June 11, 2013

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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 Petitioners, the undersigned concerned citizens, hereby submit this Citizen Petition under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 C.F.R. §§ 5.10, 10.30. The Petitioners request that the Commissioner of Food and Drugs take administrative action to implement Obama Administration policy by fostering a transition to abuse-deterrent opioids and promoting greater access to treatment for opioid addiction and, more specifically, Medication-Assisted Treatment ("MAT"), as set out below.

I. Actions Requested

The Petitioners ask the Food and Drug Administration ("FDA") to foster a transition to abuse-deterrent opioids, patient access to addiction treatment, and more specifically, MAT, by taking the following administrative actions:

- Immediately implement a policy, with limited exceptions¹, of rejecting New Drug Applications ("NDAs") and Abbreviated New Drug Applications ("ANDAs") for opioid drug products in solid oral dosage forms that are not backed by predictive or determinative data supporting the products' potential to reduce abuse;
- Respond in writing to this Citizen Petition with an acknowledgment that the clinical benefits of pharmacotherapies for use in MAT can include patient outcomes other than prolonged abstinence; and
- Prioritize and expedite additional detailed guidance to industry, on a case-by-case basis or otherwise, on the requirements for assessments of effectiveness and abuse deterrence.

II. Statement of Grounds

A. Opioid Abuse Epidemic & Obama Administration Policy

According to the Centers for Disease Control and Prevention ("CDC"), prescription drug abuse is an epidemic in the United States.² There are 33 long-acting and approximately 45 short-acting opioid analgesics presently available on the market. In 2010, approximately 16,651 people in the United States died as result of

² Leonard Paulozzi, et al., *CDC Grand Rounds: Prescription Drug Overdoses—A U.S. Epidemic*, CENTERS FOR DISEASE CONTROL AND PREVENTION, Jan. 13, 2012, *available at* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm.



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¹ Consistent with the Stop Tampering of Prescription Pills Act of 2013, exceptions to the rule that all new opioids must contain abuse-deterrent properties would include a finding that the medication either prevents or alleviates a drug shortage or otherwise addresses a significant unmet public health need in a special needs population. Stop Tampering of Prescription Pills Act of 2013, H.R. 486, 113th Cong. § 2(b) (2013).

unintentional overdoses involving prescription opioid pain relievers.³ According to the Office of National Drug Control Policy ("ONDCP"), prescription drug abuse is "the Nation's fastest-growing drug problem."⁴ Since 2003, more overdose deaths have involved opioid analgesics than heroin and cocaine combined.⁵ According to FDA experts, long-acting and extended-release opioid pain relievers are "extensively misprescribed, misused, and abused, leading to overdoses, addictions, and even deaths across the United States."⁶ The economic impact of prescription drug abuse is \$72.5 billion each year in health care costs alone."⁷

Opioid abuse is not limited to products for the treatment of pain.⁸ Medications used for the treatment of addiction, of which there are approximately 40 on the market, including methadone and buprenorphine products, are also subject to increasing diversion and abuse.⁹ Six times as many people died of methadone overdoses in 2009 than a decade before.¹⁰ From 2003 to 2008, the estimated national number of buprenorphine items secured in law enforcement operations increased more than 250-fold.¹¹ The number of emergency department visits for buprenorphine products doubled between 2007 and 2009.¹² The number of accidental pediatric exposures to buprenorphine is also on the rise, showing a 13-fold increase between 2009 and 2011, according to one study.¹³

In response to this epidemic, the Executive Office of the President and federal agencies have supported a transition to abuse-deterrent opioids, which are designed to make product manipulation more difficult or to make abuse of the manipulated product less attractive or rewarding.¹⁴ Examples include products with physical or chemical barriers to thwart common tactics of drug abusers like chewing, crushing, cutting, grating, or grinding; and subcutaneous implants, which can provide sustained drug delivery and minimize the risks of post-dispensing diversion and consequent abuse, as well as accidental exposure.¹⁵

In 2011, the ONDCP singled out as a top priority in its action plan the research and development ("R&D") of abuse-deterrent formulations of opioid medications.¹⁶ The ONDCP's most recent National

- ⁴ Epidemic: Responding to America's Prescription Drug Abuse Crisis, OFFICE OF NATIONAL DRUG CONTROL POLICY (2011), available at http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan_0.pdf.
- LEONARD PAULOZZI, supra note 2.
- ⁶ FDA Acts to Reduce Harm from Opioid Drugs, FDA CONSUMER HEALTH INFORMATION available at

www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM251895.pdf.

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, FDA, Apr. 2013, available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. To obtain the number of opioids for addiction treatment. Petitioners searched by active ingredient using the terms "buprenorphine," "methadone," and "naloxone."

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf.

Id.; FDA PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE, PROBUPHINE, (Mar. 21, 2013), available at

http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/psychopharmacologicdrugsadvisorycommittees/commit e/ucm344374.pdf.

³ Press Release, Centers for Disease Control and Prevention, Opioids Drive Continued Increase in Drug Overdose Deaths (Feb. 20, 2013), available at http://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html.

See Prescription Drug Abuse and Overdose: Public Health Perspective, CENTERS FOR DISEASE CONTROL AND PREVENTION, Oct. 24, 2012, available at http://www.cdc.gov/primarycare/materials/opoidabuse/docs/pda-phperspective-508.pdf.

⁸ List of Extended-Release and Long-Acting Opioid Products Required To Have an Opioid REMS, FDA, Apr. 22, 2013, available at http://www.fda.gov/DrugSafety/InformationbyDrugClass/ucm251735.htm; Short-Acting Opioids, Opioids 911, available at http://opioids911.org/opioidproducts.php.

¹⁰ CDC Vital Signs, Prescription Painkiller Overdoses: Use and Abuse of Methadone as a Painkiller, CENTERS FOR DISEASE CONTROL AND PREVENTION, (July 2012), available at http://www.cdc.gov/vitalsigns/MethadoneOverdoses/. ¹¹ DEA, Special Report: Methadone and Buprenorphine, 2003-2008, available at

http://www.deadiversion.usdoj.gov/nflis/methadone buprenorphine srpt.pdf.

¹² Opioid Drugs in Maintenance and Detoxification Treatment of Opiate Addiction, 77 Fed. Reg. 72752, 72752 (Dec. 6, 2012) (to be codified at 42 C.F.R. pt. 8).

¹³ Drug to Treat Opioid Addiction Places Children at Risk for Accidental Exposure, University of Utah Health Science Center, Dec. 14, 2012, available at http://www.newswise.com/articles/drug-to-treat-opioid-addiction-places-children-at-risk-for-accidentalexposure.

¹⁴ Guidance for Industry; Abuse-Deterrent Opioids—Evaluation and Labeling, FDA (Jan. 2013) available at

¹⁶ Epidemic: Responding to America's Prescription Drug Abuse Crisis, supra note 4.

Strategy, released in April 2013, also includes a specific action item on abuse-deterrent formulations, calling for expedited research, through grants, partnerships with academic institutions, and priority NDA review by the FDA.¹⁷ The Director of ONDCP, Gil Kerlikowske, recently stated that only abuse-deterrent formulations of opioids should be available on the market.¹⁸ In December 2012, the FDA's Anesthetic and Analgesic Drug Products Advisory Committee recommended that the FDA deny approval of an NDA for an opioid analgesic because the drug lacked abuse-deterrent features.¹⁹

On April 16, 2013, Douglas C. Throckmorton, M.D., deputy director of the FDA's Center for Drug Evaluation and Research, wrote in FDA Voice that the FDA will encourage an ongoing dialogue with manufacturers as they consider developing abuse deterrent opioid analgesic products, stating "... in essence, we'll let manufacturers know where we want them to go, but not prescribe how exactly to get there. Our general goal, overall, is to encourage development of abuse-deterrent opioid products.²⁰

Obama Administration policy also calls for expanding access to addiction treatment. In fact, substance use disorder services are one of the ten categories of essential health benefits that the Affordable Care Act aims to expand.²¹ The Executive Office of the President and various federal agencies have more specifically prioritized MAT, an approach that uses FDA-approved pharmacological treatments, in combination with psychosocial treatments, for patients with opioid use disorders. In the National Strategy, the ONDCP stated that it has supported and continues to support "the development of new medications to treat addiction and the implementation of MAT protocols."²² It further stated: "Steps such as the continuation of stable opioid doses or MAT with either buprenorphine or methadone are recommended."23

The Substance Abuse and Mental Health Services Administration ("SAMHSA") reports that "as part of a comprehensive treatment program, MAT has been shown to improve survival, increase retention in treatment, decrease illicit opiate use, decrease hepatitis and HIV seroconversion, decrease criminal activities, increase employment, [and] improve birth outcomes with perinatal addicts."24 According to ONDCP, "it is crucial that providers in both primary and specialty care settings become trained in Medication-Assisted Treatment."²⁵ SAMHSA provides grants for physician training in MAT.²⁶ The National Institute on Drug Abuse ("NIDA") provides grant support for academic, industry, and government research to identify, evaluate, and develop new medications, including abuse-deterrent opioids, to treat substance use disorders.²⁷

http://www.newsday.com/news/health/tamper-proof-pills-sought-for-opioid-drugs-1.4995484.

¹⁷ National Drug Control Strategy, OFFICE OF NATIONAL DRUG CONTROL POLICY (2013), available at http://www.whitehouse.gov//sites/default/files/ondcp/policy-and-research/ndcs 2013.pdf.

³ Kevin Deutsch, Tamper-Proof Pills Sought for Opioid Drugs, NEWSDAY, Apr. 2, 2013, available at

¹⁹ David Pittman, A Panel Gives Thumbs Down to Opioid, MEDPAGE TODAY, Dec. 7 2012, available at

http://www.medpagetoday.com/PainManagement/PainManagement/36334.

²⁰ Douglas C. Throckmorton, The Science of Abuse-Deterrence—Progress Toward Creating Safer Opioids, FDA VOICE, Apr. 16, 2013, available at http://blogs.fda.gov/fdavoice/index.php/2013/04/the-science-of-abuse-deterrence-progress-toward-creating-saferopioids/.

Kevin Deutsch. supra note 18.

²² National Drug Control Strategy, supra note 17.

²³ Id.

²⁴ Pharmacotherapy for Substance Use Disorder, SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION http://www.dpt.samhsa.gov/medications/medsindex.aspx.

²⁵ Office of National Drug Control Policy, Medication-Assisted Treatment for Opioid Addiction Healthcare Brief (Sept. 2012), available at http://www.whitehouse.gov/sites/default/files/ondcp/recovery/medication_assisted treatment 9-21-20121.pdf

⁶ FY 2013 Cooperative Agreement for the Physician Clinical Support System - Medication Assisted Treatment, SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION, available at http://www.samhsa.gov/grants/2013/ti-13-003.aspx.²⁷ Division of Pharmacotherapies and Medical Consequences of Drug Abuse: What We Do, NATIONAL INSTITUTE ON DRUG ABUSE

available at http://www.drugabuse.gov/about-nida/organization/divisions/division-pharmacotherapies-medical-consequences-drugabuse-dpmcda.

B. Transition to Abuse-Deterrent Opioids

To reduce the prescription drug abuse epidemic, pharmaceutical companies have begun developing and marketing medications incorporating novel technologies intended to discourage abuse. Abuse-deterrent medications have emerged as a means for supporting opioid access while limiting abuse and its consequences.²⁸ Several different types of abuse-deterrent medications have emerged including physical barriers to tampering, agonist-antagonist formulations, aversion, prodrugs, and alternative methods of administration, such as subcutaneous implants.²⁹ Each of these types has the potential to reduce specific forms of prescription opioid abuse.³⁰ Abuse-deterrent medications have the potential to reduce the public health burden of prescription opioid abuse, but they will require not only technically successful formulations, but also appropriate scientific assessment, widespread market penetration, and rational expectations of their benefits.³¹ The ability of abuse-deterrent products to meaningfully impact the prescription drug abuse 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 tamper-resistant properties.³²

1. Oxycodone

In December 1995, the FDA approved an extended-release formulation of oxycodone ("OC") for the management of moderate to severe pain where use of an opioid analgesic is appropriate.³³ In January 2001, approximately five years after the launch of OC, the Drug Enforcement Administration published an Information Bulletin describing abuse and diversion of OC as a significant problem.³⁴ OC was often abused by manipulating the product to defeat its extended-release mechanism, causing the oxycodone to be released more rapidly.³⁵ In addition to intentional abuse, there were instances in which OC was inadvertently misused by legitimate patients or their caregivers, for example, by crushing the product to sprinkle it onto food or to administer it through a gastric tube.³⁶ Such behavior is particularly dangerous and is associated with serious adverse events including addiction and death.³⁷ In response, the manufacturer reformulated OC to make the opioid medication more difficult to cut, break, chew, crush or dissolve to rapidly release the active ingredient.³⁸ The FDA approved the reformulated version of extended-release oxycodone ("OCR") in April 2010.³⁹ By August 10, 2010, the manufacturer had discontinued OC and had begun distributing only the new OCR tablets.

Other drug manufacturers nevertheless submitted ANDAs proposing to commercialize OC in generic form.⁴⁰ ANDA applicants must show that the drug for which they are seeking approval has the same active ingredient, route of administration, dosage form, strength and, with some exceptions, labeling as the

³⁴ Id.

²⁸ 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.²⁹ Id.

³⁰ *Id*.

³¹ Id.

³² 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]"); Katz, supra note 28 (noting that "earlier generation, more abusable opioids must become relative unavailable" in order for newer abuse deterrent formulations "to realize their public health benefits").

³³ Purdue Pharma Citizen Petition, July 13, 2012, available at http://www.hpm.com/pdf/blog/FDA-2012-P-0760.pdf.

³⁵ 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).

³⁶ Id. ³⁷ Id.

³⁸ Purdue Pharma Citizen Petition, *supra* note 33.

³⁹ *Id*.

⁴⁰ Oxycodone Determination, 78 Fed. Reg. 23273 at 23275.

medication they seek to duplicate, which is referred to as the reference listed drug ("RLD").⁴¹ Before approving any ANDAs, the FDA must determine whether the RLD was withdrawn from the market for reasons of safety or effectiveness. If so, the FDA may not approve the ANDA.⁴²

The manufacturer of OCR and other parties filed citizen petitions asking that the FDA determine whether OC was withdrawn from the market for safety or effectiveness reasons.⁴³ In response, on April 16, 2013, the FDA concluded that OCR posed a lower potential for abuse by certain routes of administration, namely snorting and injection, than OC, and that OC was withdrawn from sale for reasons of safety or effectiveness.⁴⁴ As a result, the FDA would not consider for approval ANDAs based on the approval of the original, discontinued version of OC.⁴⁵ The decision barred from the market generic versions of OC that lack abuse-deterrent features. The decision established that the FDA recognizes that an opioid's benefit/risk profile can change due to the availability of an alternative product with a lower potential for abuse.⁴⁶

The FDA also approved new labeling for OCR that describes the abuse-deterrent properties of the reformulated product. OCR received a Tier 3 Label, which is one that makes a claim that the product is expected to result in a meaningful reduction in abuse.⁴⁷ The new labeling states that OCR is imbued with "physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)."⁴⁸

2. Oxymorphone

On June 22, 2006, the FDA approved the original formulation of extended-release oxymorphone ("OP"), an opioid for the treatment of pain.⁴⁹ In recognition of reports of the misuse and abuse of the original OP, the manufacturer, like the maker of OCR, reformulated the product, incorporating in the new extended-release oxymorphone ("OPR") abuse-deterrent technology that the manufacturer describes as virtually identical to that used in OCR.⁵⁰ In December 2011, the FDA approved the new version of OPR and such medication reached the market in February 2012.⁵¹ On May 31, 2012, the maker of OP notified the FDA that it had discontinued the original formulation. On August 13, 2012, it requested that the FDA determine that OP was removed for safety and effectiveness reasons, and that until such determination was made, the FDA should suspend approval of ANDAs referring to OP and not approve any additional ANDAs referring to OP.⁵²

In response, on May 10, 2013, the FDA stated that there was insufficient data to conclude that OPR offered safety advantages over OP, and concluded that OP was not withdrawn from sale for reasons of safety or effectiveness.⁵³ The FDA cited shortcomings in data regarding OPR's reduced potential for abuse as the basis for its decision, describing the data as "inconclusive" and "preliminary," citing that it was not possible to "draw meaningful conclusions" because the manufacturer included only two to three quarter-years of data following the introduction of OPR.⁵⁴ The FDA stated that while it considers the development of abuse-

⁴¹ Response to Citizen Petition, Docket No. FDA-2012-P-0895 (May 10, 2013), available at

http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0895-0014.

⁴² Oxycodone Determination, 78 Fed. Reg. 23273 at 23275.

⁴³ Id.

⁴⁴ Response to Citizen Petition, *supra* note 41.

⁴⁵ Oxycodone Determination, 78 Fed. Reg. 23273 at 23274.

⁴⁶ Response to Citizen Petition, *supra* note 41.

⁴⁷ Guidance for Industry: Abuse-Deterrent Opioids-Evaluation and Labeling, supra note 14.

⁴⁸ OxyContin Label, FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

⁴⁹ Complaint at 2, Endo Pharmaceuticals Inc. v. U.S. Food & Drug Administration, 1:12-cv-01936 (D.D.C. Nov. 20, 2012).

⁵⁰ Id.

⁵¹ Id.

⁵² Id. at 4.

⁵³ Response to Citizen Petition, *supra* note 41.

⁵⁴ Id.

deterrent formulations a high public health priority, such properties must be supported by adequate data and emphasized the importance of a case-by-case determination taking into account the totality of the evidence for a particular drug at issue.⁵⁵ The decision allowed generic versions of OP that lack abuse-deterrent features to remain on the market and expressly stated that additional generic versions of the discontinued OP may be approved.

3. Buprenorphine

For over a decade, buprenorphine has been deemed safe and effective for opioid addiction treatment.⁵⁶ Given that buprenorphine can be misused, abused, or diverted to the black market, on October 1, 2009, the National Institutes of Health ("NIH") awarded a two-year grant in the amount of \$7.6 million to a company developing an abuse-deterrent buprenorphine implant for the treatment of opioid addiction.⁵⁷ The buprenorphine implant is designed to provide a therapeutic level of buprenorphine to an opioid-dependent patient for up to six months.⁵⁸ A study reported in the Journal of the American Medical Association ("JAMA") heralded the buprenorphine implant as an important advancement in opioid addiction based on promising findings.⁵⁹ The article highlighted data from a 163-patient trial, which showed that patients receiving the buprenorphine implant had significantly less illicit opioid use, experienced fewer symptoms of withdrawal and craving, stayed in treatment longer and had greater overall improvement when compared to placebo patients over the course of the six-month study.⁶⁰

In a letter to the FDA dated March 13, 2013, the American Society of Addiction Medicine expressed its conclusion that the buprenorphine implant "has been shown to be safe and effective for the treatment of opioid dependence."⁶¹ The ONDCP's 2013 National Drug Control Strategy states that the buprenorphine implant has the potential to eliminate the need for a daily dose of buprenorphine and reduces the potential for diversion and abuse.⁶² On March 21, 2013, the FDA's Psychopharmacology Drugs Advisory Committee voted for approval of the medication, recognizing the favorable benefit-risk profile and voting in favor of both the effectiveness and safety of the implant.⁶³ The Committee acknowledged that the buprenorphine implant has the potential to meet an important public health need because implants are more difficult to divert, and because young children are less likely to be accidentally exposed to an implant than to sublingual formulations.⁶⁴

Despite this consensus, on May 1, 2013, the FDA withheld approval for the buprenorphine implant, informing the manufacturer that it must submit new clinical data to establish the medication's effectiveness for the FDA to reconsider the application.⁶⁵ Specifically, the FDA stated: "Even after allowing four months for

http://www.titanpharm.com/press/2013/13-21-2013-Titan-PDAC-Positive-Vote-PR-FINAL.htm.

⁵⁵ Id.

⁵⁶ About Buprenorphine, SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION, available at http://buprenorphine.samhsa.gov/about.html.

⁵⁷ Press Release. Titan Announces Award of NIH Grant for Probuphine Clinical Development (Oct. 1, 2009) available at http://www.reuters.com/article/2009/10/01/idUS179808+01-Oct-2009+BW20091001.

³⁸ FDA PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE, supra note 15.

⁵⁹ Important Events in NIDA History, NATIONAL INSTITUTES OF HEALTH, available at,

http://www.nih.gov/about/almanac/organization/NIDA.htm. ⁶⁰ Press Release, Titan Pharmaceuticals Inc—Presents Phase 3 Probuphine™ Data at Society For Neuroscience Annual Meeting, (Nov. 17, 2010) available at http://www.titanpharm.com/press/2010/101117-press-rel-Q3-probuphine-data.htm. ⁶¹ Letter from Stuart Gitlow, President of American Society of Addiction Medicine, to Margaret A. Hamburg, Sec'y of HHS (Mar.

^{13, 2013)} available at http://www.asam.org/docs/advocacy/fda-Probuphine-hearing-

comments asam 14march2013.pdf?sfvrsn=0#search= percent22buprenorphine percent20wait percent20list percent22. ² National Drug Control Strategy, supra note 17.

⁶³ Press Release, Titan Pharmaceuticals Announces FDA Advisory Committee Recommends Approval of Probuphine for the Treatment of Adult Patients with Opioid Dependence, Titan Pharmaceuticals, Mar. 21, 2013, available at

⁶⁴ FDA PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE, supra note 15.

⁶⁵ John Carroll, Updated: FDA Steamrolls Over Panel Vote, Spurns Titan's Addiction Drug Probuphine, FIERCEBIOTECH, May 1, 2013. available at http://www.fiercebiotech.com/node/332782/print.

engagement in treatment, only three [buprenorphine implant]-treated patients were fully abstinent from opioids."⁶⁶

The company developing the abuse-deterrent buprenorphine implant is a small company with just 13 employees.⁶⁷ At the end of 2012, the company had only \$18 million in the bank, while its stock was selling at \$1.25 per share.⁶⁸ The stock plunged to \$0.45 per share on May 1, 2013 – the biggest decline in 17 years – after the FDA ruled that it was withholding approval for the medication.⁶⁹ According to the company's 2012 report to the Securities and Exchange Commission, it is possible that the company will not have sufficient funds available to complete the FDA approval process and commercialize the buprenorphine implant.⁷⁰

C. Petitioners' Position

The Petitioners support the FDA's efforts to provide drug sponsors with the regulatory clarity necessary to develop and assess abuse-deterrent formulations of opioids. Moreover, the Petitioners respect the FDA's thoroughness in carefully assessing available scientific data and information on safety, effectiveness, and abuse deterrence. Nevertheless, recent FDA actions indicate that the FDA is not acting in a manner that adequately reflects the urgency of the prescription drug abuse epidemic, and that the FDA is not optimally exercising its regulatory authority to advance the Obama Administration policies supporting a transition to abuse-deterrent opioids, patient access to addiction treatment, and more specifically, MAT.

1. Reject NDAs and ANDAs for Opioids That Are Not Abuse-Deterrent

The Petitioners oppose the FDA's May 10, 2013 decision that additional ANDAs that refer to OP may be approved and introduced to the U.S. market. This action conflicts with and undermines Obama Administration policy and the FDA's pronouncement that the development of abuse-deterrent formulations is a high public health priority.

When promising evidence for an abuse-deterrent approach exists but not enough data have been gathered to draw conclusions about the particular approach, the FDA should dedicate its resources toward working on an expedited basis with manufacturers to help them to collect and report the data necessary to support a conclusion, if possible, that an abuse-deterrent product has a lower abuse potential by certain routes of administration than a prior formulation. Allowing ANDAs for generic versions of withdrawn, non-abuse-deterrent opioids to proceed expends vital, yet limited, FDA resources. More importantly, it poses severe public health and safety threats.

The availability of more generic, non-abuse-deterrent opioids will increase the supply of relatively lowcost drugs that people are willing and able to abuse. An increase in consumption will follow. Serious public health and safety consequences can include increases in pharmacy thefts, criminal diversion, violence, drug abuse, unintentional overdoses, and deaths.⁷¹

⁶⁶ Id.

⁶⁷ Titan Pharmaceuticals, Annual Report (Form 10-K) (Feb. 18, 2013).

⁶⁸ Panel Banks Titan's Probuphine But Voices Abuse Concerns, EP VANTAGE, Mar. 22, 2013, available at

http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=406094§ionID=&isEPVantage=yes; Press Release, Jason Napodana, PropThink: Titan Files NDA on Probuphine; Partner Waits, (Oct. 29, 2012) available at

http://www.reuters.com/article/2012/10/29/idUS151764+29-Oct-2012+HUG20121029.

⁶⁹ Anna Edney, Titan Plunges After FDA Rejects Drug-Addiction Treatment, BLOOMBERG, May 1, 2013, available at

http://www.bloomberg.com/news/2013-05-01/titan-s-probuphine-fails-to-win-approval-for-opioid-addiction.html.

⁷⁰ See Titan Pharmaceuticals, Annual Report (Form 10-K) (Feb. 18, 2013).

⁷¹ Brief of Center for Lawful Access and Abuse Deterrence as Amici Curiae Supporting Plaintiff, Endo Pharmaceuticals Inc., v. U.S. Food & Drug Administration, No. 1:12-cv-01936 (2012).

The marketing of more abuse-prone opioids will reverse the gradual progress brought about by the replacement of traditional opioids with abuse-deterrent forms and will undercut efforts to shift the market from the more easily abused drugs to the new, less readily abused medications with tamper-resistant features.⁷² Given mandatory generic-drug-substitution laws and third-party payor policies, the widespread dispensing and utilization of generic, non-tamper-resistant versions of OP and other medications without abuse-deterrent features will preclude the new formulations from attaining their full public health potential.⁷³ For example, it will compromise the monitoring and analysis of the epidemiological benefits of the new products.⁷⁴

The will to invest in the significant R&D necessary to bring more of these innovative products to market will also be substantially reduced.⁷⁵ It will be extremely risky for a company to invest in the costly R&D of novel technologies to reduce prescription drug abuse and treat drug addiction only to be twofold undercut first by a federal regulatory body that does not fully exercise its authority to foster a market transition to abuse-deterrent opioids, and second by competitors intent on profiting from formulations that are more easily abused.

There are approximately 75 opioid analgesics and 40 opioids for addiction treatment presently available on the market.⁷⁶ The ability of new, abuse-deterrent products to meaningfully impact the prescription drug abuse epidemic depends on their availability for prescribing and dispensing, as well as a corresponding reduction in the availability of traditional products that are not formulated to have similar tamper-resistant properties.⁷⁷ Rather than increase the availability of widely abused prescription drugs, as the FDA is poised to do based on its May 10, 2013 decision, an approach more consistent with the FDA's mission to protect the public health and safety, White House Policy, and market realities, is to approve only NDAs and ANDAs for opioids for which predictive or determinative data supports the products' potential to reduce abuse.

Implementation of this important policy is also necessary to prevent the public health risks associated with the potential approval of the pending NDA 202880 for a non-abuse-deterrent formulation of single-entity extended-release hydrocodone ("non-ADF HC"). As the first approval of a single-entity extended-release formulation of hydrocodone, the approval of non-ADF HC is likely to open the door to a whole new category of highly-abusable versions (both brand and generic) of one of the most commonly prescribed and widely abused opioid drug products. The approval of non-ADF HC would open a significant new opportunity for prescription opioid diversion and abuse. After the brand-name product's three-year exclusivity period, non-abuse-deterrent generic versions of that drug would flood the market. The approval of non-ADF HC could also, under some circumstances, actually delay the introduction of the single-entity, extended-release hydrocodone drug products currently under development that have been designed with abuse-deterrent features.⁷⁸

Recognizing the extraordinary risk that non-ADF HC presents, the FDA Anesthetic and Analgesic Drug Products Advisory Committee, which considered the non-ADF HC NDA on December 7, 2012, voted 11 to 2

 ⁷² STEPHANIE BEASLEY, Advocates Say Generics, Like Brands, Must Adopt Abuse-Deterrent Formulas, FDA Week, Nov. 30, 2012, available at http://www.claad.org/downloads/CLAAD-Advocates-Say-Generics-FDA-12-12.pdf.
 ⁷³ Letter from Center for Lawful Access and Abuse Deterrence, et al., to Margaret A. Hamburg, Commissioner of Food and Drugs,

¹³ Letter from Center for Lawful Access and Abuse Deterrence, et al., to Margaret A. Hamburg, Commissioner of Food and Drugs, FDA, (Oct. 18, 2012), *available at* http://www.claad.org/downloads/Coalition-letter-to-FDA-re-ADF-conditions-101812.pdf. ⁷⁴ *Id*.

⁷⁵ Id.

⁷⁶ List of Extended-Release and Long-Acting Opioid Products Required To Have an Opioid REMS, supra note 8; Short-Acting Opioids, supra note 8.

⁷⁷ See, e.g., Budman, supra note 32; Katz, supra note 28.

⁷⁸ The scope of the three-year exclusivity that might attach to the non-ADF HC NDA is not clear. However, if that exclusivity were to extend to 505(b)(2) NDAs for an abuse-deterrent single-entity, extended-release hydrocodone formulation, the result could be a significant delay in the availability of safer products. Moreover, even if the exclusivity for non-ADF HC does not delay approval of abuse-deterrent versions of hydrocodone (or after the exclusivity expires), the approval and launch of abuse-deterrent alternatives would not prevent the continued sale of non-ADF HC (or generic versions of it) unless the manufacturer of non-ADF HC voluntarily ceased marketing or the FDA were to withdraw the approval of non-ADF HC on safety grounds.

to recommend that the FDA reject that application.⁷⁹ The committee agreed that standards for opioid product approval should be raised in light of the current public health concerns of abuse and misuse.⁸⁰ The committee stated that the FDA should not approve ER/LA opioids without tamper-resistant or abuse-deterrent formulations.⁸¹

The FDA should accept its advisory panel recommendation and refuse to approve the non-ADF HC NDA on safety grounds based on the fact that it has no abuse-deterrent features.

2. Acknowledge Array of Clinical Benefits of MAT

An abuse-deterrent buprenorphine implant can advance two important national public health goals: a transition to opioids less prone to diversion and abuse, and patient access to MAT. The FDA's rationale for its May 1, 2013 decision to withhold approval for the buprenorphine implant is inconsistent with established scientific-medical principles and Obama Administration policy, and again fails to recognize the urgency of the opioid abuse epidemic. The FDA stated that a reason for its postponing approval of the buprenorphine implant was the lack of abstinence among patients treated with the implant, yet it is well established in scientificmedical literature and professional practice that abstinence is not the only desirable end result that MAT can provide to patients.⁸² In fact, SAMHSA's overview of MAT does not recognize abstinence as a clinical outcome.83

Although abstinence should be an ultimate goal of addiction treatment, MAT often yields a higher rate of other kinds of success.⁸⁴ Scientific peer-reviewed studies establish that MAT can lead to substantial benefits aside from abstinence, such as retention in treatment, reduction in illicit substance use, improved psychiatric status, greater social adjustment, and increase in functional state and quality of life.⁸⁵ Other benefits include decreased craving; blocking of withdrawal symptoms; reduced likelihood of overdose and death; decrease in risk behaviors, such as non-sterile injections and unsafe sexual activity (which can result in the transmission of HIV and Hepatitis C); lower criminality; and improved function as determined by the Addiction Severity Index, which looks to employment, family, psychiatric health, legal status, and alcohol or other drug use.⁸⁶

Maintenance Treatments: Blending Conference Session, 23 J. OF SUBSTANCE ABUSE TREATMENT 93 (2002); Miranda W. Langendam, et al., The Impact of Harm-Reduction-Based Methadone Treatment on Mortality Among Heroin Users, 91 AM. J. OF PUB. HEALTH 774, No. 5 (2001); G.K. Hulse, et al., The Quantification of Mortality Resulting from the Regular Use of Illicit Opiates, 94(2) ADDICTION 221 (1999); D. Dwayne Simpson, et al., Drug Abuse Treatment Retention and Process Effects on Follow-Up Outcomes, 47 DRUG & ALCOHOL DEPENDENCE 227 (1997); S. Darke et al., Fatal Heron "Overdose": a Review, 91:30 DRUG ADDICTION 327 (1996); J.R.M. Caplehorn, et. al., Retention in Methadone Maintenance and Heroin Addicts' Risk of Death, 89 ADDICTION 203 (1994); M. Davoli et al., Risk Factors for Overdose Mortality: A Case-Control Study Within a Cohort of Intravenous Drug Users, 22 INT'L J. EPIDEMIOL 273 (1993); L. Gronbladh, et al., Mortality in Heroin Addiction: Impact of Methadone Treatment, 82 ACTA PSYCHIATRY SCAND. 223 (1990); Russell K. Portenoy, et al., Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 Cases, 25 PAIN 171 (1986).

86 E.g., Parran, supra note 84; C. Leonardi, et al., Multi-Centre Observational Study of Buprenorphine Use in 32 Italian Drug Addiction Centres, 94 DRUG & ALCOHOL DEPENDENCE 125 (2008); Maremmani, supra note 84; David C. Lott, HIV Risk Behaviors During Pharmacologic Treatment for Opioid Dependence: A Comparison of Levomethadyl Acetate Hydrochloride, Buprenorphine, and Methadone, 31 J. OF SUBSTANCE ABUSE TREATMENT 187 (2006); Kreek, supra note 85; Langendam, supra note 85; Antonios

⁷⁹ FDA. Summary Minutes of Meeting of the Anesthetic and Analgesic Drug Products Advisory

Committee, December 7, 2012, at 6, available at http://www.fda.gov/downloads/AdvisoryCommittees/Committees/MeetingMaterials/ Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM336475.pdf.

⁸⁰ Id. ⁸¹ Id.

⁸² Carroll, supra note 65.

⁸³ Pharmacotherapy for Substance Use Disorders, supra note 24.

⁸⁴ T.V. Parran, et al., Long-Term Outcomes of Office-Based Buprenorphine/Naloxone Maintenance Therapy, 106 DRUG & ALCOHOL DEPENDENCE 56 (2010); Icro Maremmani, et al., Substance Use and Quality of Life Over 12 Months Among Buprenorphine Maintenance-Treated and Methadone Maintenance-Treated Heroin-Addicted Patients, 33 J. OF SUBSTANCE ABUSE TREATMENT 91 (2007). ⁸⁵ E.g., Parran, supra note 84; Maremmani, supra note 84; Mary Jeanne Kreek, et al., History and Current Status of Opioid

Additionally, outcomes can be measured in terms distinct from abstinence, such as reduction in daily use⁸⁷ and fewer days of use per month.⁸⁸

Many studies have found that MAT may not yield prolonged abstinence. For instance, one study established that abstinence-oriented interventions work only in a subgroup of motivated patients with stable living conditions and adequate social support.⁸⁹ In another study, when 858 patients were questioned on the topic of abstinence, only 50 percent of them reported that their goal was to achieve total abstinence from illicit opioids, and 50 percent of the participants used an illicit opioid at least once a month during the treatment.⁹⁰ In yet another study, the average rate of patient retention using MAT was only 44 percent after 24 weeks.⁹¹ Retention in maintenance treatment can be significantly improved by changing dosage policy and reorienting programs from the objective of abstinence.⁹² Acknowledging such, SAMHSA has defined "recovery" as "non-linear, characterized by continual growth and improved functioning that may involve setbacks."⁹³

As the FDA's Psychopharmacology Drugs Advisory Committee acknowledged, patients treated with the buprenorphine implant were less likely than patients who received a placebo to require supplemental treatment of subjective symptoms of withdrawal or craving.⁹⁴ Scientific-medical literature shows a significant, high correlation between dropping out of opioid addiction treatment and the severity of withdrawal symptoms, establishing that the worse the withdrawal symptoms are, the less likely the patient is to remain in treatment.⁹⁵ Subjects with more severe withdrawal symptoms drop out of treatment earlier and have worse outcomes than subjects with lower levels of withdrawal.⁹⁶ Another study established a strong correlation between the duration of maintenance treatment using buprenorphine and decrease in heroin cravings.⁹⁷ Thus, the buprenorphine implant's ability to reduce withdrawal symptoms and cravings can be expected to lead to increased chances of treatment retention, evidencing yet other clinical benefits aside from abstinence.

Abstinence-oriented interventions work only in a subgroup of motivated patients.⁹⁸ In fact, research suggests that about half of patients undergoing treatment for opioid-related substance-use disorders seek to achieve total abstinence.⁹⁹ Nevertheless, addiction treatment generally, and MAT more specifically, can help improve survival, increase retention in treatment, decrease illicit opioid abuse, decrease hepatitis and HIV seroconversion, decrease criminal activities, increase employment, and improve birth outcomes with perinatal addicts.¹⁰⁰ Abstinence should not be the exclusive clinical outcome the FDA considers when assessing the

Paraherakis, An Abstinence-Oriented Program for Substance Use Disorders: Poorer Outcome Associated with Opiate Dependence, 45 CAN J. PSYCHIATRY 927 (2000); Hulse, supra note 85; Simpson, supra note 85; Darke, supra note 85; Caplehorn, supra note 85; Davoli, supra note 85; Gronbladh, supra note 85; Portenoy, supra note 85.

⁸⁷ Simpson, *supra* note 85.

⁸⁸ E.g., Valerie Gruber, et al., A Randomized Trial of 6-Month Methadone Maintenance with Standard or Minimal Counseling Versus 21-Day Methadone Detoxification, 94 Drug & Alcohol Dependence 199 (2008); Maremmani, supra note 84.

⁸⁹ Michael Soyka, et al., Retention Rate and Substance Use in Methadone and Buprenorphine Maintenance Therapy and Predictors of Outcome: Results from a Randomized Study, 11 INT'L J. OF NEUROPSYCHOPHARMACOLOGY 641 (2008).

⁹⁰ Karen L. Sees, et al., Methadone Maintenance vs. 180-Day Psychosocially Enriched Detoxification for Treatment of Opioid Dependence: A Randomized Controlled Trial, 10 J. OF AM. MED. ASS'N 283 (2008).

⁹¹ Soyka, supra note 89.

⁹² Caplehorn, *supra* note 85.

⁹³ SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION, SAMHSA'S WORKING DEFINITION OF RECOVERY, available at http://store.samhsa.gov/shin/content/PEP12-RECDEF/PEP12-RECDEF.pdf.

⁹⁴ FDA PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE, *supra* note 15.

⁹⁵ Parran, *supra* note 84; Soyka, *supra* note 89.

⁹⁶ Douglas M. Ziedonis, et al., Predictors of Outcome for Short-Term Medically Supervised Opioid Withdrawal During a Randomized, Multicenter Trial of Buprenorphine—Naloxone and Clonidine in the NIDA Clinical Trials Network Drug and Alcohol Dependence, 99 DRUG & ALCOHOL DEPENDENCE 28 (2009).

⁹⁷ Mark K. Greenwald, et al., Opioid Reinforcement in Heroin-Dependent Volunteers During Outpatient Buprenorphine Maintenance, 56 DRUG & ALCOHOL DEPENDENCE 191 (1999).

⁹⁸ E.g., Soyka, *supra* note 89.

 $^{^{99}}E.g.$, Sees, supra note 90.

¹⁰⁰ E.g., Parran, supra note 84; Lott, supra note 86; Paraherakis, supra note 86; Hulse, supra note 85; Caplehorn, supra note 85.

effectiveness of a pharmacotherapy for use in MAT. No medication is appropriate or yields optimal results for all patients, but it is nonetheless imperative to bring to market those medications that provide some clinical benefit for some patients. Indeed, the FDA recently recognized that the non-abstinence-based MAT approach should be affirmatively encouraged in the case of nicotine replacement therapy ("NRT") - actively encouraging companies to submit NDA supplements to broaden the indications for use of NRT to permit longterm use and to provide for use in conjunction with other nicotine-containing products, including cigarettes.¹⁰¹ Even limited approval and availability of an abuse-deterrent buprenorphine implant will enable some physicians and patients to determine whether such a treatment option will help the patient attain the clinical benefit he seeks. It can improve some lives and enable the drug sponsor to conduct additional clinical research that could ultimately improve others.

A failure to acknowledge the wide array of potential clinical benefits of MAT and a related withholding of approval for abuse-deterrent medications to treat opioid dependence can have devastating effects on pharmaceutical companies, which in turn, can further slow the transition or even reverse progress toward the adoption of abuse-deterrent medications in the marketplace. Delaying approval of NDAs based on an inadequate understanding of scientific-medical literature and professional practice creates a disincentive for pharmaceutical companies to develop abuse-deterrent medications in the future. The development process is time-consuming, risky, and costly. A delay in providing guidance or finding that a product is safe and effective or more abuse-deterrent than prior formulations can put a small pharmaceutical company out of business. A lack of regulatory clarity and efficiency can discourage other pharmaceutical companies from investing in new abuse-deterrent formulations because it makes the process for developing new medications even more expensive and the chance of approval and favorable determination of relative abuse deterrence is even more unpredictable.

As discussed above, the nascent market for abuse-deterrent opioids is highly vulnerable to regulatory uncertainty. It is possible that the company developing the abuse-deterrent buprenorphine implant will not have sufficient funds available to complete the FDA approval process and commercialize the buprenorphine implant.¹⁰² This result will harm patients and the public at large by denying individuals with opioid dependence an option for treatment that combines a medication well established as safe and effective with a means of administration that inherently reduces the potential for diversion, abuse, and accidental exposure. Such an outcome will also frustrate the Obama Administration policies supporting a transition to abusedeterrent opioids, patient access to addiction treatment, and more specifically, MAT. The Obama Administration's NIH grant in the amount of \$7.6 million to support the abuse-deterrent buprenorphine implant will have yielded failure.

3. Prioritize and Expedite More Specific Guidance

The FDA's April 16, 2013 decision to bar generic versions of OC for their lack of abuse-deterrent features represents a first step in the transition to abuse-deterrent opioids. The Petitioners thank the FDA for making the right policy determination: After a product proves to be abuse deterrent, generics without abusedeterrent features may not reference such product.

The Petitioners defer to the FDA on medical and scientific data necessary to establish that a new medication poses a lower risk for abuse by certain routes of administration than its prior formulation. We urge the FDA to follow through with Dr. Throckmorton's April 16, 2013 assurance that the agency will let manufacturers know where it wants them to go as they develop abuse-deterrent opioids. More specifically, in light of the divergent outcomes of the petitions to determine that OC and OP were removed for safety reasons,

¹⁰¹ Modifications to Labeling of Nicotine Replacement Therapy Products for Over-the-Counter Human Use, 78 Fed. Reg. 19718 (Apr. 2, 2013). ¹⁰² Titan Pharmaceuticals, Annual Report (Form 10-K) (Feb. 18, 2013).

the FDA should provide additional detailed guidance to industry, on a case-by-case basis or otherwise, on its expectations for assessments of abuse deterrence. Doing so will help the pharmaceutical industry to proceed swiftly and with greater clarity as to scientific and regulatory requirements necessary to develop and commercialize products that deter common forms of abuse.

In cases in which the FDA has previously denied a drug sponsor's petition for a determination that its reformulated product has a relatively lower abuse potential, or that its product was removed for safety reasons, the FDA should prioritize and expedite its ongoing dialogue with manufacturers and follow-on product review. Doing so advances Obama Administration policy and reflects the urgency of the prescription drug abuse epidemic.

Similarly, if it is possible for the company developing the abuse-deterrent buprenorphine implant to continue its efforts to obtain FDA approval of the product, the FDA should prioritize and expedite an ongoing dialogue with the sponsor, as well as acknowledge the array of clinical benefits of MAT other than prolonged abstinence, as established in scientific-medical literature and recognized by SAMHSA. Doing so advances Obama Administration policy and reflects the urgency of the prescription drug abuse epidemic.

III. Conclusion

For the reasons discussed above, the Petitioners ask the FDA to foster a transition to abuse-deterrent opioids, patient access to addiction treatment, and more specifically, Medication-Assisted Treatment, by taking the following administrative actions:

- Immediately implement a policy, with limited exceptions¹⁰³, of rejecting NDAs and ANDAs for opioid drug products in solid oral dosage forms that are not backed by predictive or determinative data supporting the products' potential to reduce abuse;
- Respond in writing to this Citizen Petition with an acknowledgment that the clinical benefits of
 pharmacotherapies for use in MAT can include patient outcomes other than prolonged abstinence;
 and
- Prioritize and expedite additional detailed guidance to industry, on a case-by-case basis or otherwise, on the requirements for assessments of effectiveness and abuse deterrence.

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 drug abuse is \$72.5 billion each year in health care costs alone.¹⁰⁴ The actions requested in the petition will have a positive impact on the economy because they will contribute to a reduction in the societal costs of prescription drug abuse by fostering a transition to abuse-deterrent opioids, patient access to addiction treatment, and more specifically, MAT.

¹⁰³ Consistent with the Stop Tampering of Prescription Pills Act of 2013, exceptions to the rule that all new opioids must contain abuse-deterrent properties would include a finding that the medication either prevents or alleviates a drug shortage or otherwise address a significant unmet public health need in a special needs population. Stop Tampering of Prescription Pills Act of 2013, H.R. 486, 113th Cong. § 2(b) (2013).

¹⁰⁴ See Prescription Drug Abuse and Overdose: Public Health Perspective, supra note 7.

VI. 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: May 10, 2013. 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: none. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

The undersigned certify, that, to the best of our 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 the Petitioner that are unfavorable to the petition. Thank you for your attention to this important public health matter. The Petitioners look forward to your prompt responsive actions and written reply.

Sincerely,

Michael C. Barnes

Michael C. Barnes For the Organizations Identified Below

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