CLAAD Center for Lawful Access and Abuse Deterrence

July 3, 2017

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

CITIZEN PETITION

In accordance with President Trump's recent call for expanding access to abuse-deterrent medications,[1] the Petitioner, the undersigned concerned citizen, hereby submits this Citizen Petition under the Federal Food, Drug and Cosmetic Act (FDCA), the Public Health Services Act, or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs (Commissioner) under 21 C.F.R. § 5.10. The Petitioner requests that the Commissioner take administrative action to foster a market transition to opioid analgesic drug products with abuse-deterrent labeling as set forth below.

I. Actions Requested

The Petitioner asks the U.S. Food and Drug Administration (FDA) to foster a transition to opioid analgesics with abuse-deterrent labeling (ADOs) by requiring manufacturers of certain oral opioid analgesics not in abuse-deterrent formulations to convert their products to ADOs by a specific date. The FDA is authorized to withdraw approval of brand and generic non-abuse-deterrent opioids pursuant to section 505(e) of the FDCA and its implementing regulations.[2] Specifically, we request that, once the FDA has approved three oral, immediate-release (IR) or three oral, extended-release/long-acting (ER/LA) ADOs with the same active moiety (*e.g.*, three oral, abuse-deterrent ER/LA morphine medications), all oral opioids without abuse-deterrent properties with that same active moiety and release profile (*e.g.*, all oral, non-abuse-deterrent ER/LA morphine medications) either be converted to an ADO within three years of the approval date of the third ADO or otherwise be removed from the market after such three-year period if they have not been converted to an abuse-deterrent formulation. Given that the FDA has already granted abuse-deterrent labeling to three oral, abuse-deterrent, ER/LA morphine and oxycodone medications, we request that manufacturers of oral, non-abuse-deterrent, ER/LA morphine and oxycodone formulations be required to convert their medications to ADOs within three years of the date of this Citizen Petition or else have their products removed from the market on July 3, 2020.

[1] *Trump Holds White House Meeting with Sheriffs*, USA Today, (Feb. 7, 2017), http://www.usatoday.com/videos/news/nation/2017/02/07/trump-holds-white-house-meeting-sheriffs/97590032/.
[2] 21 U.S.C. 355(e); 21 C.F.R. 314.162; 21 C.F.R. 5.10, 5.82.

II. Statement of Grounds

A. The Opioid Overdose Epidemic

An estimated 25.3 million Americans experience persistent pain and have a legitimate need for treatment.[3] Opioids have been demonstrated to help manage pain when other treatments have not provided enough pain relief.[4] For some of these individuals, prescription opioids are the best treatment for their pain.[5] At the same time, opioid overdose is a public health epidemic in the United States.[6] An estimated 11.6 million Americans abuse opioids each year.[7] Moreover, the number of opioid-related overdose deaths in the United States continues to rise each year; 62 Americans die each day of a prescription opioid-related overdose.[8]

A patient with pain should try non-pharmacologic treatments first, and if necessary, be prescribed a non-controlled medication and then a lower-scheduled controlled medication before receiving a higher scheduled one.[9] Patients who need prescription opioid analgesics should be prescribed medications with abuse-deterrent properties when deemed medically appropriate. Taking such precautions could reduce the risk of the patient accidentally misusing (*e.g.*, chewing) their opioid medication and progressing to more dangerous drugs and reinforcing routes of abuse.[10]

B. Overview of ADOs

ADOs are designed to make a product more difficult to manipulate and/or reduce the attractiveness or drug-liking qualities of the medication through methods such as physical or chemical barriers, agonist/antagonist combinations, aversion, and delivery systems.[11] Abuse-deterrent technologies can also make it harder to get a product into an abuseable form to access alternative (*e.g.*, intranasal, intravenous) routes of abuse.[12]

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[3] *Americans Are in Pain: Analysis of Data on the Prevalence and Severity of Pain from National Survey*, NATIONAL INSTITUTES OF HEALTH, (August 11, 2015), https://nccih.nih.gov/research/results/spotlight/081515.
[4] *National Pain Strategy*, U.S. DEP'T OF HEALTH & HUMAN SERVS, (Mar. 18, 2016), https://iprcc.nih.gov/docs/drafthhsnationalpainstrategy.pdf.
[5] *Id.*
[6] *The U.S. Opioid Epidemic*, U.S. DEP'T OF HEALTH & HUMAN SERVS, (Apr. 8, 2016), http://www.hhs.gov/opioids/about-the-epidemic/#us-epidemic.
[7] *Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health*, SUBSTANCE ABUSE & MENTAL HEALTH SERVS. ADMIN., (Sept. 2015), http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf.
[8] *Opioid Data Analysis*, CENTERS FOR DISEASE CONTROL AND PREVENTION, (Feb. 9, 2017), https://www.cdc.gov/drugoverdose/data/analysis.html.
[9] Dowell D. Haegerich, Chou R., *CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016*, MMWR RECOMM REP (2016), https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm.
[10] Wilson M. Compton, *The Effect of an Abuse-deterrent Opioid Formulation (OxyContin) on Opioid Abuse-related Outcomes in the Postmarketing Setting*, CLIN PHARMACOL THER, (Sept. 2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5102571/.
[11] Nathaniel Katz, *Abuse-deterrent Opioid Formulations: Are They a Pipe Dream?*, 10:11-18 CURRENT RHEUMATOLOGY REPORTS (2008), *available at* http://primeinc.org/downloads/supplements/MCWG_7.pdf.
[12] *Abuse-deterrent Opioids—Evaluation and Labeling: Guidance for Industry*, U.S. FOOD AND DRUG ADMINISTRATION (April 2015), http://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

For example, individuals might crush an extended-release opioid to take the product intranasally. Without the abuse-deterrent properties, if such individuals crushed and inhaled an opioid intranasally, then the active ingredient would likely release at an accelerated rate, which could result in overdose, or worse, death. Additionally, opioids without abuse-deterrent properties are easier to manipulate for purposes other than abuse, which can also be risky.

ADO manufacturers must go through a rigorous process to demonstrate that their medication is expected to meaningfully deter expected routes of abuse before they can obtain abuse-deterrent labeling from the FDA. This process includes providing evidence from an extensive battery of in vitro studies as well as in vivo studies evaluating all potential routes of abuse (oral, nasal, intravenous).[13]

By preventing individuals from using substances via altered routes of administration, ADOs can limit associated prescription opioid overdoses,[14] which could result in significant personal and public health benefits. While current technologies do not yet deter the most common source of abuse (*i.e.*, swallowing too many pills) or prevent the risk of abuse altogether, they do meaningfully deter or lower the risk of abuse incrementally.[15] For example, the most common transition pathway from oral opioid abuse to intravenous abuse is (1) starting with oral ingestion of pills, either taken whole, chewed, or manipulated; (2) moving to crushing and insufflation (snorting) of pills; (3) and potentially, crushing and injecting prescription medications to get a quicker and more intense euphoric effect.[16]

ADOs can also reduce the risk of post-dispensing diversion, *i.e.*, the unlawful transfer of a legally prescribed controlled medication from the individual for whom the medication was prescribed to another person for illicit use. Diversion of controlled prescription medications costs the health insurance industry $72.5 billion per year, which includes fraud claims, costs related to the development of a substance use disorder (SUD) resulting from using diverted drugs, and costs resulting from comorbidities that occur in those with SUDs.[17] Given that abuse-deterrent properties can reduce the ability of an individual to manipulate the product, the demand for ADOs among those seeking to manipulate and abuse diverted opioids can be expected to be lower. For example, if an ADO takes significantly more time and resources to manipulate than opioids without abuse-deterrent properties, then the ADO effectively increases the cost of abuse of that formulation, which lowers the demand that fuels drug diversion. If the market were to transition away from non-abuse-deterrent opioid analgesics, the supply of prescription opioids sought by those who intend to divert the medication would also be reduced.

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[13] *FDA Facts: Abuse-deterrent Opioid Medications*, U.S. FOOD AND DRUG ADMINISTRATION (Jan. 17, 2017), http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm514939.htm.

[14] Larochelle MR, Zhang F, Ross-Degnan D, Wharam JF, *Rates of Opioid Dispensing and Overdose After Introduction of Abuse-Deterrent Extended-Release Oxycodone and Withdrawal of Propoxyphene*, JAMA INTERN MED. 175(6):978-987, (2015), http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2276923.

[15] *Abuse-deterrent Opioids—Evaluation and Labeling: Guidance for Industry*, U.S. FOOD AND DRUG ADMINISTRATION (April 2015), http://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

[16] Wilson M. Compton, *Relationship Between Nonmedical Prescription-Opioid Use and Heroin Use*, 374 N Engl. J Med 154 (2016), http://www.nejm.org/doi/full/10.1056/NEJMra1508490?rss=mostEmailed#t=article.

[17] Kathryn L. Hahn, *Strategies to Prevent Opioid Misuse, Abuse, and Diversion that May Also Reduce the Associated Costs*, 4(2) Am Health Drug Benefit 107 (2011).

C. Overview of Federal Policy on ADOs

The Trump Administration has prioritized expanding access to ADOs. By executive order on March 29, 2017, President Trump proclaimed that "it shall be the policy of the executive branch to combat…opioid abuse, addiction, and overdose."[18] The order established the President's Commission on Combating Drug Addiction and the Opioid Crisis to study the scope and effectiveness of the federal response to the opioid crisis and SUDs, and to make recommendations for improving that response. The commission has been tasked with identifying and reporting on best practices for addiction prevention, which include health care provider education and evaluation of prescription practices.[19] In addition, President Trump has also called on the FDA to speed up the approval of ADOs.[20] Recently, during a meeting with county sheriffs, President Trump said he would work to expand the use of medications with abuse-deterrent properties as part of his administration's efforts to reduce opioid abuse and overdoses.[21]

The FDA, in its Opioids Action Plan, has also stated that expanding access to ADOs is one part of the strategy to reduce misuse and abuse of opioids while ensuring that individuals with legitimate needs have lawful access to medications that safely and effectively treat their pain.[22] Furthermore, in its "Abuse-Deterrent Opioids—Evaluating and Labeling: Guidance for Industry," the FDA stated, "[o]ne potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse."[23] Given that the administration considers ADOs to be safer opioid analgesics, the development and approval of ADOs should remain a high public health priority for the FDA.[24]

Currently, nine ER/LA opioid analgesics have FDA-approved abuse-deterrent labeling: two crush/extraction resistant oxycodone; one oxycodone and naloxone; one oxycodone and naltrexone; two crush/extraction resistant morphine; one morphine and naltrexone; and two crush/extraction resistant hydrocodone.[25] The FDA also recently approved an IR opioid analgesic with abuse-deterrent labeling, crush/extraction resistant oxycodone. Once approved, all products with abuse-deterrent labeling must then conduct postmarketing studies to evaluate their use in the real world with the goal being to demonstrate actual reduction of misuse, abuse, and related adverse clinical outcomes, including addiction, overdose, and death.

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[18] *Presidential Executive Order Establishing the President's Commission on Combatting Drug Addiction and the Opioid Crisis*, The White House (March 29, 2017), https://www.whitehouse.gov/the-press-office/2017/03/30/presidential-executive-order-establishing-presidents-commission.
[19] *Id*.
[20] K.C. Myers, *Trump's Policies on Addiction Crisis Remain Uncertain*, Cape Cod Times (Nov. 17, 2016), http://www.capecodtimes.com/news/20161117/trumps-policies-on-addiction-crisis-remain-uncertain.
[21] *Trump Holds White House Meeting with Sheriffs*, USA Today (Feb. 8, 2017), http://www.usatoday.com/videos/news/nation/2017/02/07/trump-holds-white-house-meeting-sheriffs/97590032/
[22] *Fact Sheet – FDA Opioids Action Plan*, U.S. Food and Drug Administration, (Last updated September 13, 2016), https://www.fda.gov/newsevents/newsroom/factsheets/ucm484714.htm.
[23] *Abuse-deterrent Opioids—Evaluation and Labeling: Guidance for Industry*, U.S. Food and Drug Administration (April 2015), http://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.
[24] *Id*.
[25] *FDA Facts: Abuse-deterrent Opioid Medications*, U.S. Food and Drug Administration (Jan. 17, 2017), http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm514939.htm.

D. Transition to ADOs

The FDA has publicly stated that it looks forward to a future in which most or all opioid medications are available in formulations that are less susceptible to abuse than the formulations that lack abuse-deterrent properties.[26] In response, pharmaceutical companies have begun developing and marketing medications incorporating novel technologies intended to deter abuse and address this public health imperative.

The ability of ADOs to meaningfully impact prescription drug abuse and the opioid overdose epidemic depends on their availability for prescribing and dispensing, as well as a corresponding reduction in the availability of competing products that are not formulated to have similar abuse-deterrent properties.[27]

The dual transition is not occurring. The presence of opioids without abuse-deterrent properties creates an environment that makes it difficult for ADOs to be adopted broadly. Moreover, generic manufacturers lack adequate incentives to bring generic ADOs to market while new non-ADO generic products continue to obtain approval. To date, no generic opioid has obtained FDA-approved abuse-deterrent labeling. In March 2016, the FDA released "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry" (Draft Guidance), intended to encourage generic drug manufacturers to develop ADO counterparts.[28] The Draft Guidance noted that where an ADO is available, having a corresponding non-abuse-deterrent generic opioid on the market could create a situation in which individuals who abuse opioids may "preferentially seek out and abuse such easier-to-abuse generics."[29] The guidance emphasizes that moving forward, generic drug manufacturers seeking approval of their product must make sure that the generic is "no less abuse-deterrent" than their brand counterpart on the market (*i.e.*, reference-listed drug or "RLD").[30] Additionally, in June 2017, the FDA released draft guidance on priority reviews for

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[26] *Id.*

[27] *See, e.g.*, S.H. Budman et al. *Can abuse deterrent formulations make a difference? Expectation and Speculation*, HARM REDUC. J. 6:8 (2009) (observing that the "maximum impact of these [abuse deterrent formulations] will most likely not be seen until, at the very least, most of the opioid analgesics prescribed are [abuse deterrent formulations]"); Nathaniel Katz, *Abuse-deterrent Opioid Formulations: Are They a Pipe Dream?*, 10:11-18 CURRENT RHEUMATOLOGY REPORTS (2008), http://primeinc.org/downloads/supplements/MCWG_7.pdf. (noting that "earlier generation, more abusable opioids must become relative unavailable" in order for newer abuse deterrent formulations "to realize their public health benefits").

[28] *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, (Mar. 2016), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf.

[29] *Id.*

[30] Alison Gilchrist, *FDA Draft Guidance Encourages Access to Abuse Deterrent Generic Pain Drugs*, Pharmacy Times (May 19, 2016), http://www.pharmacytimes.com/publications/issue/2016/may2016/fda-draft-guidance-encourages-access-to-abuse-deterrent-generic-pain-drugs.

generic drugs.[31] The FDA will expedite the review of generic drug applications until there are three approved generics for a given drug product.[32]

Generic manufacturers with non-abuse-deterrent opioid analgesics on the market need further incentives to make the change. FDA Commissioner Scott Gottlieb has stated that the opioid overdose epidemic is the "biggest crisis facing the agency," and the FDA must "push the policy boundaries for approval of safer opioids and other alternatives to reduce the opioid overdose epidemic."[33] Dr. Gottlieb has also previously urged the FDA to foster a transition to ADOs. In 2012, Dr. Gottlieb stated that "[s]ome of the most widely abused drugs, including oxycodone, have been re-engineered in tamper-resistant formulations and introduced in place of their original versions. Rates of abuse have fallen sharply as a consequence."[34] However, by allowing the "older, riskier versions back onto the market," the FDA "will undermine efforts undertaken by industry and policymakers to design the new tamper-resistant drugs as a way to combat the problem."[35] Dr. Gottlieb concluded that

> Allowing the market to be flooded with cheap, generic versions of outdated formulations will only feed the problems that we have begun to resolve with better technology. The creation of abuse-deterrent formulations fulfilled an important public health goal. Policymakers demanded the creation of these new drugs. We should leverage the benefits of this technology, and not undermine its purpose.[36]

Furthermore, Janet Woodcock, director of the agency's Center for Drug Evaluation and Research, recently reiterated the importance of incentivizing the development of ADOs:

> [W]hat we need to do, we think, is incentivize innovator development of various abuse deterrent formulations. The current ones…are kind of version 1.0 and surely we can do better, right. And so there has to be probably some incentives there. And then generics, we need a pathway so that the generics understand what they would have to do to show that they source exactly the same as the innovator, because uptake of these abuse deterrent formulations is lower because there are a lot of old opioids on the market that are very inexpensive that are not abuse deterrent. And that is often for health systems the preferred opioid to use to save money, so we need a progression of incentives and also a clear pathway. But the innovation needs to go from the innovators, the people who are out there trying to figure out better ways to deter abuse.

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[31] News Release, *FDA Tackles Drug Competition to Improve Patient Access*, U.S. FOOD AND DRUG ADMINISTRATION, (June 27, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm564725.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

[32] *Id.*

[33] Anna Edney, *Opioid Epidemic is FDA's Top Priority, Says Pick to Head Agency*, BLOOMBERG (April 5, 2017), https://www.bloomberg.com/politics/articles/2017-04-05/trump-s-pick-to-lead-fda-defends-investment-work-to-senate-panel.

[34] Sen. Tom Coburn & Scott Gottlieb, M.D., *Prescription for Trouble*, AMERICAN ENTERPRISE INSTITUTE, (Dec. 18, 2012), https://www.aei.org/publication/prescription-for-trouble-2/.

[35] *Id.*

[36] *Id.*

To achieve the FDA's goal of creating and approving "safer opioids," the FDA should require manufacturers of non-abuse-deterrent opioids to act swiftly and adapt their products to ADO versions within three years, as described below. Shifting the market toward all ADOs is in the best interest of both patients and communities that continue to be impacted by the misuse and abuse of prescription opioids.

E. Petitioner's Position

Pursuant to its authority under the FDCA and its implementing regulations, the FDA should foster a transition to ADOs by requiring manufacturers of certain opioids without abuse-deterrent labeling to convert their products to ADOs.

Specifically, once the FDA has approved three IR or three ER/LA oral form ADOs with the same active moiety (*e.g.*, three oral, abuse-deterrent, ER/LA morphine medications), all oral opioids without abuse-deterrent properties with that same active moiety and release profile (*e.g.*, all oral, non-abuse-deterrent, ER/LA morphine medications) should either be converted to an ADO within three years of the approval date of the third ADO or otherwise be removed from the market after such three-year period if they have not been converted to an abuse-deterrent formulation. Given that the FDA has granted labeling to three oral, ER/LA abuse-deterrent morphine and oxycodone medications, manufacturers of oral, non-abuse-deterrent, ER/LA morphine and oxycodone formulations should be required to convert their medications to ADOs within three years of the date of this Citizen Petition or else have their products removed from the market on July 3, 2020.

This requirement would create a strong incentive for manufacturers of non-abuse-deterrent opioids to begin immediately to incorporate abuse-deterrent technology. It would be beneficial to the public because waiting for three ADOs with the same active moiety to obtain FDA-approved labeling creates robust competition to address potential access and pricing concerns.

The FDA has the authority to issue and enforce this requirement. The FDA continues to monitor the safety profile of drugs after first approving them.[37] Where appropriate, the FDA may take safety into consideration when weighing a drug's benefits and risks.[38] To date, the FDA has withdrawn 59 previously approved drugs from the market for reasons of safety or effectiveness.[39]

1. FDA's Authority

The FDA has the authority to withdraw drugs from the market. An approved medication may be withdrawn voluntarily by the manufacturer, by FDA request to the manufacturer, or by

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[37] *FDA/CDER Final Response to Endo Pharmaceuticals Inc Petition Denial*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (May 10, 2013), https://www.regulations.gov/document?D=FDA-2012-P-0895-0014.
[38] *Id.*
[39] *Withdrawn List*, U.S. FOOD AND DRUG ADMINISTRATION (last visited Jan. 31, 2017), http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454B1_03_TOC.htm.

the FDA under statutory authority.[40] The FDA may require the withdrawal of both brand and generic non-abuse-deterrent formulations, and has used this authority in the past to remove other medications from the market.[41]

The FDCA requires the FDA to publish a list of all approved drugs.[42] Under the FDCA and its implementing regulations, the FDA may remove drugs from the list if it withdraws or suspends approval of the drug's New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for safety or effectiveness reasons or determines that the listed drug's manufacturer withdrew the drug from sale for safety or effectiveness reasons.[43] If, at any time, the drug's benefits no longer outweigh the drug's risks, the FDA is required to withdraw approval of the drug's application after due notice and the opportunity for a hearing by the applicant.[44]

2. Oxycodone

In December 1995, the FDA approved an ER formulation of oxycodone for the management of moderate to severe pain where use of an opioid analgesic was appropriate.[45] After reaching the market, the manufacturer learned that consumers were diverting and abusing the product by manipulating it to defeat its extended-release mechanism, causing the oxycodone to be released more rapidly.[46] Individuals were also inadvertently misusing the medication by crushing the product and sprinkling it onto food or administering it through a gastric tube.[47] Such behavior is particularly dangerous and is associated with serious adverse events, including overdose and death.[48] In response, the manufacturer reformulated its ER oxycodone product to make the opioid medication more difficult to cut, break, chew, crush, or dissolve to rapidly release the active ingredient.[49] The FDA approved the reformulated version of ER oxycodone in April 2010.[50] By August 10, 2010, the manufacturer discontinued the non-abuse-deterrent form and began distributing only the new tablets.

Other drug manufacturers nevertheless submitted ANDAs proposing to commercialize non-abuse-deterrent ER oxycodone in generic form after the non-abuse-deterrent ER branded

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[40] *Safety: Background and Definitions*, U.S. FOOD AND DRUG ADMINISTRATION (Last updated June 24, 2009), https://www.fda.gov/Safety/Recalls/ucm165546.htm.
[41] The Secretary of HHS has delegated authority to the FDA to withdrawal approval of a drug after a hearing. 21 U.S.C. § 355(e); 21 C.F.R. §§ 5.10(a)(1), 5.82.
[42] 21 U.S.C. § 355(j).
[43] 21 U.S.C. § 355(j)(7)(C); 21 C.F.R. 314.162.
[44] *How Does FDA Decide When a Drug Is Not Safe Enough to Stay on the Market?*, U.S. FOOD AND DRUG ADMINISTRATION, (last visited Jan. 31, 2017), http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194984.htm.
[45] Purdue Pharma Citizen Petition, (July 13, 2012), *available at* http://www.hpm.com/pdf/blog/FDA-2012-P-0760.pdf.
[46] Oxycodone (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn from Sale for Reasons of Safety or Effectiveness, 78 Fed. Reg. 23273, 23274 (FDA Apr. 18, 2013) (determination).
[47] *Id.*
[48] *Id.*
[49] Purdue Pharma Citizen Petition, (July 13, 2012), http://www.hpm.com/pdf/blog/FDA-2012-P-0760.pdf.
[50] *Id.*

oxycodone was withdrawn from the market.[51] FDCA regulations state that a person may petition the FDA to determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness.[52] Accordingly, in August 2012, the manufacturer of branded ER oxycodone and other parties filed citizen petitions asking that the FDA determine that the non-abuse-deterrent ER oxycodone was withdrawn from the market for safety or effectiveness reasons.[53]

In response, on April 16, 2013, the FDA concluded that reformulated ER oxycodone posed a lower potential for abuse by certain routes of administration—namely snorting and injection—and that *non-abuse-deterrent ER oxycodone was withdrawn from sale for reasons of safety or effectiveness*.[54] As a result, the FDA would not consider for approval ANDAs based on the approval of the original, discontinued version of ER oxycodone.[55] The decision barred generic versions of ER oxycodone that lacked abuse-deterrent properties from the market and established that the FDA recognized that an opioid's benefit/risk profile could change due to the availability of an alternative product with a lower potential for abuse.[56] With this decision, the FDA also approved new labeling for the reformulated ER oxycodone that described the abuse-deterrent properties of the reformulated product.

Likewise, the FDA should make the same determinations for other oral, non-abuse-deterrent opioids currently on the market where three or more corresponding oral ADOs with the same active moiety and release profile are available. The FDA should use its authority to determine that oral, non-abuse-deterrent opioids of a specific moiety are unsafe for use in light of the approvals of three oral, abuse-deterrent versions of that same opioid moiety with the same release profile.

3. FDA's Previous Concerns in Response to Petitioner's 2014 Citizen Petition

In responding to the undersigned's 2014 Citizen Petition requesting that the FDA transition the entire market to ADOs by a certain date, the FDA listed certain concerns. To begin, the FDA stated it was unrealistic to transition the entire market to ADOs because the science of abuse-deterrent technology was in its early stages and still rapidly evolving. The data was not sufficiently mature at that time to confirm expectations of deterring abuse, including whether formulations aimed at making abuse via injection or intranasal route more difficult achieved those goals.

The FDA's response was given three years ago, at a time when only one opioid analgesic medication had received FDA-approved abuse-deterrent labeling. Since then, nine other abuse-deterrent opioid analgesic medications have received such labeling. Additionally, post-market

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[51] Oxycodone Determination, 78 Fed. Reg. 23273 at 23275.
[52] 21 C.F.R. 314.161.
[53] Oxycodone Determination, 78 Fed. Reg. 23273 at 23275.
[54] Response to Citizen Petition, Docket No. FDA-2012-P-0895 (May 10, 2013), http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0895-0014. (emphasis added)
[55] Oxycodone Determination, 78 Fed. Reg. 23273 at 23274.
[56] Response to Citizen Petition, Docket No. FDA-2012-P-0895 (May 10, 2013), http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0895-0014.

research has been conducted showing that an ADO does incrementally deter abuse.[57] These technologies are no longer in a nascent stage, and they continue to demonstrate incremental improvement with regard to abuse-deterrent properties and corresponding safety improvements.

Our current petiton provides manufacturers of non-abuse-deterrent opioids with three years from the date of this Citizen Petition or the date of a third ADO approval, to remove their product and replace it with an ADO, leaving adequate time for transition. A three-year time period is reasonable given the advancement in technology and the urgency of the opioid overdose epidemic. In 2015, when Health Canada, Canada's federal department responsible for the nation's public health, proposed that manufacturers transition to ADOs with a phase-in period of three years to provide "sufficient time for product reformulations and necessary supply chain adjustment," several U.S. Congress members expressed concern that the three-year timeline was too long given the urgency of the opioid overdose epidemic.[58]

In its response to the undersigned's 2014 Citizen Petition, the FDA also noted that ADOs had yet to have an impact on the most common form of abuse—swallowing intact tablets or capsules. The FDA also noted this concern in its "Abuse-Deterrent Opioids—Evaluating and Labeling: Guidance for Industry." However, the most common transition pathway from oral opioid abuse to intravenous abuse is (1) starting with oral ingestion of pills, either taken whole, chewed or manipulated; (2) moving to crushing and insufflation of pills; and (3) potentially crushing and injecting prescription medications to get a quicker and more intense euphoric effect. Therefore, deterring chewing as well as crushing in order to snort and inject can help slow the progression of abuse by limiting access to more dangerous routes of abuse that provide a much faster and more intense euphoria.[59]

Furthermore, the FDA stated in its response that it would continue to take a product-by-product approach. This method was intended to balance the public health interest in the development of drug products with abuse-deterrent properties with the need to preserve access to a range of therapeutic agents (both brand and generic) for patients in pain. The undersigned's proposal would allow the FDA to continue taking a product-by-product approach rather than requiring an entire market shift all at once.

III. Conclusion

For the reasons discussed above, the Petitioner asks the FDA to exercise its authority under the FDCA and its implementing regulations to foster a transition to ADOs. Specifically, the FDA would require that, once the FDA has approved three oral IR or three oral ER/LA ADOs with the same active moiety, all oral opioids without abuse-deterrent properties with that same active moiety and release profile either be converted to an ADO within three years of the approval date of the third ADO or otherwise be removed from the market after such three-year

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[57] PM Coplan, *The Effect of An Abuse-deterrent Opioid Formulation (OxyContin) on Opioid Abuse-Related Outcomes in the Postmarketing Setting* (June 22, 2016), https://www.ncbi.nlm.nih.gov/pubmed/27170195.
[58] Kristy Kirkup, *U.S. Congress Members Express Concern Over Canadian Oxycodone Rule*, THE STAR, (July 24, 2015), https://www.thestar.com/news/canada/2015/07/24/us-congress-members-express-concern-over-canadian-oxycodone-rules.html.
[59] *See* Wilson M. Compton, *Relationship Between Nonmedical Prescription-Opioid Use and Heroin Use*, 374 N ENGL. J. MED. 154 (2016).

period if they have not been converted to an ADO. Given that the FDA has granted labeling to three oral, abuse-deterrent, ER/LA morphine and oxycodone medications, manufacturers of oral, non-abuse-deterrent, ER/LA morphine and oxycodone formulations should be required to convert their medications to ADOs within three years of the date of this Citizen Petition or else have their products removed from the market on July 3, 2020.

IV. Environmental Impact

The Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. §§ 25.30(h), 25.31(h).

V. Economic Impact

The economic impact of prescription opioid abuse alone is $55 billion each year in health and social costs.[60] Additionally, $20 billion is spent annually on emergency department and inpatient care for opioid poisonings.[61] The action requested in the petition will have a positive impact on the economy because it will contribute to a reduction in health care costs and societal costs of prescription drug abuse by fostering a transition to ADOs. For example, the introduction of a new formulation of extended-release oxycodone with abuse-deterrent technology has been associated with an annual medical cost savings of approximately $430 million in the U.S.[62] Furthermore, a budget impact model quantifying the potential cost savings associated with a hypothetical opioid formulation designed to resist or deter common methods of extraction estimated potential cost savings to third party payers at up to $1.6 billion annually.[63]

VI. Certification

I, the undersigned Petitioner, certify that, to the best of my 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 me that are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information that is unfavorable to the petition was 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: May 10, 2017. If I received or expected to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expected to receive those payments from the following persons or organizations: The Center for Lawful Access and Abuse Deterrence's activities are funded through support from our commercial coalition members, which are listed on our website. I

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[60] *The Opioid Epidemic: By the Numbers*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, (June 2016), https://www.hhs.gov/sites/default/files/Factsheet-opioids-061516.pdf.

[61] *Id*.

[62] Rossiter LF, et al, *Medical cost savings associated with an extended-release opioid with abuse-deterrent technology in the U.S.*, J MED ECON, (4):279-87. doi: 10.3111/13696998.2014.897628 (April 17, 2014), https://www.ncbi.nlm.nih.gov/pubmed/24559196.

[63] Katz, N. P., et al, *Prescription Opioid Abuse: Challenges and Opportunities for Payers*, AM. J. MANAG. CARE, 19(4), 295–302, (2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680126/.

verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

I certify, that, to the best of my knowledge and belief, this petition includes all information and views upon which this petition relies, and that it includes representative data and information known to me that is unfavorable to the petition. Thank you for your attention to this important public health matter. I look forward to your prompt responsive actions and written reply.

Respectfully,

Center for Lawful Access and Abuse Deterrence