November 18, 2019

Food and Drug Administration
Docket ID: FDA-2019-N-2514
Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction
Comments to the Docket on Public Hearing Questions

The U.S. Pain Foundation is pleased to respond to the FDA's request for comments on questions posed at the hearing on standards for future opioid approvals and incentivizing new pain relief options on September 17, 2019, and published in the Federal Register. The U.S. Pain Foundation is the largest 501 (c) (3) organization for people who live with chronic pain from a myriad of diseases, conditions and serious injuries. Our mission is to connect, support, educate and advocate for those living with chronic pain, as well as their caregivers and healthcare providers.

The first set of questions posed by the FDA have to do with whether new sponsors of opioid analgesics should have to demonstrate some comparative advantage relative to existing opioid analgesics. And if so, how stringent should the requirement be, to which existing products should new opioids be compared and what would be the impact on patients, providers and the public health?

According to the CDC, an enormous number of Americans—nearly 20 million—are living with pain so debilitating that it significantly interferes with their ability to function on a daily basis (e.g. engage in work, self-care, social, and recreational activities).[1] In fact, the same study found that 14.5 million of the 19.6 million living with high-impact chronic pain are unemployed—likely because they are physically unable to engage in work. A portion of these individuals with severe pain have been unable to find relief from other treatment options and may depend on opioid medications to have any quality of life.

Unfortunately, some efforts aimed at reducing addiction and overdose have had an unintentional chilling effect on pain care. We have heard from an increasing number of pain patients that they have been forced to taper off opioid medication or, even worse, suddenly cut off from medication that they have depended on for any quality of life. In many cases, these patients did not show signs of misuse or abuse; rather, clinicians felt pressured to do so because of external factors. Indeed, the FDA in April of this year issued a warning to the nation's doctors about the increase in suicides and other serious, adverse events in people living with chronic pain who have been abruptly cut off from opioid medications.

[1] https://www.cdc.gov/mmwr/volumes/67/wr/mm6736a2.htm

It's important to note that each individual reacts to medication differently, even medications in the same classification and for the same indication. A medication may cause intolerable side effects and provide little relief in one individual, while another medication may be well tolerated by and clinically helpful for the same individual. With this in mind, while we would like to see new opioids have an advantage over existing opioids, we do not believe a comparative advantage over *every other* opioid medication for the same indication should be a requirement. For example, suppose a new opioid fulfills a patient need for a portion of the population likely to use that medication. Suppose that attribute of the medication is already available in some opioids, but not the ones that portion are likely to be prescribed. Would we not allow that medication on the market because that attribute is available in another medication, even though it is not typically prescribed for that particular segment of patients?

We all want better and safer treatment options for people living with pain. We think it does make sense for the FDA to *encourage* innovation in any new opioid products. The types of advantages we would like to see are: lower side effects profiles, less abuse potential, and greater efficacy. A new opioid with a lower risk of respiratory depression, a decreased effect on mood (including the sensation of feeling "high"), a reduction or elimination of gastrointestinal side effects (such as constipation or nausea), and reduced drowsiness or fatigue would be beneficial to those pain patients who depend on opioids for pain relief. While data from Massachusetts and the CDC show that a majority of overdose deaths currently result from illicit drugs like illicit fentanyl, cocaine, heroin and polypharmacy,[2,3] a new prescription opioid with a novel superior abuse-deterrent technology would still be a worthy advantage. In addition, an opioid with superior efficacy, particularly over a sustained period, at the same dose—relative to other opioids for its indication—would also present an advantage.

The FDA's second set of questions has to do with whether new pre-approval incentives are needed to better support and encourage the development of new non-opioid therapeutics to treat pain. And, if so, what new incentives would be most effective?

New pre-approval incentives are *urgently* needed in the pain space. The opioid crisis has revealed decades of underinvestment in research aimed at understanding the mechanisms and treatment of pain. We have no completely effective therapies that will eliminate chronic pain and only a handful of mediocre ones that help relatively small numbers of specific patients. It should come as no surprise that we have had to rely on imperfect treatments for pain relief. The FDA needs to make a concerted effort to encourage and expedite the approval of new pain therapeutics in the pipeline.

[2] https://www.mass.gov/doc/opioid-related-overdose-deaths-among-ma-residents-august-2019/download
[3] https://www.drugabuse.gov/related-topics/trends-statistics/infographics/fentanyl-other-synthetic-opioids-drug-overdose-deaths

In August of 2019, the FDA's Dr. Janet Woodcock and Dr. Peter Marks authored an article, entitled "Delivering Promising New Medicines Without Sacrificing Safety and Efficacy," in which they describe the FDA's expedited programs for drug approval.[4] In answer to the FDA's question about what incentives should be available to new pain therapeutics, we believe that four of the programs described in that article and in greater detail in the 2014 "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics"[5] should be made available to new pain therapeutics. Those programs are: *fast track designation, breakthrough therapy designation, accelerated approval and priority review designation*. We also support the use of *novel clinical trial designs*, use of *real world evidence* and *patient experience data* as well as *surrogate, intermediate clinical and clinically significant endpoints,* to the extent these measures are demonstrable, in the review and approval of new pain therapeutics as well as medical devices. The expedited programs and endpoints, including eligibility criteria, are further described in the February 2019 Guidance document adapting expedited programs to regenerative medicine therapies entitled, "Expedited Programs for Regenerative Therapies for Serious Conditions."[6]

The FDA has also asked what new authorities it might need in order to offer pre-approval incentives to new pain therapeutics. However, under the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act Section 3001 (Public Law 115-271), Congress has given the FDA authority to use existing expedited designations—as well as novel clinical trial designs, use of real world evidence, patient experience data and varied endpoints—in the approval process for "non-addictive medical products to treat pain or addiction." Congress directed the FDA to issue Guidance to "help address challenges to developing non-addictive medical products to treat pain or addiction." Most importantly, Congress has allowed the FDA to apply the eligibility criteria, if it chooses to do so, of "serious disease or life-threatening disease or condition" and "unmet medical need" to pain.[7]

The SUPPORT Act says the FDA may consider "pain, pain control or pain management" in assessing whether a disease or condition is considered a "serious or life-threatening" one. In the "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics," the FDA has defined a serious disease or condition as follows:

> "A serious disease or condition is a disease or condition associated with morbidity that has a substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be

[4] https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/delivering-promising-new-medicines-without-sacrificing-safety-and-efficacy

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions

[7] https://www.congress.gov/115/bills/hr6/BILLS-115hr6enr.pdf

sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."[8]

Chronic pain, especially high-impact chronic pain, is indeed a "serious disease or condition" in accordance with the above definition. One of the core underlying principle of the landmark 2011 Institute of Medicine Relieving Pain in America report is that "chronic pain can be a disease in itself: "Chronic pain has a distinct pathology causing changes throughout the nervous system that often worsen over time. It has significant psychological and cognitive correlates and can constitute a serious separate disease entity."[9]

Chronic pain, by its very definition, is pain that continues six months or more.[10] Although the morbidity associated with chronic pain by the Guidance definition need not be irreversible if it is persistent or recurrent, most chronic pain sufferers report pain that continues for years or even a lifetime. As stated above, high-impact chronic pain is pain associated with substantial restriction of participation in work, social and self-care activities[11] and, as such, has a negative impact on day-to-day functioning. Indeed, painful arthritic, musculoskeletal and back/spine disorders are the leading causes of disability in the United States.[12]

The SUPPORT Act also says the FDA may consider the risk of addiction of controlled substances approved to treat pain when establishing "unmet medical need." FDA Guidance defines "unmet medical need" as a condition whose treatment or diagnosis is not addressed adequately by available therapy. The Guidance further states an unmet medical need includes an immediate need for a defined population or a longer-term need for society.

I have spoken earlier in this document of the inadequacy of existing treatments for debilitating chronic pain. The urgency for new therapeutic options is clear: chronic pain is the leading cause of long-term disability in the United States;[13] at least 10 percent of all suicides involve someone with chronic pain;[14] and people with pain are are four times more likely to experience mental health disorders, like depression and anxiety.[15] And,

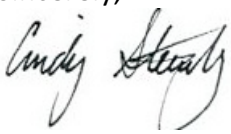
[8] https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf
[9] https://www.nap.edu/read/13172/chapter/1
[10] https://www.cdc.gov/mmwr/volumes/67/wr/mm6736a2.htm
[11] https://www.iprcc.nih.gov/sites/default/files/HHSNational_Pain_Strategy_508C.pdf
[12] https://www.boneandjointburden.org/docs/BMUS%20Impact%20of%20MSK%20on%20Americans%20booklet_4th%20Edition%20%282018%29.pdf
[13] https://jamanetwork.com/journals/jama/fullarticle/2678018
[14] https://annals.org/aim/fullarticle/2702061/chronic-pain-among-suicide-decedents-2003-2014-findings-from-national
[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3000181/

arguably the most effective treatments we have available for the most severe chronic pain—opioid analgesics—come with the risk of addiction for those with substance use disorder.

In the past decade, there has been an exciting explosion of novel drug development and approvals in the areas of oncology and rare diseases. Sadly, for those whose lives have been devastated by chronic pain, little has changed in the availability of new treatment options (save for the introduction of calcitonin gene-related peptide drugs for migraine). Certainly, this has a lot to do with the level of public and private investment in research and development into cancer and rare diseases. Congress' investment in the HEAL Initiative, particularly biomarker discovery and validation; a pain clinical trials network; the discovery of novel targets for pain; and human-cell based screening platforms will hopefully lead to promising molecules that can be developed into new treatments through private investment.

However, it is also the case that a majority of new rare disease and cancer drug approvals have used at least one of the FDA's expedited development and review programs and tools.[16] We encourage FDA's Division of Anesthesia, Analgesia and Addiction to engage in the kind of communication and collaboration with drug innovators that has led the Oncology Division to approve a plethora of new cancer treatments over the past decade. We eagerly look forward to reviewing how the FDA plans to address the challenges of developing new, non-addictive medical products to treat pain in a new Guidance as required by Congress in the SUPPORT Act. We hope that the FDA will place a priority on speeding new therapeutic options for chronic pain through the approval process. For millions of Americans, struggling every day with relentless chronic pain, effective new options can't come soon enough.

Sincerely,



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[16] https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/delivering-promising-new-medicines-without-sacrificing-safety-and-efficacy