Committee on Energy and Commerce
Implementing the 21st Century Cures Act: An Update from FDA and NIH
November 30, 2018

FDA Questions for the Record

We have restated your questions below in bold, followed by our responses.

The Honorable Michael Burgess

1. **A goal of 21st Century Cures was to help the transition between research generated by NIH and regulated by FDA. Are there areas where this could be improved? One challenge is that NIH funds new clinical trials that may become difficult to complete because a new drug is approved mid-way through the trial for the condition being researched. Could a "memorandum of understanding" allow for pre-approval data to be shared from FDA to NIH earlier in the process to improve coordination of research and regulation?**

As public health agencies within the Department of Health and Human Services, FDA and the National Institutes of Health (NIH) may generally share with each other most information in the possession of either agency. Sharing of information between FDA and NIH is subject to prohibitions against disclosure of non-public information and must include appropriate safeguards to prevent unauthorized disclosure, which are incorporated into existing memorandums of understanding between the two agencies. That being said, FDA evaluates whether information can be disclosed on a case-by-case basis. Although FDA may be able to share certain confidential information with NIH, that information may not be able to be shared with an NIH grantee, contractor, or cooperative research and development partner. Given that NIH studies may involve commercial entities (e.g., funding or IND sponsor), it is critical for FDA to consider whether disclosure of non-public information to NIH could cause commercial harm to the applicants who submitted the information to FDA.

FDA approval of a new treatment does not generally impact the status of ongoing trials in a disease area unless the treatment provides an improved safety and/or efficacy profile relative to the investigational treatment. In those cases, it could be unethical to deprive a clinical trial participant of the opportunity to obtain the newly approved treatment. After approval of a new treatment, FDA may reach out to trial sponsors if any modifications are needed for ongoing trials to treat the same disease for which the new treatment is indicated. Often, whether the newly FDA-approved treatment is safer or more effective than an investigational treatment in an NIH-funded trial will not have been established at the time of approval; under those circumstances, it would generally be appropriate to continue conducting the trial.

2. **The Least Burdensome Provisions of the FDA Modernization Act of 1997 have been in statute for some time. This concept-that FDA should regulate medical devices in the least burdensome manner, while not sacrificing patient safety-is critical to ensuring that we have reasonable regulation, and avoid the issue of regulation for regulation's sake.**

21st Century Cures included a provision to require FDA to conduct an audit on training and use of least burdensome requirements during review of medical devices. Can you tell us what FDA has been doing to implement this section of the law?

FDA has taken several steps to implement the Least Burdensome provisions of the 21st Century Cures Act (Cures Act). As required under the Cures Act, FDA has provided training on the least burdensome requirements to all employees (including supervisors) involved in the review of device premarket submissions, and has conducted an audit of the training.

FDA has also taken steps to improve our application of the least burdensome principles more broadly. FDA believes that least burdensome principles should be widely applied across the total product lifecycle for medical devices to remove or reduce unnecessary burdens so that patients can have earlier and continued access to high-quality, safe, and effective devices and we can more effectively use our limited resources on actions that will improve the health and quality of life of patients.

In recent draft guidance, FDA defines "least burdensome" to be the minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time. The least burdensome principles are based on sound science, the letter and intent of the law, the use of alternative approaches, and the efficient use of resources to effectively address regulatory issues. FDA has significantly broadened the scope of least burdensome principles by expanding their application to all aspects of the total product life cycle for medical devices rather than just select premarket activities. Beyond the requirements of the Cures Act, FDA's Center for Devices and Radiological Health (CDRH) has required that all of its employees, not just employees involved in medical device review, receive training on the least burdensome provisions and principles. CDRH required that its entire staff be trained because it believes the least burdensome concept is foundational to its work with respect to the regulation of medical devices.

3. **Supplemental indications, or additional uses for a drug, can be added to the product label when the sponsor provides the necessary data to the FDA to support these new uses. In many cases, the FDA treats each application associated with a drug the same, whether it is the first indication or the eighth indication. Given that aspects of a drug, such as its toxicity profile, becomes better understood over time, a provision was included in 21st Century Cures to improve the efficiency of reviewing potential new uses of a drug by allowing the FDA to review summaries of data rather than internally re-analyzing the complete raw datasets themselves. I understand this is completely up to the FDA to determine when this approach is appropriate, and the review team would have access to the full data at any point. Has this provision been used? How frequently? Do you foresee instances where this can improve efficiency?**

Authority added under section 3031 of the 21st Century Cures Act provides that FDA may rely on qualified data summaries to support approval of a supplemental application for a qualified indication of a drug if certain conditions are met. FDA intends for the initial focus of FDA's

implementation of this authority to be on supplemental applications for oncology drugs. We are currently in the process of evaluating criteria for identifying supplemental applications that may qualify for this type of review and the appropriate processes for facilitating and evaluating such review.

4. Patient-focused drug development was an aspect of 21st Century Cures that garnered a significant amount of attention. The law requires the FDA to provide guidance on the use of relevant patient experience and patient input data, including with respect to the structured risk-benefit assessment framework, to inform regulatory decision making. The 21st Century Cures Act provides a timeframe of 5 years for the FDA to issue such guidance. Could you share your thoughts on the impact patient experience perspective data will have on the drug development front, particularly with respect to the risk-benefit framework?

FDA considers information from patients about what matters most to them in living with their disease to be of the utmost importance. As such, FDA conducted 24 patient-focused drug development (PFDD) meetings over the past five years. These meetings confirmed the Agency's perspective that patients are experts in what it is like to live with their disease and that drug development and patients would benefit from greater integration of patients' voices in drug development. Patients are uniquely positioned to inform FDA's assessment of the *severity of a disease condition* and the *degree of unmet medical need* based on their report of experience with currently available therapies. These are the first two of five key considerations that FDA weighs within its framework for assessing the benefit and risk of a medicine.

Patients may also be able to more formally and systematically report on their experience of benefits and risks while participating in clinical studies of investigational drugs. These reports can inform other key considerations of the benefit-risk framework: the evidence of *benefit* and *risks*, based on data collected in clinical trials, and potential approaches to *risk management* to ensure that expected benefits outweigh risks for patients taking the medicine.

Patient experience data has the potential to inform a number of aspects of drug development. These data can inform a sponsor's development of a target product profile for an investigational drug. They can inform the development of data collection instruments that will capture the patient's experience more systematically, and they can inform the development of targeted endpoints that can be used to assess therapeutic benefit. In addition, patient experience data may be collected to inform the design and planning of clinical trial operations to facilitate patient enrollment and sustained involvement in studies by making them more convenient and less burdensome for patients who participate. All of these opportunities contribute to the quality of a drug development program and the evidence collected to assess the benefit versus risk of the new medicine.

The range of potential uses of patient experience data call for a corresponding range of data collection and analysis methods that will be sufficiently rigorous to ensure the quality to achieve the desired goal of patient impact on drug development and regulatory decision making. The guidance that FDA will be developing to implement section 3002 of the 21st Century Cures Act,

will provide drug sponsors and the patient advocacy community with a set of tools to collect and utilize patient experience data that are fit for this purpose.

FDA's actions in patient-focused drug development include:

- Holding 24 PFDD meetings, each focusing on a different disease area.

- Outlining the steps FDA will take over the next five years to provide guidance on collecting patient experience data and using such data and related information in drug development. (See "Plan for Issuance of Patient-Focused Drug Development Guidance Under 21st Century Cures Act."[1])

- Developing "The Voice of the Patient: A Series of Reports from FDA's Patient-Focused Drug Development Initiative"[2] and "Voice of the Patient" blog.[3]

- Establishing a new Patient Engagement Collaborative[4] to incorporate perspectives from patients, caregivers, and advocates into the FDA's regulatory decision-making processes.

How patients feel and function in their daily lives is a crucial component of determining the risk-benefit balance in treating diseases. FDA considers patient-identified disease impacts and measures of benefit and burden as early as possible in the drug development and review processes. Improved methodologies for accurately measuring these factors will advance the ability of FDA to systematically incorporate patient feedback into the risk-benefit framework.

The Honorable Cathy McMorris Rodgers

When asked about the scope of pharmacy practice this summer, you noted that a prescription provides a "line of demarcation" defining the practice of pharmacy and that "the statute clearly defines in my mind the line of demarcation for the legitimate practice of pharmacy." This statement is consistent with the policies expressed in the guidance document entitled "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act," which states that unless a limited exception applies "to qualify for exemptions under section 503A, the drug product must be compounded after the licensed pharmacist or licensed physician receives a valid prescription order for an individual patient." Unfortunately, this view differs with FDA policies over the past two years. The agency has redefined the distribution of a sterile compounded preparation to include patient specific dispensing in the draft MOU and repackaging guidance (among other guidances). This, in my opinion, appears to run counter to the DQSA's statutory language, the Food Drug and Cosmetic Act, as well FDA's traditional interpretation of the

[1] *https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf*
[2] *https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm*.
[3] *https://blogs.fda.gov/fdavoice/index.php/2014/05/fdas-voice-of-the-patient-listening-to-those-most-affected-by-their-disease-and-treatments/*
[4] *https://blogs.fda.gov/fdavoice/index.php/2017/07/patient-reps-bringing-the-voice-of-patients-to-fda/*

definitions of "distribute" and "dispense" and will reduce access to compounded sterile preparation prescriptions.

1. **Please share with the committee your thoughts on the definitions of "dispense" and "distribute", and how you plan to align the MOU and other guidance with Congress' and your understanding of pharmacy practice.**

The proposed policy articulated in the draft standard memorandum of understanding (MOU) concerning the term "distribution" is consistent with the policy articulated in the final guidance, "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act."[5] In that guidance, the Agency explained that compounding under section 503A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) can occur either after the receipt of a valid prescription order for an identified individual patient (section 503A(a)(1)), or in limited quantities before the receipt of a valid prescription order for an identified individual patient (section 503A(a)(2)). The guidance explains that section 503A does not provide for the *distribution* of a compounded drug before, or without, receiving a valid prescription for an identified individual patient.

FDA proposed that the term "distribution" for the purposes of the draft standard MOU means that a compounded human drug product has left the facility in which the drug was compounded, which includes dispensing a drug directly to a patient. In comments regarding the draft standard MOU, some members of the pharmacist community asserted that the definition of distribution should exclude dispensing. According to these comments, this is in part because some in the pharmacist community understand distribution to refer to the shipment of compounded drug products *without* patient-specific prescriptions, and dispensing to refer to the shipment of compounded drug products *with* patient-specific prescriptions. However, to qualify for the exemptions under section 503A of the FD&C Act, a compounder must obtain a prescription for an identified individual patient (section 503A(a)). The definition of distribution in the draft standard MOU is consistent with the prescription requirement under section 503A, described in FDA's final guidance document on this subject.

We note that FDA received more than 3,000 comments on the draft standard MOU, including many comments regarding the term "distribution," and comments describing overall access concerns. FDA is taking these comments into consideration as we work diligently to issue a revised draft standard MOU in the coming months.

With respect to FDA's repackaging guidance, FDA issued the final guidance in January 2017,[6] after taking into consideration all of the public comments that it received. FDA believes that the policies articulated in this and other final guidances, including the use of the term "distribution," are in the best interest of the public health.

The Honorable Marsha Blackburn

[5] *https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf*.
[6] *https://www.fda.gov/downloads/Drugs/Guidances/UCM434174.pdf.*

1. **I was glad to speak with you back in July when you called to tell me about your implementation of my SOFTWARE Act with the Pre-Cert for Software Pilot Program and the announcement of the companies selected to participate. Could you please provide this committee with an update on the pilot program, including feedback from the nine participating companies? What lessons has the agency learned so far about how best to regulate innovative, low-risk devices and software?**

FDA has completed its initial visits to all nine pilot participants. The feedback was positive and all of the participating companies are engaged. FDA looks forward to building a program that best serves public health by fostering the development of innovative, safe, and effective digital health products. We have learned the ways in which excellent companies in the digital health space are the same and the ways in which they are different from one another. We intend to propose a streamlined, risk-based approach that capitalizes on the commonalities and allows for differences that support positive innovation. We held a public meeting in January where FDA presented its finding to date; sought other perspectives; and incorporated input from a broader set of stakeholders – including patients, providers, payers, and others in industry. .

The Honorable Ben Ray Luján

Thank you for your response on November 7, 2017, to my letter asking the Food and Drug Administration (FDA) to take concrete steps to enable and communicate the availability of safe and effective, non-opioid drug products. As you know, millions of Americans require clinical treatment for pain relief. I was glad to see that we are in agreement about the importance of combating the opioid epidemic, as you wrote in your November 7 letter. 1

In light of FDA's belief that all healthcare providers involved in the management of pain should be educated about the safe use of opioids, I would appreciate information related to the following questions:

1. **You wrote, "For the first time, FDA announced its intention to require immediate-release (IR) opioid analgesic products to be subject to the same REMS requirements." You also note that you expect the modified REMS to include revisions related to prescriber education.**

    a. **What is the agency's timeline to finalize a modified REMS? What considerations is the agency taking into account when considering changes to the education requirements related to the REMS?**

FDA expects to finalize the modified REMS approximately 1 year following issuance of the REMS Notification letters (issued September 28, 2017). FDA considered stakeholder feedback on the education component of the Opioid Analgesics REMS received:

- At the joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) held on May 3-4, 2016

- At the May 9-10, 2017, public workshop - Training Health Care Providers on Pain Management and Safe Use of Opioid Analgesics – Exploring the Path Forward
- To Docket No. FDA–2017–D–2497 - Draft Revisions to the Food and Drug Administration Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioids

Based on the stakeholder feedback, the content of the "Blueprint" for education will be expanded to include principles related to 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. The education will also be expanded to other healthcare professionals who are involved in the management of patients with pain, including nurses and pharmacists, which is in addition to prescribers of opioid analgesics.

2. **You wrote, "The new training will be aimed at making sure providers are prescribing opioids only for properly indicated patients, and only under appropriate clinical circumstances […as] part of a broader effort to take new steps to make sure providers are properly informed about suitable prescribing and the risks and benefits associated with opioid drugs.**

   a. What additional activities does FDA's broader effort include? Who within FDA is responsible for this broader effort to inform providers about suitable prescribing?

FDA's Opioid Policy Steering Committee is considering novel ways to reduce the number of new cases of opioid addiction. FDA recently held a public hearing entitled, "Opioid Policy Steering Committee: Prescribing Intervention – Exploring a Strategy for Implementation." The purpose of the public hearing was to receive stakeholder input on how FDA might, under its Risk Evaluation and Mitigation Strategy (REMS) authority, improve the safe use of opioid analgesics by curbing overprescribing to decrease the occurrence of new addictions and limit misuse and abuse of opioid analgesics.

Recent studies suggest that prescriptions for opioid analgesics are frequently dispensed for a number of tablets that exceed those needed for adequate pain control, particularly for acute pain. The Steering Committee is exploring, by means of FDA's REMS authorities, the option of facilitating appropriate prescribing by requiring sponsors to implement a prescriber intervention at the point when the prescriber determines an opioid analgesic prescription is necessary for a patient. For example, a REMS could impact prescribing by requiring that sponsors ensure that prescribers provide specific documentation for a prescription above a specified amount. Such a documentation requirement would be designed to ensure that prescribers consider whether the amount prescribed is appropriate for the patient and, if above the specified amount, document that necessity.

The Steering Committee is also considering whether to require sponsors to create a system that would leverage a nationwide database to be more effective in helping healthcare providers identify potential misuse and abuse (e.g., doctor shopping) and facilitate safe use of opioid analgesics (e.g., real-time identification of potential harmful drug-drug combinations). Such an

approach could be integrated into the healthcare provider's workflow to minimize burden on the health care system.

In addition, the Steering Committee is seeking input on whether, consistent with the Agency's statutory authority, FDA should require sponsors to take additional measures to ensure that healthcare providers, their patients, and patient caregivers and family members are educated on safe storage and disposal and the risks of misuse, abuse, and addiction associated with opioid analgesics (for example, a public health campaign targeted at these groups).

Finally, FDA is working with medical professional societies to potentially create expert guidelines about what appropriate prescribing and dispensing should be for different medical needs. These efforts align with those of the Centers for Disease Control and Prevention (CDC). If guidelines were in place and had sufficient scientific support, and FDA reviewed the scientific support for these guidelines and determined that it was sufficient to support updates to product labeling, then we could potentially use our current authority to adjust product labeling, thereby promoting more appropriate prescribing.

3. **You wrote, "There have been a small number of non-opioid drug shortages over the past few years, but there continue to be multiple alternative options available to patients."**

    a. **What are these multiple alternative options to non-opioid drugs that are available to patients? How many alternative options to non-opioid drugs are available to patients?**

Alternatives to opioids (e.g., non-opioid drugs) to treat various types of pain, along the spectrum of severity, include the following approved non-opioid products:

- NSAIDs (non-steroidal anti-inflammatory drugs) of which there are many (ibuprofen, diclofenac, ketorolac, etc.)
- duloxetine (Cymbalta) is included in the class of drugs called selective serotonin/norepinephrine reuptake inhibitors (SNRIs), and is approved for diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain
- milnacipran (Savella, also an SNRI) for fibromyalgia
- gabapentin (Neurontin, Gralise), pregabalin (Lyrica), and carbamazepine (Tegretol) (originally approved as anticonvulsants, each are indicated for treatment of specific types of neuralgia and other neuropathic pain)
- topical lidocaine (local anesthetic), and capsaicin
- ziconotide by intrathecal infusion for chronic pain.

4. **You wrote, "There are few existing classes of analgesics." In Division Director of the Division of Anesthesia, Analgesia, and Addiction Products Dr. Sharon Hertz's March 1, 2016 presentation to the FDA Science Board, she listed existing analgesics as opioids,**

nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antidepressants, local anesthetics, and "other (capsaicin and ziconotide)."[7]

a. Are these six classes a comprehensive list of existing analgesic drug classes? If not, what additional or alternative classes are there?

This list is comprehensive at this time.

5. You wrote, "Drug developers may encounter both clinical and nonclinical challenges specific to their drug development program."

a. What are some examples of clinical and nonclinical challenges that drug developers have faced?

Examples of clinical challenges include difficulty enrolling subjects, study designs, finding qualified study sites to conduct studies. An example of a nonclinical challenge is identifying appropriate pain models for study. Nonclinical models tend to be poorly predictive of clinical success in this area.

b. Is there a trend of where in the development or regulatory processes the challenges are faced?
For example, are the challenges primarily in the review or in the post-market phase?

Most challenges in the development or regulatory processes occur premarket.

c. What are some potential incentives to increase the number of non-opioid drugs in the pipeline?

Where applicable, the expedited review programs FDA has in place to aid development may apply to some non-opioid analgesics under development and can assist industry in more efficient drug development. More information about FDA's expedited review programs can be found on our website.[8]

d. Is the main challenge increasing the number of drugs entering the pipeline, or increasing the number of drugs coming out of the pipeline?

One of the biggest challenges for new analgesics is identifying new targets that have high specificity for pain pathways so that the product works, with as little affinity for non-pain targets as possible to reduce the risk of side effects. This limits the number of drugs entering

[7] Hertz, Sharon, Division of Anesthesia, Analgesia and Addiction Products, OND, CDER, FDA, "Challenge of developing new pain medicines – developing novel analgesics and abuse-deterrent formulations," March 1, 2016, *https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM489207.pdf.*

[8] *https://www.fda.gov/ForPatients/Approvals/Fast/default.htm*

the pipeline. The Agency works closely with sponsors from the earliest stages of development to provide advice based on our vast experience with analgesic drug development, to permit the most efficient development program possible, and to advance the approval and marketing of safe and effective pain drugs.

e. Do you consider FDA barriers to be clinical or nonclinical?

As discussed above, examples of clinical challenges include enrolling subjects, study designs, finding qualified study sites to conduct studies and examples of nonclinical challenges include identifying appropriate pain models for study as nonclinical models tend to be poorly predictive of clinical success in this area. These challenges for drug developers can result in both clinical and nonclinical data limitations as those developers make submissions to FDA.

6. You wrote, "The Agency is open to working with sponsors who are interested in developing new potential treatments."

Have any sponsors already asked FDA to work together to develop new potential treatments? If so, what did FDA respond?

FDA is committed to the principles of open government and transparency. At the same time, FDA must comply with its obligations to keep certain information in its possession confidential. We do not publicly release correspondence regarding potential new treatments before the approval of an application. Therefore, FDA is unable to publicly disclose specific data used in making recommendations for a particular treatment.

From a broader perspective, FDA has past and ongoing work in the development of novel treatments for pain and opioid overdose, supported through our participation in the ACTTION public private partnership (PPP)[9] 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.

- The Consortium for Addiction Research on Efficacy and Safety (CARES) is working to create consensus on the design and analysis of addiction clinical trials, which would be a valuable step towards reducing barriers to drug development.
- The Agency and the National Institute on Drug Abuse (NIDA) are discussing mechanisms to collect data to support the use of new endpoints for trials of drugs intended to treat opioid substance use disorder.
- FDA and NIDA are also working to encourage the development of non-opioid pain medications, and we have been involved in discussions hosted by the National Institutes

[9] The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks Initiative (ACTTION) aims to streamline the discovery and development process for new analgesic drug products for the benefit of the public health. This multi-year, multi-phased initiative will address major gaps in scientific information which can slow down analgesic clinical trials and analgesic drug development (see *http://www.acttion.org/*).

of Health (NIH) and the Foundation for NIH (FNIH) in a series of meetings to facilitate development of non-addictive pain treatment. These efforts will be pursued in partnership with FDA and the Centers for Medicare and Medicaid Services (CMS) to ensure that products can quickly move from discovery and development to approval and implementation in clinical practice.

- The Coalition for Accelerating Standards and Therapies (CFAST) is an initiative to accelerate clinical research and medical product development by facilitating the creation and maintenance of data standards, tools and methods for conducting research in therapeutic areas important to public health.

7. You wrote, "Moving forward, we strongly encourage manufacturers and drug developers to contact the Division of Anesthesia, Analgesia, and Addiction Products in the Center for Drug Evaluation and Research so that we can provide targeted advice specific to their drug development program."

Have any manufacturers contacted DAAAP in CDER to request targeted advice specific to their drug development programs? Has FDA provided targeted advice specific to drug development programs?

As stated above, FDA must comply with its obligations to keep certain information in its possession confidential. We do not publicly release information pertaining to anything under review until it has been approved. We encourage sponsors to contact us early and often in their drug development program and work closely with them to assure that thresholds of safety and effectiveness are addressed in submissions provided to FDA.

8. You wrote, "For more information, please see our draft guidance entitled *Analgesic Indications: Developing Drug and Biological Products,* which, when finalized, will provide the Agency's recommendations on such development."

The draft guidance was released in February 2014, "for comment purposes only." It had a 60-day comment period. Since February 2014, approximately 190,000 Americans have died due to opioid overdoses.[10] Is FDA currently in the process of finalizing the guidance? If available, when does FDA anticipate publishing the finalized guidance?

Subsequent to the release of the draft guidance, our advisory committees have provided advice about analgesic development that we have been working to translate into useful guidance for industry. We are also incorporating input from the National Academies of Sciences, Engineering, and Medicine (NASEM) 2017 report, "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use", particularly, how to frame the risk/benefit analysis to demonstrate the many public health factors that are taken into consideration when making regulatory decisions about new analgesic products. Even

[10] "1,396 days between February 2014 and November 2017; according to CDC estimates, 50,000 Americans died from an opioid overdose in 2016, which is 137 people per day, Time Magazine, "Here's what it would cost to fix the opioid crisis, according to 5 experts," *http://time.com/money/5032445/cost-fix-opioid-crisis/*".

though the draft guidance has not yet been finalized, FDA works with individual sponsors on development issues.

9. You wrote, "We have been involved in discussions with the National Institutes of Health in a series of meetings to facilitate development of non-addictive pain treatment."

What is the structure of this series of meetings? Who is the designated point person at FDA and who is the designated point person at NIH for these meetings? Can I communicate directly with those point people for the meetings? What are the goals of these meetings? Are these meetings open to the public? How many meetings are in the series? How many have already been held? How many are scheduled to occur? When do these meetings occur? Where do these meetings occur?

NIH is the lead HHS agency providing support for cutting-edge research on pain and opioid misuse, addiction, and overdose. NIH is exploring ways to work with private sector partners to promote safe, effective, non-addictive strategies to manage pain as part of a broader public-private partnership aiming to at cut the time needed to develop new therapeutics to help end the opioid crisis.[11] NIH is also exploring ways to facilitate development of additional treatments for opioid use disorder. To advance the efforts, since June 2017, NIH has held three seminal meetings with the pharmaceutical industry, researchers, FDA and other experts in pain and addiction. NIH has been in discussions with over 30 companies and FDA in a joint effort to advance this initiative. Meetings were held on December 11 and 12, 2017 to bring stakeholders together to identify areas of scientific opportunity that could be pursued in collaboration with industry partners.

10. You wrote, "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," referring to "programs, such as Fast Track and Breakthrough Therapy Designation, which are intended to facilitate the development and expedite the review of products that, for example, are intended to treat a serious condition for which there is an unmet medical need."

How many non-opioid products are currently under review for management/treatment of pain? Of the current products under review, how many/what percentage have applied for and been awarded one of these designations? Are there other tools at your disposal to move these applications through in a timely fashion? If not, what can Congress do to help? In addition to new product approvals, please describe how manufacturers can seek new indications, expanded labels and/or different concentration approvals for non-opioid products already available to patients.

As noted above, FDA must comply with its obligations to keep certain information in its possession confidential. We do not publicly release correspondence regarding potential new treatments before the approval of an application. Therefore, FDA is unable to publicly disclose specific data regarding any products that may be under review.

[11] *https://www.nih.gov/research-training/medical-research-initiatives/opioid-crisis/public-private-partnership*.

Currently, both opioid and non-opioid FDA-approved drugs are available for the management of pain. There are also medical devices indicated to treat specific types of pain, such as intrathecal pumps that have been cleared to administer morphine and ziconitide for chronic pain.

The Commissioner has made addressing the opioid addiction epidemic among one of his highest priorities. FDA understands the value in, and supports the development of, new treatment options for pain, and continues to work with the medical device and drug industries to explore new options for patients in pain, especially options that have improved safety profiles and are less likely to result in addiction or abuse. The tools in our expedited programs have been helpful in facilitating the development and expediting the review of products. For example, FDA approved Evzio, the first auto-injector formulation of naloxone, and Narcan Nasal Spray, a nasal spray formulation of naloxone hydrochloride, in less than four months under expedited review. These are the first approved opioid overdose treatments specifically designed so that they can be administered by family members or caregivers in the community. FDA also approved Narcan Nasal Spray as a 2 mg formulation for the emergency treatment of known or suspected opioid overdose through an expedited pathway.

Manufacturers can seek new indications, expanded labels and/or different concentration approvals for non-opioid products already available to patients by following the requirements set forth in 21 CFR 314.70 and by reviewing our guidances, such as *Guidance for Industry: Changes to an Approved NDA or ANDA*.[12]

[12] *https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf.*