Food and Drug Administration responses to Questions for the Record
Committee on Energy and Commerce
October 25, 2017 hearing entitled "Federal Efforts to Combat the Opioid Crisis: A Status Update on CARA and Other Initiatives"

The Honorable Michael C. Burgess

1. **As we continue to treat those addicted to opioids, we must also prevent new patients from abusing pain medication, which often leads to addiction. Opioids with abuse-deterrent formulations (ADFs) help deter opioid misuse. Do you agree that abuse-deterrent technology has a role to play in addressing the opioid crisis?**

As we continue to confront the staggering human and economic toll from opioid abuse and addiction, we are focused on taking actions that reduce the scope of new addiction by decreasing unnecessary exposure to opioids. At the same time, we also must take steps to help those with acute and chronic pain who need access to medicines, including opioids, get access to improved alternatives. Until we are able to find new non-opioid forms of pain management for those who need treatment for pain, it is critical that we also continue to promote the development of opioids that are harder to manipulate and abuse, and take steps to encourage their use over opioids that do not offer any form of abuse deterrence.

2. **The FDA's Opioid Action Plan calls for accelerating prescribers' uptake of opioids with abuse-deterrent formulations. Impediments such as prior authorization, formulary placement, non-medical switching and "fail first" policies can prevent patients from accessing abuse-deterrent formulations and are counterproductive to addressing opioid abuse prevention. Several states such as West Virginia, Massachusetts, Florida, Maryland, and Maine, have recognized the benefits of abuse-deterrent opioids and passed laws to remove formulary barriers to these drugs.**

    a. **What is the federal government doing to ensure that providers have access to abuse-deterrent products when appropriate?**

    FDA supports the development of opioid drugs that have progressively more-effective abuse-deterrent formulations to reduce the opportunity for manipulation and abuse, and is taking a number of new steps to advance the opportunity for abuse deterrent formulations of opioid drugs to become a more viable alternative to formulations that are more prone to manipulation and subsequent abuse. Transitioning from the current market, dominated by conventional opioids, to one in which most opioids have abuse-deterrent properties, holds significant promise for a meaningful public health benefit.

    Recognizing the importance of generic drugs to ensure patient access, FDA also must lay out a viable path for the entry of generic versions of abuse deterrent drugs. The Agency recently issued a final guidance to assist industry in their development of generic versions of

approved ADF opioids. This guidance includes new recommendations about the type of studies companies should conduct to demonstrate that the generic drug is no less abuse-deterrent than its brand-name counterpart. We are also taking additional steps beyond the new guidance to help developers of generic ADFs navigate the regulatory path to market as quickly as possible and make the review process more efficient and predictable. For example, we are developing appropriate, improved testing methodologies for evaluating complex features like abuse deterrence for both brand name (innovator) and generic opioid drug products. In addition, we are also taking a flexible, adaptive approach to the evaluation and labeling of ADF opioids.

b. Should all patients have access to abuse-deterrent technology at parity with other opioids?

Although insurance companies and other payors often rely in part on FDA's approval of medications in making their coverage decisions, the Agency does not have authority to intervene in such decisions.

The Honorable Joe Barton

1. The techniques for managing acute pain are different from the techniques for managing chronic pain. In fact, some specialties, like dentistry, rarely (if ever) have to treat patients for chronic pain. Even the types of opioids that would be prescribed—long acting versus short acting—are different. The CDC guideline and the current FDA REMS strategy have both focused on managing chronic pain, but what are you doing to help promote more judicious prescribing among those who are not in the business of managing chronic pain?

To reduce the rate of new opioid addiction, we need to decrease overall exposure to opioids for both acute and chronic pain. This means using our regulatory authorities to address how opioids are prescribed. We need to make sure that only appropriately indicated patients are prescribed opioids, and that the prescriptions are written for durations and doses that properly match the clinical reason for which the drug is being prescribed in the first place.

Given what we already know about the scope of current prescribing, and the subsequent patterns of abuse, it is clear that there should be fewer prescriptions being written for opioids. When opioids are prescribed, more of these prescriptions should be written for shorter durations of use. I believe there are still too many thirty-day prescriptions being written for conditions like dental procedures or minor surgery, which should require very short-term use, if they require an opioid prescription at all. Therefore, we are exploring whether FDA should take additional steps to make sure that general prescribing, and the number of opioid doses that an individual patient can be dispensed, is more closely tailored to the medical indication.

Among other steps, FDA is soliciting public input on these questions. The Agency is exploring whether and how it should use its authorities to better address issues related to prescribing and dispensing, as part of the HHS Opioid Strategy to advance the practice of pain management.

2. **What are you doing to promote the delivery of preventive services that help to control acute pain and stop such pain from becoming chronic?**

As part of the HHS Opioid Strategy to support cutting-edge research on pain and addiction and to advance the practice of pain management, FDA is committed to working with sponsors and with researchers who are developing non-opioid and non-addictive pain medications to bring these new options to patients as expeditiously as possible. FDA has a number of programs, such as Fast Track and Breakthrough Therapy Designation, which are intended to facilitate the development and review of products that, for example, are intended to treat a serious condition for which there is an unmet medical need. Novel non-opioid medications with the potential to provide effective pain relief, and that satisfy the applicable legal criteria, may be appropriate candidates for such programs. We have issued Fast Track Designation for more than 30 non-opioid analgesics and Breakthrough Therapy Designation for 12 non-opioid analgesics.

The Honorable Gus Bilirakis

1. **Many patients who suffer from opioid addiction also have other co-morbidities that require the use of other medications and medical devices. As a result, care coordination can play a major role in helping stem drug abuse but also promote basic medical safety.**

   a. **In what ways is data currently being used to advance this end?**

   FDA collects post-market safety data that can include information about other medications patients may be using along with the drug in question, and this information may be used to better educate patients and providers about the benefits and risks of using a drug in combination with another drug. As an example of ongoing data collection, FDA has required post-marketing studies of the holders of new drug applications for extended-release and long-acting (ER/LA) opioid analgesics. These NDA holders are currently conducting a series of ten observational studies and one clinical trial to provide data to better understand the risks of misuse, abuse, addiction, overdose, and death associated with long-term opioid analgesic use in patients prescribed ER/LA opioid analgesics. Risk factors for these adverse outcomes, which can include co-morbidities and other prescribed medications, will also be examined in these studies. FDA expects to have the data from these studies and trial by early or mid-2020.

   b. **In what role can interoperability of medical devices and the systems to which they report play in increasing safety and efficiency in patient care?**

The ability of devices to communicate effectively with other devices while providing clear and useful information to users is a major component of device safety and efficiency of patient care. Interoperability in healthcare has the potential to encourage innovation and facilitate new models of health care delivery by promoting the availability and sharing of information across systems even when products from different manufacturers are used. Interoperable devices can improve patient care, reduce errors and adverse events, and encourage innovation. FDA supports interoperability when data can be exchanged between devices safely and securely.

FDA recently issued a guidance document titled "Design Considerations and Premarket Submission Recommendations for Interoperable Medical Devices" that outlines our current thinking on how device manufacturers should consider interoperability when designing a device. With respect to interoperability, we recommend device developers consider the type of data being exchanged, anticipated users, how to mitigate any risks identified, how best to label a device intended to be used in an interoperable setting, how to verify and validate data exchanges work correctly, how to label an interoperable device, and the use of standards. FDA has a robust standards program that has supported the use of standards related to interoperability. In 2013, we recognized an initial set of standards manufacturers could use to improve patient care by making sure devices work well together. We have since recognized additional standards related to interoperability and encourage their development and use.

More broadly, FDA is participating in the development of the National Evaluation System for health Technology (abbreviated as NEST), which will link various sources of data collected as part of routine clinical care—including data from electronic health records, medical claims, and medical device registries—to improve the quantity and quality of information that can be used to support decision-making by a variety of medical device users and evaluators. FDA can use such information to support decisions related to marketing and surveillance of medical devices; insurance companies can use such information to support coverage and payment decisions; hospitals can use such information to support quality improvement activities; and device manufacturers can use such information to support a new or revised indication for a new or existing product. NEST will support interoperability by harmonizing data that are collected from devices and data about how devices are used.

2. **Many patients who suffer from opioid addiction also have other co-morbidities that require the use of other medications and medical devices. As a result, care coordination can play a major role in helping stem drug abuse but also promote basic medical safety.**

   a. **In what ways is data currently being used to advance this end?**

      See response to 1a

   b. **In what role can interoperability of medical devices and the systems to which they report play in increasing safety and efficiency in patient care?**

See response to 1b

3. **Last August, FDA authored a blog post titled: "FDA Supports Greater Access to Naloxone to Help Reduce Opioid Overdose Deaths." Can you provide this Committee with an update on the development of an over-the-counter version of naloxone?**

Prevention and treatment of opioid overdose is an urgent public health priority, and FDA recognizes the need to improve access to naloxone for the emergency treatment of known or suspected overdoses until emergency medical help arrives. As part of the HHS Opioid Strategy, the Agency is focusing on: 1) expanding the utilization of naloxone; 2) accelerating the development and availability of new naloxone formulations and user friendly products; and 3) identifying and disseminating the best practice naloxone delivery models and strategies. FDA is reviewing options, including over-the-counter (OTC) availability, to make naloxone more accessible to treat opioid overdoses, building on the Agency's recent approval of intranasal naloxone. To lay the groundwork for naloxone to be available more broadly, FDA is supporting research to facilitate the development of labeling for a potential OTC version of naloxone aimed at encouraging manufacturers to develop OTC naloxone products. In addition, FDA has contacted every maker of an approved naloxone product and offered to meet with them to discuss the OTC process, and several have taken us up on this offer.

The Honorable Chris Collins

1. **The opioid epidemic is a serious public health crisis, but the FDA has not prioritized non- opioid pain medications in the same way as antibiotics to treat drug-resistant bacteria. The Generating Antibiotic Incentives Now (GAIN) Act passed in 2012 to spur the development of new antibiotics to fight drug-resistant bacteria in hospitals and communities gave the FDA a path to qualify infectious disease products for Fast Track Designation and Priority Review. In 2013, the CDC estimated that 23,000 die each year due to resistant infections. In 2015, a total of 33,091 persons in the United States died from drug overdoses involving opioids and yet similar actions have not been taken.**

   a. **Has the agency considered taking the same approach with the opioid epidemic?**

FDA is committed to working with sponsors and with researchers who are developing non-opioid and non-addictive pain medications to bring these new options to patients as expeditiously as possible. FDA has a number of programs, such as Fast Track and Breakthrough Therapy Designation, which are intended to facilitate the development and review of products that, for example, are intended to treat a serious condition for which there is an unmet medical need. Novel non-opioid medications with the potential to provide effective pain relief, and that satisfy the applicable required criteria, may be appropriate candidates for such programs. We have issued Fast Track Designation for more than 30 non-opioid analgesics and Breakthrough Therapy Designation for 12 non-opioid analgesics.

2. **The opioid epidemic is a serious public health crisis, but the FDA has not prioritized non- opioid pain medications in the same way as antibiotics to treat drug-resistant bacteria. The Generating Antibiotic Incentives Now (GAIN) Act passed in 2012 to spur the development of new antibiotics to fight drug-resistant bacteria in hospitals and communities gave the FDA a path to qualify infectious disease products for Fast Track Designation and Priority Review. In 2013, the CDC estimated that 23,000 die each year due to resistant infections. In 2015, a total of 33,091 persons in the United States died from drug overdoses involving opioids and yet similar actions have not been taken. Has the agency considered taking the same approach with the opioid epidemic?**

See response to 1

The Honorable David McKinley

1. **Police, fire fighters, and other emergency personnel are the first to arrive on an opioids-related scene. These professionals are there to protect us, but they are at risk of being exposed to potent opioids and their synthetic analogues, such as fentanyl and carfentanyl. What's being done to protect these first responders, what more can be done, and what do you need from Congress?**

FDA recognizes the need to improve access to naloxone for the emergency treatment of known or suspected overdoses and accidental exposure until emergency medical help arrives. The Agency is focusing on: 1) expanding the utilization of naloxone; 2) accelerating the development and availability of new naloxone formulations and user friendly products; and 3) identifying and disseminating the best practice naloxone delivery models and strategies. FDA is reviewing options, including over-the-counter (OTC) availability, to make naloxone more accessible to treat opioid overdoses, building on the Agency's recent approval of intranasal naloxone. FDA is facilitating the development of labeling for a potential OTC version of naloxone, which is currently only available by prescription.

To help facilitate the potential availability of OTC naloxone, FDA has developed a draft model naloxone drug facts label (DFL) and an accompanying simple pictogram that would be placed next to the DFL to correspond with the DFL directions, and FDA has initiated label comprehension testing to determine whether consumers can easily understand the information. This study is currently ongoing.

In addition, HHS contributed to the development of the Fentanyl Safety Guidance for First Responders that was released in Fall 2017, which is available here: *https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final%20STANDARD%20size%20of%20Fentanyl%20Safety%20Recommendations%20for%20First%20Respond....pdf*.

2. **Dr. Gottlieb, your testimony describes significant efforts by the FDA to address the opioid crisis in the US, including encouraging use of non-addictive forms of pain management. Yet, the FDA announced in a press release dated January 14, 2014 that the agency would take regulatory action to restrict access to OTC acetaminophen to prevent inadvertent overdose, despite the fact that half of Americans are contraindicated for non- steroidal anti-inflammatory drugs (NSAIDs) and may only take acetaminophen. Given the need to respond to the opioid crisis with non-addictive treatment options for patients, does FDA still intend to take regulatory action limiting access to OTC acetaminophen?**

Yes, FDA remains focused on helping to ensure safe use of acetaminophen in adults and children. To achieve this goal, FDA is working on a proposed rule intended to reduce the recommended daily adult dose of acetaminophen in OTC pain relief products consistent with the previous action for prescription combination drug products containing acetaminophen to a dose that is still effective for pain relief, but will reduce the likelihood of liver damage. Acetaminophen is currently the most common cause of drug-induced liver injury in the US.

FDA also is working on a proposed rule addressing acetaminophen dosing instructions in the labeling of OTC acetaminophen products for children that are based upon weight as well as age to reduce unintentional overdose. FDA has previously issued guidance recommending that the concentration of single-ingredient liquid acetaminophen products used in children be standardized to reduce dosing errors and to require warning statements on the labels of acetaminophen-containing prescription drugs to let consumers know that rare but serious skin reactions may occur with acetaminophen. In addition, manufacturers of OTC acetaminophen-containing products have voluntarily implemented safety-related changes to their labeling.

While working on rulemaking on these issues, FDA has provided public advisories and guidance to industry to make the public and drug manufacturers aware of the risks discussed above. FDA has also worked to educate consumers about the risks of taking multiple acetaminophen-containing products at the same time.

3. **Dr. Gottlieb, as you know, over-the-counter (OTC) pain relievers taken as directed provide a safe and non-addictive alternative to the use of opioids. Advocates for patients that can only take acetaminophen to manage pain and for whom non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated are aware of the importance of balancing the need for OTC pain relief options with education on safe use of these medications and awareness of all pharmacologic and nonpharmacologic pain relief options as part of their pain management plan. What is the FDA currently doing to educate both providers and patients living with pain about the safe use of OTC pain relief options, as well as other safe and effective pain management options, and to make these materials easily accessible and interpretable by these populations?**

FDA supports expanded availability of safe nonprescription pain relievers as alternatives to opioids. Beginning with the labels of products that contain these pain relievers which clearly lay out their efficacy, FDA works both to inform the public of information on safe use of currently available nonprescription pain relievers, and to support industry efforts to develop new and improved OTC pain relievers.

FDA continually monitors safety reports and medical literature pertaining to OTC pain medicines; meets frequently with sponsors of current and potential OTC pain relievers to give these manufacturers advice and support for development programs for new and improved OTC pain relievers; and routinely updates Drug Facts labeling and issues communications to providers and consumers on important safety topics.

4. **As you know, over-the-counter (OTC) pain relievers can serve as safe and non-addictive alternatives to opioids. It's important that patients are aware of all options as part of their pain management plan. What is the FDA currently doing to educate both providers and patients about the safe use of OTC pain relief options, as well as other safe and effective pain management options, and to make these materials easily accessible and interpretable by these populations?**

See response to 3

5. **Your testimony describes significant efforts by the FDA to address the opioid crisis in the US, including encouraging use of non-addictive forms of pain management. Yet, the FDA announced in a press release dated January 14, 2014 that the agency would take regulatory action to restrict access to OTC acetaminophen to prevent inadvertent overdose, despite the fact that half of Americans are contraindicated for non-steroidal anti-inflammatory drugs (NSAIDs) and may only take acetaminophen. Given the need to respond to the opioid crisis with non-addictive treatment options for patients, does FDA still intend to take regulatory action limiting access to OTC acetaminophen?**

See response to 2

<u>The Honorable Buddy Carter</u>

On June 13th, the FDA put out a release titled "Statement from FDA Commissioner Scott Gottlieb, M.D. – FDA is taking new steps to help assess opioid drugs with abuse-deterrent properties." This is part of their commitment to take actions on opioids.

1. **The FDA released a statement in June focusing on ways to deter opioid abuse and in that announcement. What are you doing to pursue those actions and combat opioid abuse?**

FDA continues to have an important role to play in addressing this crisis under the five-point HHS Opioid Strategy. Among other efforts, some of the steps we are initially focused on relate to three broad areas. First, lowering overall exposure to opioid drugs and, in turn, reducing the number of new cases of addiction. Second, enabling more opportunities for those currently addicted to opioid drugs to seek medication-assisted treatment (MAT) – the use of medication combined with counseling and behavioral therapies – that can help them recover. And third, helping to expedite the development of progressively more-effective abuse deterrent formulations of opioid drugs, and better still, non-opioid alternatives for the treatment of pain. Some examples of the actions FDA is taking to address the crisis include:

We are committed to making sure that FDA's decisions to approve new opioid drugs, as well as decisions related to how we evaluate the post-market safety of currently marketed medicines, are made within a benefit-risk framework that considers not only the outcomes of opioids when used as prescribed, but also the public health effects of the inappropriate use of these drugs.

FDA supports the development of opioid drugs that have progressively more-effective abuse-deterrent formulations to reduce the opportunity for manipulation and abuse, and is taking a number of new steps to advance the opportunity for abuse deterrent formulations of opioid drugs to become a more viable alternative to formulations that are more prone to manipulation and subsequent abuse. Transitioning from the current market, dominated by conventional opioids, to one in which most opioids have abuse-deterrent properties, holds significant promise for a meaningful public health benefit.

FDA is committed to using all of the Agency's authorities to advance both non-addictive and non-pharmacologic treatments for pain,. This includes programs such as the Fast Track and Breakthrough Designations that are intended to facilitate development and to expedite review of products that, for example, are intended to treat a serious condition for which there is an unmet medical need. We are working to provide additional guidance to innovators who are pursuing non-opioid alternatives for the treatment of pain. Our steps also include a more careful consideration of non-drug alternatives for pain, such as medical devices that can deliver more localized analgesia.

To reduce the rate of new opioid addiction, we need to decrease overall exposure to opioids. This means using our regulatory authorities to address how opioids are prescribed. We need to make sure that only appropriately indicated patients are prescribed opioids, and that the prescriptions are written for durations and doses that properly match the clinical reason for which the drug is being prescribed in the first place. We are exploring whether FDA should take additional steps to make sure that general prescribing, and the number of opioid doses that an individual patient can be dispensed, is more closely tailored to the medical indication.

FDA is updating the existing Risk Evaluation and Mitigation Strategy (REMS) on extended release opioid analgesics, and for the first time, extending these same regulatory requirements (including prescriber training) to the manufacturers of IR opioid analgesic products. The new,

updated REMS will include modifications to FDA's existing Blueprint for prescriber education to broaden information on pain management, including the principles of acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic).

FDA's Opioid Policy Steering Committee is also considering whether there are circumstances when FDA should require some form of mandatory education for health care professionals, and how the agency would pursue such a goal, and the agency has issued a public notice to solicit input on a detailed series of questions related to these goals.

2. You announced that you would be engaging with "external thought leaders." What were the results of that meeting?

The public workshop held on July 10-11, 2017, involved discussion on a central question related to opioid medications with abuse-deterrent properties: do we have the right information to determine whether these products are having their intended impact on limiting abuse and helping to curb the epidemic? We recognize that the science of abuse deterrence is relatively new. Both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. That is why we are also focusing our efforts on determining how effective the current abuse-deterrent products are in the real-world setting and better understanding the attitudes and beliefs of health care professionals and those who are prescribed these products. While these innovative formulations are designed to make it harder for people to manipulate the opioid drug so they cannot be abused, it is important that prescribers and patients understand that these drugs are not "abuse-proof," and they do not prevent addiction, overdose, or death. To address these issues, among other steps, we are currently conducting a study to evaluate whether the nomenclature we use to describe these drugs, by labeling them "abuse deterrent," is accurately conveying their benefits.

<u>The Honorable Ryan Costello</u>

1. What effect will increased patient access to medical technologies have on limiting long-term opioid therapies?

Medical devices have a potential role both in pain management and in treating opioid use disorders. Depending on the cause of the pain, FDA-approved or cleared devices may offer an alternative or adjunct to treatment with opioids or other analgesics, and FDA encourages physicians to consider the needs of the patient and whether an appropriate device should be used as part of a patient's treatment plan.

FDA is committed to working with clinical investigators and companies to bring novel technologies to market for the treatment of pain as an alternative to opioids or to treat opioid use disorder.

2. **What are the current policies of CMS, Tricare, and commercial insurance carriers when evaluating surgical procedures and medical technologies? Is opioid use reduction part of that evaluation process?**

FDA defers to CMS.

3. **What statutes exist that require clarity and transparency into the levels of evidence required for positive payer policies for medical technologies, surgical procedures, and medical interventions? Can statutes be developed and implemented that would standardize these requirements?**

FDA defers to CMS.

The Honorable Pete Olson

1. **Of the grant funding provided for in CARA, how much funding has been allocated to state prescription drug monitoring programs (PDMPs)? Do you think states need additional federal grant funding to improve their PDMP or to fund clinical workflow integrations?**

FDA defers to SAMHSA or other components of HHS.

The Honorable Bill Johnson

1. **Innovative non-opioid treatments for pain are being developed that can prevent addiction before it starts. How is the FDA working to accelerate approval of such treatments? How can we better align the approval process with federal reimbursement policies for approved innovative medications and devices, so that once new treatments are approved, patients are not barred from accessing them because they are not covered by Medicare?**

FDA is committed to working with sponsors and with researchers who are developing non-opioid and non-addictive pain medications to bring these new options to patients as expeditiously as possible. FDA has a number of programs, such as Fast Track and Breakthrough Therapy Designation, which are intended to facilitate the development and review of products that, for example, are intended to treat a serious condition for which there is an unmet medical need. Novel non-opioid medications with the potential to provide effective pain relief, and that satisfy the applicable legal criteria, may be appropriate candidates for such programs. We have issued Fast Track Designation for more than 30 non-opioid analgesics and Breakthrough Therapy Designation for 12 non-opioid analgesics.

Although insurance companies and other payors often rely in part on FDA's approval of medications in making their coverage decisions, the Agency does not have authority to intervene in such decisions.

2. **You've been supportive of abuse-deterrent technologies as one means of deterring early users from progressing to more dangerous methods of consuming prescription drugs, and CARA encouraged FDA to enhance development and approval of abuse-deterrent formulations. However, even though 60% of all branded, extended-release, long-acting opioids have an abuse-deterrent formulation, virtually all of those prescriptions involve one specific opioid product – Oxycodone. When will the FDA update its existing Branded Guidance and publish product guidance for Generic abuse-deterrent formulations to incentivize additional product designs and generics, which may be as effective and less costly?**

Transitioning from the current market, dominated by conventional opioids, to one in which most opioids have abuse-deterrent properties, holds significant promise for a meaningful public health benefit. But to transition this market more quickly to the ADFs, and consider permanently withdrawing the older formulations that lack abuse-deterrent features in the event these products were judged to be less safe – there are a number of factors we must consider. One of the factors that the FDA would consider relates to generic access. We must have the potential to improve access to the newer formulations, for appropriately selected and monitored patients, through the introduction of generic competitors or else the market could be left without sufficient supplies to meet market demand.

In order to support this transition and encourage advancements in this area, in November 2017, the FDA issued a final guidance to assist industry in their development of generic versions of approved ADF opioids. This guidance (available at *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf*) includes new recommendations about the type of studies companies should conduct to demonstrate that the generic drug is no less abuse-deterrent than its brand-name counterpart.

The final guidance for industry entitled "Abuse-Deterrent Opioids — Evaluation and Labeling" was issued in April 2015 *(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf*). We periodically assess the need for updated or revised guidance for industry and may update this guidance in the future if appropriate.

3. **Dr. Gottlieb, I introduced legislation, with my colleague on this committee Doris Matsui, to address teen abuse of DXM, the active ingredient in most cough medicines, by prohibiting sales to people under 18. Will you commit to working with us to advance this policy?**

HHS will be happy to provide technical assistance on the bill if requested.

The Honorable Richard Hudson

1. **FDA has proposed streamlining of the drug approval process for discovery in the area of Pain Management. What efficiencies could be gained by a standardized data and analytics platform that was the same as the submission standard?**

The availability of a standardized data and analytics platform could make analyses more efficient, but the review of data is not often a limiting factor in the drug approval process. Such standardization would improve the ability to look at data across different products to look for similarities and differences that may have clinical relevance.

The Honorable Susan Brooks

1. **I have heard you say that preventing drug use before it begins is the is the most cost-effective way to reduce drug use and its consequences. In your opinion, what are the characteristics of successful prevention intervention programs? Besides lack of resources, what are the barriers to implementing intervention programs?**

FDA defers to SAMHSA or other components of HHS.

The Honorable Ben Ray Lujan

Addressing the opioid epidemic is going to require a multi-faceted approach. We cannot cure opioid addiction through law enforcement or treatment alone. We must also work to address the problem at the start. This means we should also be adopting policies and practices to reduce the amount of opioids that are available in circulation, and educating health care providers on opioids, pain management, and non-opioid pain alternatives.

Approximately 80 percent of the legal global opioid supply is consumed in the United States. Based on 2015 sales, the top five opioid products were made by Purdue Pharma, Johnson & Johnson, Insys Therapeutics, Mylan and Depomed, according to sales. A 2016 survey by the National Safety Council revealed that about 99 percent of physicians exceed the recommended three-day dosage limit, with a quarter of them writing prescriptions for a full month and thus overprescribing these types of medications.

Members of this Committee have called for additional prescriber education and training to this effect and I want to learn more about what role FDA and DEA can play in this process.

1. **Dr. Gottlieb, you recently announced that the FDA is taking the step to require immediate release opioid formulations be subject to the more stringent Risk Evaluation and Mitigation Strategy (REMS) program that extended release and long-acting opioid**

formulations are subject to today. The REMS for these products requires that training be available to health care providers. Will you walk us through the REMS requirements for these products, and specifically discuss the training that is available to health care practitioners under the REMS?

Since 2012, manufacturers of extended release and long-acting (ER/LA) opioid analgesics have been subject to a REMS, which requires, as its primary component, that training be made available to prescribers of those products. To meet this requirement, the sponsors of the ER/LA opioid analgesics have been providing unrestricted grants to accredited continuing education providers for the development of education courses for health care professionals based on content outlined by FDA, which the agency calls the "Blueprint." FDA is now extending these REMS requirements to the immediate release (IR) manufacturers.

While some of the ER/LA manufacturers also make IR opioids, this action will greatly expand the number of products covered by the REMS. The existing REMS currently includes 64 ER/LA opioid analgesic products. Once the action is finalized, an additional 277 IR opioid analgesics will be subject to these REMS requirements.

In addition to expanding the REMS to include IR products, FDA is modifying the content of the educational "Blueprint" required under the REMS. The agency is adding content on pain management, including non-opioid alternatives. This includes principles related to the acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). The revised Blueprint will also cover information about the safe use of opioids, and basic information about addiction medicine and opioid use disorders.

For the first time, this training will also be made available to other health care professionals who are involved in the management of patients with pain, including nurses and pharmacists, which is in addition to prescribers of opioid analgesics. FDA believes that all health care professionals involved in the management of patients with pain should be educated about the safe use of opioids so that when they write or dispense a prescription for an opioid analgesic, or monitor patients receiving an opioid analgesic, they can help ensure that the product is properly indicated for the patient and used under appropriate clinical care.

2. **Is training under the REMS mandatory for health care practitioners today?**

Currently, this training is not mandatory for health care practitioners.

3. **Can you give us a sense of how many health care practitioners have voluntarily participated in the training available under the REMS?**

As of 2/28/2017[1] there have been 430,859 health care practitioner participants in the training available under the ER/LA REMS. Of these participants, 208,040 completed all components of an educational activity and met the education provider's criteria for passing. Of the participants who completed all components of an education activity and met the education provider's criteria for passing, 88,316 were individual clinician participants who were registered with the DEA to prescribe schedule II and/or III controlled substances and who wrote at least one ER/LA opioid prescription in the past year.

4. I understand that FDA is considering whether mandatory education might be appropriate. Dr. Gottlieb, what are your thoughts on mandatory training? Is this something that you would support, and if so, how would FDA operationalize such a requirement?

FDA's Opioid Policy Steering Committee is considering whether there are circumstances when FDA should require some form of mandatory education for health care professionals, and how the agency would pursue such a goal. The agency's purpose is to reduce overall exposure to opioids by making certain that prescribing doctors are properly informed about appropriate prescribing recommendations, that providers understand how to identify the risk of abuse in individual patients, and know how to get addicted patients into treatment. The agency has issued a public notice to solicit input on a detailed series of questions related to these goals. FDA has also been scheduling meetings with provider organizations and sponsors engaged in dispensing drugs – including health systems and pharmacy chains, in an effort to solicit additional input on new strategies.

In 2015, 33,000 Americans died from opioids. According to the CDC, almost half of those deaths were from prescription opioids. The New York Times reports that in 2016, overdoses from all drugs was the leading cause of death of people under the age of 50. Drug overdoses now kill more Americans each year than at the height of the HIV epidemic and the worst year for auto accident deaths. The Times and drug use experts attribute the sharp rise in all drug overdose deaths to the rise of opioids. What we need to fight this epidemic is continued and reliable long- term investments in prevention, treatment, recovery, and monitoring.

The President's budget proposal for fiscal year 2018, coupled with other administration initiatives, takes several steps back in the fight against opioid addiction, including a cut in funds for SAMHSA. Overall, the President's proposed budget cuts HHS by 16.2 percent, the CDC by 17 percent and NIH by 19 percent. It cuts funding for addiction research, treatment and prevention. Even the White House Office on National Drug Control Policy would take a 95 percent hit.

[1] Quarterly update data is unaudited and provided by CE providers directly to the REMS Program Companies (RPC). Collection and reporting of participants and completers is not required by the REMS Implementation Guidelines.

5. **Commissioner Gottlieb, do you have all of the tools you need to stop the opioid epidemic?**

FDA intends to take whatever steps we can, under our existing legal authorities, to ensure that exposure to opioids is occurring under appropriate clinical circumstances, and for appropriate patients.

6. **Commissioner Gottlieb, given the 31 percent cuts to FDA in the President's budget proposal, what programs relating to the opioid epidemic will be cut? Which programs would have been expanded that will now not be?**

FDA is committed to addressing the opioids crisis using all available tools and strategies, and will continue to work with Congress to ensure we have adequate resources to carry out our mission.

Opioid addiction is not a new problem. Misuse of and addiction to pharmaceuticals has existed for centuries, ever since morphine was heralded in the 1850s as a solution to our opium addiction problem– until it, in turn, morphine became a larger problem, as did heroin, and then methadone. Today, we understand the importance of pain relieving agents, but as my constituents continue to perish at alarming rates due to these drugs, we need to be working together to address the crisis. The public and private sectors can and should work together to swiftly address the opioid epidemic. The Reagan-Udall Foundation for the FDA is an independent 501(c)(3) not-for-profit organization created by Congress for the purpose of advancing regulatory science that is necessary to helping the FDA accomplish its mission. The Foundation was created by Congress in the Food and Drug Administration Amendments Act of 2007 (FDAAA) to address regulatory science challenges of the 21st century. The central focus of the Foundation is to assist in the creation of new, applied scientific knowledge, tools, standards, and approaches the FDA needs to evaluate products more effectively, predictably, and efficiently, and thereby enhance the agency's ability to protect and promote the health of the American public.

7. **Understanding what we know now about this issue, what further information or support do you need from pharmaceutical manufacturers to more aggressively combat this crisis?**

   FDA is committed to working in partnership with industry to ensure that exposure to opioids is occurring under only appropriate clinical circumstances, and for appropriate patients. As described in the response to question 1, FDA has notified manufacturers of immediate-release opioids that they will be subject to the same REMS requirements that currently apply to extended release/long-acting opioids, including that training be made available to prescribers of these products. IR manufacturers will be required to inform prescribers and other health care providers involved in the treatment and monitoring of patients with pain

(e.g., pharmacists, nurses) of the existence of the REMS and the need to successfully complete the necessary training.

In addition, there is a critical need to encourage the development of novel treatments for chronic pain, including non-opioid alternatives, as well as new and innovative treatments for substance use disorders in order to augment our currently limited treatments. Encouraging the development of these products requires both scientific and translational development. FDA has previously, and is currently, working in these areas, including through our participation in the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership (PPP) and other PPP and consortia initiatives in a wide variety of areas relevant to pain treatment, opioids, substance use treatment, drug safety, and accelerated drug development.

8. **How are you engaging the Reagan-Udall Foundation to develop effective, innovative regulatory responses to the opioid crisis?**

FDA's partnership with the Reagan-Udall Foundation for the FDA has focused on a number of key initiatives, including the Innovation in Medical Evidence Development and Surveillance (IMEDS) Program and the Expanded Access Navigator tool. We look forward to continuing this partnership to advance FDA's vision of collaborative innovation to address regulatory science challenges of the 21st century.

There are multiple forms of opioid painkillers, including abuse-deterrent formulations (ADFs) and extended-release/long-acting (ER/LA) formulations. Now, in addition to expanding the REMS to include immediate-release (IR) products, FDA is modifying the content of the educational "Blueprint" required under the REMS. The agency is adding content on pain management, including non-opioid alternatives. The content includes principles related to the acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). The revised Blueprint will also cover information about the safe use of opioids, and basic information about addiction medicine and opioid use disorders.

But education alone will not be enough. Patients need to be able to access effective products without the risk of addiction. Non-opioid pain alternatives include biologics in the pipeline, such as fasinumab (an NGF antibody for osteoarthritis and chronic lower back pain, in Phase 3 development by Regeneron) and tanezumab (an NGF antibody for osteoarthritis and chronic lower back pain, in Phase 3 development by Pfizer and Eli Lilly). Tanezumab is the first NGF inhibitor to receive Fast Track designation from the FDA.

9. **How will you be working with the Centers for Medicare and Medicaid Services, Indian Health Services, and the Department of Veterans Affairs to arrange for inclusion in the relevant reimbursement schedules of biologics as non-opioid pain alternatives?**

Although insurance companies and other payors often rely in part on FDA's approval of medications in making their coverage decisions, the Agency does not have authority to intervene in such decisions. We defer to CMS for further information on this topic.