Deadly Synthetic Drugs:

The Need to Stay Ahead of the Poison Peddlers

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Introduction

Chairman Grassley, Ranking Member Leahy and Members of the Committee, I am Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to appear before you today to discuss the important role that FDA has in supporting the efficient and scientific assessment of substances to protect the public health, as well as supporting needed drug development. New illicit synthetic drugs are flooding the U.S. market, and many pose significant health risks. Many of these substances are used for their psychoactive effects, and have contributed to serious injuries and deaths. We appreciate the efforts of the Committee to address this public health challenge, and we are committed to doing our part. My testimony today will cover the role of FDA in the drug scheduling process, including emergency control of new and dangerous "street" drugs, and other issues related to synthetic drugs, including our work to help address their potential harms, and our work to help identify their potential value to scientific research.

FDA's Role in Scheduling Decisions

While the Drug Enforcement Administration (DEA) is the lead Federal agency responsible for regulating controlled substances and enforcing the Controlled Substances Act (CSA),[1] HHS has a number of responsibilities under the CSA, several of which are performed by FDA on behalf of HHS. As a part of this work, FDA conducts a scientific and medical evaluation, sometimes referred to as an "eight-factor analysis," which forms the basis of the HHS recommendation to DEA about the appropriate level of controls for a substance with the potential to be abused.

[1] 21 U.S.C. § 801, *et seq.*

This analysis includes the following considerations for a drug or other substance: (1) its actual or relative potential for abuse;[2] (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history or current pattern of abuse; (5) the scope, duration, and significance of abuse; (6) what, if any, risk there is to the public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled under the CSA.[3]

This scientific evaluation involves the careful analysis of many kinds of data:

1) Data on chemical synthesis and solubility;

2) Data on drug absorption, receptor binding and metabolism;

3) Data to investigate whether animals will develop physical dependence, whether they will work to self-administer the drug; and, whether an animal can distinguish a given drug from other controlled substances.

4) Clinical studies, including the conduct of a study to assess the drug's abuse potential;

[2] The term "abuse" is not defined in the CSA; however, the legislative history of the CSA suggests the following factors, which FDA considers in determining whether a particular drug or substance has a potential for abuse: (a) individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; (b) there is a significant diversion of the drug or substance from legitimate drug channels; (c) individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances; and (d) the substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance; thus, making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community. (The Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970), reprinted in U.S.C.C.A.N. 4566, 4603.

[3] *See* 21 U.S.C. § 811(c).

5) Review of human adverse events (relating to the drug's ability to cause physical dependence, alter moods, cause hallucinations, etc.) from clinical trial reports and from post-marketing experience if applicable.

After integrating these data, the scientific and medical evaluation prepared by FDA is then sent to the National Institute on Drug Abuse (NIDA) for concurrence. Once concurrence is obtained, FDA, through the Commissioner, forwards the evaluation and recommendation to the Assistant Secretary for Health (ASH/HHS).

The official recommendation on scheduling is transmitted from HHS to DEA, which makes the final determination of the appropriate schedule for the substance by scheduling the substance through the rulemaking process prescribed by statute.[4] Under the CSA, controlled substances are listed in one of five schedules, depending on their abuse potential, among other criteria. Important for today's discussion, drugs in schedule I are the most tightly controlled, and are those that a) have a high potential for abuse; b) have no currently accepted medical use in treatment in the United States; and c) lack an accepted safety for use under medical supervision.

FDA also has a role in the "emergency" scheduling provision in the CSA,[5] which allows for DEA to place certain substances not already scheduled, and not subject to an investigational new drug application, into a schedule on a temporary basis to address an imminent hazard to the public health. Under these circumstances, HHS receives notice from the Attorney General (through DEA) of the proposed action. FDA then reviews the records of drugs being investigated for therapeutic use and begins work to support permanent scheduling.

[4] *See* 21 U.S.C. § 811.
[5] 21 U.S.C. § 811(h)

For completeness, there are other scheduling mechanisms that I will not discuss in greater detail given the limited, if any, role FDA has. For instance, many substances were controlled legislatively under the CSA at the time the law was enacted in 1970. Scheduling also can and has been done through subsequent legislation. The scheduling of anabolic steroids is an example of scheduling through legislation. In addition, there is scheduling to fulfill international treaty obligations.

FDA's Internal Process Related to Scheduling

The scientific and medical evaluation process to determine the appropriate level of control for a substance is complex, involving the balancing of the interests of various agencies in support of public health. There is a critical need to protect the public from the dangers posed by drugs and substances of abuse and at the same time to provide access to these drugs and substances to researchers for potential drug development. Working through these different issues requires close cooperation and careful attention to the available data to make the best decisions.

Recognizing the importance of the scientific aspects of scheduling, CDER has dedicated resources within the Controlled Substances Staff (CSS), focused on assessing abuse potential. This group works with the medical review divisions of CDER's Office of New Drugs and makes scheduling recommendations for new drugs being developed for medical treatments that are coming on the market. In addition, CDER relies on the CSS to respond to DEA requests to schedule new substances. These requests can be in the form of emergency scheduling actions (discussed above), or through Citizen Petitions submitted to DEA related to adding, removing, or changing schedules of substances under the CSA. The result of these reviews can be to support the emergency scheduling of dangerous illicit drugs, if these substances do not fall under investigational new drug applications (INDs) or new drug applications (NDAs). They can

also result in a recommendation to increase the level of control on a drug, such as the recommendation to move hydrocodone combination products from Schedule III to Schedule II. Finally, the review can result in recommendations to reduce, or even eliminate, controls. For example, naloxone (an important drug in the treatment of opioid overdose) was initially a scheduled drug but, given its absence of abuse potential, was removed from the scheduling.

To support drug development in this area and facilitate scientific assessment of drugs of abuse, in 2010 FDA published draft guidance on the assessment of the abuse potential of drugs.[6] Following public meetings and comment, we intend to finalize the guidance in 2016. The guidance has standardized the study and evaluation of the abuse potential of new substances through a systematic series of nonclinical and clinical studies. The guidance contains advice on the study of new drugs under development for medical treatment in the United States.

FDA's Role in Investigations and Enforcement Actions with Regard to Controlled Substances

Finally, in addition to its role in scheduling drugs, FDA sometimes works with the Department of Justice (DOJ), including DEA, and other state and Federal agencies on criminal investigations involving the illegal sale, use, and diversion of controlled substances. FDA recognizes that DEA is the lead Federal Government Agency for enforcement matters related to the diversion of controlled substances. Historically, FDA has deferred to DEA regarding the illegal sale and use of illicit drugs of abuse that have no currently-accepted medical use (i.e., Schedule I substances).

Assessing the Abuse Potential of New Psychoactive Substances

[6] *Draft Guidance for Industry: Assessment of Abuse Potential of Drugs* - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

We are greatly concerned about the new emerging public health threat of new psychoactive substances (referred to as NPS), that involve:

1. New synthetic chemicals that elicit cannabimimetic effects;

2. New substances that are sold as innocuous products such as "bath salts," but may contain highly dangerous substances that elicit stimulant effects with serious, even lethal outcomes; and

3. New psychedelic stimulants and hallucinogens being sold on the street that are responsible for hospital emergency department admissions and Medical Examiner reports.

FDA has been actively engaged with DEA in assessing the abuse potential of substances of concern. Recently, we completed a process to allow us to share confidential information efficiently to facilitate our important work together. Between 2011 and 2016, we have responded to all DEA requests for a recommendation regarding permanent scheduling of approximately 20 substances. Most of these substances were emergency-controlled initially and then permanently controlled under the CSA.

Working together, we have made progress in improving the process of scheduling these substances. With enactment of the "Synthetic Drug Abuse Prevention Act of 2012,"[7] Cannabimimetic Agents were added to Schedule I of the CSA. The term "Cannabimimetic Agents" refers to a substance that is a cannabinoid receptor type 1 (CB1 receptor) agonist. Under this Act, scheduling was performed using binding studies and functional assays for the specific chemical structural classes listed in the law. This greatly simplified the type of scientific

[7] Title XI, Subtitle D, of the Food and Drug Administration Safety and Innovation Act (FDASIA), P.L. 112-144.

data that is needed to evaluate these substances for control in Schedule I. FDA has been able to evaluate 16 cannabimimetic substances for CSA control by this simplified approach. We have also applied a comparable approach to evaluating 13 new cathinones (the so-called "bath salts") and several new CNS stimulants/hallucinogens for control relying on reduced amounts of scientific data. These are highly dangerous substances, and FDA determined that these substances, sold on the street as substitutes for other controlled substances, in addition to producing euphoria and hallucinations, were responsible for other behavioral and toxic effects that are typical of cannabinoids and CNS stimulants. Reported adverse effects included paranoia, panic reactions, confusion, insomnia, agitation, and memory loss. Reported severe toxic effects have included convulsions and coma with hyperthermia, tachycardia, diffuse bleeding, acidosis, rhabdomyolysis, and anuria.

The emergence of the synthetic cannabinoids and cathinones, as well as a number of new tryptamine derivative substances with CNS hallucinogenic properties, has increased our focus on these products in recent years. In 2012, the first of the synthetic cannabinoids (cannabimimetic substances) and tryptamine derivatives with CNS hallucinogenic properties and new stimulants were scheduled. Since then, recognizing their dangers, we have continued to expeditiously review and recommend scheduling of additional analogs of these substances in support of the work DEA is doing to keep them off the streets.

In light of the harm to the public health observed from many of these rapidly emerging new substances, and because chemists can rapidly alter the chemical structures to stay ahead of the efforts to control these substances, we recognize the difficult challenges in this area. Placing substances that lack an accepted medical use and have a large potential for drug abuse and harm to the public health into Schedule I make those substances illegal to manufacture,

possess, or distribute, except for their use in legitimate research,1 and subject to DEA controls and enforcement. However, the chemical structures and pharmacological activity targeted by NPS manufacturers overlap not only with illicit, potentially dangerous, Schedule I substances, but also with many drug substances that research may show have legitimate therapeutic uses.

For this latter group compounds, the requirements placed on the conduct of research using Schedule I drugs may act as a disincentive to research and an appropriate balance needs to be struck. Overall it is important to balance the pressing need to address the important public health risk posed by the illicit use of some of these compounds and the important need to develop new therapies and improved scientific understanding. Science can form the basis for timely decisions regarding the appropriate controls over these compounds.

FDA is committed to working with DEA and NIDA to support development and rapid assessment of the science in this area, and to support efforts to enhance the timely assessment of new substances for potential scheduling.

We hope that as the Committee explores ways of addressing this problem, you will continue to give the relevant Federal agencies an opportunity to share perspectives on proposed responses, including science-based solutions, that would address the threat to public health and safety posed by such compounds, while at the same time provide needed access to these drugs and substances to researchers for potential drug development.

Thank you for the opportunity to appear before you today. I am happy to answer any questions.