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.

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