulation and whether the effect is present with intact product as well as with manipulated product. When food is expected to increase exposure, subsequent abuse potential studies by the oral route should be conducted in the fed state to maximize the potential systemic exposure.

As a part of these studies, adverse events should be collected. For example, if the manipulated formulation is abused by snorting, it would be important to assess adverse events related to intranasal tolerability.

C. Clinical Abuse Potential Studies (Category 3)

Clinical studies of abuse potential, Category 3, are also an important methodology for assessing the relative abuse potential of a new drug for purposes of scheduling under the Controlled Substances Act.[5]

The preferred design is a randomized, double-blind, placebo-controlled and positive comparator-controlled crossover study. These studies generally are conducted in a drug-experienced abuser population. The use of a pre-qualification phase (see section 2 below) to identify subjects who can distinguish active drug from placebo reproducibly is a common enrichment strategy used to improve the power of the study to distinguish difference between treatments.

For drugs with abuse-deterrent properties, the purpose of a clinical abuse potential study is to assess the impact of the potentially abuse-deterrent formulation on measures that predict how probable it is that the formulation will be attractive to abusers ("liked"). Accordingly, certain methodological aspects of these studies should be adapted to that objective, as discussed below.

1. Blinding

Clinical studies of abuse potential should use a randomized, double-blind, placebo-controlled and positive comparator-controlled crossover design. Because study subjects are recreational drug users and familiar with the effects of the drug substances being studied, the double–dummy technique or other techniques should be used to ensure the blinding of all tests when possible. However, alternative designs may be suitable when the blinding of the study drug and the positive control cannot be maintained. For example, a parallel design may be useful when studying the intranasal route of administration, where subjects may be able to see the differences in volume or color between test drug and placebo or positive comparator.

Options for assisting with blinding include the administration of the crushed study drug in a narrow neck, opaque container with a pre-inserted straw to facilitate snorting of the drug. Though subjects might not be able to see the sample, due to the physical properties of samples and even differences in weight among samples, un-blinding may still occur. When the study involves intranasal administration of a crushed product, every effort should be made to produce

[5] See FDA draft guidance for industry, *Assessment of Abuse Potential of Drugs*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

samples with similar particle size distribution and the details of the preparation of the samples should be provided in the study protocol.

2. Pre-qualification Phase

The purpose of the pre-qualification phase is to increase the power of a study to detect differences in the abuse potential of the various formulations of drug and placebo.[6] In general, the pre-qualification phase should ensure that subjects can distinguish between placebo and an IR version of the same opioid drug as the abuse-deterrent formulation, using the same route of administration as planned for the assessment in the clinical phase. The positive control should include a strength that is lower than or equal to the lowest strength selected for the assessment during the clinical phase. For example, a 15 mg dose of opioid could be used in the pre-qualification phase when a 30 mg dose will be assessed in the clinical phase.

Qualifying criteria that help identify subjects with an acceptable placebo response and an acceptable response for the positive control should be pre-specified in the study protocol. After a range for an acceptable placebo response is set, an acceptable response for the positive control should be chosen so that there is no overlap of responses. For example, if a difference in drug liking scores between placebo and the positive control of 15 or higher is set and an acceptable placebo E_{max}[7] response range is set between scores of 40 and 60 on a bipolar scale,[8] liking scores for the positive control that successfully define a suitable subject for the treatment phase would be those equal to or higher than 75 on a bipolar drug liking scale.

3. Assessment Phase

The potentially abuse-deterrent formulation should be compared to a formulation that serves as a positive control,[9] and the positive control should be compared to placebo to validate the study. For an IR product with potentially abuse-deterrent properties, the positive control should be an IR formulation of the same opioid. For an ER formulation with potentially abuse-deterrent properties, the positive control could be an IR formulation of the same opioid, an ER formulation of the same opioid, or, if unavailable, a manipulated form of another ER opioid known to be abused. Examples of a manipulated opioid include crushed ER tablets administered orally or placed into an oral solution. The study should include at least two strengths of the positive control.

Pharmacokinetic data should be collected to correlate with the pharmcodynamic outcomes described in section 7.

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[6] An additional advantage of a pre-qualification phase is that it helps subjects to be familiarized with and trained in the use of various scales and questionnaires that measure subjective effects.

[7] E_{max} refers to the maximum pharmacodynamic response.

[8] On a bipolar drug liking scale, 50 = neutral, 100 = maximum liking, and 0 = maximum dislike).

[9] A positive control in general is an opioid with a similar pharmacological profile or, in some cases, on a similar adverse event profile.

325 *4. Subjects*
326
327 Studies should be conducted in opioid-experienced abusers who have experience with the
328 particular route of abuse being studied. Subjects should not be physically dependent and should
329 not be currently seeking or participating in treatment for drug abuse.
330
331 Detailed characteristics of the study population with respect to past and current drug use and
332 abuse should be captured (e.g., drugs abused, drug of choice, duration of abuse or abstinence).
333
334 *5. Dose Selection, Manipulation Mode, Comparators, Route of Administration, and*
335 *Sample Preparation*
336
337 The selection of the route(s) of administration should be based on epidemiological data showing
338 that a selected route is a relevant route of abuse. For each route of administration, the potentially
339 abuse-deterrent formulation and comparator should be manipulated to cause the highest release
340 of the opioid and the highest plasma levels. The dose of the opioid selected for the study should
341 be known to produce high levels of liking in opioid-experienced abusers.
342
343 The intranasal and intravenous routes of administration present additional challenges. For
344 studies using the intranasal route of administration, the preparation of the samples is extremely
345 important. The potentially abuse-deterrent formulation and comparator study drug should be
346 produced with similar particle size distribution based on a detailed protocol for the preparation of
347 the samples.[10]
348
349 For studies using the intravenous route of administration, the oral formulations may not be safe
350 for intravenous use. In place of the manipulated oral formulation, a solution for injection should
351 be prepared using commercially available products that are safe for intravenous use. The amount
352 of the opioid should be based on extrapolation from in vitro extraction studies of manipulated
353 solid formulations.
354
355 *6. Outcome Measures and Data Interpretation*
356
357 In abuse potential studies, the primary method for evaluating the subjective effects of drugs
358 should be through the use of standardized instruments. A Statistical Analysis Plan should be
359 included in the study protocol.
360
361 *7. Instruments to Assess Drug Abuse Potential*
362
363 In typical abuse potential studies, several instruments have been used to measure subjective
364 responses predictive of the likelihood of abuse. These instruments include:
365

[10] Available safety-related information on the use of the various excipients through the intranasal route should be provided. Additionally, some sponsors have conducted intranasal tolerability studies prior to the abuse potential studies to evaluate irritation of the nasal cavity, nasal congestion, and discharge, among other measures.

- Visual Analogue Scales (VAS) – used for drug liking, good effects, bad effects, and other drug abuse-related effects
- Profile of Mood States

Using these instruments, for the evaluation of the abuse potential of a potentially abuse-deterrent formulation, the VAS for drug liking should be the primary measure as it appears to correlate most directly with potential for abuse. Other measures of particular interest include:

- Assessment of overall drug liking[11]
- Assessment of high
- Assessment of likelihood to take the drug again

These measures can be assessed using either a unipolar or bipolar scale, and a rationale should be provided for the choice for a particular scale. In general, we recommend use of a bipolar scale for the primary measure of drug liking.

8. Data Interpretation

For clinical studies of abuse potential conducted on potentially abuse-deterrent opioid drug products, the primary analysis should be the difference in means of the E_{max}.[12]

Additional pharmacodynamic measures, including positive subjective effects other than drug liking (e.g., take drug again, high, overall drug liking) and other subject-rated assessments, are generally considered secondary endpoints. Other subject-rated assessments of interest include: alertness; drowsiness; nausea; and, when the intranasal route is used, intranasal irritation, burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion.

Some sponsors provide descriptive statistics including mean, standard error, median, and interquartile range, calculated for all pharmacodynamic endpoints by time and treatment. (See section on Statistical Analysis for further guidance.) What constitutes a clinically significant difference in drug liking, between the manipulated and intact versions of the potentially abuse-deterrent formulation and positive control, is an area requiring further research and will be evaluated on a case-by-case basis. Analysis of postmarketing data on abuse levels associated with the potentially abuse-deterrent formulation being studied will help to support the findings from abuse potential studies.

In addition, when interpreting results from human abuse potential studies, attention should be given to the profile of subjective effects produced by the manipulated and intact formulation in

[11] 'Overall drug liking' measures the user's retrospective assessment of a drug, whereas 'VAS for drug liking' measures the user's immediate assessment.

[12] In general, the primary endpoint of interest is drug liking, and the E_{max} is captured within 8 hours after dosing. However, the timeframe of measuring the maximum response will be determined by the pharmacokinetic and pharmacodynamic parameters of the formulations studied.

terms of onset, peak duration of activity, and offset. The rate of rise of drug onset for the intact and manipulated potentially abuse-deterrent formulation should be given appropriate weight in the overall analysis of the abuse deterrent properties. A more rapid onset of action or a shorter time-to-reach peak effect is generally associated with greater abuse potential.[3] Regarding the duration of effect, it may be difficult to interpret the abuse potential of a formulation that produces a sustained liking effect when taken intact or after manipulation, though lower than that produced by the IR comparator formulation.

The overall assessment of abuse potential should be based on the pattern of findings across all of the measures. In addition, qualitative aspects of the findings, such as the steepness of the drug liking response and duration of the liking effects associated with manipulated formulations, should be taken into consideration, along with other positive effects and negative effects.

9. Statistical Analysis

a. Background

The overall goal of a clinical study of abuse potential is to assess a number of abuse potential outcome measures (e.g., drug liking VAS) in the potentially abuse-deterrent formulation relative to a formulation of the drug without abuse-deterrent properties (positive control). Substantial decreases in the responses for the potentially abuse-deterrent formulation compared to the positive control are evidence of deterrence.

The positive control (C) would typically be an appropriate opioid analgesic that has history of misuse and abuse. The test drug (T) would be the potentially abuse-deterrent formulation.

A clinical study of abuse potential should be validated by comparing the responses to C with those of placebo (P). Thereafter, the assessment of the abuse-deterrence properties of T is of primary interest. This can be achieved by comparing the difference in means between C and T with a *margin* for abuse potential measures and comparing the difference between C and T relative to C in drug liking on a bipolar VAS.

The statistical analysis of the data in a clinical study should begin with descriptive statistics comprising tabulations and graphs, which include tables of the means (or medians), standard error, and other summary statistics: minimum, Q1, median, Q3, and maximum of the responses of interest for each treatment. Useful graphs include mean time course profiles, heat-maps, and continuous responder profiles.

b. Primary Analyses

The primary analysis of abuse-deterrent effects should be based on the comparison of means (or medians) between crushed, chewed, or otherwise modified T and C with an abuse-deterrence margin. That is,

$$H_0 : \mu_C - \mu_T \le \delta_1 \text{ versus } H_a : \mu_C - \mu_T > \delta_1$$

where $\delta_1 > 0$. Because C is an opioid drug, the validation test also needs a margin, say δ_2. That is,

$$H_0 : \mu_C - \mu_P \le \delta_2 \text{ versus } H_a : \mu_C - \mu_P > \delta_2$$

where $\delta_2 > 0$.

The actual values of δ_1 and δ_2 may vary according to abuse potential measures and the route of drug administration. Before conducting a study, the sponsor should review the literature and consult with appropriate experts, and then propose the values of δ_1 and δ_2 to the FDA for discussion. We also suggest the use of 95% confidence intervals to assess both the differences $\mu_C - \mu_T$ and $\mu_C - \mu_P$.

c. Secondary Analyses

In addition to the primary analysis, an analysis of the percent reduction for the potentially abuse-deterrent formulation relative to C from each individual study subject for drug liking VAS on a bipolar scale from 0 to 100, the most important abuse potential measure, is recommended for the clinical abuse potential studies. One definition for percent reduction for individual subjects is as follows:

$$\%reduction = \frac{c_i - t_i}{c_i - p_i} \times 100\%,\ i = 1, 2, ..., n,$$

where c_i, t_i and p_i are the E_{max} values for C, T, and P from the *i*th subject, respectively; n is the sample size.

Nevertheless, this definition is problematic because for two subjects having the same E_{max} values for T and C ($t_1 = t_2$ and $c_1 = c_2$), the larger the placebo response, the greater the percent reduction. A more appropriate definition of percent reduction can be derived by replacing p_i by the neutral score 50 on a bipolar scale; that is,

$$\%\text{ reduction} = \frac{c_i - t_i}{c_i - 50} \times 100\%,\ i = 1, 2, ..., n$$

Note that even though most abuse potential studies have a pre-qualification phase, approximately 10% of subjects still have placebo responses p_i over 65, with 5% over 77 in the assessment phase. Consequently, it may be necessary to penalize subjects with large values of p_i in computing percent reduction. For example, the percent reduction could be multiplied by an adjustment factor that equals 1 when p_i is around 50 or less and decreases from 1 when p_i is large. Sponsors should discuss with FDA the need for an adjustment factor in computing percent reduction and an appropriate formula for defining the penalty to be applied prior to finalizing the study protocol.

Two approaches for assessing the deterrent effects using percent reduction are provided below.

Responder Analysis

A *responder* is defined as a subject who had at least a certain prespecified level of reduction, for example, 30% or 40% reduction, in E_{max} for T relative to C. A proportion test may be used to test the null hypothesis that 50% or fewer subjects are responders. That is,

$$H_0 : p^* \leq 50\% \text{ versus } H_a : p^* > 50\%$$

where p^* denotes the percentage of responders. The 95% confidence interval of p^* may also be calculated.

Analysis of the Median Percent Reduction

The median of the percent reduction (*ptr*) is a descriptive measure of central tendency of *ptr*. At most 50% of subjects have *ptr* less than the median, and at most 50% of subjects have *ptr* greater than the median. If the median of *ptr* is equal to 30%, for example, it means that approximately 50% of subjects have greater than or equal to a 30% reduction.

For assessing deterrent effects, we may test

$$H_0 : median(ptr) \leq DR\% \text{ versus } H_a : median(ptr) > DR\%$$

DR denotes deterrent reduction. If the distribution of *ptr* is symmetric, the Wilcoxon-signed rank test can be used to test the null hypothesis that the $median(ptr) \leq DR\%$, and a 95% confidence interval for the median based on this test may be readily calculated using standard methods.

Sponsors should pre-specify one of the two analysis methods for the percent reduction in their statistical analysis plan in addition to the primary analysis in their clinical studies, and discuss with FDA the definition of a responder in the responder analysis or the value of DR% used in the analysis of the median percent reduction prior to finalizing the study protocol.

V. POSTMARKETING STUDIES (CATEGORY 4)

Premarketing studies focus on assessing the potentially abuse-deterrent properties of a product under controlled conditions. The goal of postmarketing studies, Category 4, is to determine whether the marketing of the potentially abuse-deterrent formulation results in a significant decrease in population-based and use-based estimates of abuse compared to estimates of abuse if only formulations without abuse-deterrent properties are marketed.

Because data on the actual impact of an abuse-deterrent formulation on drug abuse are limited, the optimal design features of postmarketing epidemiologic studies capable of detecting a change in the occurrence of abuse and abuse-related clinical outcomes (addiction, overdoses, poisonings, and death) as a result of the drug product's abuse-deterrent formulation have not yet been established.

A wide range of interrelated behavioral, clinical, and societal factors contribute to drug abuse, and the impact of drug abuse can be manifested in a variety of ways. As a result, data on drug abuse can come from a variety of sources and measure a wide range of markers of drug abuse. Sponsors may thus choose to conduct multiple formal studies, using a variety of data sources and outcomes, and also to collect other informal or supportive data. Sponsors should submit to FDA proposals for formal studies and proposals intended to provide supportive data that are supportive of the assessment of abuse deterrence.

Formal studies have the following characteristics:

1. They use outcomes that provide meaningful measures of abuse deterrence.
2. They produce estimates of abuse deterrence that are nationally representative, or are based on data from a large geographic region.
3. They assess overall <u>and</u> route-specific abuse and abuse deterrence.
4. They are sufficiently powered to assess meaningful changes in drug abuse.

Data that are considered supportive of the evaluation of abuse deterrence can be used to provide additional context on societal, behavioral, and clinical aspects of abuse. Supportive data may rely on sources that capture diversion events, attitudes, and practices (e.g., tampering) of abusers and other information that may not directly be considered abuse (e.g., data concerning the street value of prescription drugs, information about drug use and misuse from social websites). Supportive data can contribute to the totality of evidence relating to abuse deterrence.

The epidemiologic methods and data sources that underlie formal postmarketing studies to evaluate the effect of abuse-deterrent formulations are evolving, and best practices have not been established. Based on the current state of this field, we provide below some basic guidelines on recommended study design features that will allow FDA to evaluate the results of formal studies of potentially abuse-deterrent formulations.

1. The study hypothesis and its relationship to assessing abuse deterrence should be clearly stated. The study hypothesis should also include the route(s) of abuse that will be studied.
2. Drug abuse should be carefully defined in the protocol.
3. An understanding of each data source is important to the design and interpretation of the study. A description of each data source should be provided in the protocol and should include if and how the data source captures drugs, study outcomes, drug formulation, and route of administration of abuse.
4. If a study in a non-U.S. population is pursued, sponsors should describe each country's data sources; health care use; system of health care delivery; and national policies, patterns, and cultural implications for drug abuse and how these differences could affect the study interpretations.

5. The choice of population(s) in each study should be carefully considered. The populations included in the study should be described in the protocol. At least one study should include a high-risk population, such as a population of known drug abusers.

6. The choice of the outcome measure(s) should be justified. Outcomes should include both reported abuse and clinical outcomes that are consequent to abuse. Outcomes of reported abuse should include prevalence and frequency (e.g., days of abuse in past 30 days) of abuse. Clinical outcomes should include prevalence or rates of overdoses, poisonings, addiction, and death; severity of overdoses, poisonings, and addiction; and duration of addiction.

7. The relevance of the outcome measure(s) should be explained. If cross-study comparisons are planned, the outcome measures in these studies should be as similar as possible.

8. The choice of comparator is critical for determining if a reduction in drug abuse is the result of a product's abuse-deterrent properties or the result of other factors (e.g., educational programs, changes in law enforcement policies, or other interventions). If an abuse-deterrent formulation of a previously marketed product is introduced onto the market, a comparison of abuse rates before and after the introduction of the abuse-deterrent formulation can provide important information about abuse deterrence. Use of other opioid products as concurrent comparators can help to clarify whether observed reductions in drug abuse are the result of interventions other than the introduction of an abuse-deterrent formulation. Sponsors should clearly list all proposed opioid comparators and describe the rationale behind their inclusion. When branded and generic versions of a comparator are marketed, they should be included in the study because many data sources used in abuse studies identify only active ingredients and do not distinguish between branded and generic products or among multiple generic products.

9. Understanding the background rates of drug abuse is important for protocol design and interpretation of study results. A baseline assessment of the prevalence of drug abuse for formulations lacking abuse-deterrent properties should be conducted.

10. It is important to control for variables that may affect how the product is used and also for confounders. Examples of confounders to consider include geographic variability and demographic characteristics.

11. Submissions should discuss how the availability of each opioid and the size of the at-risk population will affect the analysis, study design, and interpretation.

12. Submissions should provide specific information regarding the statistical analyses in the protocol, including pre-specified hypotheses, methodologies, and sample size estimates.

13. Qualitative assessments should use available instruments that are shown to be valid measures of the type of drug abuse defined in the protocol and appropriate to the targeted study population. If outcome assessment methods must be developed specifically for a study, they should be tested in a pilot study before their use in the main investigation.

14. Assessment of the abuse outcome measures should consider both the average level and the trend over time in the measures. Segmented regression[13] and interrupted time series[14] measures can be useful for this purpose.
15. Outcome measures should be observed for a sufficient time to adequately characterize the trend. If seasonal and other temporal patterns are present, then analysis of the trend may require longer observational periods.
16. The accuracy of outcome measures will also influence the required observational period. Outcome measures with large uncertainty (due to bias or variability) may require longer observational periods.
17. Changes in the average level of the outcome measures within a defined period of time can be estimated with only a few observations if the uncertainties of the measures are well characterized and there is sufficient statistical power. A change in the average level observed in a limited time period does not preclude favorable or unfavorable trends.
18. Interim analyses are encouraged, but results should be considered as tentative in light of their preliminary nature.

As is the case for formal studies, best practices for collecting and submitting additional supportive data are still evolving. However, below are some basic recommendations relating to supportive data.

1. The goal of the supportive data should be clearly stated, and the rationale for how these data contribute to a sponsor's portfolio of abuse-related studies should be clearly stated.
2. The sponsor should clearly describe how supportive data are representative of the population from which it is derived or sampled, if such information is available.
3. The sponsor should clearly describe how the exposure and outcome are measured and describe the evidence that demonstrates the performance of the outcome assessment in measuring drug abuse as defined in the protocol, if such information is available.
4. Analysis of supportive data based on geographically-diverse settings are strongly encouraged. Analyses with overlapping geographic areas between formal studies and supportive data should be considered.
5. Sponsors should clearly state in the protocol whether the supportive data are intended to be descriptive or analytic in nature. A description of the statistical power and related sample size should be provided.

[13] Wagner A.K., S.B. Soumerai, F. Zhang, D. Ross-Degnan, 2002, Segmented regression analysis of interrupted time series studies in medication use research, *Journal of Clinical Pharmacy and Therapeutics* 27:299-309.

[14] Crosbie J., 1993, Interrupted time-series analysis with brief single-subject data, *Journal of Consulting and Clinical Psychology*, 61(6):966-974).

VI. LABELING

Including information about a product's demonstrated abuse-deterrent properties in labeling is important to inform health care providers, the patient community, and the public about the product's predicted or actual abuse potential. Accordingly, FDA encourages sponsors to seek approval of proposed product labeling that sets forth the results of physiochemical, physiologic, pharmacodynamic, pharmacokinetic, and/or formal postmarketing studies and appropriately characterizes the abuse-deterrent properties of a product.

To date, FDA has limited data correlating the potentially abuse-deterrent properties of certain opioid drug products with actual reduction in abuse or adverse events associated with abuse. When the data predict or show that a product's potentially abuse-deterrent properties can be expected to, or actually do, result in a significant reduction in that product's abuse potential, these data, together with an accurate characterization of what the data mean, should be included in product labeling.[15] This information should be communicated as clearly and transparently as possible. It is critical that labeling claims regarding abuse-deterrent properties be based on robust, compelling, and accurate data and analysis, and that any characterization of a product's abuse-deterrent properties or potential to reduce abuse be clearly and fairly communicated.

Labeling language regarding abuse deterrence should describe the product's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter. For example, a formulation that limits an abuser's ability to crush a tablet and to extract the opioid may be labeled as limiting manipulation for the purpose of snorting or injection, if the data support such a claim. For this characterization to be accurate and not misleading, however, appropriate caveats are likely to be necessary. For example, it may be necessary for the labeling to explain that the product's abuse-deterrent properties only make abuse more difficult, not impossible, and that these properties provide no deterrence against other forms of abuse (such as swallowing the intact tablet).

FDA may also require caveats based on the types of studies performed or on the extent to which those studies accurately predict real-world effects. For example, when data supporting a product's potential to reduce abuse derive from premarketing studies that FDA determines are reasonably predictive but not determinative of reduced abuse, the labeling might include a statement such as:

> *This information is based on the above-described laboratory and clinical studies, which may not accurately predict the product's actual abuse potential. Postmarketing studies of the actual abuse patterns associated with this product are ongoing, and this information may be modified based on the results of such studies.*

In the past, FDA has required descriptions of abuse-deterrence studies in labeling to be accompanied by statements that, for example, the clinical significance of the studies is unknown and that there is "no evidence" that the product's potentially abuse-deterrent properties actually

[15] Abuse-deterrence information will be included in subsection 9.2 (Abuse) of the DRUG ABUSE AND DEPENDENCE section.

reduce the product's abuse potential. However, we believe the approach discussed in this section – which focuses on targeted data and a flexible, adaptive approach to labeling - will be beneficial to public health.

FDA encourages sponsors to develop abuse-deterrent formulations based on advances in the relevant science and technologies. As abuse-deterrence technologies improve, FDA expects that it will allow claims related to abuse deterrence commensurate with those improvements. On the other hand, FDA is concerned that abusers may adapt to abuse-deterrent formulations and discover methods of defeating them. Accordingly, FDA will take a flexible, adaptive approach to the labeling of these products. If and when abusers can overcome a technology such that it no longer has a meaningful effect in deterring abuse, FDA may require labeling revisions.

There are four general tiers of claims available to describe the potential abuse-deterrent properties of a product.

Tier 1: The Product is Formulated with Physicochemical Barriers to Abuse

Tier 2: The Product is Expected to Reduce or Block Effect of the Opioid When the Product is Manipulated

Tier 3: The Product is Expected to Result in a Meaningful Reduction in Abuse

Tier 4: The Product has Demonstrated Reduced Abuse in the Community

These tiers generally correlate with the four categories of study data described above. However, in order to provide as complete a picture as possible of a product's abuse-deterrent properties, FDA generally expects sponsors to provide data from Categories 1, 2, *and* 3 in order to be eligible for Tier 1, Tier 2, or Tier 3 claims. For example, Category 1 data alone likely will not be sufficient to support a Tier 1 claim; Category 2 or 3 data (or both) may be needed to ensure that a Tier 1 claim is not misleading.

That said, some products intended to deter abuse will not require data from each of the four study categories in order to be eligible for an abuse-deterrence claim. One example is a prodrug of an opioid for which there are Category 1 and 2 data demonstrating that it cannot be abused because it is not active until it has been metabolized in the gastrointestinal tract or the systemic circulation after oral ingestion. Based on these data, it may not be necessary to perform Category 3 studies to obtain approval for Tier 1 and/or Tier 2 claims related to deterring abuse via injection or insufflation**.**

The goal of product labeling for abuse-deterrent opioid formulations is to accurately reflect the available data regarding the expected or known impact of the abuse-deterrent formulation on abuse of the product while also accurately conveying any uncertainty regarding that impact. As discussed below, the nature of the claims available for a particular product will depend on the types of studies performed and the results of those studies. FDA is not able to provide specific guidance on the magnitude of effect that would be sufficient to support each type of claim. Labeling claims therefore will be assessed on a case-by-case basis, depending on the data presented.

Tier 1: Claims that a Product is Formulated with Physicochemical Barriers to Abuse

As discussed in Section IV, various physicochemical barriers to abuse may be initially assessed in Category 1 premarketing studies. The specific properties that resist manipulation and/or that result in the release of components of the formulation that may limit its ability to be abused should be described. In addition, the specific route or routes of administration affected by these abuse deterrence properties should be described.

An example of a Tier 1 claim could be:

> *These data demonstrate that, when the intact formulation is ground in a coffee grinder, the resulting particle size makes insufflation extremely difficult; and when those particles are heated they form a gelatinous substance that cannot be drawn up into a syringe or insufflated. Therefore, it appears that injection or snorting of the manipulated drug product would be difficult. However, abuse of this product is still possible by the oral route.*

This statement would be followed by an appropriate acknowledgment that data from laboratory studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and that this information may be modified based on the results of such studies.

Tier 2: Claims that a Product is Expected to Reduce or Block the Effect of the Opioid When the Product is Manipulated

As discussed in Section IV, pharmacokinetic data may also be used to demonstrate a product's abuse deterrence. An example of a Tier 2 claim could be:

> *These data demonstrate that, when the intact product is heated in a solvent suitable for injection and the resulting solution is injected, the opioid antagonist component is released into the systemic circulation at a pharmacokinetic exposure level that may result in blocking of the opioid's agonist effects, or in a mild to moderate degree of opioid withdrawal in an opioid-tolerant individual. However, abuse of this product is still possible by the oral route.*

This statement would be followed by an appropriate acknowledgment that data from laboratory and clinical studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and this information may be modified based on the results of such studies.

Tier 3: Claims that a Product is Expected to Result in a Meaningful Reduction in Abuse

As discussed in Section IV, data from appropriately designed, conducted, and analyzed human abuse potential studies may demonstrate a meaningful degree of reduction in abuse potential. If a sponsor seeks a Tier 3 claim that a product can be expected to result in a meaningful reduction in abuse, that claim generally will need to be supported by data from Category 1, 2, and 3 studies.

The Agency believes that reductions in drug "liking" generally are likely to result in meaningful reductions in abuse. However, data from Category 1 and 2 studies should serve as the basis for performing the Category 3 studies and will provide important supportive information in understanding the results of a Category 3 study. If data from Category 3 studies are robust, Tier 3 labeling claims and data regarding the design, conduct, and data from Category 3 studies may be included in the product labeling.

An example of a Tier 3 claim could be:

> *These data demonstrate that the inclusion of the opioid antagonist component in the product's formulation results in a decrease in euphoria and "liking" when a solution of the product in a suitable solvent for injection has been heated and the resulting solution injected parenterally. Based on these findings, this product's specific formulation may result in reduced abuse by parenteral injection. However, abuse of this product is still possible, including by the oral route or by snorting when the product is crushed.*

This statement would be followed by an appropriate acknowledgment that data from laboratory and clinical studies may not fully predict real-world abuse potential, that post-marketing studies are ongoing, and this information may be modified based on the results of such studies.

Tier 4: Claims that a Product has Demonstrated Reduced Abuse in the Community

As discussed in Section V, post-marketing data from a variety of sources can demonstrate that a product's abuse-deterrent properties cause persistent and relevant reduction in its abuse. These data include data from appropriately designed, conducted, and analyzed formal post-marketing studies, as well as data from supplemental sources on the abuse of the product (e.g., data concerning the street value of prescription drugs).

FDA is currently considering formal studies plus a variety of supplemental data as sources that may be acceptable to provide evidence that a product's formulation has had an actual impact on its abuse. FDA anticipates that data from Category 1, 2, 3, and 4 studies (including both formal studies and supporting data) would be needed to support a Tier 4 claim. The combined results from all of these studies would be described in the product labeling, including specific study designs, conduct, analyses, and study data.

An example of a Tier 4 claim could be:

> *These data have demonstrated a reduction in abuse of this opioid in the community setting compared to the levels of abuse, overdoses, and deaths that occurred when only formulations of the same opioid without abuse deterrence properties were available. This reduction in abuse appears to be due to the product's particular formulation, which deters parenteral injection and snorting of the manipulated product. However, such abuse of this product is still possible, and the product's abuse deterrence properties do not deter abuse associated with swallowing the intact formulation.*

This statement would be followed by an appropriate acknowledgment, if applicable, that postmarketing studies are ongoing and that this information may be modified based on the results of those studies.

VII. ADDITIONAL RESEARCH NEEDS

As has been discussed above, the science of abuse deterrence is relatively new. Both the technologies involved and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. This means that FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. It also means there is considerable room for additional scientific work that could advance the development and assessment of abuse-deterrent formulations. In particular, the agency encourages additional research on the following topics:

- Characterization of the quantitative link between changes in the pharmacokinetics of opioids in different formulations and results of a clinical abuse potential study with those same formulations.
- Characterization of the best assessment methods to employ when analyzing a clinical study of abuse potential.
- Characterization of the quantitative link between the outcomes from a clinical study of abuse potential comparing formulations and the effect on those same formulations on abuse in the community.
- Further understanding of the best study methods to employ to assess the effect of an abuse-deterrent formulation on the rates of abuse in the community.

Progress on these topics could facilitate the ability of sponsors to propose, and FDA to approve, labeling that would give a more complete picture of the anticipated effect of abuse-deterrent formulations. Ultimately, progress in these areas could facilitate product development by reducing the amount of information that is needed to accurately assess an abuse-deterrent formulation and predict its impact on abuse in the community.