Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
"The Overdose Crisis: Interagency Proposal to Combat Illicit Fentanyl-Related Substances"
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The Honorable Frank Pallone, Jr. (D-NJ)

1. **In 2018, DEA took action to place all fentanyl-related substances (FRS) into Schedule I as a class. Your testimony notes that the Drug Enforcement Administration (DEA) had asked the Department of Health and Human Services (HHS) to conduct an eight-factor analysis on the FRS class and make a scheduling recommendation, but the Food and Drug Administration (FDA) concluded that such an analysis was not possible. Why was this the case, and how has this influenced the FDA's position on permanent class-wide scheduling of FRS?**

   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. We continue to support the scheduling process outlined in the Controlled Substances Act (CSA) and the important role HHS plays in that process, but we believe the Biden Administration proposal would appropriately balance the pressing need to address the important 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.

2. **The Administration's proposal on would place all FRS into Schedule I class-wide, but would also create an expedited process for removing individual fentanyl-related substances from the schedules or moving them to a lower schedule if it is found that they do not fit the criteria for Schedule I substances.**

   a. **According to your testimony, substances related to fentanyl that are within certain chemical structure parameters would all be placed into Schedule I under the Administration's proposal. Under class-wide scheduling, is it possible that substances with unknown and potentially no pharmacological**

effects will be preemptively scheduled in the most restrictive class?

Yes, this proposal would codify the 2020 DEA order, under which the entire FRS class was added to schedule I of the CSA based on their structural similarity to fentanyl, without prior assessment of their pharmacological effects.

b. **If a substance does not have a pharmacological effect, what risk does it pose to public health? How many FRS within the class-wide definition would pose little to no threat to public health?**

If a substance does not have a pharmacological effect, it would pose little or no risk to the public health in terms of potential for abuse. It is not possible to determine with data available today how many FRS would lack fentanyl's pharmacological effect, but 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.

c. **How would the process included in the Administration's proposal to remove or reschedule FRS operate and how is it different that the process under current law? Why does the FDA believe it is a critical component of the Administration's proposal?**

In the case of removing a substance from scheduling or moving it to a less restrictive schedule, the current process generally entails a consideration of all eight factors as required to support new scheduling, re-scheduling, and de-scheduling actions for a given substance. This process occurs through rulemaking and can be time-consuming. Under the Biden Administration proposal, if data show an individual FRS doesn't share the pharmacology and therefore the abuse potential of fentanyl and therefore doesn't belong in schedule I (which is for substances with high potential for abuse), HHS can make a determination that it should be either removed from scheduling entirely or moved to schedule III.

Because of the danger posed by fentanyl-related substances, we agree that a more expedited process (scheduling the entire FRS class via legislation) is appropriate when accompanied by the ability of HHS to determine on an expedited basis that an individual FRS that doesn't share the pharmacology and therefore the abuse potential of fentanyl should be descheduled or rescheduled. This approach ensures that scientific data will continue to have a role in the scheduling process.

3. **Some have suggested that there be a requirement of pharmacological effect in the class-wide definition of a "fentanyl-related substance." Was this something the interagency working group considered as a part of the proposal? And if so, why was it not included in the Administration's proposal on FRS that was considered during the December 2 hearing?**

We defer to ONDCP on any questions regarding the operation of the interagency working group.

4. **This year the country has witnessed a high of 100,000 overdose deaths. I recognize that this is a complex and multifaceted problem that requires a multifaceted solution. It is important that we consider all possible strategies to combat this crisis. What additional policies should be considered to reduce overdose deaths?**

   Addressing the overdose crisis is among FDA's highest priorities. It will take carefully developed, coordinated, and sustained action by multiple stakeholders to reduce the incidence of drug misuse, abuse, addiction, overdose, and death, while preserving appropriate access to these drugs for patients who need them. As part of these efforts, FDA recognizes that opioids are being used in combination with controlled substances such as benzodiazepines and stimulants. Confronting the challenge and complexity of polysubstance use will be critical to the success of our health policy solutions moving forward. FDA will continue to pursue actions and activities aligned with the HHS Overdose Prevention Strategy, the National Drug Control Strategy and the SUPPORT Act. Specifically, FDA intends to:

   - Advance the development of overdose reversal agents
   - Advance the development of novel treatments for substance use disorders
   - Advance the development of non-addictive alternative treatments for conditions that would typically require prescription of a controlled substance
   - Address safe use of controlled substances for patients who need them
     - Advocate for evidence-based use of these medications for appropriate treatment
     - Explore public and prescriber education strategies to promote safe use
   - Anticipate potential unintended consequences of regulatory actions that may worsen the overdose crisis, and design mitigation strategies that support our policy actions
   - Evaluate whether the approval standard for opioids should be modified to address the special public health risks posed by these products

<u>The Honorable Anna G. Eshoo (D-CA)</u>

1. **Please describe how social media is used to facilitate the trafficking of fentanyl, fentanyl-related substances, and other opioids.**

   a. **Has the FDA observed an issue with private, peer-to-peer sales often facilitated in private groups?**

      FDA has observed the use of platforms such as Telegram, WhatsApp, Snapchat, and Wickr. Specifically, the agency has observed illicit transactions occurring on these platforms. Of note, suspects are using the chat functions inside of social media platforms to communicate about drug sales. FDA Office of Criminal

Investigations (OCI) special agents have made undercover purchases of counterfeit drugs though these apps.

b. Has the FDA observed formal, monetized advertisements on social media services for illicit drugs? Is this problem wide-spread?

Yes, this has occurred on social media services such as Reddit, Twitter, Instagram, YouTube, and Facebook (Meta). We believe this is a common, wide-spread problem. FDA has observed on at least one platform that, after an individual searches for a certain drug, he/she will receive ads, from other users of that platform, informing them that those users are selling the drugs for which the individual searched.

c. To what degree and how often does the FDA coordinate with social media companies to combat the sale of opioids on social media?

FDA sends abuse complaints to social media companies regarding specific users posting ads for illegal drug sales. The purpose of the abuse complaint is to alert the social media platform of the posting so that it can take any voluntary action it deems appropriate. In most instances, the social media companies ultimately decide to pull the posting after receiving the abuse complaint.

d. Which social media companies has the FDA worked with?

FDA has worked with Microsoft, Google, Facebook (Meta), WhatsApp, Twitter, LinkedIn, and Instagram, among others.

e. How does the FDA collaborate with social media companies?

FDA has hosted three Online Opioid Summits since 2018. These summits provide stakeholders a unique opportunity to collaborate, leverage expertise and explore meaningful ways to help reduce the availability of opioids online. The most recent Online Opioid Summit, held on Sept. 9, 2021, was part of the agency's continued efforts to find and implement innovative solutions to prevent the illegal sale of opioids through internet platforms and services. Summit attendees included internet stakeholders, including social media companies, government entities, academia, and other important partners within the internet ecosystem.

Discussions during the virtual meeting addressed topics including the evolving landscape of online opioid purchasing, such as younger and more vulnerable populations being exposed to these dangerous opioids through social media and other online platforms; ways to enhance cross-industry and global collaboration; successes and novel solutions implemented since prior summits; and new ways to continue to prevent the illegal sale of opioids through internet platforms and services.

f. Have social media companies been receptive to the FDA outreach?

FDA has found that social media companies are generally receptive to agency outreach. With COVID-related issues, they have been very cooperative. During our interactions with the social media companies, we stress the public health risks associated with the illegal sale of opioids and encourage them to implement their own processes to proactively curb such sales.

g. Which social media companies have been the most productive partners on responding to issues involving illicit drug sales?

We have found most social media companies to be responsive once they learn of specific issues.

h. Are there legal, technical, personnel, or other barriers to effectively coordinating to combating the sale of opioids on social media?

Illicit activity is more difficult for law enforcement to detect when encrypted communication platforms or private chat/messaging features of social media platforms are used to facilitate illegal sales of opioids. Further, unlike most federal law enforcement agencies, OCI does not have administrative subpoena authority, which limits our ability to investigate online. FDA's cybercrime investigators cannot quickly identify subscriber information for any social media account or suspect domain name because companies and domain name registrars will not share subscriber or even basic "Whois" data without a subpoena. Given this, in many cases, OCI's ability to readily ascertain the identity of website operators depends on how quickly OCI can work with DOJ on the issuance of a grand jury subpoena to the social media platforms or domain name registrars for this information. Additionally, some social media platforms do not readily provide or publicly disclose service addresses or legal points of contact, which makes sending legal process, such as subpoenas, more difficult for law enforcement.

2. From June 2020 to January 2021, the FDA and the National Telecommunications and Information Administration (NTIA) administered a pilot program to curb access to illegal online opioid sales by working with domain name registries.

a. What was the outcome of this program?

As the result of a successful 120-day pilot program launched in 2020 with FDA, the National Telecommunications and Information Administration, and domain name registries, nearly 30 websites illegally offering opioids for sale became inaccessible to the public.

b. Will FDA and NTIA continue or expand this program? Why or why not?

The pilot program has proven to be an effective tool in maximizing the impact of efforts to limit the illegal sale of unapproved opioids online. FDA hopes to continue this effort to help prevent illegal online opioid sales.

c. Was the participation of private domain name registries effective?

Under the pilot, the FDA notified registries that participated in the pilot – Public Interest Registry, Registry Services (formerly Neustar) and Verisign – when the agency sent a warning letter to a website operator and the website operator did not respond adequately within the specified timeframe. The registries reviewed FDA's notifications and assessed whether to take further voluntary action, including possible domain name suspensions or blocks. As noted above, as a result of the pilot program, nearly 30 websites illegally offering opioids for sale became inaccessible to the public.

The Honorable Lisa Blunt Rochester (D-DE)

1. **In response to my question about whether there is precedent for a class-wide scheduling approach that is based solely on chemical structure, you testified that the Anabolic Steroids Act of 1990 was based only on structure. But that law, codified at 21 U.S.C 801(41)(A), defines "anabolic steroid" as any drug or hormonal substance that is chemically *and* pharmacologically related to testosterone. Based on these criteria, in 2009, the DEA began evaluating three substances for scheduling identified as methyldrostanolone, prostanozol, and adrenostreone.[1] Although three compounds were reviewed, only two were scheduled (methyldrostanolone and prostanozol).[2] Neither the notice of proposed rulemaking in November 2011 nor the Final Rule issued in July 2012 referenced adrenosterone.**

   a. Since adrensoterone is chemically related testosterone, was it not scheduled because it was also not pharmacologically related to testosterone? Do you wish to clarify your testimony?

   The Anabolic Steroid Control Act of 2004 (ASCA) defines an anabolic steroid as any drug or hormonal substance that is chemically and pharmacologically related to testosterone, subject to certain exceptions. The DEA evaluates whether a

[1] *See, eg.,* Joseph T. Rannazzisi. Sept 2009:

"DEA is reviewing three other substances identified as methyldrostanolone, prostanozol, and adrenostreone. All three are found in the dietary supplement market and two of these products are believed to be more potent than testosterone."

[2] 21 CFR 1300.01.

substance meets the definition of an anabolic steroid [21 USC 811 (i)]. DEA may be able to provide clarifications concerning their actions on adrenosterone.

The Honorable Brett Guthrie (R-KY)

1. **As you know, methadone is still only given at treatment centers that must be visited once a day – which can be a burdensome and disruptive model to individuals' lives. However, there are products in development that would allow methadone to be given orally once per week – improving ability to receive and comply with treatment, reducing the risk of relapse, and providing a better quality of life. What actions can your agency take to speed development and uptake of these kinds of products, and how can the federal government at-large play a bigger role in supporting innovative dosage forms?**

   FDA encourages development of products that facilitate and reduce the burden of adherence to medications for opioid use disorder. We have approved long-acting depot formulations of naltrexone and buprenorphine and continue to work with pharmaceutical sponsors to encourage development of additional products of this nature. Products that address an unmet medical need in the treatment of a serious condition may be eligible for our various expedited programs, including Fast Track Designation and Priority Review.

The Honorable Richard Hudson (R-NC)

1. **The COVID-19 pandemic has tragically led to an increase in the number of overdose deaths in the United States. While a growing percentage of these deaths are caused by fentanyl and synthetic opioids, far too many overdoses and substance use disorders are also attributable to leftover prescriptions in medicine cabinets.**

   During the 115th Congress, a provision I championed was included in H.R. 6, the SUPPORT for Patients and Communities Act, which was signed into law in 2018. Section 3032, Safety-enhancing packaging and disposal features, provided FDA with the authority to require certain opioids be dispensed with at-home disposal solutions. While you have spoken favorably in regard to this provision on multiple occasions, the Food and Drug Administration (FDA) has unfortunately not taken any concrete steps towards implementation.

   a. **Considering the number of deaths, we are witnessing related to overdoses from leftover prescriptions, can you provide a comprehensive status update on the Food and Drug Administration's (FDA) plans to implement the disposal provisions included in Section 3032 of the SUPPORT Act? Please ensure this status update includes a description of next steps, an estimated timeline, as well as a detailed overview of the FDA's implementation plan.**

      FDA is actively considering how to use this disposal authority. In June 2021 the Duke-Margolis Center for Health Policy, in coordination with FDA, convened a

workshop, Exploring Options for Safe and Effective In-Home Opioid Disposal, to explore opioid disposal products available to consumers and consider the potential impact and benefits of FDA requiring that a disposal product be provided to patients with their opioid prescriptions. Subsequent to this meeting, the Agency sought additional information on mail-back envelopes from the DEA, the U.S. Postal Service, and companies that manufacture commercially available mail-back envelopes and operate mail-back envelope programs. FDA intends to publish a proposal for comment on potential use of the SUPPORT Act section 3032 disposal authority soon.[3] Following consideration of comments received on this proposal, a workshop or meeting with key stakeholders may be valuable. If FDA determines that a specific use of the disposal authority is appropriate, warranted, and meets applicable statutory requirements (including that the disposal packaging or system render the drug "nonretrievable" as defined in DEA regulations at 21 CFR 1300.05), we would require a risk evaluation and mitigation strategy (REMS) or REMS modification applicable to manufacturers of affected products.

2. **During a 12-month period ending in April 2021, an estimated 100,306 drug overdose deaths occurred in the United States, of which 8 in 10 of these deaths were opioid-related. Naloxone serves as a powerful tool to combat the crisis and increasing accessibility and awareness of this product remains a drastic need and has been a focus of the Food and Drug Administration (FDA).**

   The patient-provider relationship is a critical component in aiding those who are unaware both of their risk for an accidental opioid overdose, as well as the lifesaving nature of naloxone. In an October 2020 article in Pain Medicine News, Prescribing Naloxone: Tips for Conversations With Patients, you provided background and context on prescribing naloxone, as well as tips for healthcare providers when having a conversation with their patients related to naloxone. You have also previously mentioned that a priority of FDA is to encourage manufacturers to pursue approval of over-the-counter naloxone products.

   a. **Have you considered any possible unintended downstream consequences of moving naloxone to an over-the-counter product? i.e. Will an at-risk patient or caregiver who is not provided with the appropriate background information on the potentially lifesaving product still manage to utilize it efficiently and effectively?**

      FDA and experts in treatment of substance use disorders agree that widespread availability of naloxone is an essential part of efforts to reduce the high number of opioid overdose deaths occurring in the United States. Nonprescription status of naloxone would be one way of increasing availability.

[3] For updated developments on this issue, see: https://www.fda.gov/news-events/press-announcements/fda-considers-new-approach-improve-safe-disposal-prescription-opioid-analgesics-decrease-unnecessary

Naloxone generally has a low incidence of adverse effects, and experts agree that the possible life-saving benefit of naloxone makes it appropriate to administer naloxone in an opioid overdose situation, even with a risk of adverse effects, however small. The potential benefits far outweigh the risks.

In order for a drug to be nonprescription, it must be labeled appropriately such that a consumer can use the drug safely and effectively without any help from a healthcare professional. Sponsors of potential nonprescription products conduct scientifically rigorous consumer behavior studies to demonstrate that consumers understand the proposed nonprescription labeling, how to use the drug appropriately, and what the risks of the drug are.

Because of the high number of opioid deaths occurring in the United States, to encourage the development of nonprescription naloxone products, FDA took the unprecedented step of designing a model Drug Facts label (DFL) for a potential nonprescription naloxone product, and had that DFL tested in a rigorously conducted Label Comprehension Study. The study showed that consumers were able to use the label to identify a person who might have an opioid overdose, to know to give naloxone for it, to call 911, to stay with the person until 911 personnel arrive, and to recognize what potential side effects might occur.

Information regarding the study can be found at: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-efforts-support-development-over.

The scientific validity and public health importance of the study were acknowledged by its publication in the New England Journal of Medicine, the nation's premier medical journal.

The model DFL is available to sponsors of potential nonprescription naloxone products, and substantially reduces development time and cost for sponsors. There are several different kinds of devices to administer naloxone (e.g., nasal sprays, autoinjectors, vials and syringes, etc.). A sponsor can use the model DFL (which includes all information needed other than device-specific information), add device-specific instructions, and conduct human factors testing to confirm consumers understand how to use the particular device. If their human factors program is successful and their naloxone product otherwise meets FDA's standards, the sponsor could then submit an application to FDA for approval for nonprescription marketing.

For more information on FDA's many efforts regarding naloxone, please see https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-about-naloxone.

b. Due to state standing orders, are individuals currently able to walk into a pharmacy and obtain naloxone? Is this generally covered by their insurance?

Naloxone remains a prescription drug in all states and the District of Columbia (DC). However, all states and DC have some type of naloxone access law, including standing orders, under which anyone can enter a pharmacy and purchase naloxone using one of these systems.

However, despite these standing order provisions, naloxone uptake has remained low. People still report encountering difficulty obtaining naloxone due to various reasons, including embarrassment over the stigma of having to ask at the pharmacy counter for a drug known to be used for overdoses, reluctance of some pharmacists to dispense it, lack of knowledge of availability of the standing order program, lack of pharmacy stocking of naloxone, confusion and unwillingness among pharmacists to dispense naloxone despite the standing orders, and other reasons.

Thus, these state standing order programs, while well-intended and somewhat helpful, have not led to a substantial uptake in naloxone. Naloxone is still not getting into as many hands as it needs to.

FDA does not regulate insurance coverage, and thus cannot answer the question about whether insurance companies are covering the cost of naloxone dispensed via state standing order systems.

c. As Congress continues to consider policies to address the opioid crisis, can you provide additional context and policy rationale for the FDA's recent actions to encourage manufacturers to pursue approval for over-the-counter naloxone products?

Please see the responses to questions a. and b. We believe that wider availability of naloxone (e.g., nonprescription naloxone on the shelves of all kinds of retail establishments and through online retailers) could result in fewer opioid overdose deaths. Nonprescription availability might overcome some of the barriers noted above that still exist under state standing order prescription systems. Sponsors of potential nonprescription naloxone products will have to demonstrate that the labeling of their product is adequate for consumers to understand how to use the product safely and effectively, without the supervision of a healthcare professional.

d. How does the FDA's push to over-the-counter naloxone products parallel the recent proposal by the Biden Administration to ensure certain at-home over-the-counter COVID-19 rapid tests be offered to individuals at no cost? Recent reports have indicated early hurdles to implementation – either compelling individuals with private insurance to first pay the costs upfront

and then later submit for reimbursement or requiring individuals covered by Medicare and Medicaid to travel to designated healthcare clinics to access the tests for free. Would you anticipate similar hurdles if naloxone were to move to over-the-counter?

There is no connection between the recent federal program for free COVID-19 tests, and FDA's efforts regarding potential nonprescription naloxone. To our knowledge, neither the Administration nor Congress has proposed to provide free naloxone to the public. If Congress intends to propose legislation for such a program, FDA would be happy to provide technical assistance if asked. FDA does not have authority regarding reimbursement policies.

While FDA cannot predict with certainty what will happen with regard to consumer out-of-pocket costs if naloxone becomes an over-the-counter product, we can look to the history of what has happened when other types of products, (e.g., nonsedating antihistamines for allergies, and proton pump inhibitors for heartburn) have switched from prescription to nonprescription. In general, insurance companies have stopped covering the product, but overall healthcare system costs and individual costs have actually gone down. Some reasons for this reduced cost include higher volume sales reducing per unit cost; rapid market-based competition with multiple products quickly entering the nonprescription marketplace; and reduction in associated consumer costs such as doctor visits, parking, travel, and time off work with loss of income.

In addition to convenience, symptom relief, and reduction of healthcare system costs, nonprescription availability of drugs can sometimes have other public health benefits. For example, after the widespread availability of nonprescription proton pump inhibitors for heartburn, the incidence of esophageal cancer in the U.S. decreased. FDA hopes that nonprescription availability of naloxone can have the highly desired public health benefit of decreasing opioid overdose deaths.