
Authors (alphabetically): Elizabeth Eisenhauer, Brett Green, Tara Pickens, Jeremy Sutherland, Mariam Taleb

Summary
This Comment addresses The Food and Drug Administration’s request for information regarding general issues concerning the availability of a draft guidance for industry entitled “Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products—Content and Format.” The guidance is intended to assist applicants in writing the DRUG ABUSE AND DEPENDENCE section of the labeling, as described in the regulations for the content and format of labeling for human prescription drug and biological products. The recommendations in the proposed draft guidance aim to ensure that the labeling is clear, concise, useful and informative, and, to the extent possible, consistent in content and format within and across drug and therapeutic classes.

First, this Comment provides background on the current state of affairs surrounding the opioid epidemic, underscoring the urgent need for action. Second, this Comment raises concerns regarding the inadequacies present in physician-patient communications and variability in labeling standards for medications given to patients. Third, this Comment highlights the necessity for greater enforcement of standards across manufacturing companies and pharmaceutical dispensaries. Finally, this Comment recommends new legislation to appropriately address the need for improved labeling standards citing both the HELP (Health, Education, Labor and Pensions) Committee and the Ways and Means Subcommittee on Health as appropriate for drafting such legislation. Ultimately, we conclude that guidance for industry is insufficient given the level of crisis at hand and legislation to enforce warning and labeling standards for medicines with potential for abuse should be drafted to proportionately address the problem.

Introduction
The Penn State Science Policy Society is a coalition of graduate degree students with a common interest in exploring the relationship between science and policy, and in having an active role in such interactions. We approach this from a spectrum of levels: community outreach and education, engaging with policymakers and advocating in scientific issues, while informing fellow scientists on the importance of their voice in science policy. With the vast breadth of complex and often technical issues policymakers must address, it is regularly necessary that external scientists be consulted or incorporated into the decision process. For this reason, we submit the present comment to policymakers as a reference tool and guide.

Background
Drug addiction and abuse is on the rise in the United States and over 19 million Americans battled a substance abuse disorder in 2017. The over-prescription of opioid-based pain relievers has led to a dramatic increase in the occurrence of opioid addiction, overdoses, and heroin usage. There is a strong correlation between prescription opioid use and heroin use, with 4 out of 5 heroin addicts reporting their abuse started with prescribed opioids. Hydrocodone and oxycodone consumption doubled and increased by 500%, respectively, from 1999 to 2011. The opioid-related overdose death rate nearly quadrupled during this time frame and the United States Centers for Disease Control and Prevention (CDC) listed opioid overdose prevention as one of the top five public health challenges in 2014. Heroin overdose deaths among whites between 18 – 44 increased by 171% since 2001, and from 1999 – 2017, almost 400,000 Americans died from overdosing on prescription and illicit opioids.
In 2006, the Food and Drug Administration (FDA) amended the requirements on the content and format of labeling for Human Prescription Drug and Biological Products. It was recognized that health care practitioners had difficulty accessing, reading, and using the information provided to them when prescribing medications, and this led to errors. The amendment of part 201 (21 CFR part 201) included a new “Highlights of Prescribing Information” section, which offers a brief introduction on the prescription medication and a “Boxed Warning” to apprise the practitioners of the dangers associated with that medication. As shown in Figure 1, this did nothing to lessen the frequency with which opioid-based pain relievers are abused and we are facing a widespread epidemic that is destroying the lives of U.S. citizens and their families. We need to revisit the required labeling and the verbiage used to inform our citizens of the dangers associated with these drugs.

Figure 1: 3 Waves of the Rise in Opioid Overdose Deaths. Since the revision of the content and labeling for Human Prescription and Biological Products in 2006, the number of deaths per 100,000 citizens due to overdose of commonly prescribed opioids has continued to increase, and the number of deaths attributed to heroin abuse and other synthetic opioids has increased dramatically. As adapted from the National Vital Statistics System Mortality File.

Physician-Patient Communication
Given the urgency of the crisis at hand, the need to properly inform patients regarding a drug’s potential for abuse is more pressing than ever and studies have shown that physicians have often been found to inadequately perform their duties when conveying instructions for medications. Moreover, physicians and pharmacists frequently fail to provide information using language that can be understood by patients. Thus, the problem is two-fold. Therefore, the last remaining opportunity for advising is the accompanying print materials given to patients such as the container label, patient package inserts, consumer medication information, medication guides, etc. Unfortunately, however, many of these valuable documents have been shown to be too complicated, and written at a level too difficult for most patients to comprehend and use. Professional guidance regarding a given drug’s potential for abuse is inadequate and while FDA-2019-D-1917 addresses the need for attention on this issue, it in no way requires manufacturers or pharmacies to adhere to any standard.

Variability in Labels
Variability in medication labeling has been shown to impact patient interpretation of instructions, and the effect is most significant in patients with limited health literacy. In a 2007 study that included 4 large US cities, Shrank et al. found considerable variability in medication labeling, especially in the content of instructions and warnings. In the most extreme cases, some pharmacies failed to include warning stickers or medication guides. In 2015, patients in Chicago and Atlanta were shown to have limited knowledge of the active ingredients in their acetaminophen-containing analgesics. Again, high variability was found in labeling and warning information on the patients’ medications. A lack of consistency in medicinal
labeling is enabled by the absence of standard labeling enforcement. While recommendations are useful, there is evidence that labeling guidelines as a stand-alone strategy may not be adequate to prevent the misuse of medications.

**Call for Legislation**

Ultimately, while the authors recommend changes to the scope and strength of FDA-2019-D-1917, we also recognize that many of the most urgent changes to labeling must have the force of law behind them. We would recommend that the Senate HELP committee and the Ways and Means Subcommittee on Health draft new laws that would require labels to be uniform in structure and language, with standards developed by the agency. Clarity and uniformity will allow physicians and patients alike to make informed decisions. We would also recommend that this legislation require lay language to be included to describe dependence risks and symptoms, so that patients could better understand both risks and dependence itself. It is our duty – the medical doctors, physician assistants, pharmacists, nursing staff, federal agencies, and concerned scientists – to use our knowledge regarding the science to require language on prescription drug labeling to be more informative, direct, and administered to patients in a manner that makes them more aware of the dangers associated with opioid-based prescription medications.

**Citations**