U.S. FOOD & DRUG ADMINISTRATION

STATEMENT

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON ENERGY AND COMMERCE

SUBCOMMITTEE ON HEALTH

U.S. HOUSE OF REPRESENTATIVES

THE OVERDOSE CRISIS: INTERAGENCY PROPOSAL TO COMBAT ILLICIT FENTANYL-RELATED SUBSTANCES

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Chair Eshoo, Ranking Member Guthrie, members of the Subcommittee: 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 comprehensive approach to the scheduling of fentanyl-related substances (FRS) developed by the Office of National Drug Control Policy (ONDCP), the Department of Justice, and the Department of Health and Human Services, and the important role that FDA plays in scheduling illicit substances that pose a danger to public health while also supporting needed drug development.

FDA remains committed to addressing the national opioid and overdose epidemic on all fronts, with a significant focus on supporting primary prevention by eliminating unnecessary initial prescription drug exposure and inappropriate prolonged prescribing; encouraging harm reduction through innovation and education; advancing development of substance use disorder treatments; and protecting the public from unapproved, diverted, and counterfeited drugs presenting serious overdose risks.

As the Committee is well aware, new illicit synthetic drugs derived from fentanyl are flooding the U.S. and are being mixed with heroin and other drugs. The result has been a dramatic increase in opioid-related deaths in the U.S. in recent years, further exacerbated by the current COVID-19 pandemic. 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 with respect to FRS, and our support for the interagency

proposal which we think will advance efforts to reduce the supply and availability of illicitly manufactured FRS while supporting their availability, under appropriate circumstances, for scientific research and drug development.

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 critical responsibilities under the CSA, several of which are performed by FDA on behalf of HHS. FDA takes its scientific role very seriously. As a part of this work, FDA conducts a scientific and medical evaluation of drugs and other substances, sometimes referred to as an "eight-factor analysis," which forms the basis of the HHS recommendation to DEA about the appropriate level of control for a substance with the potential to be abused (also called "scheduling"). This analysis includes the following considerations for a drug or other substance: (1) its actual or relative potential for abuse; (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.[2]

The scientific and medical evaluation prepared by FDA is sent to the National Institute on Drug Abuse (NIDA) at NIH for concurrence. Once concurrence is obtained, FDA forwards the

[1] 21 U.S.C. § 801*, et seq.*
[2] *See* 21 U.S.C. § 811(c).

evaluation and recommendation to the Assistant Secretary for Health (ASH/HHS). Following final review by the ASH on behalf of 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.[3]

FDA also has a role in the temporary scheduling provision under section 201 of the CSA,[4] which allows for DEA to place certain substances that are not already scheduled, or that are not subject to an approved application or an investigational new drug application, into schedule I on a temporary basis to avoid an imminent hazard to the public health. Under these circumstances, HHS receives notice from the Attorney General that DEA plans to place a drug or substance into schedule I on a temporary basis. FDA then reviews the records of drugs approved or being investigated for therapeutic use and conveys to DEA whether or not we have any objection to the proposed temporary order to place the substance in schedule I. In the large majority of cases in which DEA proceeds with the temporary order, DEA will request from HHS a full eight-factor analysis on the substance, and FDA begins work to consider permanent scheduling once DEA initiates that process.

In the case of FRS, DEA issued a temporary order on February 6, 2018, controlling the entire FRS class (defined as all substances related to fentanyl that are within certain chemical structure parameters and that are not otherwise controlled and are not approved or exempted under the

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

Federal Food, Drug, and Cosmetic Act) for a period of two years. Congress has extended the order on three occasions, most recently extending the order through January 28, 2022.

On February 4, 2020, DEA asked HHS to conduct an eight-factor analysis on the FRS class and make a scheduling recommendation for the class. Following careful evaluation, FDA concluded that such a finding is not possible for FRS as a class because: (1) the class is vast in the number of hypothetical covered substances; (2) data on the pharmacological effect and epidemiological data showing harms and overdose deaths are available for fewer than 30 FRS substances; and (3) among the individual FRS for which pharmacological activity has been studied, FDA has identified examples of substances lacking in mu-opioid agonist activity, the presumed pharmacology that would lead to opioid-related harms.

Recognizing the danger posed by fentanyl-related substances, however, we have continued to expeditiously review and recommend scheduling of individual analogues of these substances in support of the work DEA is doing to keep them off the streets. In addition, 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 of the drugs to stay ahead of the efforts to control these substances, we have worked closely with our interagency colleagues on a legislative approach that would control the FRS class while minimizing the impact of the control action on research and drug development by providing for the rapid decontrol of individual members of the FRS class, as appropriate, when new data becomes available.

Under the interagency proposal, the entire FRS class would be legislatively added to schedule I of the CSA based on the presumption that their pharmacology, and therefore their potential for

abuse, will mirror that of fentanyl due to their structural similarity. This would provide law enforcement with the tools they need to promptly respond to the trafficking and manufacture of illicit synthetic fentanyl-like products. But because the chemical structures targeted by illicit opioid manufacturers for expected fentanyl-like pharmacological activity may not always demonstrate pharmacology like fentanyl or warrant control as dangerous schedule I substances, we have also proposed a new process by which an FRS could be moved to a lower schedule, or de-scheduled entirely, if the data show it doesn't belong in schedule I.

This proposal is based on our experience with the opioid class, including FRS, where we have seen that small changes in chemical structure can result in significant changes in pharmacological effects. An example is the structural similarity of many conventional schedule II mu-opioid agonists derived from thebaine (i.e., morphine-like structures such as oxycodone, hydrocodone, etc.), where small structural changes also lead to compounds such as naltrexone and naloxone with mu-opioid antagonist activity. Because of this, and because we believe some members of the FRS class could have important therapeutic potential, we need a science-based mechanism to rapidly remove that substance from schedule I if sufficient evidence emerges that a particular FRS does not share fentanyl's pharmacological effects.

Under the decontrol provision in the interagency proposal, HHS would consider one of the eight factors normally required for scheduling recommendations (the scientific evidence of the substance's pharmacological effect), and, to the extent evidence exists, three other factors listed in the CSA (its actual or relative potential for abuse; the state of current scientific knowledge regarding the substance; and the risk to the public health). With regard to the pharmacological

effects, the proposal identifies a three-part assessment focused on the substance's mu-opioid activity. There are two potential outcomes that would reduce the controls over a given substance if appropriate. First, if this process leads HHS to conclude that the substance has less potential for abuse than substances in schedule V (the least restrictive schedule under the CSA), HHS would convey that conclusion to the Department of Justice (DOJ) and provide its analysis, and DOJ would be required to remove the substance from the CSA schedules within 90 days. Second, if the process leads HHS to conclude that the substance has some potential for abuse, but less than that of substances in schedules I and II, HHS would likewise convey the conclusion to DOJ and provide its analysis, and DOJ would be required, within the same time period, to remove the substance from schedule I and reschedule it in schedule III.

The CSA, at section 201(a)-(b), does have a process for removing an individual substance from the schedules, or for moving a substance from a more restrictive to a less restrictive schedule. That existing process would be preserved under the bill. However, because that process entails a consideration of all eight factors as required to support new scheduling, re-scheduling, and de-scheduling actions for a given substance, and because it must take place through rulemaking, and can be time-consuming, we have proposed a streamlined process for decontrol of an FRS from a more restrictive to a less restrictive schedule as new scientific information is collected.

We believe the proposed approach would appropriately balance the pressing need to address the public health risk posed by the illicit use of some of these compounds and the similarly important need to support scientific research into these substances to develop new therapies and improved

scientific understanding. We feel the interagency proposal strikes an appropriate balance between these two priorities and is deserving of your consideration.

FDA stands ready to do its part to address the public health challenges presented by the FRS class. Thank you for the opportunity to appear before you today. I am happy to answer any questions.