

1 Testimony before the Massachusetts Drug Formulary Commission

2 by

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8 Thank you for the opportunity to address the members of the Commission in writing. In addition to  
9 some verbal remarks, I submit this written testimony for the record.

10 This testimony will provide information to the members of the Commission about a) some relevant  
11 drug-related definitions, b) the procedure used to schedule drugs with abuse potential and c) the  
12 processes outlined in FDA's Guidance to Industry (1 April 2015) entitled Abuse-Deterrent Opioids—  
13 Evaluation and Labeling for how drug developers must test the effects of formulations intended to deter  
14 certain methods of abuse, how FDA will evaluate the results of those studies, and, if certain criteria are  
15 met, how FDA will allow the label, or Full Prescribing Information (FPI), of an opioid analgesic drug  
16 product to describe the abuse-deterrent properties and their associated claims.

17 **Definitions**

18 I will employ a number of specific terms that are relevant to the testimony and offer definitions to  
19 facilitate accurate understanding of my testimony. I shall use the term *drug substance* in the meaning of  
20 21 CFR 314.3, that is: an active ingredient that is intended to furnish pharmacological activity or other  
21 direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the  
22 structure or any function of the human body. Contrast this with *drug product* which, according the CFR,  
23 refers to a finished dosage form, for example, tablet, capsule, or solution that contains a drug substance,  
24 generally in association with one or more other ingredients. For example, the Tylenol® brand includes  
25 several different *drug products* (eg, regular strength tablets, extra strength caplets, bi-layer tablets,  
26 infants' oral suspension, children's oral suspension, children's chewable tablets), but they all contain the  
27 same *drug substance* (acetaminophen), although in different amounts.

28 **Scheduling**

29 Drug substances with abuse potential are *scheduled* by a procedure outlined in the federal Controlled  
30 Substances Act (Title II, Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended  
31 {Pub. L. No. 91-513, 84 Stat. 1236}. The Controlled Substance Act (CSA) provided for regulation of  
32 manufacture, importation, possession, and distribution of certain drug substances (and other chemicals)  
33 by consolidating various pre-existing laws, combining federal agencies, and serving as the implementing  
34 legislation to allow the US to fulfill its obligations under the United Nations' Single Convention on

Narcotic Drugs. Scheduling a drug substance under the CSA subjects it to certain restrictions, for example, whether it can be refilled or prescribed by telephone. Individual practitioners (eg, physicians, dentists, advanced practice registered nurses) must be licensed by their State(s) of practice and have State authority to prescribe controlled substances and then must become registered with the federal Drug Enforcement Administration (DEA) to lawfully prescribe, administer, or dispense drug products containing scheduled drug substances.

The CSA established a system of placing certain drug substances that have “stimulant, depressant, or hallucinogenic” effects into one of five schedules, based on acceptable medical uses and the drug’s abuse or dependency potential. Technically, the scheduling determination is made by the Attorney General, with scientific input from the Secretary of Health and Human Services. In practice, however, these duties are delegated to the DEA and the Controlled Substances Staff (CSS) of the Food and Drug Administration. Notable, however, is that DEA is “bound” by the scientific and medical evaluation of FDA. The CSS must consider eight factors in their medical and scientific evaluation of a drug substance (the “8 Factor Analysis”). The factors comprising this analysis are: the drug substance’s actual or relative potential for abuse; scientific evidence of its pharmacological effects; the state of current scientific knowledge regarding the drug; its history and current pattern of abuse; the scope, duration, and significance of abuse; what, if any, risk there is to the public; its psychic or physiologic dependence liability (ie, risk of addiction or physical dependence); and whether the substance is an immediate precursor of another controlled substance.

Drugs in **Schedule I** are those that have high abuse potential *and* have no currently-accepted medical use in the US. **Schedule II** drugs are those with a currently-accepted medical use, high abuse potential, and their abuse may lead to severe physical dependence or psychological dependence (addiction). **Schedule III** drugs have a currently-accepted medical use, have less abuse potential than the drugs in Schedules I and II, and their abuse may lead to moderate or low physical dependence *or* high psychological dependence (addiction). **Schedule IV** drugs have a currently-accepted medical use, lower abuse potential than drugs in Schedule III, and their abuse may lead to limited physical dependence or psychological dependence, relative to drugs in Schedule III. Drugs in **Schedule V** have a currently-accepted medical use, lower abuse potential than drugs in Schedule IV, and their abuse may lead to limited physical or psychological dependence, relative to drugs in Schedule IV. Schedule V drugs include some drugs to treat diarrhea, some cough suppressants, and some anti-epileptics. Non-scheduled drugs include all other prescription medicines and over-the-counter drugs.

#### Selected Drugs Scheduled under the CSA

Schedule	Examples
I	heroin, LSD, marijuana, MDMA (ecstasy), methaqualone, peyote
II	cocaine, hydrocodone, fentanyl, methamphetamine, morphine, oxycodone, amobarbital
III	buprenorphine, codeine (<90mg/unit), ketamine, testosterone
IV	alprazolam, pentazocine, tramadol, zolpidem
V	codeine (<2mg/mL); diphenoxylate; pregabalin; ezogabine

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69 **FDA Abuse-Deterrent Opioids—Evaluation and Labeling**

70 The White House Office of National Drug Control Policy (ONDCP) issues an annual National Drug Control  
71 Strategy (NDCS). In 2011, ONDCP issued a supplement to the NDCS specifically focused on abuse of  
72 prescription medicines. This outlined a detailed strategy for the Executive branch agencies with various  
73 elements of this supplemental strategy being assigned to an agency or several agencies. The FDA was  
74 assigned two tasks relative to my testimony today:

- 75 1) Perform expedited reviews of New Drug Applications (NDAs) for:  
76 a. Analgesics with no abuse potential  
77 b. Abuse-deterrent formulations for opioid medications and other drugs with abuse  
78 potential.  
79 2) Provide guidance to drug developers on the development and assessment of potentially abuse-  
80 deterrent drug formulations.

81 FDA issued the final version of its Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and  
82 Labelling on 1 April 2015. The Guidance lays out FDA’s current thinking about the studies that should be  
83 conducted to demonstrate whether a formulation has abuse-deterrent properties. Importantly for the  
84 Commission’s deliberation is that FDA acknowledges in the Guidance that both the *science* of abuse-  
85 deterrent technology and the *methods* by which FDA evaluates drug products intended to deter abuse  
86 are relatively new and are evolving.

87 The Guidance includes four groups of studies, called Categories, that characterize whether a drug  
88 product embodies *meaningful* abuse deterrence. Studies in three Categories are performed prior to the  
89 approval of a drug application. The fourth Category comprises studies that can be conducted only after a  
90 drug has been approved and is in clinical use.

91 Category 1 studies are *in vitro* manipulation and extraction studies which evaluate the ease of defeating  
92 physical and chemical properties of a formulation. Category 1 studies can involve testing crush  
93 resistance up to the breaking point of an oral solid dosage form (eg, a tablet or capsule) or using various  
94 combinations of solvents and temperatures to determine what fraction of the drug substance can be  
95 extracted from a solid dosage form.

96 Category 2 studies are done in human volunteers who, in controlled settings, are administered an intact  
97 dosage form, a manipulated tablet or capsule, a placebo, and a suitable comparator. The plasma levels  
98 of drug substances over time are measured to provide a sense of how likely it is that drug abusers will  
99 seek out the new formulation.

100 Category 3 studies are done in drug-liking volunteers who, in the case of opioid analgesics, are not  
101 physically-dependent on opioids. These studies involve similar administration protocols at Category 2,  
102 although different routes may be used to more-closely simulate known drug-abuse methods, such as  
103 intranasal insufflation (“snorting”). Since the subjects are drug-liking, they are assessed with tools that

measure drug liking, willingness to take each drug again, street value of each drug, etc., which are known to be fairly predictive of real-world behaviors.

Once a drug has been approved and is available for use, various Category 4 studies (epidemiology studies, etc.) will be required to assess how effective an opioid with abuse-deterrent properties is in deterring its abuse in the community setting.

Depending on how a particular drug performs on the studies FDA requires in Categories 1-3, FDA will allow the following to appear in an opioid drug product's FPI: a) a description of some abuse-deterrent studies, their high-level results, and what FDA thinks of those results, b) statements describing what FDA considers to be meaningful abuse-deterrent properties of the drug product, and c) claims associated with those properties. FDA states in the Guidance that "*abuse-deterrent properties* are defined as those properties shown to meaningfully **deter** abuse, even if they do fully **prevent** abuse." (emphases in original)

Since implementation of the "Physician's Labeling Rule" in early 2006, all new products have the information in their FPIs in numbered sections which are uniform across drug products. As an example, section 1 is always **Indications and Usage**, section 2 is always **Dosage and Administration**, etc. If the drug product has abuse potential, its FPI will include a section 9, entitled **Drug Abuse and Dependence**. By contrast, antibiotics, statins, etc. do not have a section 9, because they do lack abuse potential, as defined by FDA. The sections are further subdivided into subsections, numbered with decimals.

FDA has stated that, if abuse-deterrent properties and associated claims are allowed for a drug product, they will appear in section 9.2 **Abuse**. To date, FDA has placed this information in a subsection, entitled *Summary*, at the end of section 9.2. An example of abuse-deterrent properties and associated claims from an approved, but not marketed opioid analgesic product that incorporates an opioid antagonist to provide abuse deterrence is:

Based on the in vitro study results, it is expected that abuse of oxycodone from physically and chemically manipulated <PROPRIETARY NAME> tablets will be deterred by the inability to separate the two active components.

The data from the clinical abuse potential studies indicate that <PROPRIETARY NAME> has pharmacologic properties that are expected to reduce abuse via the intranasal and intravenous routes of administration.

A number of drug developers have tried to design opioid analgesics with abuse-deterrent properties, but not all have succeeded. Thus, the definitive way to determine if a specific drug product possesses what FDA considers to be meaningful abuse-deterrent properties is to look for that information at the bottom of section 9.2 **Abuse** of the product's FPI.

Thank you for the opportunity to participate today. I am pleased to answer any questions the Commission members have.