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Abuse-Deterrent Opioids: Study Requirements

(Part 2 of a 3-Part Series)

Introduction

As one component of a multifaceted approach to addressing opioid abuse and misuse, the FDA and pharmaceutical manufacturers are taking steps to help deter opioid abuse through the development of abuse-deterrent (AD) formulations.[1-3] These new formulations are designed to deter abusers from manipulating the product in order to create a "dump" effect and an associated rapid high.[2,3]

Part 1 of this 3-part series on AD opioids reviewed the approaches to the development of AD technology and the need to continually strike a balance between ensuring effective pain control and reducing the risk for opioid abuse and misuse. Various approaches include incorporation of physical or chemical barriers, addition of a sequestered opioid antagonist, employment of a noxious component (ie, aversion), the use of unique drug delivery systems, development of new molecular entities and prodrugs that lack opioid activity until undergoing metabolism within the body, a combination of 2 or more of the above, or novel approaches not included in the other categories.[1] Part 2 of this series focuses on a different aspect of the development of these agents, namely premarket and postmarket studies for demonstrating the potential to reduce opioid abuse.

FDA Guidance for Industry

In April 2015, the FDA issued a final guidance document that outlined the recommendations for the evaluation and labeling of AD opioids.[1] The purpose of the document is to assist pharmaceutical manufacturers in developing formulations of opioids with potentially AD properties in the interest of improving public health and safety.[1] In particular, the document provides guidance regarding how studies should be conducted to demonstrate that a given formulation has AD properties, how studies could be executed and evaluated, and how to describe them and "their implications in product labeling."[1] The guidance also states that the FDA is prepared to undertake a "flexible, adaptive approach" when assessing the study data and potential labeling of AD formulations given the relatively new science of abuse deterrence.[1]

In an effort to clarify terminology, the guidance document defines AD properties as deterring but not necessarily preventing abuse. Additionally, the document distinguishes between *abuse*—intentional non-therapeutic use of an opioid to achieve a desirable effect—and *misuse*—intentional therapeutic use of an opioid in an inappropriate way.[1,4]

The guidance describes 4 separate categories of studies for evaluating potential AD opioid formulations: Categories 1 through 3 refer to premarket studies, and the development plans of AD formulations should generally include data from all of them, and category 4 refers to postmarket studies.[1] The guidance document also provides general considerations regarding study design of premarket studies. It states that the design of these studies should include appropriate positive controls and comparator drugs, outcome measures, data analysis, and subject selection.[1] Additionally, the most common potential routes of abuse for an opioid and design studies should be considered when evaluating use of AD formulations via those routes.[1] The FDA document points out that sponsors should be aware that the results of category 1 studies may influence the category 2 study design, and the results of category 2 studies may affect the need for, and design of, category 3 studies.[1] Data from all 3 study categories may not always be needed; however, in most cases, data from all of the categories will be appropriate when considering the effect of the AD technology and the potential risk for abuse.

Category 1: Laboratory-Based Manipulation And Extraction Studies

The goal of category 1 studies is to assess the ease with which the potentially AD properties of an opioid formulation can be compromised.[1] When designing these studies, sponsors should consider not only how abusers may attempt to overcome the AD properties of the medication but also the ways that patients may alter the formulation in order to change the rate or amount of opioid released.[1]

A variety of different studies can be performed at this stage of development that evaluate simple and sophisticated mechanical and chemical approaches to manipulating a dosage formulation.[1] These may include evaluating the preparation of an immediate-release formulation for alternative routes of administration; separating the opioid antagonist from the agonist, and compromising the controlled release of an opioid from an extended-release formulation for alternative routes of administration.[1]

The assessment should include the simplicity with which the formulation may be cut, crushed, grated, or grinded, as well as the effects of exposure to hot and cold temperatures.[1] Additionally, an appraisal of the ease of solubilizing and extracting the opioid from the intact and manipulated product, including the effects of time, pH, temperature, and agitation on this process, should be considered.[1] Beyond these general assessments, route-specific data also should be evaluated, including particle size distribution (to assess the potential to be snorted); vaporization and degradation temperature of the opioid in salt and base form (for formulations that may be smoked or inhaled); and the opioid concentration in, and viscosity of, a small volume of fluid (for those products that may be injected).[1]

Category 2: Pharmacokinetic Studies

The goal of category 2 studies is to evaluate the in vivo properties of the AD formulation by comparing pharmacokinetic (PK) properties of the "manipulated formulation with the intact formulation and with manipulated and intact formulations of comparator drugs" using one or more routes of administration.[1] The effects of food and alcohol on the PK properties of the formulation also should be assessed if needed.[1,5] The FDA recommends that the following PK parameters should be measured for the parent opioid and any active metabolite[1]:

- Terminal elimination half-life ($T_{1/2}$)
- Maximum serum concentration (C_{max})
- Time to maximum serum concentration (T_{max})
- Area under the curve (AUC_{0-t} and $AUC_{0-\infty}$); and
- Any relevant partial AUC measurements (eg, AUC from 0 to 30 min)

Additionally, how quickly the serum concentration of the opioid can increase should be evaluated because this property may contribute to the potential for abuse.[1] Finally, adverse event data should be collected as a routine component of conducting category 2 studies.[1]

Category 3: Clinical Abuse Potential/Human Abuse Liability Studies

Although category 3 studies aid in evaluating the abuse potential of a new medication for purposes of scheduling under the Controlled Substances Act, the main purpose of these studies with regard to AD formulations is to assess the drug liking of the formulation.[1,5] As such, various study methodologies should be adapted to achieve this objective. The Table summarizes the methodologic aspects of CAP/HAL studies. Overall, the preferred design for category 3 studies is a randomized, double-blind, placebo-controlled trial, along with a positive comparator–controlled crossover study performed using a drug-experienced abuser population.[1,5] Generally, the primary end point of interest in these studies is drug liking.

Category 4: Postmarket Studies

Postmarket studies are designed to determine whether or not the availability of an AD formulation results in a significant reduction in estimates of abuse, as well as related clinical adverse outcomes compared with estimates of abuse if only formulations without AD properties were available after marketing approval.[1] The optimal study design of postmarket epidemiologic studies (eg, study variables, design features, and analytical techniques) has not been fully determined because data on the effect of AD formulations on actual drug abuse are limited.[1]

The FDA guidance document categorizes postmarket evaluations as being formal studies or supportive information.[1] Formal studies should have the following characteristics per the FDA guidance document[1]:

- Hypothesis-driven, population-based observational evaluations that use outcomes that provide meaningful measures of abuse deterrence.
- Provide outcomes that can be used to assess reductions in abuse, misuse, addiction, overdose, and death.
- Estimates of abuse deterrence that are nationally representative in nature, or are at least representative of a larger geographic area.
- Assessment of overall and route-specific abuse and abuse deterrence.
- Sufficient power to detect a significant reduction in drug abuse.

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Table. Methodologic Aspects of Category 3 Studies

Study Design Aspect	Comments
Blinding	• Because the study population is usually recreational drug users who are familiar with the effects of opioids, the use of a double-dummy technique or other approach may be necessary to ensure blinding. • Depending on the route of drug administration, unique challenges to ensuring blindness may occur (ie, maintaining a similar particle-size distribution when evaluating intranasal administration of a crushed product).
Prequalification phase	• The purpose is to "increase the power of a study to detect differences in the abuse potential of various formulations of drug and placebo." • This phase should ensure that enrolled individuals can tell the difference between placebo and an immediate-release formulation of the same opioid as the AD formulation, using a route of administration that is similar to what will be used in the assessment phase.
Assessment phase	• The AD formulation is compared with a "positive control," which is an opioid with a similar pharmacologic or safety profile; the positive control also is compared with placebo to validate the study.
Subjects	• Individuals should be experienced drug users who have a history of abuse via the route of administration under evaluation. • Generally, physically dependent individuals should not be enrolled unless the formulation being studied renders such data as meaningful. • Individuals who are currently seeking or receiving treatment for drug abuse also should be excluded.
Route of administration, dose selection, manipulation mode, and sample preparation	• Epidemiologic data on the route(s) of administration by which abuse occurs should guide the choice of route evaluated in the study. • For each route of administration, the AD formulation and the comparator should be manipulated to result in the highest release of the opioid and, subsequently, the highest serum drug level. • The selected dose should be known to produce high "liking" levels in opioid-experienced abusers. • Intranasal and IV routes of administration may be particularly challenging to study.
Outcome measures and data interpretation	• Standardized instruments should be used to evaluate the subjective effects of drugs.
Instruments to assess drug abuse potential	• VAS: primary measure for drug liking as it correlates most directly with abuse potential; the "VAS for drug liking" measures the user's immediate assessment • Profile of Mood States • Other measures of interest: assessment of overall drug liking, assessment of high, and assessment of likelihood of taking the drug again • The assessment of overall drug liking examines the user's retrospective assessment of a drug versus the immediate assessment seen with the VAS. The VAS measures the drug liking difference on a scale of 1 to 100 between the active formulation and the comparator. • The broader the difference, the less "liked" it is, thus the more effective the product is in achieving abuse potential.
Data interpretation	• Primary end point: difference in E_{max} means for drug liking • Secondary end points: address subject-rated assessments (eg, drowsiness and intranasal irritation) and route-specific assessments • Assessment of subjective effects on onset and offset of action and peak duration period
Statistical analysis	• Primary analysis: comparison of E_{max} means between AD opioid formulation and non-modified opioid • Secondary analysis: percent reduction in drug liking on the VAS between AD opioid formulation and non-modified opioid

AD, abuse deterrent; **E_{max},** maximum effect; **VAS,** visual analog scale
Based on reference 1.

The guidance document contains basic guidelines regarding study design features for formal studies.[1] Highlights from these guidelines include a clearly stated hypothesis; a description of each data source and how it will be used to assess outcomes; careful consideration of study population; well-defined study outcomes including clinical adverse events; rationale in selecting appropriate comparators to determine if a reduction in drug abuse is attributed to the AD formulation or other factors; and statistical and interim analyses.[1]

Conclusion

The FDA guidance document on AD opioids provides pharmaceutical manufacturers with an overview of the agency's current thinking regarding study recommendations for developing AD formulations. The FDA acknowledges that the science of abuse deterrence is relatively new and therefore a flexible, adaptive approach is needed when evaluating study design and results from studies involving these products. Additionally, the methods by which new molecular entities are evaluated will need to adapt as other formulations are assessed.

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