PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.

March 6, 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. § 10.20 and 10.30 to the U.S. Food and Drug Administration ("FDA") requesting that the Commissioner of the FDA take the following action.

A. ACTION REQUESTED

PMRS requests that the FDA take the following actions:

- Revoke approval of OxyContin's indication for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate" and all supporting chronic use labeling.

- Revoke approval of all extended-release (ER) opioids indicated for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."

- Revoke approval of all immediate-release (IR) opioid drug product labeling supporting use for the treatment of chronic pain. Instead, labeling must state indication is for acute pain for a limited duration.

B. STATEMENT OF GROUNDS

I. FDA approved OxyContin and other opioids for treatment of chronic pain despite absence of substantial evidence

On July 18, 2001, the FDA approved, without requiring substantial evidence, supplement S-022 to OxyContin new drug application (NDA) 20-553, for labeling updates to OxyContin. This supplement changed the indication for OxyContin from treatment of acute pain to chronic pain. The FDA justified the approval of the NDA supplement (sNDA) and indication change on the grounds that "additional stronger warnings about the potential for misuse and abuse" were

needed.[1] The FDA did not conduct or require the sponsor to conduct sufficient testing to reasonably conclude that substantial evidence existed to change the indication from acute to chronic.[2] Such approval in the absence of substantial evidence violates the Federal Food, Drug and Cosmetic Act (FD&C Act).

> For a new drug or indication to be approved under section 505(b) of the FD&C Act, the FDA must rely on "substantial evidence."[3] No such showing of substantial evidence, however, appears to have been made to change the indication for OxyContin from treatment of acute pain to chronic pain. 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."[4] The FD&C Act requires, but the sNDA approval lacks, substantial evidence for expanding OxyContin's indication.

There were significant legal deficiencies in processing NDA 20-553/S-022 which led to an approval that is not consistent with applicable law; the most compelling being no evidence was cited or relied upon by the FDA regarding the change. The FDA merely stated the reason for changing OxyContin's indication from acute to chronic treatment was "INDICATIONS were simplified to reinforce the appropriate patient population for whom this product is intended."[5] The appropriate patient population was defined by the FDA as "patients suffering with chronic pain."[6] Included in the label change, the FDA also required the addition of a Box Warning to address the "concern over growing abuse, misuse and diversion of OxyContin tablets."[7]

In the end, the FDA approved the change to OxyContin's indication in the absence of substantial evidence. Accordingly, the approval of NDA 20-553/S-022 exceeded the FDA's statutory authority and must be revoked. The following is a brief summary of the relevant regulatory history of OxyContin and other opioids.

The FDA had previously approved NDA 20-553 on December 12, 1995, OxyContin (oxycodone hydrochloride) extended-release tablets for "moderate to severe pain where use of an opioid

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[1] U.S. Food and Drug Administration, *Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse*, January 23, 2017, p. 7, accessed March 2, 2017 from https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM332288.pdf.

[2] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin® NDA 20-533, *S-022 Administrative Document:*, *Regulatory Project Manager Review*, July 18, 2001, p. 1, accessed March 2, 2017 from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/020553_S022_OXYCONTIN_AP.pdf

[3] 21 U.S. Code §355 (d) (2012)

[4] U.S. Food and Drug Administration, *Guidance for Industry—Analgesic Indications: Developing Drug and Biological Products*, February 2014, p. 2, accessed on March 2, 2017 from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384691.pdf

[5] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin® NDA 20-533, S-022 *Administrative Document: Division Director's Review of Labeling Supplement and Basis for Action*, July 16, 2001, p. 2, accessed on March 2, 2017 from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/020553_S022_OXYCONTIN_AP.pdf

[6] *Id*. at p. 5

[7] *See* n. 2 at p. 1

analgesic is appropriate for more than a few days." The FDA justified the approval of an extended-release tablet for acute treatment on a basis in which "[d]elayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug"[8] Both the indication and justification, originally included in the drug product labeling, were reversed upon approval of the supplement.

Sixteen years later, there is still insufficient scientific or substantial evidence for using opioids in the treatment of chronic pain. The CDC confirmed this fact in the CDC's 2016 opioid prescribing guidelines.

> "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."[9]
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> "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."[10]
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> "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."[11]

The FDA has also approved and labeled other extended-release opioids for chronic treatment of pain without substantial evidence. Specifically, the FDA has approved other extended-release opioids for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate,"[12] despite evidence since the 1990s of the lack of documented effectiveness of opioids in the treatment of chronic pain.[13] Just as OxyContin's approval has never been in compliance with applicable law, all other opioid drug products with the same indication are in violation as well.

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[8] *Physician's Desk Reference* (53rd Ed., 1999, p. 2572) Label for OxyContin®, *Drug Abuse and Dependence (Addiction.)*

[9] 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 March 2, 2017 from https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf

[10] 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, pp. 1501-1504, accessed March 2, 2017 from http://www.nejm.org/doi/pdf/10.1056/NEJMp1515917

[11] *Id.* at p. 1503

[12] Food and Drug Administration, *Highlights of Prescribing Information OxyContin®*, December 2016, accessed on March 2, 2017 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022272s034lbl.pdf

[13] *See* n. 10 at p. 1501

Lastly, and also in violation of the Federal Food, Drug, and Cosmetic Act, the FDA has added supporting labeling for chronic treatment for immediate-release opioids despite the lack of substantial evidence of efficacy and safety.[14]

II. The Seed of the Opioid Epidemic – FDA Approval of Opioids for Chronic Use

In 1987, the FDA approved the first extended-release (ER) opioid, MS Contin, for acute use. The drug was previously marketed without approval, under a provision of the Code of Federal Regulations permitting an extended-release drug to be sold based on an immediate-release formulation, so long as the extended-release formulation is not of a greater potency than the immediate-release formulation.[15] The approval of MS Contin established a precedent; an ER drug could be submitted for an acute indication and would be approved.

In 1995, OxyContin became the second ER drug approved for an acute indication, labeled for treatment of "moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." Upon its approval, the agency certified "delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug."[16]

The approval of OxyContin also significantly increased the quantity of active drug in each dose beyond any amount which had previously been marketed. Percodan, on the market since 1950, contained less than 5 mg of oxycodone HCl per dose. The new product, OxyContin, contained quantities of oxycodone HCl up to 40 mg in 1995 and by 2000 had 160 mg in a single tablet. The quantity of active drug now available in a single tablet would have required ingesting more than 30 tablets just 5 years prior. This quantity of active drug with a recognized abuse potential available for sale had never been seen before.[17]

By the early 2000s "[r]eports of overdose and death from prescription drug products, especially opioids, began to rise sharply, with OxyContin at the center of the problem. For instance, the number of people who admitted to using OxyContin for non-medical purposes increased dramatically from approximately 400,000 in 1999 to 1.9 million in 2002 and to 2.8 million in 2003. By 2009, about 1.2 million emergency department (ED) visits were related to misuse or abuse of pharmaceuticals, an increase of more than 98% since 2004 and more than the number of

[14] U.S. Food and Drug Administration, *Highlights of Prescribing Information Roxicodone®*, December 2016, Section 2.2, accessed March 3, 2017 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021011s006lbl.pdf

[15] The Pink Sheet, *Purdue Frederick MS Contin Sustained Release Morphine Sulfate Marketing Without FDA Approval is Justified By Agency's Acutrim Decision, Firm Says*, February, 18 1985, accessed March 2, 2017 from https://pink.pharmamedtechbi.com/PS007871/PURDUE-FREDERICK-MS-CONTIN-SUSTAINED-RELEASE-MORPHINE-SULFATE-MARKETING-WITHOUT-FDA-APPROVAL-IS-JUSTIFIED-BY-AGENCYS-ACUTRIM-DECISION-FIRM-SAYS

[16] *See* n. 8 at p. 2572

[17] U.S. Food and Drug Administration, *Labeling for Percodan®*, 2016, accessed on March 3, 2017 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/007337s049lbl.pdf; U.S. Food and Drug Administration, *Labeling for OxyContin®*, 2008, accessed on March 3, 2017 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020553s059lbl.pdf; *See also*, n. 23 at pp. 5, 8

ED visits related to use of illicit drugs such as heroin and cocaine. Most prominent among these prescription drug-related deaths and ED visits were opioid pain relievers (OPR), especially OxyContin."[18]

"FDA had worked with sponsors for more than a decade to implement risk management programs for a number of opioid products. However, data demonstrated that these programs did not adequately manage the risks of misuse, abuse, addiction, and overdose. More was needed."[19]

In May of 2000, the FDA issued a Warning Letter to Purdue Pharma L.P. (manufacturer of both MS Contin and OxyContin), instructing the company to cease and desist misleading advertisements for OxyContin in violation of the Federal Food, Drug, and Cosmetic Act.[20]

"Beginning in 2001 and ongoing, inter-agency collaboration occurred to develop public education regarding prescription drug abuse. The involved agencies included FDA, SAMHSA, the Center for Substance Abuse Treatment (CSAT), and the National Institute on Drug Abuse (NIDA)."[21]

On July 18, 2001, OxyContin Supplement S-022 was approved by the FDA, expanding the original acute indication approved in 1995 to "the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an **extended period of time** [emphasis added]."[22] At the same time, the FDA removed the abuse-deterrent language granted in the original label.

"The label was also changed to say that OxyContin is not appropriate for 'as needed' pain or in the immediate-post operative period if the pain is mild or not expected to persist for an extended period of time."[23]

"A Boxed Warning was added to reinforce the most important warnings, and information in the DRUG ABUSE AND DEPENDENCE section was updated. OxyContin's manufacturer, Purdue Pharma, agreed to implement a Risk Management Program (RMP) to try to reduce the misuse and abuse of OxyContin and issued a Dear Healthcare Professional Letter about changes to the label."[24]

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[18] *See* n. 1 at pp. 5-6
[19] *Id.* at p. 7
[20] U.S. Food and Drug Administration, *FDA Warning Letter to Purdue Pharma L.P.*, May 11, 2000, accessed on March 2, 2017 from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/UCM166015.pdf
[21] *See* n. 1 at p. 7
[22] *See* n. 5 at p. 3
[23] *Id.*
[24] *Id.*

In January 2003, the FDA issued another Warning Letter to Purdue Pharma L.P., "for misleading advertisements. Among many other details, the warning specified that the ads left out and minimized the serious safety risks associated with OxyContin and promoted it for uses beyond those which had been proven safe and effective. Specifically, the letter pointed out that the advertisements failed to clearly present information from the products label's Boxed Warning regarding the potentially fatal risks and the danger of abuse."[25]

By 2007, Purdue Pharma L.P. had developed an abuse-deterrent extended-release oxycodone, also named OxyContin.[26]

Also in 2007, "[t]he Food and Drug Administration Amendments Act (FDAAA) became law, providing the Agency with a wide array of new authority designed to enhance drug safety. One of these is the authority to require Risk Evaluation Mitigation Strategies (REMS) in order to ensure the benefits of the drugs continue to outweigh their risks. REMS are intended to require manufacturers to implement various safety measures for certain drugs. This new law helped provide the basis for a future comprehensive REMS program for all FDA-approved Extended-Release (ER)/Long Acting (LA) opioid products."[27]

In the years since, the FDA has met with manufacturers and held a number of public advisory committee meetings to garner public and industry comments to implement in the final comprehensive REMS (enacted in 2012).[28]

In 2008, an advisory committee was convened to discuss the merits of the new controlled-release (CR)[29] formulation as well as a history of the original OxyContin's use, misuse, and abuse. Notable conclusions from this meeting:[30]

> "Although it was initially believed that the PK characteristics of a CR formulation would reduce the reinforcing properties, experience has shown that defeat of the CR mechanisms is associated with abuse"[31]

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[25] *Id.*
[26] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin NDA 022272 Approval Letter, April 5, 2010, accessed March 2, 3017 from http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022272s000ltr.pdf
[27] *See* n. 1 at p. 8
[28] *Id.* at p. 11
[29] Prior to 2014, OxyContin was designated a controlled-release (CR) tablet but is now labelled as being extended-release (ER).
[30] Anjelina Pokrovnichka M.D., U.S. Food and Drug Administration, *History of OxyContin: Labeling and Risk Management Program*, Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, November 13 & 14, 2008, pp. 11-12, accessed on March 2, 2017 from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM248776.pdf
[31] *Id.* at p. 11

> "Warning against crushing may have alerted abusers to a method for misuse. Label language suggesting that OxyContin had lower abuse potential may have impacted product use or prescribing"[32]

This new reformulated OxyContin was approved as a 505(b) NDA in 2010.[33]

In 2013, the FDA amended the OxyContin labeling once more:[34]

> OxyContin receives abuse-deterrent labeling a second time (after having been removed in 2001) despite known flaws in the formulation, including, in relevant part: "The controlled-release properties of ORF [OxyContin Re-Formulated] can be overcome with chewing and swallowing."[35]
>
> OxyContin label language suggesting that OxyContin has lower abuse potential, at least with respect to injection and the intranasal route is applied.[36]

Another labeling change to all ER opioids (including OxyContin) in 2014 updated the indication for "pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."[37] The labeling still misleads the medical community that the drug is safe and efficacious for "long-term" treatment without an adequate and well-controlled clinical trial to demonstrate the claims made.

In March 2016, the CDC published the *CDC Guideline for Prescribing Opioids for Chronic Pain*. "[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."[38]

One year later, the FDA has yet to take action to reduce prescriber reliance on extended-release opioids for chronic pain.

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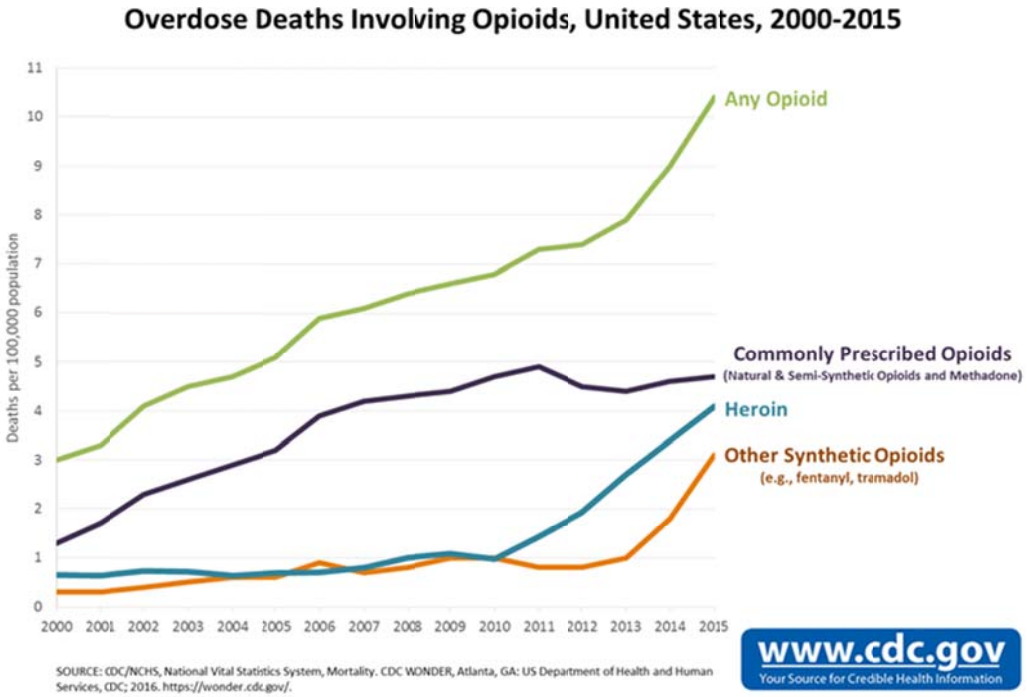
[32] *Id.* at p. 12
[33] *See* n. 25
[34] Food and Drug Administration, *Highlights of Prescribing Information OxyContin®*, April 2013, accessed on March 2, 2017 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf
[35] U.S. Food and Drug Administration, *Division Director Review: OxyContin Tablets, Reformulated*, February 6, 2013, p. 3, accessed on March 2, 2017 from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014SumR.pdf
[36] *See* n. 34
[37] FDA News Release, *FDA Announces Safety Labeling Changes and Postmarket Study Requirements for Extended Release and Long Acting Opioid Analgesics*, September 10, 2013, accessed on March 4, 2017 from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm
[38] *See* n. 10 at p. 1501

III. Public Impact - Opioid Morbidity and Mortality

"Addiction 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."[39]

The United States is experiencing an iatrogenic opioid epidemic that continues to rage out of control. According to the Centers for Disease Control and Prevention, "Since 1999 the number of overdose deaths involving opioids (including prescription opioids and heroin) quadrupled… 91 Americans die every day from an opioid overdose."[40] In the same period of time "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."[41] The increase in deaths from opioid overdose is directly proportional to the increase in volume of prescription opioids sold. The dramatic growth in overdose deaths can be seen in the following graph.



[39] 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 March 2, 2017 from http://www.nejm.org/doi/full/10.1056/NEJMra1507771#t=article

[40] Center for Disease Control and Prevention, *Understanding the Epidemic*, accessed March 02, 2017 from https://www.cdc.gov/drugoverdose/epidemic/ (*internal citation omitted).*

[41] *Id.*

"Prescription opioids continue to be involved in more overdose deaths than any other drug."[42]

"Overdose 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. Overall, 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".[43]

The use of opioids for treatment of chronic pain is best summarized by the then-Director of the CDC, Dr. Thomas Frieden, M.D., M.P.H. and Debra Houry, M.D., M.P.H.:[44]

> "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."
>
> "Whereas the benefits of opioids for chronic pain remain uncertain, the risks of addiction and overdose are clear."
>
> "We know of no other medication routinely used for nonfatal conditions that kills patients so frequently."

IV. 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 OxyContin was safe and effective in the treatment of chronic pain when there was never ANY evidence to justify 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 lack of empirical data of efficacy for chronic pain. Conventional wisdom changed when high-dose OxyContin was unlawfully approved for chronic pain and extended duration, and this sowed the seeds of the opioid epidemic.

Ultimately, the FDA's action to approve extended-release 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" to justify these changes. The FDA approvals, including changing the approved indication for OxyContin from an acute indication to chronic pain treatment, were done without substantial evidence. Since being wrongfully approved for chronic pain treatment

[42] Center for Disease Control and Prevention, *Opioid Data Analysis*, accessed March 02, 2017 from https://www.cdc.gov/drugoverdose/data/analysis.html
[43] *See* n. 10 at pp. 1502-1503
[44] *Id.* at p. 1501-1503

prescription, it is estimated that opioids have killed over 200,000 people.[45] In modifying the OxyContin indication without substantial evidence, the FDA 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 immediately (i) revoke the approval of OxyContin's indication for "the management of pain severe enough to require daily, around the clock, long-term opioid treatment and for which alternative treatment options are inadequate" and all supporting chronic use labeling; (ii) revoke the approval of all extended-release opioids that are indicated for "the management of pain severe enough to require daily, around the clock, long-term opioid treatment and for which alternative treatment options are inadequate," and (iii) revoke the approval of all immediate-release opioid drug product labeling supporting the use of the treatment of chronic pain.

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.

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 the best of my knowledge and belief, this petition includes all information and views upon which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully Submitted,

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[45] National Institute on Drug Abuse (NIDA), *Overdose Death Rates*, accessed March, 02 2017 from https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates