April 11, 2022

Food and Drug Administration
Docket ID: FDA-2021-N-0556
Development of Non-Opioid Analgesics for Acute Pain: Guidance for Industry
Comments to the Docket

The U.S. Pain Foundation appreciates the opportunity to respond to the Food and Drug Administration's (FDA) request for comments on Development of Non-Opioids Analgesics for Acute Pain: Draft Guidance for Industry. The U.S. Pain Foundation is a national 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.

FDA has issued this Guidance to fulfill its statutory requirement under section 3001(b) of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act, which directs the FDA to issue or update existing guidance to help address challenges to developing nonaddictive medical products to manage pain.

The U.S. Pain Foundation is pleased that FDA has released this draft Guidance on Acute Pain. Using FDA's temporal definition of acute pain as "pain lasting up to 30 days, typically in response to some form of tissue injury, such as trauma or surgery", then by definition chronic pain, defined as pain lasting more than 3 months, is always preceded by acute pain. While we, of course, understand and support the importance of developing novel therapeutics for acute pain, the time-limited nature of acute pain measured in days in relation to the typical life expectancy of Americans, measured in decades is small, and for most healthy adults relatively insignificant over the course of a lifetime. Also, the intensity of acute pain is typically greatest at the onset of injury, surgery, infection or other trauma and lessens with healing and thus its burden in terms of morbidity is small.

We are not going to comment on the specifics of this Acute Pain Guidance other than to say that it appears to cover the requirements of the statute in terms of trial design, outcome measures and endpoints, product labeling including reductions in opioid analgesics and eligibility for FDA's expedited review programs. We are especially pleased to see comments throughout the document welcoming and encouraging sponsors to initiate "early and regular discussions" with FDA on a range of important topics such as secondary efficacy endpoints (line 190), biomarkers (line 224-6), safety considerations (line 250), use of electronic health data (line 356-7), clinical trial design and labeling (361-3), and the use of expedited programs (line 372-3). Given these comments, we expect that FDA is responsive in a timely manner to acute pain developers inquiries and requests for meetings on these and other topics covered in the Guidance and will be interested to hear from developers as to how these discussions are progressing.

One general recommendation we have given the number of topics that FDA has asked for discussion about is the development of a Communication Plan between sponsors and FDA on specific topics such as those listed thoughout the document and others that may arise during development with regular meetings scheduled. We view these communications as essential to meeting FDA's mission to speed innovations that make medical products safer, more effective and more affordable and ensure that novel acute pain therapeutics are available to patients at the earliest possible date.

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The U.S. Pain Foundation is focused on representing the interests of the 50 million Americans living with chronic pain and as such we have two important points to make in regard to FDA and pain therapeutics. The first is that we are eagerly awaiting FDA's Chronic Pain Guidance. Although, we understand that the pandemic has likely consumed critical FDA resources during the past 2 years, the SUPPORT Act was signed into law in 2018 and it has taken until now to have a draft of FDA's Acute Pain Guidance. We hope that the Chronic Pain Guidance which is critical to fulfilling FDA's statutory requirements under section 3001(b) of the SUPPORT Act will be released for comment in the next few months. We have been encouraged to hear in recent months about a handful of sponsors with non-opioid products for chronic pain in the development pipeline. But, any sponsor willing to put the enormous resources required to bring a product to market in the notoriously challenging field of pain, needs FDA Guidance to steer development efforts and better understand what FDA requires in all aspects and phases of development in order to ultimately gain approval to market the drug.

The second key point we would like to make is that 50 million Americans and especially the approximately 20 million living with high-impact chronic pain need FDA to play a more proactive role in encouraging innovation in the chronic pain space.

It is hard to overstate the devastating, increases in pain and suffering experienced by the millions of Americans living with high-impact chronic pain over the past 6 years since the CDC Opioid Prescribing Guideline (Guideline) was released. In 2015, prior to the release of the Guideline, the NIH reported that there were between 5 and 8 million Americans on opioid therapy for chronic pain[1]. After the widespread adoption of the Guideline in the subsequent years, tens of thousands of pain patients on stable doses of opioid medication were force tapered off which has led to an inhumane crisis of egregious harms including sudden loss of access to medication triggering withdrawal, dismissal from physician practices, inability to find medical care, extreme anxiety, depression and despair, loss of function and quality of life and hundreds of documented suicides.

The U.S. Pain Foundation has received thousands of calls, e-mails, and letters over the past six years from desperate pain patients who were forced off opioid therapy that allowed them to function and are now so debilitated by unrelenting pain that they are unable to work, sleep, or take care of their families. We hardly need to detail the extent and serious nature of this problem to this agency because by April of 2019 the problem had gotten so bad that FDA took the rare step of issuing a warning and requiring label changes to guide gradual tapering to the nation's prescribers stating that, "The U.S. Food and Drug Administration has received reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased. These include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide." [2]

[1] **National Institutes of Health Pathways to Prevention Workshop: The Role of Opioids in the Treatment of Chronic Pain** Feb 17, 2015. https://www.acpjournals.org/doi/abs/10.7326/m14-2775. Accessed April 5, 2022

[2] https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes Accessed April 5, 2022.

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In September of 2021, the AMA reported that opioid prescriptions in the US had decreased by more than 44% and total MME has decreased by more than 55%.[3] According to an HHS Report to Congress in April 2020, at least thirty-three states have adopted statutory limits on opioid analgesic prescriptions. It is doubtful that any of these codified restrictions will be repealed anytime soon and highly unlikely that there will be a renewed willingness on the part of physicians to prescribe opioids again to chronic pain patients in this pervasive climate of fear of loss of licensure.

Opioids certainly do not help everyone with chronic pain and for those they do help, they do not completely eliminate the pain and they come with side effects and well known risks for some. There is no cure for chronic pain and a dearth of truly effective and safe treatments. People living with debilitating chronic pain, at present, struggle over many years or a lifetime to piece together an individualized treatment regimen combining pharmacological and non-pharmacological treatments in the hopes of finding a combination of treatments that will reduce the pain enough such that they can eek out a life worth living. Sadly, especially now compounded by the pandemic, millions of Americans are isolated and struggling with relentless chronic pain and cannot find help. There is a tremendous unmet need for effective non-opioid treatments for pain.

There have not been any novel therapeutic breakthroughs for chronic pain approved in more than a decade with perhaps the exception of CGRP medications for migraine. We believe that FDA could and should do a lot more to encourage the development of novel therapeutics. In particular, we encourage FDA to convene a series of stakeholder meetings including FDA Analgesic Division representatives, developers, researchers, patients and patient advocates to stimulate ideas and spark innovation on range of critical topics such as novel clinical trial designs for pain, improving measurement tools for pain, the development of new endpoints and biomarkers for assessing pain and assessment of benefits and risks of potential treatments to name just a few of a plethora of topics in pain therapeutics that would greatly benefit from a rich exchange of ideas.

In addition, Congress has greatly increased the country's investment in pain research at the NIH with the HEAL Initiative as well as direct increases in funding for pain research to individual institutes. The stated goal of most of these substantial investments is to ultimately speed the development of new therapeutics as alternatives to opioids. We encourage FDA to increase its engagement in these research efforts to ensure that research advances and developments benefit from FDA's expertise in advancing novel treatments through the development pipeline. For example, NIH's Early Phase Pain Investigation Clincal Network (EPPIC-NET) Program that is part of the HEAL Initiative could benefit from FDA's expertise in pain endpoints and clinical trial design.

We hope the FDA will give our recommendations serious consideration as it moves forward with this important work that represents hope to so many suffering with debilitating chronic pain. Should we be able to provide additional information or assist the FDA's efforts in any way, please feel free to contact me using the information listed below.

[3] https://end-overdose-epidemic.org/wp-content/uploads/2021/09/IQVIA-opioid-prescription-trends-chart-Sept-2021-FINAL.pdf

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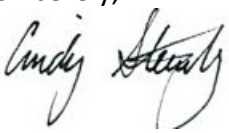
Sincerely,



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