

September 3, 2019

Dockets Management Staff (HFA-305)
Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Submitted via <https://www.regulations.gov/>

Re: Docket No. FDA-2019-D-1917; “Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format; Draft Guidance for Industry”

Dear Food and Drug Administration:

These comments are submitted in response to the Federal Register Notice of the availability of the Draft Guidance document “Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Draft Guidance for Industry” and the associated request for comments.

We submit these comments as scientists with the consulting firm **Pinney Associates**. We have extensive experience in advising both branded and generic pharmaceutical companies on the development and assessment of drugs with abuse potential, including developing abuse potential assessments for regulatory submission, and developing and executing post-marketing risk management plans and Risk Evaluation and Mitigation Strategies (REMS) for controlled substances. 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.

We commend the Food and Drug Administration (FDA) for providing specific definitions for the terminology to be used in prescription labeling and for its efforts to harmonize labeling about abuse, misuse, addiction, dependence, and tolerance. Although numerous experts could produce sound alternatives or variations on these definitions, consistency of language across drug products and labeling is very important and long overdue – *especially* because leading experts and organizations are not consistent with their own definitions. It is not so much a matter of which definitions are the best, but more of making sure that definitions are reasonable and understood so that the resultant labeling for these drugs will, to the greatest degree possible, speak in one language. Drug developers would be wise to use this consistent language and definitions from the beginning of drug development to the development of the label. Implementation of this harmonization effort will provide prescribers with important, comparable information to use in their decision-making and consultations with their patients.

The terms proposed for use in professional labeling will be most beneficial to patients if prescribers clearly understand the terms and can adequately explain them to their patients. Once finalized, FDA should take steps to ensure that prescribers accurately understand these terms and assist prescribers’ efforts to communicate accurately with patients what these terms mean for patients and how to take these drugs safely and

effectively. We also recommend that these definitions and supporting information (perhaps including the Guidance itself) be included in curricula for physicians, nurse practitioners, physician assistants, dentists, podiatrists, and other health care providers.

It is important to emphasize that all the information included in Section 9 of prescription labeling (DRUG ABUSE AND DEPENDENCE) must be based on the best available data. The data needed for many aspects of the label must come directly from the New Drug Application, particularly from the clinical trials that were conducted to develop the drug and upon which approval is based. Below we address key elements of these defined terms with regard to important considerations for obtaining the necessary data that would make the use of these definitions most beneficial to prescribers and their patients.

Physical Dependence and Withdrawal

We fully concur with FDA that it is no longer adequate to base decisions about whether physical dependence may occur, nor assess the nature of the symptoms of physical dependence, solely through adverse event (AE) assessments. Rather, as described in the 2017 Guidance, studies must be designed to determine if physical dependence symptoms occur with drug administration, and AE data must be collected more systematically. More recently, animal studies designed according to the 2017 Guidance have been increasingly conducted to determine whether a drug may produce physical dependence, and the results of these studies should be used to inform the design of clinical studies. The design of nonclinical and clinical studies to determine if a drug may produce physical dependence and withdrawal and appropriate characterization of the symptoms would ideally be based on *a priori* discussion of the study approach with FDA's Controlled Substance Staff (CSS).

Withdrawal symptoms are the hallmark measures to determine if physical dependence has been produced and are a part of the pharmacology of many drugs regardless of whether the drug is considered to carry significant abuse potential and regardless of whether the person showing signs of withdrawal has a Substance Use Disorder (SUD) (commonly called "addiction"). As stated by FDA (lines 360-361): "Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug" and (lines 365-371) "Physical dependence is associated not only with the repeated use of known drugs of abuse, but with drugs with no abuse potential as well. For example, physical dependence to propranolol (a beta blocker used for the management of hypertension) is known to occur, and abrupt discontinuation may be followed by a "propranolol withdrawal syndrome" resulting in increased blood pressure (temporarily higher than before starting propranolol), headache, chest pain, palpitations, and sweating."

FDA's recommended labeling and discussion related to physical dependence and withdrawal is vital information because the concepts are widely misunderstood. As a result of the misunderstandings, doctors often assume that their patients have developed an addiction simply because they experience withdrawal symptoms when they miss doses or stop taking the medication altogether. The unintended consequence of this misinterpretation is that prescribers may make different prescribing decisions than they might otherwise, and/or patients might seek to prematurely discontinue pain management that could improve their quality of life and recovery from, for example, the

surgery or trauma contributing to their pain (Hsu, Mir, Wally and Semour, 2019; Vallerand, Cosler, Henningfield, and Galassini, 2015).

Including information about withdrawal symptom risk and approaches to minimize and treat withdrawal in the prescribing information will greatly benefit prescribers, but all healthcare professionals should be educated on this topic. Specifically, it is vital that all health professionals understand both that a withdrawal syndrome is not sufficient evidence of the presence of an SUD, as well as the fact that withdrawal is a disorder in its own right that might merit intervention. A better understanding of these concepts guided by improved drug labeling may help health professionals to minimize the risk of its occurrence, and appropriately diagnose and treat withdrawal as discussed in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (APA DSM-5) (APA, 2013).

For all medicines that can produce physical dependence and withdrawal, it is therefore vital that healthcare professionals and patients understand that withdrawal symptoms might occur when drug doses are missed or a patient stops taking the drug for any reason, so that patients and their healthcare providers can be prepared to minimize such risk and treat it appropriately when it occurs. Also important is an understanding that the occurrence of withdrawal symptoms does not indicate abuse or addiction. Misunderstanding of the meaning of withdrawal has impacted treatment decisions by healthcare professionals and safe and effective use of prescribed medicines by patients.

Even though physical dependence and withdrawal are not necessarily indicative of abuse potential in isolation of other abuse potential signals (e.g., as is the case with many antidepressants, some cardiovascular drugs and others), physical dependence and withdrawal are important to document and communicate to prescribers and patients so that they can be managed when a drug is discontinued. Certainly, physical dependence and withdrawal can be factors in abuse potential and contribute to SUDs, and we agree with FDA's statement in its 2017 Abuse Potential Guidance (p.4) that "if a drug has rewarding properties, the ability of that drug to induce physical dependence or tolerance may influence its overall abuse potential." (FDA, 2017). This, in turn, is consistent with APA DSM-5 that withdrawal is neither necessary nor sufficient for a diagnosis of SUD, but it is a factor that may be indicative of a more severe SUD (APA, 2013).

Abuse Potential

FDA's 2017 Abuse Potential Guidance describes the data needed for most aspects of the label to address the abuse potential, development of physical dependence, and withdrawal signs and symptoms.

The draft guidance on Drug Abuse and Dependence complements the Abuse Potential Guidance by proposing the approach by which labeling may include information, data, and study findings relevant to abuse potential. This is of great interest to drug developers, patients, healthcare providers, and, increasingly, policy makers. Such labeling is complementary to scheduling in the case of drugs placed in the Controlled Substances Act (CSA) and may help differentiate drugs within the same schedule. This differentiation can be invaluable to health professionals making decisions about which drugs might be most appropriate for a particular patient (Dasgupta, Henningfield, Ertischek and Schnoll, 2011).

Addiction

Addiction is the most commonly used term for what has come to be more technically known as Substance Use Disorder in APA's DSM-5 (APA, 2013) and Dependence in the World Health Organization's International Classification of Diseases, tenth edition (WHO ICD-10) (WHO, 1994). Thus, it is important to provide a definition that will be understood by lay persons as well as health professionals.

FDA's proposed definition is as follows (FDA, 2019, p.9): "Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence."

We believe that FDA's definition is a reasonable distillation of the scientific understanding as communicated by the National Institute on Drug Abuse (NIDA) (2018), Goodman and Gilman's Pharmacological Basis of Therapeutics (O'Brien, 2011), and the more technical diagnostic criteria of APA's DSM-5 and WHO's ICD-10 (APA, 2013; WHO, 1994).

Although FDA's definition implies a more severe form of an SUD than the 2-3 symptoms that meet criteria for SUD at the "mild" level of severity, in practice the term addiction is used by the lay public for relatively benign substance use behaviors such as daily caffeine intake, daily consumption of a serving of wine or beer with dinner as well as for life-threatening alcohol, opioid and cocaine patterns of use. Thus, we suggest that FDA make clear that its definition of addiction is not intended to replace SUDs, nor does it imply a subset of SUDs for diagnostic, therapeutic, or medical disease coding for insurance purposes. Rather that it is a term that is widely used in general communications and warnings, used much as other general terms when technical language might be less impactful and less generally understood, e.g., "cancer," "heart attack," "kidney disease," and "overdose."

We also suggest that FDA encourage health professionals to be careful not to use the term addiction for patients who have become physically dependent and tolerant to prescribed drugs when the evidence indicates that they are complying with the prescribed dosing and not displaying evidence of aberrant behaviors indicative of an SUD. As noted above, conflating physical dependence and withdrawal with addiction can contribute to unintended consequences, such as patients being afraid to appropriately use a medicine important to their health and well-being, as well as to recover from trauma or surgery as discussed earlier. A better understanding of these concepts, including how to assess aberrant behaviors potentially indicative of substance abuse and an SUD (Chou, Fanciullo, Fine, et al., 2009) should contribute to improved care of patients and public health.

Concluding Comment

Once again, we commend FDA for this important proposed guidance and urge that it be quickly finalized. Labeling that conveys more accurate information about abuse, addiction, physical dependence and withdrawal is important for patients, prescribers, caregivers and families, as well as pharmaceutical developers. It is also among the many steps needed to more effectively minimize the occurrence and risks of substance use related problems for individual patients and at the societal level.

We encourage FDA to work with other federal agencies including NIDA, the Substance Abuse and Mental Health Services Administration, and the Centers for Disease Control and Prevention to revise their communications and harmonize their efforts with FDA's approach even where they do not use identical definitions. We will be pleased to provide any additional assistance at the request of FDA.

Sincerely,
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