



November 18, 2019

The Honorable Admiral Brett P. Giroir, M.D.  
Acting Commissioner  
Division of Dockets Management (HFA- 305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

*Re: Input on Potential Role for Abuse-Deterrent Formulations of Central Nervous System Stimulants (Docket No. FDA-2019-N-3403)*

Dear Acting Commissioner Giroir:

Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD) appreciates the opportunity to comment on the above captioned notice regarding the development and evaluation of abuse-deterrent formulations of central nervous system (CNS) stimulants.

CHADD was founded as a tax-exempt organization in 1987 in response to the frustration and sense of isolation experienced by parents and their children with ADHD. At that time, one could turn to very few places for support or information. Many people seriously misunderstood ADHD. Many clinicians and educators knew little about the disability, and individuals with ADHD were often mistakenly labeled “a behavior problem,” “unmotivated,” or “not intelligent enough.” In the more than thirty years since, CHADD has become recognized as the national clearinghouse for objective ADHD information and operates the National Resource Center on ADHD, an evidence-based program funded by the U.S. Centers for Disease Control and Prevention.

**CHADD’s General Comments:**

We appreciate the Food and Drug Administration’s efforts to explore whether the agency could be doing more to address misuse of prescription CNS stimulants. We recognize that CNS stimulants are susceptible to abuse, particularly by those who are using them for nonmedical purposes. CHADD is part of the Coalition to Prevent ADHD Medication Misuse (CPAMM), a diverse group of organizations working to help prevent the misuse, abuse and diversion of prescription stimulant medication. More broadly, CHADD is committed to being part of solutions aimed at reducing the misuse of ADHD medications.

Given their susceptibility to abuse, CHADD is interested in the prospect that abuse-deterrent formulations (ADFs) could have public health benefits and, if done correctly, could even have direct benefits for those prescribed CNS stimulants to treat ADHD. We also have serious reservations, however, about potentially negative consequences of ADFs on individuals and families dealing with ADHD, especially as it pertains to reducing access to ADHD medications,



making them more expensive, further stigmatizing the disorder, and other unintended consequences.

As FDA scientists and policymakers have long recognized and frequently reaffirmed, prescription medications—including CNS stimulants—are a primary treatment option to safely and effectively reduce the core symptoms of ADHD. Quite often, the response to ADHD medications varies for each individual, and patients frequently must try several medications to identify the medication that provides the maximum clinical benefit with the fewest side effects. It is CHADD's position that all individuals with diagnosed ADHD should have access to the full range of safe and effective prescription medications indicated to treat ADHD. In light of the rampant misconceptions about ADHD treatment, the stigma surrounding the disorder, and other external pressures, individuals with ADHD often face significant barriers to accessing prescribed medications. We respectfully urge FDA to consider these systemic burdens on the ADHD population, and the important differences between prescription stimulants and abuseable agents used for other therapeutic indications, when issuing any future statements or policies on this topic.

In its notice, FDA has suggested that comparisons may be drawn between ADFs of opioids and stimulants, while also noting that the scope of association with misuse and abuse, illness, and death is different for prescription opioids than for prescription stimulants. As noted by the agency, serious consequences of prescription stimulant misuse and abuse appear to be considerably less frequent than for prescription opioids, even after accounting for the lower prescription volume of stimulants. A nationally representative household population study of adults age 18 or older from the 2015 and 2016 National Surveys on Drug Use and Health found that among U.S. adults, 6.6 percent used prescription stimulants overall, with 4.5 percent using without misuse. While 1.9 percent misused without use disorders, only 0.2 percent had use disorders.<sup>1</sup>

In addition, as other federal, state and local regulators increasingly take action on controlled substances, CHADD remains concerned about the unintended consequences for individuals prescribed CNS stimulants. As Congress and state legislatures draft legislation to confront the opioid epidemic, additional restrictions are being placed on the prescribing, coverage, and use of controlled substances. Multiple state and local bodies—including city councils and state boards of medicine—have imposed new taxes and fees, instituted tough penalties on prescribers, and even placed stringent restrictions on the use of these prescription medications. For example, one state recently advanced policies to limit the prescribing of controlled substances to no more than a five-day supply.<sup>2</sup> Another state policy required all physicians licensed in the state who

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<sup>1</sup> Wilson M. Compton et al., *Prevalence and correlates of prescription stimulant use, misuse, use disorders, and motivations for misuse among adults in the U.S.*, 175(8) AM. J. PSYCHIATRY 741-755 (Aug. 2018).

<sup>2</sup> 2017 Ga. Laws 7436S (SB 81 Jeffrey Dallas Gay, Jr. Act.).



distribute, prescribe, administer, or dispense controlled substances to incorporate abuse mitigation strategies including urine testing.<sup>3</sup> Lumping CNS stimulants in with policies designed to thwart opioid abuse is having far-reaching implications that CHADD worries are further stigmatizing ADHD, reducing medication adherence or even deterring diagnoses, and ultimately leading to more untreated ADHD. The costs and challenges associated with untreated or undertreated ADHD are substantial.

Individuals prescribed ADHD medications and their families frequently come to CHADD with complaints about the challenges of obtaining access to ADHD medications. The status of CNS stimulants as controlled substances results in serious supply disruptions stemming from manufacturing quotas and recurring drug shortages. There are now various drug-drug combinations and formulations with FDA approval, such as long-acting formulations and doses for nocturnal use. The diverse formulations, combined with the proliferation of pharmacy benefit utilization management strategies, result in byzantine formulary coverage policies that leave many families perplexed and ultimately exposed to unanticipated and inexplicable out-of-pocket costs. In a recent survey of more than 1,000 CHADD members, more than half of respondents indicated that they or a family member diagnosed with ADHD experience challenges accessing their prescribed ADHD medications.<sup>4</sup> Even as more ADHD medications become multiple-source products, individuals with the diagnosis experience great hardship with timely and affordable access to their prescribed medications.

It is imperative that any FDA actions to invite and approve ADF formulations of prescription stimulants not exacerbate current coverage and access hardships. The Institute for Clinical and Economic Review (ICER) released a report that found the average annual cost of an ADF prescription was approximately twice as much as a non-ADF prescription. The report also found that if all opioid medications were made with ADFs, it would increase both patients' and payers' costs by millions of dollars per year.<sup>5</sup> Prescription stimulants have become more affordable over time, and CHADD is concerned that potential action from the agency prompting drug development in new formulations could undermine this trend.

Still, the pursuit of ADFs of CNS stimulants holds potential to reduce misuse, abuse and diversion. We therefore ask that FDA take an iterative approach to exploring the possibilities for these formulations. The agency should carefully consider all comments it receives, and pursue

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<sup>3</sup> Alabama Bd. Med. Examiners, Proposed Rule 540-X-4-.09, Risk and Abuse Strategies by Prescribing Physicians (Apr. 2018).

<sup>4</sup> CHADD, Health Insurance Survey 2016 (unpublished Nov. 2016).

<sup>5</sup> INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW, ABUSE-DETERRENT OPIOIDS: EVIDENCE REPORT (June 2017), available at <https://icer-review.org/announcements/adf-evidence-report/>.



direct engagement with stakeholders, prior to issuing any formal policies. CHADD would welcome the opportunity to be part of any discourse or to help convene experts on the topic.

### **CHADD's Responses to FDA Prompts:**

Below, CHADD puts forward initial responses to the prompts included in FDA's notice. FDA's notice in the Federal Register was reviewed by CHADD's public policy committee (PPC) and professional advisory board (PAB) – leading experts in medicine, psychology, education and other professions who play an integral part in keeping the organization abreast of the latest developments enabling CHADD to disseminate the most current scientifically based and authoritative information about ADHD. Based on the input of our PAB members, we reached out to other leading academic, research, and clinical experts for additional input on the questions FDA raised.

We welcome the opportunity for an ongoing dialogue with FDA on these issues.

### **Natural history of stimulant use disorders**

*FDA has provided a summary of its current understanding of abuse and misuse of prescription stimulant products in the United States. We are seeking new or additional information and perspectives on prescription stimulant misuse and abuse and associated harms. We are particularly interested in data on the natural history of stimulant use disorders, including the risk of developing addiction and of transitioning to abuse of illicit stimulants*

It is clear that there is a dearth of empirical information on the natural history of stimulant misuse, dependence and addiction. As with other substances, a subset of the population prescribed these agents is likely to be at risk. There is greater data on stimulant use disorder, which includes syndromes of misuse and addiction to agents like cocaine and non-prescription stimulants, but this research is occasionally inclusive of study populations with patterns of prescription stimulant misuse. CHADD shares the agency's desire for more data specific to prescribed medications.

### **Patterns of prescription stimulant misuse**

*Taking into account the patterns and consequences of prescription stimulant misuse and abuse by both patients and others who may access the drugs, discuss whether ADF stimulants could be expected to meaningfully reduce prescription stimulant abuse and associated harms. For which specific patient populations, if any, might it be beneficial to prescribe ADF stimulants? In particular, please discuss whether and to what extent ADF stimulants might be expected to deter the various routes of abuse (e.g., oral, intranasal, injection) associated with prescription stimulants, and also whether such products, if approved and marketed, could be expected to meaningfully reduce the incidence or progression of stimulant use disorder.*



It is of interest to CHADD and clinicians we have consulted to have an agent available that could target ADHD without risk of development of dependency. Future research might reveal, for example, that it is possible to reduce dependency development with concurrent blockade of opiate receptor effects. It would also be of interest to have an agent that could target ADHD with lower risk of misuse or abuse. Conceptually, the latter approach seems more difficult to achieve given the fact that the mechanism that produces cognitive accommodation in individuals with ADHD will have effects on the brain that some individuals may seek for non-treatment reasons – the experience of more focus, for example, may be something that people seek when they don't have an identifiable medical indication for focus improvement.

As compared to illicit stimulants, FDA-approved drugs are formulated to mitigate certain types of abuse, such as overuse. As compared to illicit drugs, which have a dose response and can give users a recurring “high” after a short amount of time, FDA-approved prescription CNS stimulants keep the exchange of neurotransmitters in the synapses constant for longer periods of time, which limits the ability of users to frequently abuse them for recurring effect. Research has demonstrated that methylphenidate, one of the leading prescription CNS stimulants, cannot be abused like cocaine. Specifically, positron emission tomography (PET) scan studies reveal that when administered via the same route, methylphenidate and cocaine have equally fast uptake in the brain, which corresponds to the experience of a “high.” However, methylphenidate has much slower clearance, such that further self-administration of methylphenidate cannot induce another “high” as rapidly, thereby limiting motivation for repeated use.<sup>6</sup> For additional literature regarding differences in brain effects of methylphenidate and illicit drugs, see Swanson and Volkow (2003).<sup>7</sup>

There may also be approaches to product formulation that can further mitigate misuse by certain routes of administration. For example, lisdexamfetamine (LDX) is the inactive prodrug to dexamphetamine utilized in the treatment of ADHD. Following oral ingestion, LDX is metabolized in the GI tract as l-lysine and the active d-amphetamine. Because there is no active d-amphetamine in the parent formulation, manipulation by crushing or extraction will not result in the active drug.<sup>8</sup> Agents such as lisdexamfetamine, which may have lower “liking” potential by substance abusers according to some research, may still have dose-dependent effects on mental state. At least anecdotally in prison populations, agents lacking rewarding features have currency for misuse and abuse. Moreover, it remains the case that most nonmedical uses of

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<sup>6</sup> Nora Volkow et al., *Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain*, 52 ARCHIVES GEN. PSYCH. 456-463 (1995).

<sup>7</sup> Nora Volkow & James M. Swanson, *Serum and brain concentrations of methylphenidate: implications for use and abuse*, 27(7) NEUROSCIENCE & BIOBEHAVIORAL REVS. 615-21 (2003).

<sup>8</sup> Tammi Schaeffer, *Abuse-Deterrent Formulations, an Evolving Technology Against the Abuse and Misuse of Opioid Analgesics*, 8(4) J. MED. TOXICOLOGY 400-407 (Dec. 2012).



prescription stimulants are ingested orally. Thus, it may be hard to avoid risk of abuse or diversion with an ADF.

Lastly, there is self-reported evidence that abuse of CNS stimulants for nonmedical uses, such as academic or athletic performance, is driven by factors other than chemical dependency. This evidence is particularly acute for high-risk populations, such as college students. For instance, a 2016 study on prescription stimulant misuse in college populations found that social motives were largely correlated with misuse.<sup>9</sup> There is thought that recurring abuse may initiate in part a context of perceptions and social norms that are external to the physical formulation of a compound.

### **Evaluation of ADF stimulant products in clinical studies**

*Please comment on how ADF stimulant products should be evaluated in premarket and postmarket studies to determine whether they can be expected to deter, or actually have deterred, abuse by the various routes associated with prescription stimulant abuse (oral, intranasal, intravenous, inhalation).*

Based on the background research cited by FDA and other literature that we are aware of, it would appear that the oral route remains the most common route of nonmedical uses. Thus, to prevent the majority of abuse, such agents would need to demonstrate a lack of reinforcing or off-target effects through oral use. Long-acting stimulants are considered by many in the clinical community to be relatively less abused/abusable than agents with immediate therapeutic effect. There has been interest among some in reducing clinical reliance on short-acting stimulants and preferential prescription of long-acting agents for these reasons. However, there appear to be many patients for whom existing long-acting therapies are less effective or have other drawbacks.

### **Product labeling**

*Comment on whether the potentially abuse-deterrent properties of ADF stimulants should be described in product labeling. If so, how should they be described and based on what evidence? We additionally invite comment on whether terms such as abuse deterrent stimulant and ADF stimulant could be misinterpreted by the public (including prescribers) to suggest that a product is “abuse-proof,” or carries a lower risk of addiction. Is there alternative terminology that FDA could use to more clearly describe the expected effects of these new formulations in terms of patient safety and public health?*

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<sup>9</sup> Claire E. Blevins, Robert Stephens & Ana M. Abrantes, *Motives for Prescription Stimulant Misuse in a College Sample: Characteristics of Users, Perception of Risk, and Consequences of Use*, 52:5 SUBSTANCE USE & MISUSE 555-561 (2017).



We share FDA’s concerns that the use of terminology may connote that certain products are abuse-proof, when abuse may not be completely preventable. In general, CHADD opposes, and seeks to rectify, misinformation regarding ADHD and its treatments. If patients or caregivers wrongfully assume an ADF is not capable of being abused, they may be less vigilant in ensuring the medication is not misused or diverted.

In general, the binary statement that a drug product is either “abuse-deterrent” or not may mislead the public about the current state of different ADHD medications. As the FDA is well aware, there are a variety of approved medicines indicated to treat the symptoms of ADHD, some of which are controlled substances and others of which are not. There are also approved drug products that are chemically formulated not to have an immediate effect or an effect when ingested by certain routes, such as lisdexamfetamine, that are less susceptible to abuse. We worry that implicitly categorizing all existing approved products as not abuse-deterrent could mislead the public about the different potential for misuse among current treatment options.

In addition, packaging and consumer guides may offer links to guidance for clinicians and consumers on best practices for recognizing and intervening in stimulant misuse and abuse.

### **Unintended consequences of ADF stimulants**

*Comment on any potential unintended consequences of introducing ADF stimulants to the market. For example, what is the potential for ADF stimulants to shift behavior toward more dangerous routes of abuse (i.e., injection) or to more dangerous drugs (e.g., illicit methamphetamine or other substances), or to result in increased costs for patients, payers, or health systems?*

We appreciate FDA posing this question. Potential unintended consequences of ADF drug development are CHADD’s principal concerns in this area.

It is imperative to CHADD that we ensure that effective treatments for ADHD remain widely available, covered by payers, and affordable, as this condition has significant morbidity and mortality. As discussed, prescription medications including CNS stimulants are a primary treatment option to safely and effectively reduce the core symptoms of ADHD.

CHADD is particularly troubled that individuals who are at low risk for prescription stimulant abuse could lose access to needed treatments if stakeholders misinterpret or adversely leverage actions or statements by the FDA regarding the need for abuse deterrence. As noted, individuals with prescriptions for ADHD medications have long experienced tremendous difficulties accessing medication through the application of utilization management strategies, such as step therapy, prior authorization, quantity limits, age restrictions, and other mechanisms imposed by



insurance companies. These strategies are increasingly being adopted by governmental payers as well.

Given the stigma associated with ADHD, mainstream skepticism of the disorder and its treatments, and the potential for abuse of leading ADHD medications, CHADD's members and the broader ADHD community face numerous challenges in gaining access and coverage for needed therapies. We are concerned that issuance of FDA policy calling for broad market substitution of existing therapies with newly approved formulations could exacerbate many of these preexisting challenges. In 2017, the Institute for Clinical and Economic Review (ICER) released a report, which found the average annual cost of an ADF prescription was estimated at \$4,234 compared to \$2,124 for a non-ADF prescription. ICER's report concluded that it would cost patients and insurers \$645 million over five years if all opioid medications were made with ADFs.<sup>10</sup>

Based on these circumstances, if multiple-source drug products were substituted with new ADF products, we worry that many individuals would struggle to obtain access to needed therapies. Conversely, if such wide-scale substitution did not occur, we are unclear what the utility of newly approved ADF products would be.

### **Additional actions**

*What other actions, if any, should FDA consider to reduce misuse, abuse, and related harms associated with prescription stimulants?*

While CHADD recognizes the merits of access to patient-friendly and clinician-friendly methods of tracking stimulant prescription use, as well as identifying doctor shopping or irregular use patterns, these efforts should not infringe unduly on privacy or create barriers to treatment. The agency may also wish to consider maintenance of requirements for regular medical assessment and education, such as dear clinician letters, with evidence-based methods of monitoring for signs of adverse effects such as dependence, misuse, abuse, and addiction. Identification of comorbidity and cultural factors may be useful. Clinicians have a wide range of practices and institutional policies for responding to medication stockpiles, and at the same time, patients run the risk of shortages. Policies that make it easier to destroy unused stimulants or document their destruction might remove them from the pool of potentially misused agents.

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Once again, CHADD appreciates the agency shining a light on these issues and taking the preliminary step of soliciting stakeholder input on these questions. Our professional advisory

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<sup>10</sup> ICER, *supra* note 5.





board, public policy committee, staff, and other affiliates look forward to reviewing the submissions the agency receives in response to its solicitation. We thank FDA for the opportunity to share our comments regarding the development and evaluation of ADFs of CNS stimulants and sincerely hope our comments will be considered during the review process and beyond. CHADD is available and prepared to discuss any questions regarding the aforementioned concerns.

On behalf of CHADD, thank you for accepting our comment and we look forward to working with you further.

Sincerely,

A handwritten signature in black ink, appearing to read "R. Cattoi", is written over a light blue horizontal line.

Robert J. Cattoi  
Chief Executive Officer

cc: Craig Surman, MD  
Co-Chair, CHADD Professional Advisory Board  
Scientific Coordinator for the Adult ADHD Research Program, Massachusetts General Hospital

Max Wiznitzer, MD  
Co-Chair, CHADD Professional Advisory Board  
Pediatric Neurologist, University Hospitals Rainbow Babies & Children's Hospital  
Professor of Pediatrics and Neurology, Case Western Reserve University School of Medicine

Ingrid Alpern, JD  
Co-Chair, CHADD Public Policy Committee

Jeffrey Katz, PhD  
Co-Chair, CHADD Public Policy Committee

Eli Tomar, JD MPH  
Co-Chair, CHADD Public Policy Committee