

# Pinney Associates

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September 11, 2017

Food and Drug Administration  
Division of Dockets Management  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852  
Via <https://www.regulations.gov/>

Re: Docket No. FDA-2017-N-2903

Dear Food and Drug Administration:

These comments are submitted in response to the Federal Register Notice of a Public Workshop entitled 'Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and Future Capabilities', and the associated request for comments.

I write these comments as a physician with over 30 years in academic medicine who has treated patients in pain and patients suffering from substance use disorder and addiction. I am also Vice President, Pharmaceutical Risk Management Services with the consulting firm Pinney Associates, Inc. We have extensive experience in advising both branded and generic pharmaceutical companies on the development and assessment of abuse-deterrent (AD) formulations of opioids including designing and developing protocols for *in vitro* assessment of abuse-deterrent drug formulations, developing abuse potential assessments for regulatory submission, and developing and executing postmarketing risk management plans and Risk Evaluation and Mitigation Strategies for controlled substances. These comments are my own and do not represent those of any company for which we provide or have provided consulting services. Additionally, these comments were not vetted with anyone outside of our company, nor did any outside organization compensate me for my time to prepare these comments.

I offer overall comments and then provide specific recommendations on the data and methods necessary for appropriate evaluation of AD opioids in the postmarket setting.

First, I applaud FDA's effort to incent companies to develop AD opioids and seek a path to further development of these formulations. While FDA seeks input on how to evaluate AD opioids in a postmarket setting, I think it is important for the Agency to engage in other important efforts to address two particular issues. I raise these issues here as they are potential impediments to development and acceptance of AD opioids and there are expectations that AD opioids can resolve these issues. I address each issue in turn.

## **The current epidemic of abuse of illicit heroin and fentanyl analogues.**

The rising abuse of illicit opioids (heroin and fentanyl analogues) is a serious public health problem leading to many unnecessary deaths, often in combination with abuse of

other substances. AD opioids are not directly involved in this problem, but may have contributed to the increased abuse of illicit opioids because AD opioids were effective in reducing abuse of specific prescription opioids, thus diverting abusers to illicit opioids in pursuit of the same effects (Cicero and Ellis, 2015)

(1) ). This is certainly not a desired outcome, but it was somewhat predictable.

To address the illicit opioid problem, FDA should engage in approaches to support the increased use of medications to treat opioid abuse, the development of new medications to treat opioid use disorder, and regular meetings with federal agencies and other stakeholders to develop a coordinated effort to address substance use disorders with increased use of National Institute on Drug Abuse (NIDA) approved prevention programs and treatment-on-demand.

(2) The abuse of prescription opioids, primarily by people to whom the drugs were never prescribed.

As shown in the National Survey on Drug Use and Health (NSDUH) surveys for many years, over 60% of those who abuse prescription opioids were never prescribed the medications. Sholten and Henningfield (2016) described the differences between prescribed and prescription drugs; the two should not be confused. The availability of AD opioids may have reduced abuse of prescription opioids (Cicero and Ellis, 2015; Cassidy et al., 2014) while the abuse of prescribed opioids within the patient population is low (Adams et al. 2006), yet there is a clear problem of medication leaking from the prescribed patient to the non-patient, abuser population.

To address the diversion of medications, FDA should support policies to facilitate involvement in and improvement of training on appropriate opioid prescribing and patient monitoring as well as alternate (non-opioid) effective methods for managing pain, including engaging with insurance companies and pharmacy benefit managers to lower barriers to prescribing long-acting AD opioids (e.g., patient costs, and inclusion as first tier products) and coverage of comprehensive pain management programs, which could reduce the number of pills/tablets in circulation. We note the Drug Enforcement Administration has promoted participation in National Prescription Drug Take Back Day programs to address this very issue.

The FDA began to address this issue through voluntary education of prescribers as part of the shared Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioid analgesics, but this voluntary program has not been an overwhelming success as it is difficult to change prescriber behavior, especially among those who have practiced for many years. Unfortunately, some who do change sometimes go to the extreme of ceasing opioid prescribing entirely, which is not in the best interest of patients (Sera et al., 2017). That does not mean that education efforts should cease. Going from voluntary to required education to get and maintain DEA registration is one step that can be taken. Another would be to increase training in schools for health professionals. This could be facilitated through programs like the Career Teacher program in addiction medicine (currently unfunded) and working to get increased numbers of questions on board exams related to pain management

(Institute of Medicine, 1997). Although some of these suggestions are not within the direct reach of FDA activities, the FDA should publicly support these, and other, broad efforts to address this issue.

At the July 10, 2017, FDA public workshop on how to measure the effect of abuse deterrent opioids, FDA Commissioner Dr. Scott Gottlieb stated that the opioid crisis is FDA's "highest immediate priority." He also affirmed that incentives for the development of AD opioids are critical to transform the market from more abuseable to less abuseable, and increasingly safer, pain medications. He and other FDA staff made clear that they take pride in their role in AD development and would like to see more rapid development and approvals, including approval of AD opioids that can obtain Category 4 labeling. FDA was clear that it does not have simple solutions to this challenge and was open to seeking suggestions from the panel and to Sponsor's proposals.

Opioid abuse, overdose and associated harms including death have been problems in the US for over 150 years. David Musto addressed this issue in his seminal 1973 book, *The American Disease: Origins of Narcotic Control*, which described the effect and response to opioids from the Civil War until the time the book was published. Historically, efforts to address the abuse of opioids have had rather limited effects.

Today, the FDA is attempting to address this problem with the approval of medications to treat opioid use disorder and AD formulations of extended release opioids designed to reduce dose dumping (by chewing or crushing) or the ability to insufflate or inject these formulations. The Serenity Prayer below, used to open 12-step meetings, is an important touchstone for finding the pathway forward.

God grant me the serenity to accept the things I cannot change,  
Courage to change the things I can,  
and the Wisdom to know the difference

The issues discussed above are issues that AD opioids cannot directly effect. FDA wants to understand whether AD opioids have an effect on abuse of these products.

The FDA can require companies to measure the effects that AD opioids are designed to address: chewing or crushing to get dose dumping; insufflation; and injection with each mode of abuse important to assess. These are the only the outcomes that can be addressed with an AD formulation, and they are measurable. The keys to measuring the impact of an AD opioid for the purposes of Category 4 labeling are clear criteria for assessing and evaluating these outcomes.

### **A Pathway towards Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting**

The lack of clear criteria for Category 4 labeling discourages Sponsors from seeking this labeling, and could ultimately result in loss of interest in development of AD opioid formulations. Such criteria would guide Sponsors in developing study methods, including selection of outcomes, appropriate measures, and establishing adequately powered studies. For the FDA to provide guidance to Sponsors about the criteria against which Category 4 labeling will be determined, FDA first needs to consider the goal of any AD opioid (e.g., what level of reduction in a given route of abuse would be considered a success).

The FDA has already recommended examining pre-and post-AD opioid formulation change. These data are available for only one product with Category 1-3 labelling and for which studies have demonstrated a change (Dart et al., in press). This criterion of pre- and post-ADF cannot be applied to newly approved AD opioids nor to generics, due to the lack of market penetration and pre-market data, but these issues are not insurmountable.

We offer the following specific recommendations:

- First, we suggest that FDA set a criterion of a 30% reduction in the specific measurable effects of AD opioids (e.g., dose dumping, insufflation or injection).
- Second, carefully assess the available data on the one AD opioid (i.e., OxyContin) that has pre-and post-data to determine whether it meets this criterion. If it does meet the criterion, then approve Category 4 labeling. Thereby demonstrating that Category 4 is actually achievable. If it does not meet the criterion, it will be clear as to why the labeling was not approved.
- Third, in order to demonstrate whether new products achieve that set level of reduction, we recommend that prospective RCTs be conducted to compare the AD opioid with non-AD opioids with the same active pharmaceutical ingredient (API). This will demonstrate whether or not there is a difference in the abuse of the product in the patient population. This may be difficult to achieve with the low rates of abuse within prescribed populations, but a positive effect will be very powerful. Since a randomized controlled trial (RCT) may be difficult to undertake, an alternative design is a cohort study comparing a cohort receiving the AD formulation to one receiving the same API not in an ADF.
- Fourth, the results of an RCT or cohort study could be matched with epidemiologic studies that look at the diversion of the product into the abuser population and behaviors in that population. These epidemiologic studies can provide very sensitive details regarding abuse behaviors (e.g., RADARS, NAVIPPRO).
- Fifth, monitoring of internet chat rooms will provide information about whether abusers like or dislike the AD product and whether methods proffered for defeating the formulation are easy to achieve or even plausible.
- Sixth, if epidemiologic data identify a localized outbreak of abuse of the product, ethnographic studies can be conducted to determine precisely what is occurring in the area. These combinations of studies will provide a more comprehensive picture of the effects of the AD opioid in the real world.
- Finally, the FDA has to provide a reasonable time frame for these studies, taking into account the timeframe of exclusivity for a product or giving consideration to either extending the exclusivity period to allow for the necessary time to conduct meaningful studies or giving the product some extended exclusivity if Category 4 labeling is achieved. This is complicated, but it is important, since no company will expend the time and other resources to conduct these studies without some exclusive benefit.

The FDA is in a difficult position as the public and politicians expect it to do more than it can to control the opioid crisis, which encompasses both licit and illicit opioids as well as a broad range of behaviors by patients, medical professionals, and abusers, over whom the Agency has little, if any, direct influence. By making clear what it can and cannot do and providing a path forward for existing and future products to obtain Category 4 labeling, FDA will make a significant public health contribution. By following the suggestions above, we believe that some AD products will be able to demonstrate a “meaningful change” in abuse via chewing, crushing, insufflation and injection.

I appreciate the Food and Drug Administration’s effort to advance the development of methods to support Category 4 labeling of AD opioid formulations. Thank you very much for the opportunity to provide these comments. Please contact Dr. Sid Schnoll at **Pinney** Associates at [sschnoll@pinneyassociates.com](mailto:sschnoll@pinneyassociates.com) if you have any questions or need further information.

Sincerely,



Sidney Schnoll, M.D., Ph.D.

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