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Food and Drug Administration
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
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Re: FDA Solicits Input on Potential Role for Abuse-Deterrent Formulations of Central Nervous System Stimulants: Establishment of a Public Docket: Request for Comments (Docket No. FDA-2019-N-3403)

Dear Food and Drug Administration:

These comments are submitted in response to the Federal Register Notice *FDA Solicits Input on Potential Role for Abuse-Deterrent Formulations of Central Nervous System Stimulants: Establishment of a Public Docket: Request for Comments* (Docket No. FDA-2019-N-3403).

We write these comments as scientists and regulatory experts who, as employees of Pinney Associates, Inc., provide services for pharmaceutical companies on the development and evaluation of abuse-deterrent-formulation of central nervous system (CNS)-acting drugs and drug products, including stimulants, and the postmarketing assessment and mitigation of misuse and abuse. These comments are our 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 us for our time to prepare these comments.

Introduction

We commend the Food and Drug Administration (FDA) for their efforts in working to address abuse and misuse of CNS stimulants, including exploring efforts to incentivize development of safer medicines. Incentivizing the development of abuse deterrent formulations (ADFs) of stimulants by FDA would be an important step in addressing misuse and abuse of prescription CNS stimulants. While this would not represent a panacea in addressing problematic stimulant use, new ADF stimulants may provide an incremental benefit over existing treatments and may help prevent people who abuse stimulants from transitioning to more dangerous and harmful routes of misuse and abuse, such as injection or snorting of these products.

Important to this effort is awareness that the misuse and abuse of prescription stimulants represents only a portion of problematic use of CNS stimulants; the majority of abuse of CNS stimulants occurs with the illicit drugs methamphetamine and cocaine. FDA's power to address stimulant abuse is limited to approved medicines, and even then, its regulatory and policy reach is finite, and therefore it is essential for the agency to work with other regulators, law enforcement agencies, academic experts, the public and industry to provide solutions to this public health issue.

We also believe that it is important to apply lessons learned from efforts to encourage development and prescribing of ADF opioids to future efforts surrounding ADF stimulants. This is crucial in maintaining access to needed treatment options for patients while reducing rates of abuse and misuse.

Use, Misuse, and Abuse of Prescription Stimulants

CNS stimulants most commonly are prescribed for treatment of attention-deficit/hyperactivity disorder (ADHD), but also used to treat narcolepsy and binge eating disorder.

ADHD diagnoses in the US have steadily risen over the past decade^[1] with prevalence rates being estimated at over 10% for children and adolescents, and over 4% of adults. A number of factors have contributed to the increased rates of ADHD diagnoses, including greater prescriber education regarding ADHD, increased awareness by clinicians of adult ADHD, recent changes in diagnostic criteria (including updated diagnostic criteria in the 5th edition of the DSM [DSM-5]), and increased access to health care for minorities and low-income patients^[1-3].

Stimulant medications have been found to be effective at treating ADHD for most children and have been shown to be more efficacious than non-stimulant treatments^[4, 5]. Among stimulant medications, extended-release (ER) formulations are prescribed more frequently, though use of both IR and ER formulations has been increasing steadily over time.

Looking at other individuals potentially treated with stimulants, approximately 200,000 Americans suffer from narcolepsy (<https://narcolepsynetwork.org/about-narcolepsy/narcolepsy-fast-facts/>). Binge eating disorder is the most common eating disorder among adults in the US, affecting approximately 2.8 million people (<https://www.bingeeatingdisorder.com/hcp/patient-demographics.aspx>).

History has shown that with stimulants as with opioids, increased rates of prescribing are correlated with increased incidence of nonmedical use and public health problems associated with drugs in the respective category, whether prescription or illicit in origin^[6].

The National Survey on Drug Use and Health estimated that among Americans aged 12 and older, an estimated 6.6% have used a prescription stimulant in the past year, and 1.9 percent have misused or abused a prescription stimulant^[7]. Additionally, NSDUH found that among this population, an estimated 2.0% had used cocaine and 0.7% had used methamphetamine in the past year.

In 2018, rates of past year initiates for cocaine, methamphetamine, and prescription stimulants were 0.3%, 0.1%, and 0.4% respectively. NDSUH also found that over 95% of current (past month) misusers of prescription stimulants are over the age of 18.

Data from the National Forensic Laboratory Information System (NFLIS) reported methamphetamine (24.15%) and cocaine (14.31%) to be the most and third most frequently identified drugs among drugs seized by law enforcement in 2018 (NFLIS, 2019). In comparison, amphetamine (combined illicit and licit) represented 0.81% of all drugs identified. Methylphenidate did not appear among the top 25 most frequently identified drugs.

According to the Treatment Episode Data Set (TEDS), from 1997 through 2017, methamphetamine was reported as the primary stimulant of abuse to substance abuse treatment centers, significantly more often than either “other amphetamines” or “other stimulants”.

While the published literature varies greatly in the estimated prevalence rates for prescription stimulant misuse and abuse, these studies do provide some insight into users’ motivations and trends. Commonly cited motivations for nonmedical use of stimulants include enhancing performance and productivity^[8-16]; losing weight^[8, 17-20]; and to “get high”^[8, 9, 11, 14, 15, 20-22].

Taken together, these data show that stimulant abuse in the US is not isolated to FDA approved products. Alone, FDA cannot eliminate this problem; however, encouraging development and adoption of ADF stimulants may be an important step to reduce abuse of substances under the agency’s jurisdiction.

Natural History of Stimulant Use Disorders

Stimulants are a prototypical class of drugs with abuse potential in which use is driven strongly by these drugs’ readily evident effects, including increases to alertness, attention, and energy. Identical dopaminergic effects have been observed for amphetamine, methylphenidate, and cocaine^[23], and insufflation or injection of methylphenidate may lead to similar patterns of withdrawal and toxicity symptoms as cocaine^[24]. Studies have shown intranasal and intravenous abuse of stimulants results in euphoria similar to cocaine^[25].

Compulsive, high-transition bingeing patterns may be established via stimulant use phases: 1) Initiation, in which single-dose euphoria results in classical conditioning, for which smoking and intravenous abuse are profoundly reinforcing; 2) Consolidation, in which tolerance develops leading to increased frequency of abuse, and abusers are liable to switch routes of administration to increase rapidity of response; and 3) Maintenance, in which high-dose and frequent-use patterns often lead to compulsive bingeing and considerable pathological effects^[26]. Use of drugs via these routes can increase the rate of drug effect onset, which can in turn have significant reinforcing effects^[27-29].

There are few data on the transition from nonmedical use of prescription stimulants to abuse of illicit stimulants or vice versa, but there is evidence of prescription stimulants being taken by non-oral routes, such as insufflation^[9, 10, 14, 20, 30, 31], injection, or smoking^[32, 33].

An analysis of NSDUH data suggests that nonmedical use of prescription ADHD stimulants is not commonly an initiating factor leading to the nonmedical use of other prescription medications or abuse of illicit drugs. Among those who reported nonmedical use of ADHD stimulants, illicit drug use preceded nonmedical use of ADHD stimulants in 77.6% of cases^[34].

One study interviewed 16 active users of both methamphetamine and prescription drugs to examine motivations for substituting prescription stimulants for methamphetamine. The methamphetamine users reported that they may turn to prescription stimulants due to lower perceived risk of harm compared to illicit stimulants. They did this when they were able to receive health insurance benefits that provided access to prescription

stimulants which lowered their out-of-pocket costs, or when illicit stimulants were not available. Prescription stimulants were considered easier to obtain in their social circles^[35].

A study of current high-risk prescription drug misusers 16-25 years old found that respondents were prescribed stimulants at significantly earlier ages than their first misuse of stimulants. Participants also reported initiation of misuse of prescription stimulants at significantly earlier ages than cocaine, methamphetamine, and ecstasy ($p < 0.001$). However, these high-risk participants also reported first use of marijuana and prescription opioids at earlier ages than illicit stimulants. Abuse and misuse of prescription drugs were frequently consumed as part of a broader pattern of abuse involving both prescription and illicit drugs^[36].

While the evidence linking prescription stimulant abuse to illicit stimulant abuse is sparse, the increased availability of these medicines and their similar mechanisms of action create a risk that these medications may be sought out by abusers when illicit stimulants are too expensive or difficult to obtain. FDA therefore should use its authority to shift the supply of approved stimulants to technologies that can deter the worst of harms associated with abuse of this class of drugs when taken by insufflation or injection.

Stimulant Abuse Associated Harms

Nonmedical use of stimulants can lead to several cardiovascular and psychiatric outcomes and some of which can be fatal. These effects are most often seen with non-oral routes of administration such as intranasal and intravenous routes, which can increase bioavailability, cause greater reinforcing effects, and increase the drugs' abuse potential. Use via these non-oral routes can often lead to greater rates of negative medical outcomes^[37].

Nationwide data from the American Association of Poison Control Centers (AAPCC) show that adolescents and adults who abuse prescription amphetamines face a significantly greater risk of adverse medical outcomes compared to non-abusers, although these varied depending on route of administration. Among adolescents and adults contacting poison control centers due to amphetamine adverse reactions, the odds of death were 13 times greater among nasal abusers (insufflation) and 22 times greater among intravenous abusers than non-abusers. Mean numbers of adverse medical outcomes were highest for intravenous use (2.95), followed by nasal (2.46), and oral (2.17), compared with 1.57 for non-abuse exposures. The incidence of admissions to a critical care unit was greatest among intravenous abusers (36.6%), compared with nasal abuse (21.2%), oral abuse (24.6%)^[37].

Role of ADF Stimulants

We would anticipate that ADF CNS stimulants would have some impact on prescription stimulant abuse associated harms, if prescribed to enough patients to replace currently available CNS stimulants. Data from NSDUH shows that the vast majority (78.3%) of those misusing or abusing prescription stimulants obtain them from a friend or relative, 12.7% obtain them from a doctor's prescription^[7]. As FDA cannot by itself prevent drug diversion or abuse, its best course of action may be to ensure that the products in its purview are as unattractive to abusers as possible.

As we know from opioids, FDA approval of an ADF does not result in prescribing of these products. FDA can incentivize and approve ADF CNS stimulants, but the safety of these products would only be realized if prescribed. For this, comparative labeling with the relevant safety data would facilitate appropriate prescribing. Third-party payors also have a role in making sure these products are available with a reasonable co-pay and without the requirement of first “failing” on two non-ADF stimulants before allowing for an ADF stimulant to be prescribed and covered. This is a practice which has been seen with ADF opioids and does not necessarily address abuse by those who obtain the drug without a prescription.

Premarketing and Postmarket Evaluation

Premarket testing can inform sponsors and regulators about the strengths and weaknesses of an ADF and inform how best to perform pharmacokinetic and human abuse liability studies. These evaluations should be predictive of how these products would resist tampering attempts by abusers, patients, and caregivers. Importantly, to avoid approval of ADFs with significant weaknesses, a model for comprehensive *in vitro* evaluation is needed. Such an evaluation should challenge a product in ways that are known or might plausibly be practiced by drug abusers in “real-world settings”. These studies must be developed in a way that can demonstrate that these drugs maintain efficacy while reducing the potential for abuse.

To that end, premarket evaluation of ADF stimulant products should include the following general types of assessments, commonly referred to as “domains”: physical manipulation, extraction, injectability, smokeability, dose dumping, and specialized assessments (e.g., thermal stressing, free-base isolation, solubility) when warranted for a specific active pharmaceutical ingredient (API) and formulations. A broad range of procedures are described in FDA’s 2015 Guidance, Abuse-Deterrent Opioids — Evaluation and Labeling. Although the opioid specific labeling claims do not pertain to stimulants, most of the procedures for evaluating opioid products are readily adapted to stimulants. To incentivize such testing and improved product development we encourage FDA to consider allowing comparable labeling claims to stimulant products that meet comparable standards as opioids. Then formularies and payers should be encouraged to reimburse for them.

Premarket human clinical trials similar to those recommended in the 2017 FDA Guidance on the Assessment of Abuse Potential of Drugs may also be used to assess an ADF’s relative abuse potential compared to a non-ADF product with the same API.

While premarket testing may not capture all potential drug risks, this can be supplemented with a rigorous postmarketing risk management plan.

Ideally, a strategic plan for postmarketing evaluation would be discussed prior to NDA submission, and the Sponsor would submit a proposal as part of the NDA. The goal of a postmarketing strategy would be oriented towards evaluating the impact of marketing of the ADF CNS stimulant on abuse of prescription CNS stimulants. Importantly, marketing of a prescription product can not on its own be expected to meaningfully reduce abuse of illicit CNS stimulants.

It is incumbent on FDA to establish what constitutes “meaningful reduction” for postmarketing evaluation. Changes in abuse of illicit stimulants would be of interest, but

any increases or decreases could be the result of many other factors outside the control of the Sponsor and FDA.

A postmarketing evaluation does not need to take place under the umbrella of a Risk Evaluation Mitigation Strategy (REMS). We anticipate that postmarketing evaluation would encompass utilization of national surveys and datasets, as well as brand-level data collection sources^[38, 39].

Lessons Learned from ADF Opioids

While ADF products may be available on the market, pharmacoeconomic considerations often prevent these drugs from being used to their maximum potential benefit. Because of the extensive resources required to develop these technologies as well as complying with FDA's rigorous premarket evaluation requirements, these drugs can cost more than legacy drugs, which are often generic. In the case of ADF opioids, the high cost of these products relative to non-ADF options have caused insurance companies to require documentation of a patient's risk of abuse or even a diagnosis of a use disorder prior to receiving coverage^[40, 41]. These drugs, therefore, are relegated to a treatment role after a patient has already developed a use disorder, instead of a preventative role for which most of the available technologies are best suited.

We also know that prescription medications are often diverted for abuse. That is, the patient for whom it was prescribed is not necessarily the person abusing the product. This is the case both for opioids and stimulants. An ADF may reduce diversion since these formulations would not be in high demand by abusers.

Terminology

Specialized research similar to the research undertaken to maximize understanding of over-the-counter labels would be valuable to determine the most appropriate language for describing these products in labeling. Such research could be done both with prescribers, to support prescribing information, and/or with patients, to support the patient information and Medication Guide.

Terms to be considered include "manipulation deterrent formulation" or "tamper resistant" as these terms are about the function of the specific product.

Potential Unintended Consequences

We already see methamphetamine abuse increasing. Other factors are at play outside of FDA mandate and control.

We appreciate the Food and Drug Administration's effort to consider the potential role of ADF stimulants and how to incentivize the development of these products. Thank you very much for the opportunity to provide these comments. Please contact Daniel Wang at **Pinney**Associates at dwang@pinneyassociates.com or 301-718-8440 if you have any questions or need further information.

Sincerely,

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