FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D. on the agency's 2019 policy and regulatory agenda for continued action to forcefully address the tragic epidemic of opioid abuse

For Immediate Release

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Statement

The opioid crisis is one of the largest and most complex public health tragedies that our nation has ever faced. It remains the biggest public health crisis facing the FDA. The toll of addiction, in lost lives and broken families, touches every community in America. Sadly, the scope of the epidemic reflects many past mistakes and many parties who missed opportunities to stem the crisis, including the FDA.

At the FDA, we've worked to learn from past mistakes, and we intend to make sure that we're acting forcefully enough to address new threats that could extend this crisis. Addressing the opioid crisis is a top priority of the Secretary of Health and Human Services and the entire Administration. The FDA is a key part of that effort.

We're a deliberative, science-based agency. We calibrate our policy and regulatory actions carefully, based on rigorous evidence that can often take many months and even years to collect. This defines our gold standard for regulatory decisions. But given the scope of this crisis, and its human toll, we've committed to act more quickly as we confront new risks. We've changed our approach and are taking a much more aggressive approach to regulatory action. At the FDA, we've committed to taking more rapid action in the face of new threats, like the growing prevalence of illicit fentanyl that's contributing to overdose deaths, or the continued prevalence of prescriptions being written for durations of use that are too long for the clinical circumstances for which they're intended. We've changed the way we're tackling these issues and stepped up our intervention when it comes to opioids. In this epidemic, waiting for the accumulation of definitive evidence of harm left us a step behind a crisis that was evolving quickly, and sometimes furtively, in vulnerable communities that were too often being tragically ignored.

To address this crisis differently, and more definitively, we've taken decisive steps in recent years, and have additional actions already underway for 2019, with more steps planned to begin this year.

We're committed to getting ahead of this crisis. We don't want to look back five years from now, at an even larger crisis, with regret that there were more aggressive steps that we could have taken sooner. All options are on the table. Addressing this crisis is one of the FDA's top public health priorities. With this statement, I want to assess some of the steps we've taken and outline the new actions we'll be pursuing.

FDA Actions in 2018

Prescribers have a critical role to play, and we must make sure they have essential information about opioids through drug labeling. In the fall, we expanded the extended-release and long-acting (ER/LA) opioid analgesics Risk Evaluation and Mitigation Strategy (REMS) requirements to the immediate-release (IR) opioid analgesics intended for use in an outpatient setting. We've also updated the boxed warnings in the labeling for these products to include information about the REMS.

The REMS program was also expanded to require, for the first time, that training be made available to all health care providers, including nurses and pharmacists, who are involved in the management of patients with pain (in addition to doctors who prescribe these products). The content of the education was also broadened to cover information about acute and chronic pain management, safe use of opioids or other non-opioid or non-drug treatments, and material on addiction medicine and opioid use disorders.

The FDA also developed new solutions to address the unique risks of opioids in conjunction with our request for the market withdrawal of Opana ER in 2017. We will, as needed, continue to take strong regulatory steps to seek to limit or curtail access to certain drugs, based on formally assessing the risks associated with illicit use, as we did in the case of Opana ER with the risk of intravenous abuse. As part of our effort to consider the risks associated with the illicit use of opioids as one component of how we assess the overall risk and benefit of these medicines, we also worked with Congress to secure explicit authority to take action, as needed, on the basis of a consideration of these risks. This authority was included in the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act. In 2018 we also opened a dialogue around the potential for evaluating the comparative benefits and risks of new opioids relative to other opioids already on the market. Going forward we've raised the question of whether there should be such a standard for new opioid approvals to offer some advantage over the existing armamentarium. We raised this question in the context of the approval of the sufentanil product Dsuvia. We plan continue to evaluate this concept in questions that we'll ask as part of a public docket alongside a draft guidance document that we'll be issuing to modernize the FDA's framework for assessing the risks and benefits of opioid drugs.

To reduce the rate of new addiction we need to reduce exposure to opioids. This means rationalizing prescribing, which in turn means that not only must we take steps to make sure fewer prescriptions for opioids are written, but also that when these drugs are prescribed, it's for a dose and duration of use that comports closely with the clinical circumstance and the medical need of the patient. This means no more 30 tablet prescriptions for a tooth extraction. To pursue these public health goals, we're working with stakeholders like the National Academies of Science, Engineering, and Medicine to create a scientific framework for developing evidence-based prescribing guidelines that provide specific recommendations on the proper dosing and dispensing of opioids based on specific clinical indications (like outpatient surgeries).

This will help support evidence-based guidelines in areas where they do not currently exist. This report will be ready at the end of 2019. We're also conducting a review of data from product applications, in collaboration with an academic partner, to identify where adequate evidence exists to inform new guidelines. We believe there are clinical circumstances where there's already adequate evidence to create evidence-based prescribing recommendations, and we'll pursue the development of these guidelines.

In 2018, the FDA also continued work with other federal and state partners on numerous other changes started over the past several years to achieve more appropriate prescribing. Rationalizing prescribing practices by providers remains a cornerstone of our effort to reduce the rate of new addiction. And reducing the rate of new addiction is a key element of our overall approach to address this crisis. These combined actions across many federal, state, and professional entities are having an impact. Since 2015, the estimated number of opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies (which may be the most vulnerable to abuse or diversion of prescription products) have fallen by 24 percent. Notably, prescriptions of higher strength opioids (90+ morphine milligram equivalents/unit) have fallen even more steeply since 2015, accounting for less than 1 percent of all opioid analgesic units (e.g., tablets) dispensed in 2018.

Although the appropriate use of opioids from prescription claims data cannot be determined, the risk of overdose has been shown to be intertwined with increasing dose and duration of opioid analgesic use. Overall, the estimated total number of opioid analgesic prescriptions peaked in 2012, to 260 million prescriptions from 145 million in 1997. The estimated total morphine milligram equivalents (MMEs) per prescription peaked in 2010, at 950 MMEs, before falling to 905 MMEs in 2015. However, the rate of overdose death continues to increase. This is due in part to the increasing abuse of potent adulterated or illicitly manufactured fentanyl products purchased through online channels and sold as street drugs.

As the opioid crisis has evolved, so has the nature of the threat. Opioids are still too commonly prescribed and lawful prescriptions still contribute to the development of new cases of addiction. But illicit opioids are accounting for a sharply increasing fraction of the total exposure to these drugs, and fueling a growing addiction crisis. Within the scope of our work, we're especially focused on illicit online purchases. The flow of drugs on the surface and dark web has become a significant part of the epidemic relative to prescription opioids. To address the evolving nature of this threat, since 2017, we've warned a total of 23 networks operating more than 450 websites for illegally marketing potentially dangerous, unapproved, and misbranded versions of opioid medications, including tramadol and oxycodone. Cutting off this illicit internet traffic is critical. We'll continue to pursue all available means of enforcement to stop these online drug dealers.

In 2018 we also took actions to increase our interdiction work in the International Mail Facilities (IMFs). Specifically, as the nature of this epidemic has evolved to encompass greater flows and use of illicit opioid drugs, we've expanded our enforcement efforts to include increased interdiction work aimed at stopping the illegal flow of counterfeit and unapproved prescription drugs, which in numerous cases includes opioids.

The FDA expanded the capacity of import operations, made significant investments in our Office of Criminal Investigations, and our laboratories, including our Forensic Chemistry Center. These are important investments to help us identify and stop illegal drugs seeking to enter the U.S. including through the IMFs.

Over the last two months, the Office of Regulatory Affairs (ORA) and the Center for Drug Evaluation and Research (CDER) have made significant progress to stop the activities of sophisticated bad actors who attempt to evade FDA enforcement at the border.

Among these new steps, we're pleased to report that we're implementing one of the new authorities in Section 3022 of the SUPPORT Act related to restricting entrance of illicit articles containing active pharmaceutical ingredients (APIs). This new authority (new section 801(u) of the Federal Food, Drug and Cosmetic Act) allows the FDA to treat illegal imported articles as drugs when they meet certain requirements—and stop them as needed—even in the absence of certain evidence of intended use. ORA has updated its IMF procedures to support implementation of this new authority to help prevent illegal drugs from entering our country. We're also working on new tools to identify analogues of APIs that present s significant public health concern, to make sure that this important new enforcement tool against illicit drugs has its intended effect. The FDA will begin applying the new 801(u) authority to any imported product entering the U.S. via international mail which is labeled to be or contains, or is found through

laboratory analysis to be or contains, any of the ingredients identified as presenting a significant public health concern. These new steps will make our operations in the IMFs more efficient and allow us to improve our interdiction work.

By supporting appropriate opioid prescribing, education, and labeling we're reducing excess quantities of opioid analgesics available for abuse or diversion and helping to reduce the rate of new addictions from prescribed opioids. By strengthening our enforcement and inspections of packages **purchased online (https://www.hsgac.senate.gov/imo/media/doc/Combatting%20the%20Opioid%20Crisis%20-%20Exploiting%20Vulnerabilities%20in%20International%20Mail1.pdf)** and entering the U.S. from abroad, we're helping to staunch the trafficking of even more powerful and deadly drugs (**like illegal Chinese fentanyl (/NewsEvents/Testimony/ucm623895.htm)**) and address the changing nature of this crisis. By increasing the accessibility of medication-assisted treatment (MAT), and reducing stigma associated with it, we're helping those struggling with addiction to return to lives of sobriety in their communities with dignity.

These are just some of the domains that we're working across as we address this crisis using all of our tools and authorities. We know we must treat opioids very differently than other drug classes, and Congress has supported us in that effort by granting us very specific new authorities related to opioids.

FDA Actions in 2019

These are just some of the steps that we took in 2018 to address this crisis. In 2019, we plan on taking new actions to build on these efforts, and also adapt our response to confront the changing nature of the threat. We'll continue to aggressively and compassionately **pursue new efforts (/NewsEvents/Newsroom/PressAnnouncements/ucm618831.htm)** to address this tragedy.

Reducing Misuse and Abuse of Opioid Drugs

The FDA continues to have a critical and unique role to play in preventing cases of new opioid addiction – helping to reduce avoidable exposure to opioid analgesics and thereby reduce the rate of new addiction.

We're taking new steps to reduce exposure to opioid analgesics by helping to ensure that these drugs are appropriately prescribed, with dose, quantity and treatment durations that match the indication. Passage of the SUPPORT Act has provided the FDA with important new authorities to assist in our effort to reduce the risk of addiction and misuse associated with opioid analgesics. For example, the new law allows the FDA to require certain packaging be made available for opioids and other drugs that pose a serious risk of abuse or overdose if the FDA determines that such packaging may mitigate such risks. We plan to implement the initial steps to require unit of dose packaging in the first half of 2019. Specifically, the FDA is considering use of this new authority to mandate that certain solid, oral dosage forms of immediate-release formulations of opioid analgesics indicated for treatment of acute pain be made available in short-duration packaging for outpatient dispensing. Such packaging could reduce over-prescribing by giving providers a convenient option that contains only enough drug doses for up to a few days of opioid treatment at standard dosing. Our data suggests that for many acute pain indications where opioids are used, a day or two of dispensed drug is the appropriate quantity. Small quantities in blister packaging, that comport with evidence demonstrating that a day or two of medication is sufficient, could reduce the overall amount of dispensed drugs available for misuse, abuse, and diversion.

The SUPPORT Act also allows the FDA to require manufacturers to develop disposal technologies (such as a mail-back pouches) to get unused medications out of medicine cabinets. This is another new authority that we're prioritizing for work in the first half of 2019.

We're also taking new steps to consider a framework to allow us to formally evaluate each candidate opioid in the context of how a novel opioid might fit into the overall therapeutic armamentarium that's available to patients and providers, and address the question we're frequently asked as to whether new opioid drugs should offer some comparative benefit over existing drugs. This process could include seeking revisions to statutory authorities to allow us to change the weight we give to meaningful therapeutic differentiation for proposed new opioids, including relative safety or effectiveness advantages over existing treatments.

We also plan to pursue new efforts to continue to evaluate the effectiveness of REMS programs for opioid products, including methods for data collection and assessment tools. Recently, we've heard concerns around the REMS program associated with one class of opioid products, transmucosal immediate-release fentanyl (TIRF) medicines, and whether the REMS program is working as intended. This is **a topic (/NewsEvents/Newsroom/PressAnnouncements/ucm615411.htm)** that was raised by the FDA as the focus of an August 2018 public advisory committee meeting.

These products are medically important for a specific group of patients experiencing breakthrough pain that may not be managed by their around-the-clock opioid pain medicine. But these medicines also pose serious risks. That's why the agency has sought to ensure that the TIRF REMS program is achieving its public health goal of assuring safe use and mitigating the risks of misuse, abuse, addiction, overdose, and complications due to medication errors. The agency has been actively assessing the recommendations of our advisory committee on the effectiveness of the REMS and necessary changes. Based on these recommendations, and our analysis of our own data, the FDA will soon share next steps, including modifications intended to strengthen the current TIRF REMS. The prescribing of the TIRF products has decreased dramatically from peak years in 2014 and 2015. Nonetheless, substantial risks remain if these powerful drugs are not used properly and in appropriately indicated patients. The goal of the changes we will make to the TIRF REMS programs will be to make sure the program is working to mitigate the known risks of these medicines and that these drugs are being prescribed only to opioid-tolerant patients, and that those patients understand the risks and how to use TIRF medicines safely.

Support Addiction Recovery and Reduce Overdose Deaths

To help those suffering from opioid use disorder, the FDA is prioritizing new efforts to advance the development and use of safe and effective MAT. This includes new guidance aimed at supporting the development of novel medicines as well as novel medical devices such as digital health tools, advancing new policies to promote the adoption of safe and effective MAT, and working with partner organizations/stakeholders to reduce the stigma associated with MAT.

Reducing overdose deaths also requires broadening the availability of naloxone. One potential way to improve access to naloxone is to make it available for over-the-counter (OTC) sale. FDA-approved versions of naloxone currently require a prescription, which may be a barrier for people who aren't under the care of a physician or may fear a stigma associated with seeking access to the medicine or are fearful of admitting to issues with substance abuse. Having naloxone widely available, for example as an FDA-approved OTC product, would be an important public health advance, and a need that we've been working on at the FDA.

To encourage naloxone manufacturers to enter the OTC market, the FDA took an unprecedented step of developing a model Drug Facts Labels (DFL) with easy-to-understand pictograms on how to use the drug. We proactively designed, tested and validated the key labeling requirements necessary to approve an OTC version of naloxone and make it available to patients. These steps put into the public domain much of the regulatory work needed to take naloxone OTC. One of the key components for OTC availability is now in place so that sponsors can use it to obtain approval for OTC naloxone and increase its access. These efforts should jumpstart development of OTC naloxone and promote wider access to this medicine. This year we are seeking to work with industry partners who are interested in developing these OTC naloxone products.

Research and Innovation in Non-Addictive Pain Treatments

Another critical part of our efforts for 2019 is new steps to promote the development of drugs to treat pain that are not addictive. To advance these goals, in 2019, we'll be issuing updated guidance outlining the appropriate clinical endpoints and clinical trial approaches for the development of non-opioid drugs for use in the treatment of acute and chronic pain. We'll also advance new steps to promote the development of abuse-deterrent formulations of opioids by exploring new methods for analyzing and evaluating abuse-deterrent features; further evaluating the nomenclature used to describe these abuse-deterrent features; and facilitating development of science for generic versions of these products.

Strengthen Enforcement Against Illicit Opioids

The FDA will continue to strengthen its enforcement activities that target those who unlawfully market or distribute illicit opioids and other unapproved drugs. We'll step up our efforts aimed at the interdiction of opioids being illegally shipped into the United States and will continue to increase the number of investigators, both civil and criminal, in the IMFs.

Among other new steps we'll take in 2019, the FDA is working in partnership with U.S. Customs and Border Protection (CBP) to expand information sharing and maximize each agency's inspection and detection capabilities at the border to protect the public from illegal and potentially harmful products entering the U.S. This includes real-time sharing of data obtained by scientists using field-based screening tools to test samples that are seized at the IMFs and at the border. We're working closely with our partners at CBP in this program.

Right now, seizures of opioids like fentanyl are typically reported in pounds of drug product seized. But that doesn't give a full picture of the total amount of drugs that are being illegally shipped into the U.S. because these weight-based measures don't account for potency. Some of the drugs being illegally brought into the U.S. may consist of fentanyl premixes ready for pressing into tablets, while others are super-potent formulations of compounds like fentanyl. By additional testing to develop a chemical profile of more seized samples, we can develop a better picture of the illicit drug trafficking landscape, which can better inform our policy work.

We're also going to be expanding our collaboration with internet stakeholders to crack down on illicit drugs sold online. In April, we're also planning our second Online Opioid Summit. The first Online Opioid Summit held last June initiated an open and candid dialogue with key internet stakeholders to discuss ways to take robust action to reduce the availability of opioids online. Since the initial Summit was announced, internet stakeholders have taken concrete steps to prevent the illegal sale of opioids through their platforms and services. Important actions came about as a result of this collaborative dialogue with key stakeholders.

For example, Google now deindexes websites based on our warning letters that cite the unlawful sale of opioids to U.S. consumers. Social media platforms such as Facebook and Instagram redirect users who are looking to buy opioids online to the Substance Abuse and Mental Health Service Administration National Helpline. We look forward to the second Online Opioid Summit to build on these efforts with additional, innovative steps to protect the public from opioids that are illegally being sold via the internet.

As part of the 2019 budget, the FDA also received $20 million to create a large-scale data warehouse to improve our analytic capabilities to better evaluate social and clinical trends that are affecting the trajectory of the opioid crisis. This warehouse can facilitate data analytics, including machine learning algorithms, to help better assess vulnerability points in the population through predictive analytics, identify early trends that may be contributing to the epidemic, and target early regulatory changes to address the changing opioid epidemic.

Finally, as part of our effort to clamp down on illicit sales of opioids – which includes our work to close down illegal portals on the internet and expand our presence in the IMFs – we're also doing more to secure the legitimate supply chain. This means doing more to hold distributors responsible for securing the drug supply chain. As part of this effort, we recently **announced (/NewsEvents/Newsroom/PressAnnouncements/ucm631195.htm)** that the FDA issued its first warning letter under the Drug Supply Chain Security Act (DSCSA) to **McKesson Corp (/ICECI/EnforcementActions/WarningLetters/ucm631088.htm)**. for violations highlighted by a concerning tampering incident that involved opioid medications. Under the DSCSA, manufacturers, repackagers, wholesale distributors and dispensers – which are mainly pharmacies – are all required to have systems and processes in place to quarantine and investigate suspect and illegitimate medications. These systems must be in place to respond rapidly to notifications of illegitimate products and to notify trading partners and the FDA when illegitimate products are discovered. The warning letter to McKesson outlines violations observed during **inspections (/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM616533.pdf)** that took place this past summer, including failing to: sufficiently respond to notifications that there was illegitimate product in their supply chain; quarantine and investigate suspect products; and maintain records of investigations of suspect product and disposition of illegitimate product as the law requires. This action is part of a broader policy effort to improve the security of the drug supply chain and prevent diversion of opioids. We'll continue efforts to ensure manufacturers, repackagers, wholesale distributors, dispensers and others responsible for maintaining the supply chain are taking measurable steps under the law to appropriately track and trace opioid medications as these products move through the supply chain, and to respond to incidents involving illegitimate products to protect the public health.

These are just some of the new steps we'll advance in 2019 as we continue to confront this crisis. Looking back across modern times, this is perhaps the biggest public health tragedy ever created through the deliberate actions of people. The opioid crisis took hold over the course of decades of action and inaction. Now, its scope is so large, and so devastating, its toll is self-evident. It will, unfortunately, take years of aggressive action to reverse its course for good. We won't lose our focus on this fight.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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