ORIGINAL ARTICLE

# Insights and issues from FDA Advisory Committee meetings on abuse-deterrent opioids

Christopher J. Miller, MS; Richard C. Dart, MD, PhD; Nathaniel P. Katz, MD, MS; Lynn R. Webster, MD, FACPM, FASAM

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**ABSTRACT**

*It is the current policy of the US Food and Drug Administration (FDA) to convene expert Advisory Committees to provide input on key regulatory decisions regarding opioid products, including approval and labeling of opioid abuse-deterrent formulations (ADFs). Advisory Committee meetings on ADF opioids consider whether the laboratory and clinical data submitted by the sponsor are sufficient to support marketing approval and labeling of the product with properties expected to deter abuse by specific routes of abuse (ie, oral, intranasal, intravenous). The FDA has typically followed the approval and labeling recommendations for ADFs reviewed by its Advisory Committees, highlighting the importance of these meetings in the regulatory approval process. This review describes common issues considered by Advisory Committees for ADF opioids as well as insights on how to prepare for these meetings based on recent relevant experience and regulatory decisions.*

## INTRODUCTION

As one component of a larger public health effort to address the opioid abuse epidemic, the US Food and Drug Administration (FDA) has advocated for the development of abuse-deterrent formulations (ADFs) that make abuse and misuse of opioid products more difficult or less rewarding. While the most common form of opioid abuse is via oral ingestion of intact tablets, a substantial number of individuals tamper with opioids to speed the release of the active pharmaceutical ingredient (API) or to convert the product into an abusable form (eg, insufflatable powder or injectable solution). Oral administration of an altered (eg, crushed or chewed) opioid product or administration via a nonoral route is more dangerous than intact oral abuse. Most ADFs are formulated with properties that are intended to deter abuse by tampering for oral, nasal, or intravenous (IV) administration.

The FDA Guidance for Industry on the evaluation and labeling of abuse-deterrent opioids outlines that the goal of ADFs is to meaningfully *deter* abuse, recognizing that no formulation can fully *prevent* abuse.[1] The call for ADFs has resulted in unique and complicated regulatory challenges for both sponsors and the FDA, since the development program for each formulation must be tailored to evaluate the intended abuse-deterrent properties or safety features of the product within the framework of the general guidance.

Given the evolving regulatory paradigm and public policy implications of abuse-deterrent opioid products, the FDA has relied extensively on the advice of its expert Advisory Committees during the New Drug Application (NDA) review process. In 2016, the Agency issued their Opioids Action Plan which states, "the FDA will convene an expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties."[2] Furthermore, the Plan notes that "the FDA will consult an advisory committee on ADF opioids when they raise novel issues."

From September 2015 through April 2017, there have been seven joint meetings of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management

**Table 1. Recent Advisory Committee meetings considering approval of ADF opioids (September 2015-April 2017)**

| Product | Sponsor | Release profile and active moiety | Description of product | Summary of vote (FDA decision) |
|---|---|---|---|---|
| Avridi™ | Purdue Pharma L.P. | IR oxycodone | Tablet formulation with gelling and aversive agents | 23-1 against approval (not approved) |
| Xtampza® ER | Collegium Pharmaceutical, Inc. | ER oxycodone | Microsphere-in-capsule formulation | 23-0 in favor of approval (approved with nasal and IV AD labeling) |
| Apadaz™ | KemPharm, Inc. | IR benzhydrocodone/ acetaminophen | Prodrug of hydrocodone with acetaminophen | 16-4 in favor of approval; 18-2 against labeling as AD product (not approved) |
| Vantrela™ ER | Teva Pharmaceutical Industries Ltd. | ER hydrocodone | Triple-layer polymer formulation | 14-3 in favor of approval; 14-3 in favor of oral AD labeling; 14-3 in favor of nasal AD labeling; 16-1 in favor of IV AD labeling (approved with oral, nasal, and IV AD labeling) |
| Troxyca® ER | Pfizer Inc. | ER oxycodone | Agonist/antagonist formulation with sequestered naltrexone | 9-6 in favor of approval and IV AD labeling; 9-6 against oral AD labeling; 11-4 in favor of nasal AD labeling (approved with oral, nasal, and IV AD labeling) |
| Arymo™ ER | Egalet Corporation | ER morphine | Polymer matrix tablet technology utilizing injection molding | 18-1 in favor of approval and nasal and IV AD labeling; 16-3 in favor of oral AD labeling (approved with IV AD labeling) |
| RoxyBond™ | Inspirion Delivery Sciences, LLC | IR oxycodone | Tablet formulation with physical and chemical barriers | 19-0 with 1 abstention in favor of approval; 19-1 in favor of nasal AD labeling; 16-4 in favor of IV AD labeling (approved with nasal and IV AD labeling) |

Advisory Committee (DSaRM) to consider the approval and abuse-deterrent labeling of extended-release (ER) and immediate-release (IR) opioid products (Table 1). Outside of meetings to consider product approvals, this joint Advisory Committee met four additional times since 2016 to discuss the ER/long-acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy, appropriate development plans for opioid use in pediatric patients, dosing of naloxone to reverse the effects of opioid overdose, and the epidemiologic data on IV abuse of Opana® ER.

Recent precedent suggests that the FDA will continue to hold Advisory Committee meetings for most, if not all, opioids seeking abuse-deterrent label claims for the foreseeable future. This article describes common issues from recent Advisory Committee meetings for ADF opioids as well as some of the authors' recommendations for how to address such issues based on their experience in preparing for and participating at most of these meetings.

## BACKGROUND ON FDA ADVISORY COMMITTEE MEETINGS

An FDA Advisory Committee is comprised of a panel of experts convened by the FDA to provide recommendations to the Agency on scientific issues, regulatory policy, and product approvals. The procedures and policies of Advisory Committees are described in the Code of Federal Regulations, Title 21, Part 14. The regulations state that Advisory Committees should be used when "the Commissioner concludes, as a matter of discretion, that it is in the public interest for a standing or ad hoc committee (advisory committee or committee) to hold a public hearing and to review and make recommendations on any matter before FDA and for

interested persons to present information and views at an oral public hearing before the advisory committee."[3] The Agency's priority items for its Advisory Committees include "drugs subject to active IND's and pending NDA's that offer potential therapeutic advances, that pose significant safety hazards, that present narrow benefit/risk considerations, that have novel delivery systems or formulations, that are the subject of a major scientific or public controversy, or that are the subject of special regulatory requirements, such as a limitation on clinical trials, a patient follow-up requirement, postmarketing studies, or boxed warnings."[4] Overall, the FDA regulations state that "the primary goal of the advisory committee (and outside consultant) system should be to help the agency make sound decisions based upon the reasoned application of good science."[4] While the recommendations of FDA Advisory Committees are not binding, the FDA's approval decisions are typically consistent with their guidance.[5]

Members of FDA Advisory Committees have a wide range of expertise. For example, the current roster of the AADPAC include members with expertise in adult and pediatric anesthesiology, pharmacotherapy, pain medicine, neurology, and biostatistics. The current DSaRM roster includes members with expertise in drug safety, pharmacy practice, medical toxicology, epidemiology, and statistics. These rosters of standing advisory committee members are typically supplemented with additional temporary voting members who have expertise that is not represented among the standing members of the committee. In the case of Advisory Committees for abuse-deterrent products, this expertise has often been in the areas of clinical pharmacology, public policy, and substance abuse.

Advisory Committee meetings reviewing NDAs for abuse-deterrent opioids include Closed and Open Sessions (see Table 2 for a typical agenda). During the Closed Session, the sponsor delivers a presentation and answers questions on trade secret or confidential commercial information about the formulation and its development program. Sponsors also present the specific methodologies used in the abuse-deterrent testing along with blinded codes, which are later used in the Open Session to keep tools, methods, and experimental conditions (eg, solvents, pretreatments, and temperatures) confidential. To protect the confidentiality of the information, only the sponsor, the FDA, and the voting members of the Advisory Committee are allowed to attend.

**Table 2. Typical agenda for an FDA Advisory Committee meeting for an ADF opioid**

| Time | Agenda item |
|---|---|
| 8:00 a.m. | Closed session |
| 9:30 a.m. | Call to order and introduction of committee |
| 9:35 a.m. | Conflict of interest statement |
| 9:40 a.m. | FDA introductory remarks |
| 9:45 a.m. | Sponsor presentations |
| 10:45 a.m. | Clarifying questions to sponsor |
| 11:00 a.m. | Break |
| 11:15 a.m. | FDA presentations |
| 11:45 a.m. | Clarifying questions to FDA |
| 12:00 p.m. | Lunch |
| 1:00 p.m. | Open public hearing |
| 2:00 p.m. | Charge to the committee |
| 2:05 p.m. | Questions to the committee/committee discussion |
| 3:15 p.m. | Break |
| 3:30 p.m. | Questions to the committee/committee discussion (continued) |
| 5:00 p.m. | Adjournment |

In contrast, the Open Session of the Advisory Committee meeting is open to the general public. These sessions typically include an hour-long presentation by the sponsor, a presentation by the FDA, an open public hearing where anyone may speak (usually for a period of 3-5 minutes), time for advisory committee members to ask questions to the sponsor and the FDA, and time for the committee to discuss and vote on questions posed by the FDA. The FDA voting and discussion questions at recent Advisory Committee meetings for ADF products have focused on whether the product has properties that can be expected to deter specific routes of abuse (ie, oral, intranasal, or IV) as well as whether the product should be approved for use in the United States.

The data pertinent to approval and labeling of abuse-deterrent opioids typically include pharmacokinetic bioequivalence studies and abuse deterrence studies. Per FDA Guidance, abuse deterrence

studies include in vitro physical and chemical manipulation evaluations (Category 1), as well as pharmacokinetic data (Category 2) and pharmacodynamic data (Category 3) from human abuse potential (HAP) studies.[1] While experts in their respective fields, most of the Advisory Committee members will not have training or experience in abuse deterrence outside of prior Advisory Committee meetings. Specifically, they will not usually have experience conducting in vitro experiments or HAP studies, or in the identification of abuse-related events in clinical trials. Thus, panel members rely considerably on the briefing information prepared by the sponsor and FDA in advance of the meeting as well as the presentations at the meeting itself to make their recommendations; therefore, the sponsor's briefing materials and presentations ought to provide the necessary background information to derive a sound scientific evaluation of the data while avoiding unnecessary technical details.

The FDA has typically followed the approval and labeling recommendations of its Advisory Committees for abuse-deterrent opioids, though the Agency is not bound to do so. There are some cases where the FDA's approval and labeling decisions have diverged from the recommendations of its Advisory Committees due to a difference in data interpretation or a legal issue (eg, exclusivity for an abuse-deterrent claim); some of these cases will be reviewed later in this review. Nonetheless, in the last 2 years, the FDA has approved all five of the products that have received a positive recommendation from the Advisory Committee for approval and abuse-deterrent labeling. The Agency has not approved either of the two products that did not receive a positive vote (Table 1). Therefore, a product's chances of approval and favorable abuse-deterrent labeling are closely associated with the outcome of a committee's interpretation of a short briefing document, a 1-hour presentation, and 1-2 hours of questioning. This fact underscores the importance of understanding the pivotal issues discussed at past meetings and of anticipating such issues for future meetings, to be adequately prepared.

## DESIRE FOR STANDARDIZATION OF TOOLS FOR PHYSICAL MANIPULATION STUDIES

The FDA Guidance instructs sponsors to use knowledge of the physicochemical properties of the product, as well as knowledge of the methods available to abusers, to test a range of common household tools that are representative of the different ways an abuser could manipulate a product by crushing, cutting, grating, or grinding.[1] The goals are to evaluate the product's resistance to physical manipulation, in general, and to identify the most effective tool to use as the method of manipulation in subsequent in vitro and clinical testing. The Guidance recommends that experiments be conducted with both mechanical and electrical tools such as spoons, cutters, and coffee grinders. In practice, these particle size reduction evaluations tend to be iterative in nature. An initial battery of tools are evaluated, and the most effective tools are optimized by evaluating a wider range of manipulation times, applying pretreatments (eg, freezing, baking, and microwaving), and applying multitool manipulations.

The ability to resist particle size reduction is an important characteristic for many solid oral dosage forms that rely on physicochemical barriers such as tablet hardness to deter abuse. It should be noted that resistance to particle size reduction is less pertinent for agonist/antagonist formulations where manipulation releases an antagonist to minimize the opioid's euphoric effects. Particle size reduction is also less pertinent for prodrugs whose abuse deterrence is based on the chemical engineering of the molecule rather than a physicochemical barrier (ie, prodrugs of opioids are pharmacologically inactive until they are metabolized in the gastrointestinal tract and converted into the pharmacologically active opioid). These exceptions aside, the ability to reduce the particle size of many ER opioid products increases the surface area of the tablet available for diffusion. This increase in surface size speeds the rate of release and absorption, defeating the drug's intended controlled-release properties. For both IR and ER products, particle size reduction may allow an abuser to convert the product into an abusable form for intranasal abuse (ie, an insufflatable powder) or IV abuse (ie, manipulated product that rapidly extracts in a small volume of liquid).

As Advisory Committee members have gained additional experience reviewing ADF development programs, they have expressed a desire to see a consistent use of tools in physical manipulation tests for consistency of tools used to test the physical barriers of the formulations. Advisory Committee members contend that this would allow products to be directly compared for their

resistance to physical manipulation. While the inclination to compare across products makes intuitive sense, doing so may ignore the unique properties of a particular technology. The purpose of physical manipulation experiments is to challenge the specific formulation to the limit so that an optimized particle size reduction procedure can be identified, representing a "worst-case" scenario for that product. These experiments are based on the assumption that this approach yields the best prediction of the extent to which a drug will be manipulated for abuse in the real world. Given that each product has unique physical and chemical properties (eg, active ingredients, dosage form construction, and excipients), different tools will be more effective for different types of formulations. For example, a tool that produces effective particle size reduction for a hard-to-crush tablet may be considerably less effective for a microsphere-in-capsule formulation. Advisory Committee members sometimes appear to assume that variability in choice of tools represents efforts to hide vulnerabilities in the formulations, whereas it actually represents efforts to identify unique vulnerabilities. To address the Committee's concern about standardization, sponsors should proactively describe how the selected tools were representative of the possible methods of manipulation, explain how their selection was aimed at specifically challenging their formulation, and demonstrate that the testing identified an optimal particle size reduction procedure with the most effective tool(s) and conditions. In addition, it may be beneficial for FDA to prescribe a standardized set of manipulations that are common across all formulations, where possible, with an additional battery of tests that are customized to assess potential vulnerabilities of each formulation.

## INTEREST IN CHEMICAL EXTRACTION OF THE OPIOID

Recent Advisory Committees have spent considerable time discussing the ease and speed with which the API can be chemically extracted from the abuse-deterrent product. Advisory committee members' interest in extraction relates to the potential for abusers to find more sophisticated methods to either defeat the controlled-release properties of an ER formulation for oral abuse, prepare an opioid for IV abuse or separate the opioid agonist from the antagonist (eg, naltrexone) to defeat the abuse-deterrent properties.

Addressing the issue of resistance to extraction is complicated since any oral opioid product, including ADFs, must ultimately be orally bioavailable to provide effective analgesia. Further, the FDA Guidance does not lay out clear pass-fail criteria for chemical extraction studies, which leaves the interpretation of these complicated experiments to the Advisory Committee.

The results of chemical extraction studies are best framed in the context that ADFs are intended to be abuse *deterrent* and are not abuse *proof*. It should also be recognized that sponsors test their products to failure using methods well beyond the willingness or capability of most opioid abusers. These tests include, but are not limited to, the use of toxic solvents at extreme temperatures using advanced laboratory equipment over extended periods of time. It must be acknowledged that some dedicated abusers will overcome any barriers provided by a formulation. To address this, extraction results can be positioned in the framework of whether the amount of time, effort, and knowledge required to defeat the abuse-deterrent properties would be expected make abuse more difficult or less rewarding. In the experience of the authors, a constructive approach is to frame the results of extraction studies in terms of several key factors (Table 3).

**Table 3. Factors to consider in explaining results of chemical extraction studies**

| Factors | Considerations |
|---|---|
| Yield | How much opioid is extracted? |
| Time | How much time does the product take to be extracted? |
| Solvents | There should be greater concern over effective extraction with ingestible solvents like water or alcohol than noningestible solvents like acetone. |
| Solvent volume | Is the extraction relevant for oral abuse (ie, large volume extraction) or IV abuse (ie, small volume extraction)? |
| Conditions | Does appreciable extraction only occur at high temperatures or with continuous agitation? |
| Knowledge and resources | Are complex steps required to get the solution into an abusable form (eg, is back-extraction or neutralization required prior to ingestion)?<br>Is advanced laboratory equipment required to perform the extraction? |

Providing context for experimental conditions is essential for a productive discussion of a product's abuse-deterrent properties, and to avoid the false impression that a product is easily extracted when it is not. It is also important to put the results of extraction studies in perspective with the habits and preferences of abusers in the real world. For example, at recent Advisory Committee meetings, certain Committee members have proposed that an abuser might extract an ADF opioid in a large volume solvent (eg, in bottle of soda) overnight and then either abuse or sell the solution. However, data from sources such as the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System, which has wide coverage of drug treatment centers across the United States and performs web monitoring for tampering techniques, do not indicate that individuals abuse opioids with such methods. In fact, survey data suggest that abusers have relatively little patience for conducting physical or chemical manipulations. A recent study found that more than half of recreational drug abusers would not spend more than 10 minutes tampering with an opioid product and more than 85 percent would not spend over 30 minutes.[6]

## GUIDANCE ON CLINICALLY IMPORTANT DIFFERENCE IN HAP STUDIES

HAP studies evaluate the pharmacodynamics (Category 3) of a manipulated abuse-deterrent product compared to a nonabuse-deterrent comparator for a specific route of abuse among recreational, nondependent opioid users. Subjective pharmacodynamic endpoints evaluate how subjects feel about a particular aspect of the drug-taking experience. The primary pharmacodynamic endpoint of Category 3 studies is usually Drug Liking $E_{max}$ (ie, maximum Drug Liking), though the studies also evaluate a range of other endpoints such as the Take Drug Again Assessment, Drug Effect Questionnaire, and Ease of Snorting Assessment (in the case of intranasal HAP studies). Achieving statistical significance on the key endpoints appears to factor heavily into an Advisory Committee's appraisal of the abuse-deterrent properties of a product. However, there has been increasing attention at Advisory Committee meetings on whether the treatment differences observed between the abuse-deterrent product and the nonabuse-deterrent comparator are clinically meaningful. Simply put, advisory committee members are trying to determine whether the differences observed in these carefully controlled experiments will ultimately translate to real-world, meaningful reductions in abuse and misuse.

Answering the question of clinical relevance is difficult, since a study's treatment differences will be a function of many factors. These include a formulation's inherent abuse-deterrent properties, the moiety, dose, choice of comparator (eg, non-abuse-deterrent ER product or IR API powder), and other aspects of the study design (eg, inclusion/exclusion criteria, drug discrimination requirements). These various factors also preclude reliable cross-study comparisons of the treatment differences on HAP study endpoints across different abuse-deterrent products.

Despite the limitations, there are studies which have attempted either to quantify the treatment differences in certain HAP study endpoints that could be expected to produce a meaningful change in drug-taking behavior,[7] or to correlate the treatment differences in HAP study endpoints with expected reductions in nonmedical opioid use.[8] Several recent sponsor presentations have used these studies to provide the committee with a relevant anchor with which to evaluate the clinical relevance of results from their abuse-deterrent studies. Providing these data has been useful at recent meetings. However, to increase the confidence of Advisory Committees and the FDA in the clinical relevance of the findings, further research is needed to evaluate the predictive validity of HAP studies. Similar studies supporting the predictive validity of in vitro (Category 1) studies (eg, syringeability and injectability studies) and studies that quantify abuse-related events in clinical trials are also important research priorities.

## DATA NECESSARY TO SUPPORT AN ABUSE-DETERRENT LABELING CLAIM FOR THE ORAL AND INTRANASAL ROUTES OF ABUSE

Drug Liking $E_{max}$ has been the prespecified primary endpoint for all HAP studies that have been used to support abuse-deterrent labeling for the oral and intranasal routes. However, demonstrating a statistically significant difference in this primary endpoint alone does not appear to be sufficient to support abuse-deterrent labeling. Based on comments at Advisory Committee meetings and in recent labeling decisions, it appears that the FDA considers a statistically significant difference on the Take Drug Again Assessment as a requirement

for abuse-deterrent labeling via the oral and nasal routes of administration.

For example, the oral HAP studies of Arymo™ ER and Xtampza® ER met their respective primary endpoints of demonstrating significantly lower Drug Liking $E_{max}$ versus their relevant comparators, but did not achieve statistical significance on the secondary endpoint Take Drug Again.[9,10] At the Advisory Committee for Arymo ER, the Committee voted 16-3 in favor of oral abuse-deterrent labeling based on "sufficient evidence and clear data that chewing of the product is reduced by its abuse-deterrent properties."[11] Presumably, the Advisory Committee's determination was based on the sponsor's data supporting that the hardness of Arymo ER tablets exceeded that of the maximum human bite force and was highly resistant to particle size reduction with a variety of tools.[12] (Unlike more recent meetings, the Advisory Committee for Xtampza ER did not vote on abuse-deterrent labeling for each route of abuse; rather, the Committee voted 23-0 in favor of overall approval.[13]) As of June 2017, neither Arymo ER nor Xtampza ER have labeling claims for the oral route of abuse, and both labels note that their respective oral HAP studies did not achieve statistical significance on Take Drug Again.

The FDA has clarified their position at recent Advisory Committee meetings that Take Drug Again provides important clinical context for the deterrent effect of a product and must be evaluated to provide context for the other pharmacodynamic findings.[12,14] It is also worthy to note that the results for Drug Liking $E_{max}$ and Take Drug Again $E_{max}$ are listed together in summary tables of oral and intranasal HAP studies in all abuse-deterrent labels, in effect, highlighting both as coprimary endpoints.

These recent insights into FDA's perspective lead to two important implications for the design of HAP studies of abuse-deterrent products. First, HAP studies should be powered to achieve statistical significance on both Take Drug Again and Drug Liking $E_{max}$. The Take Drug Again Assessment is a less sensitive measure (ie, with smaller effect sizes) than Drug Liking, so studies powered on the basis of Drug Liking alone will likely be underpowered to demonstrate a statistical difference from the comparator on Take Drug Again. This will require increased sample sizes, which has both practical and ethical implications. Second, products whose abuse deterrence relies primarily on physical or chemical properties (eg, resistance to particle size reduction or extraction) must incorporate those properties into the experience of subjects in HAP studies to demonstrate a difference from the comparator in Take Drug Again. The standard protocol for HAP studies is to provide the subjects with pre-manipulated product to standardize the manipulation. However, if one of the primary abuse-deterrent features of a product is its resistance to physical manipulation, subjects' willingness to "take the drug again" will be artificially inflated if they do not experience the difficulty of getting the product into an abusable form.

## EXCLUSIVITY OF ABUSE-DETERRENT CLAIMS

In January 2017, the FDA approved Arymo ER, a morphine sulfate ER tablet manufactured by Egalet Corporation, with labeling as an abuse-deterrent product by the IV route. However, despite a positive intranasal HAP study that met the key endpoints of Drug Liking $E_{max}$ and Take Drug Again, as well as an 18-1 Advisory Committee vote in favor of abuse-deterrent labeling for the nasal route, Arymo ER was not labeled as an abuse-deterrent product by the intranasal route.

This regulatory decision was explained in a press release by FDA concurrently with the approval of Arymo ER, where the Agency noted that another product, MorphaBond, had been given marketing exclusivity for labeling describing the expected reduction of abuse of single-entity ER morphine by the intranasal route due to physiochemical properties. Therefore, "due to MorphaBond's marketing exclusivity, no other single-entity morphine product submitted in an abbreviated new drug application or 505(b)(2) application can be approved for use at this time."[15] After additional interaction with the Agency, Egalet Corporation reported that the FDA is still considering their interpretation of scope of new clinical investigation exclusivity for abuse-deterrent products. Specifically, the question remains whether the 3-year exclusivity will pertain to a specific route of abuse or to a particular abuse-deterrent formulation.[16] Furthermore, the FDA has stated that it "'does not object' to Egalet Corporation's stated plans for distribution of materials that are 'based on the intranasal abuse-deterrence data in its original NDA submission' if the communications are directed only to healthcare professionals, include appropriate disclosures and are otherwise truthful and nonmisleading."[16]

Clarification of this regulatory uncertainty regarding the interpretation of exclusivity claims should be an important priority for the FDA and innovators. In this evolving area, it will be critical to strike an appropriate balance between encouraging the incremental improvement of ADFs, protecting innovation, and promoting the public health with the availability of multiple abuse-deterrent products.

## IMPORTANT CONSIDERATIONS FOR ABUSE-DETERRENT IR PRODUCTS

As of June 2017, there are nine approved ER products with abuse-deterrent properties consistent with the 2015 FDA Guidance for Industry, but only one IR product. IR opioids pose the largest problem in the prescription opioid abuse crisis, accounting for more than 90 percent of all oral opioid prescriptions. According to data from the RADARS System, IR opioids are 4.6 times more likely to be intentionally abused and 6.1 times more likely to be diverted than ER formulations.[17] Not surprisingly, abusers prefer IR products because they provide faster onset of the rewarding effects. In a recent study of 300 opioid abusers entering treatment for substance abuse, 66 percent reported a preference for IR opioids.[18]

There are several reasons why developing abuse-deterrent IR opioids has proven challenging. First, IR opioids are designed to release "immediately" and last for a short duration (3-4 hours), and the total amount of the API is less than ER opioids. The difference in amount of API between ER and IR drugs makes it more challenging to show abuse-deterrent properties with IR products regardless of the route of abuse tested.

Second, the addition of excipients (eg, nasal irritants, gelling agents) to IR formulations has led to large food effects that cause inconsistency in pharmacokinetics and delayed absorption, and therefore delayed onset of analgesia for acute pain. This issue was highlighted at the September 2015 Advisory Committee meeting for Avridi™. When taken with food, Avridi had a significant delay in absorption and $C_{max}$ when taken with food, so the proposed dosing instructions were to take Avridi on an empty stomach. The Committee did not recommend approval, despite positive intranasal abuse deterrence data, because of the anticipated difficulty of patient compliance with the food instructions, and the corresponding safety concern of patients taking additional doses if pain relief was not quickly achieved with the first dose.

The key question that remains unanswered is whether the primary evaluations required in the FDA Guidance is relevant for demonstrating abuse-deterrent properties of an IR opioid. The primary analysis of pharmacodynamic endpoints, per FDA Guidance, is based on the differences in $E_{max}$, or the maximum effect at any time. In the context of abuse-deterrent ER products, $E_{max}$ assessments measure the ability of the abuse-deterrent ER product to resist being transformed into an IR (ie, rapid rise in opioid concentrations with a high $C_{max}$), thereby reducing the maximum drug liking versus the comparator, which is typically an IR product. This paradigm is reasonable for ER opioids, but does not translate as well to IR opioids. Intranasal administration of an IR opioid leads to a faster onset of opioid concentrations and Drug Liking than intact oral administration, but not greater maximum effects.

Three IR products have been reviewed at an Advisory Committee with data to support intranasal abuse-deterrent labeling (Avridi™, Apadaz™, and RoxyBond™). Consistently, across all three programs, the $C_{max}$ values, Drug Liking $E_{max}$ scores, and Take Drug Again $E_{max}$ scores of the crushed and snorted nonabuse-deterrent comparator were similar to the abuse-deterrent product taken orally intact. The pharmacokinetic and pharmacodynamic parameters for maximum effect ($C_{max}$ and $E_{max}$), which are calculated without regard to time, do not measure the incentive of IR opioid abusers to choose the intranasal route over oral administration for a particular product. Therefore, we conclude that $E_{max}$ parameters may be less appropriate for IR opioids and that future studies of IR abuse-deterrent products should elevate the importance of Drug Liking and Drug High at early time points.

## CONSISTENCY OF PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

Recent FDA Advisory Committees sought data illustrating the consistency between the pharmacokinetic (Category 2) and pharmacodynamic (Category 3) results. For abuse-deterrent ER products, Committee members requested insights on two critical issues: namely, that the ER profile is not converted to an IR profile (ie, higher $C_{max}$ and shorter $T_{max}$) after manipulation with the most effective tool and that those pharmacokinetic results translate to

the expected differences between ADF and non-ADF products in Drug Liking and other pharmacodynamic endpoints. Highlighting the link between blood levels and subjective ratings has provided the committee with greater confidence in the validity of HAP study findings.

## DESIRE FOR DATA DEMONSTRATING REAL-WORLD EFFECTIVENESS OF ADF OPIOIDS

As Advisory Committees have recommended approval for an increasing number of abuse-deterrent products, there has been a corresponding increase in their desire for data to demonstrate that ADFs are having their expected positive public health benefit in the real world. Per FDA Guidance, these claims are formally evaluated in postmarket (Category 4) epidemiologic studies.[1] Category 4 studies are expected to evaluate at least 3 years of postmarketing data and compare results to a matching time period prior to ADF launch. To date, no ADF is labeled with Category 4 claims.

Unfortunately, the relatively slow uptake of ADFs has made it difficult to demonstrate a significant public health impact for nearly all the currently approved ADF products due to inadequate sample size for assessment of abuse-related events in relevant databases. OxyContin®, which was reformulated with abuse-deterrent properties in 2010, is the only abuse-deterrent product to date that has substantial data on the impact of an abuse-deterrent formulation on rates of abuse. OxyContin was in a unique position to evaluate the effectiveness of abuse-deterrence properties. At the time OxyContin was reformulated, it was the only ER oxycodone product on the market, and it had a high prescription volume that was rapidly transitioned to the abuse-deterrent formulation. As a result, a variety of data sources were able to evaluate the impact of the reformulation on reductions in abuse, misuse, diversion, doctor shopping, and a variety of other abuse-related measures.[19]

The FDA has disagreed with the conclusions in the article by Coplan and colleagues due to concerns over the measurement and validation of outcomes measures from the epidemiologic data sources.[12] This suggests that epidemiologic data alone will be insufficient for the Agency to provide Category 4 label claims, and that different strategies combining experimental and surveillance data will be required. The challenges of conducting these studies for ADFs has recently been reviewed.[20]

In light of these recent developments and methodological challenges, greater regulatory clarity on the design of studies that would be sufficient to achieve Category 4 labeling is needed. It will likely be several years until adequate data are generated for ADFs to support the predictive validity of premarket studies, so sponsors should be prepared to discuss the epidemiologic impact of OxyContin's reformulation if Advisory Committee members request data on the real-world impact of ADFs on abuse.

## UNINTENDED CONSEQUENCES OF ABUSE-DETERRENT PRODUCTS

In March 2017, the FDA held a 2-day Advisory Committee meeting to discuss the benefit-risk profile of Opana® ER. The meeting was called because of epidemiologic data suggesting that IV abuse of Opana ER led to an HIV outbreak in Indiana and may have caused cases of thrombotic thrombocytopenic purpura (TTP). TTP is a rare blood disorder that causes clotting in small blood vessels throughout the body. Based on preclinical data, the FDA presented a mechanistic link between TTP-like illness and the high molecular weight polyethylene oxide (HMW PEO) found in Opana ER. HMW PEO is an inactive excipient that imparts some of the abuse-deterrent properties (eg, resistance to physical manipulation, gelling properties) to several approved ADFs. The Advisory Committee interpreted the data presented at the meeting as proof or as an indication that abuse of Opana ER had shifted from intranasal to IV routes after its reformulation, and that IV exposure to HMW PEO was the likely cause of TTP-like illness. The Committee voted 18-8 with one abstention that the benefits of reformulated Opana ER did not outweigh its risks. Most members recommended additional risk management strategies be put into place to limit prescribing.[21] Ultimately, in June 2017, the FDA requested that the sponsor remove Opana ER from the market.[22]

At a subsequent Advisory Committee meeting for RoxyBond in April 2017, some members of the Advisory Committee raised questions regarding the safety of excipients in the formulation if injected, despite the fact that RoxyBond does not contain PEO. Based on these meetings, it is reasonable to expect that Advisory Committee members will

continue to ask sponsors and the FDA for additional testing to show that IV abuse of abuse-deterrent products will not lead to greater harm than non-abuse-deterrent products.

## INCREASING CONCERN ABOUT APPROVING ADDITIONAL OPIOID PRODUCTS

As more ADF opioids are considered for approval, concerns have been raised by several Committee members about increasing the number of opioid products on the market—even in abuse-deterrent forms. Their concern is that an increase in the number of products might lead to an increase in overall prescribing and, ultimately, abuse. Sponsors should be prepared to illustrate that the number of prescriptions for opioid analgesic products has actually been decreasing in the United States over the past several years despite the introduction of several ADFs into the market.

Committee members have also cited concerns that prescribers may feel more comfortable prescribing opioids in abuse-deterrent forms under the false impression that they are less addictive. This concern may be ameliorated by illustrating two key points: first, by reinforcing that the intention of ADFs is to replace non-abuse-deterrent products rather than to increase the number of prescriptions; and second, that the sponsor will accurately reflect the product's abuse-deterrent properties to patients and providers. Proactive recognition by the sponsor that ADFs are one component of a larger public health strategy to reduce opioid abuse, which also include prescribing limits, prescription drug monitoring plans, patient and prescriber education, and safe disposal programs, among others, enhances credibility and reduces the false perception that ADFs can be a "silver bullet" for the prescription opioid epidemic. However, this appeal by sponsors to a broader approach to prescription opioid abuse may be viewed with skepticism when not accompanied by a demonstrable commitment to support such approaches.

## CONCLUSIONS

FDA Advisory Committee meetings are high-stakes regulatory meetings, especially for sponsors of ADF products who find themselves in a politically charged atmosphere of prescription opioid abuse. The clinicians, academicians, and statisticians on FDA Advisory Committees for ADF products have considerable knowledge in their respective fields, though many do not have expertise in the development, testing, and evaluation of abuse-deterrent products. To provide Advisory Committee members with the background information necessary to make an informed recommendation to the FDA, sponsors should recognize and prepare to address the common issues encountered at previous meetings.

Many of the key issues encountered at recent Advisory Committee meetings stem directly from the lack of data on the predictive validity of premarket abuse deterrence studies. Given that epidemiologic data have not been sufficient to support Category 4 labeling, it is incumbent upon the FDA to collaborate with sponsors on a feasible framework to evaluate the impact of new abuse-deterrent opioids on rates of abuse in the real world. Subsequently, it will be incumbent upon sponsors of ADF products to expeditiously conduct these studies to evaluate Category 4 labeling claims and to substantiate the public health value of abuse-deterrent opioid formulations.

*Christopher J. Miller, MS, 3D Communications, Raleigh, North Carolina.*

*Richard C. Dart, MD, Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, Colorado.*

*Nathaniel P. Katz, MD, MS, Analgesic Solutions, Natick, Massachusetts; Adjunct Associate Professor, Department of Anesthesiology, Tufts University School of Medicine, Boston, Massachusetts.*

*Lynn R. Webster, MD, FACPM, FASAM, Vice President of Scientific Affairs, PRA Health Sciences, Salt Lake City, Utah.*

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