July 20, 2017

Via Electronic Submission

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned, on behalf of Pharmaceutical Manufacturing Research Services, Inc. ("PMRS") submits this petition pursuant to 21 C.F.R. §§ 10.30 and 10.31, and Section 505(q) and other provisions of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). This petition requests the Food and Drug Administration ("FDA") to refrain from approving NDA 209653, submitted by Intellipharmaceutics Corp. ("NDA 209653" or the "Intellipharmaceutics product"), with the proposed indication or any other labeling that suggests that the product is appropriate for chronic use. This petition further requests that FDA refrain from approving any other pending or future marketing application for such use.

A. ACTION REQUESTED

To protect the public health interest in ensuring the responsible prescribing and use of opioid drug products, PMRS respectfully requests that the FDA take the following action:

- Refrain from approving pending NDA 209653 with the proposed indication of "management of moderate-to-severe pain when a continuous around-the-clock analgesic is needed for an extended period of time."

- Refrain from approving all other pending or future applications for opioids indicated for chronic use, including use over "an extended period of time," use for "long-term opioid treatment," or any other labeling for chronic use.

B. STATEMENT OF GROUNDS

If NDA 209653 is approved with the proposed indication of "management of moderate-to-severe pain when a continuous around-the-clock analgesic is needed for an extended period of time," it would be misbranded and its presence on the market would negatively affect the public health, potentially further fueling the current epidemic of opioid addiction.

For the reasons discussed herein, the proposed indication is false and misleading, and lacks "substantial evidence consisting of adequate and well-controlled investigations" as required by the FD&C Act.

I. Indication of opioids for the treatment of chronic pain lacks substantial evidence

According to its guidance document on analgesic indications, the FDA defines chronic pain as "either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months."[1] However, as PMRS has articulated in a previously-filed Citizen Petition (FDA-2017-P-1359), beginning with the approval of original OXYCONTIN in 1995, the Agency has unlawfully allowed extended-release opioids to be marketed with chronic-use labeling, despite a lack of evidence to support the chronic-use indication.[2] Even today, there remains a lack of evidence that prescription opioids are effective or safe therapeutics in the chronic pain setting.[3]

Indeed, the lack of evidence to support the efficacy of prescription opioids in the treatment of chronic pain has been recognized by the CDC. In its March 2016 *Guideline for Prescribing Opioids for Chronic Pain*, the CDC acknowledged that: "[T]he guideline uses the best available scientific data to provide information and recommendations to support patients and clinicians in balancing the risks of addiction and overdose with the limited evidence of benefits of opioids for the treatment of chronic pain."[4] The CDC Guideline is the culmination of almost three years of

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[1] FDA, *Guidance for Industry—Analgesic Indications: Developing Drug and Biological Products*, February 2014, p. 2 (emphasis added), accessed on July 18, 2017 from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384691.pdf

[2] PMRS, Citizen Petition, Docket No. FDA-2017-P-1359 (Mar. 6, 2017)

[3] *See, e.g.*, FDA, Transcript, *Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop* (May 31, 2012), pp. 7-8 (statement of Janet Woodcock, M.D., Director, CDER) (commenting that, although the evidence base is strong for the efficacy of opioids for up to 12 weeks of treatment, their performance and liabilities beyond 12 weeks have not been demonstrated "in the type of evidentiary base that FDA usually has for approval for when [the Agency] grant[s] an indication"), accessed July 18, 2017 from https://www.regulations.gov/contentStreamer?documentId=FDA-2012-N-0067-0017&attachmentNumber=2&contentType=pdf

[4] Thomas R. Frieden, M.D., M.P.H., and Debra Houry, M.D., M.P.H, *Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline*, N Engl J Med, April 21, 2016, p. 1501, accessed July 18, 2017 from http://www.nejm.org/doi/pdf/10.1056/NEJMp1515917

work by the world's experts in epidemiology.[5] The Guideline is the ultimate authority on the opioid epidemic, having combined the resources and knowledge of top experts in the field, numerous rigorous studies, and a multitude of panels. Some of the CDC's recommendations and conclusions in the Guideline include:

> "The evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy." [6]

> "Most placebo-controlled, randomized trials of opioids have lasted 6 weeks or less, and we are aware of no study that has compared opioid therapy with other treatments in terms of long-term (more than 1 year) outcomes related to pain, function, or quality of life. The few randomized trials to evaluate opioid efficacy for longer than 6 weeks had consistently poor results." [7]

> "The science of opioids for chronic pain is clear: for the vast majority of patients, the known, serious, and too-often-fatal risks far outweigh the unproven and transient benefits." [8]

The FDA has also acknowledged the lack of evidence for the treatment of chronic pain using opioids in the context of the CDC Guideline:

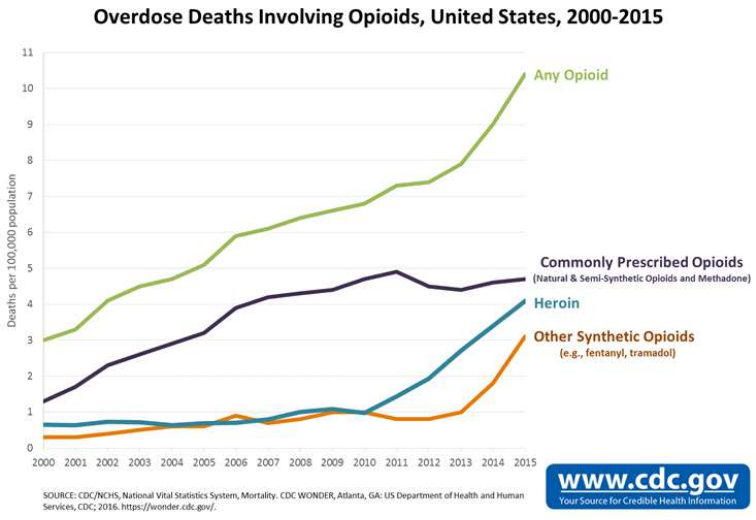
> "The FDA does its best work when high-quality scientific evidence is available to assess the risks and benefits of intended uses of medical products. Unfortunately, the field of chronic pain treatment is strikingly deficient in such evidence. A key lesson learned during the development of the CDC guideline is that there is very little research on the long-term benefits of opioids for treating chronic pain. There is, however, growing evidence of harms associated with such use, and of the benefits of other nonopioid treatment alternatives."[9]

[5] Dowell D, Haegerich TM, Chou R. *CDC Guideline for Prescribing Opioids for Chronic Pain* — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49, p. 34 accessed July 18, 2017 from https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf
[6] *See* n. 5 at 34.
[7] *See* n. 4 at 1501
[8] *Id.* at 1503
[9] Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 N Engl J Med. p. 1484 (2016) , accessed on July 17, 2007 from http://www.nejm.org/doi/full/10.1056/NEJMsr1601307

II. Public Impact – Opioid Morbidity and Mortality

As pain experts have explained, "[a]ddiction develops slowly, usually only after month of exposure, but once addiction develops, it is a separate, often chronic medical illness that will typically not remit with opioid discontinuation and will carry a high risk of relapse for years without proper treatment."[10] As such, abuse-deterrent opioids were originally approved and marketed to correct what is now known to be a flawed premise: that addiction was a consequence of abuse and misuse.[11] However, it is not the abuse of opioids that creates addicts; addiction causes abuse of opioids.

The United States is experiencing an iatrogenic opioid epidemic that continues to rage out of control. According to the CDC, "[s]ince 1999, the amount of prescription opioids sold in the U.S. nearly quadrupled, yet there has not been an overall change in the amount of pain that Americans report."[12] And, in 2015, "there were over 33,000 deaths involving opioids, equivalent to about 91 deaths per day."[13] The increase in deaths from opioid overdose is directly proportional to the increase in the volume of prescription opioids sold. The dramatic growth in overdose deaths can be seen in the following graph:



[10] Nora D. Volkow, M.D., and A. Thomas McLellan, Ph.D, *Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies*, N Engl J Med, March 31, 2016, p. 1256, accessed on July 17, 2017 from http://www.nejm.org/doi/full/10.1056/NEJMra1507771#t=article

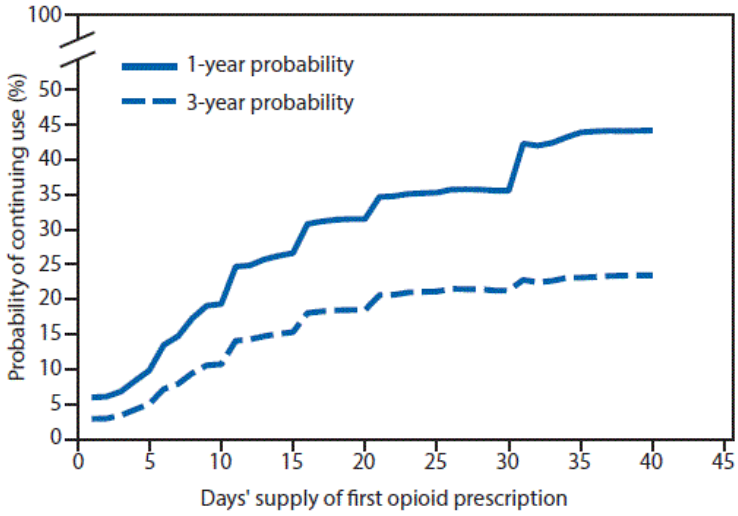
[11] "When OxyContin entered the market in 1996, the FDA approved its original label, which stated that iatrogenic addiction was "very rare" if opioids were legitimately used in the management of pain." -- Van Zee, Art. "The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy." American Journal of Public Health 99.2 (2009): 221–227. PMC. Web. 19 July 2017

[12] Center for Disease Control and Prevention, *Understanding the Epidemic*, accessed July 18, 2017 from https://www.cdc.gov/drugoverdose/epidemic/

[13] Center for Disease Control and Prevention, *Opioid Overdose*, accessed July 18, 2017 from https://www.cdc.gov/drugoverdose/index.html.

Moreover, "prescription opioids continue to be involved in more overdose deaths than any other drug, and all the numbers are likely to underestimate the true burden given the large proportion of overdose deaths where the type of drug is not listed on the death certificate." [14]

Importantly, the CDC has observed that "[o]verdose risk increases in a dose–response manner, at least doubling at 50 to 99 morphine milligram equivalents (MME) per day and increasing by a factor of up to 9 at 100 or more MME per day, as compared with doses of less than 20 MME per day."[15] Accordingly, "1 of every 550 patients started on opioid therapy died of opioid-related causes a median of 2.6 years after the first opioid prescription; the proportion was as high as 1 in 32 among patients receiving doses of 200 MME or higher."[16] With strengths as high as 80 milligrams per tablet, the Intellipharmaceutics product has the potential to deliver 240 MME when dosed BID—a total daily dose that is expected to increase the likelihood of addiction and death. The proposed labeling and extended-release formulation for NDA 209653 would also introduce additional risks to the public health, given that the anticipated duration of treatment is for extended periods of time. This is because the risk of continued opioid use is heavily dependent on the length of the patient's first opioid prescription, as measured in days. For example, the CDC reports that the one- and three-year probabilities of continued opioid use positively correlate with the number of days' supply of the first opioid prescription:[17]



[14] Center for Disease Control and Prevention, *Opioid Data Analysis*, accessed July 18, 2017 from https://www.cdc.gov/drugoverdose/data/analysis.html
[15] *See* n. 4 at 1502-1503
[16] *Id*. at 1503
[17] Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66:265–269. DOI: http://dx.doi.org/10.15585/mmwr.mm6610a1

CDC data suggests that the proposed labeling for NDA 209653, including use over "an extended period of time," would continue to create new addicts and, thus, further contribute to the opioid epidemic.

In addition, the risk of continued opioid use is also significantly higher for long-acting opioids, which includes the Intellipharmaceutics product. For instance, the CDC reports that both the one- and three-year probabilities of continued opioid use and the median time to discontinuation of opioid use are significantly higher for patients first treated with long-acting opioids:[18]

Choice of first prescription	One-year probability of continued use, %	Three-year probability of continued use, %	Median days to discontinuation
Long-Acting Opioids	27.3	20.5	63
Hydrocodone Short-Acting	5.1	2.4	5
Oxycodone Short-Acting	4.7	2.3	6

Thus, the risk to the public health of the FDA continuing to approve extended-release/long-acting opioids is significant.

Finally, former Director of the CDC, Dr. Thomas Frieden, M.D., M.P.H. and Debra Houry, M.D., M.P.H. have provided perhaps the best summary of the consequences of the use of opioids for the treatment of chronic pain:

> "Beginning in the 1990s, efforts to improve treatment of pain failed to adequately take into account opioids' addictiveness, low therapeutic ratio, and lack of documented effectiveness in the treatment of chronic pain."[19]
>
> "Whereas the benefits of opioids for chronic pain remain uncertain, the risks of addiction and overdose are clear."[20]
>
> "We know of no other medication routinely used for nonfatal conditions that kills patients so frequently."[21]

[18] Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66(10):xx
[19] *See* n. 4 at 1501
[20] *Id.* at 1502
[21] *Id.* at 1503

III. CONCLUSION

The root cause of the United States opioid epidemic is the FDA's approval of opioid drug products for the treatment of chronic pain absent substantial evidence of efficacy. Exacerbating the problem, the FDA-approved labeling provided the medical community with false reassurance that opioids are safe and effective in the treatment of chronic pain despite a lack of evidence to support such an indication. This led the medical community to change its long-held beliefs and practices about prescribing low-dose opiates only for acute injury and only for short durations due to severe risk of addiction and a lack of empirical data of efficacy for chronic pain.

Ultimately, the FDA's action to approve prescription opioids for chronic pain is in violation of the FD&C Act requirement that FDA have "substantial evidence consisting of adequate and well-controlled investigations." Since being wrongfully approved for treatment of chronic pain, it is estimated that opioids have killed over 200,000 people.[22] By approving opioids indicated for the treatment of chronic pain without substantial evidence of their efficacy for this indication, the FDA has helped to facilitate the launch of the U.S. opioid epidemic—an escalating public health crisis unprecedented in our country.

To address these concerns, PMRS requests that the FDA refrain from approving pending NDA 209653 with the proposed indication of "management of moderate-to-severe pain when a continuous around-the-clock analgesic is needed for an extended period of time," or any other labeling that suggests that the product is appropriate for chronic use. PMRS further requests that FDA refrain from approving any other pending or future marketing application for such use.

IV. INTERESTS OF PMRS, INC.

PMRS submitted a New Drug Application (NDA) on January 16, 2017 under Section 505(b)(2) of the FD&C Act for Oxycodone HCl IR ADF capsules with a proposed indication for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. This proposed indication is specifically for the management of acute pain, and not for chronic use. In addition, the dosage guidance for this NDA adheres to the CDC's recommendations for MME maximum dose and duration.

C. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

[22] National Institute on Drug Abuse (NIDA), *Overdose Death Rates*, accessed July 17, 2017 from https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

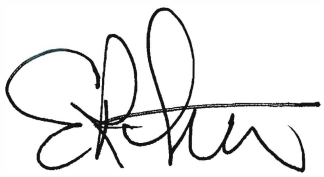
D. ECONOMIC IMPACT

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

E. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: June 30, 2017. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Pharmaceutical Manufacturing Research Services, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully Submitted,



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