DEPARTMENT OF HEALTH & HUMAN SERVICES

APR - 1 2015

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

Nathaniel Katz, MD, MS
Analgesic Solutions
232 Pond Street
Natick, MA 01760

Re: Docket No. FDA-2009-P-0252

Dear Dr. Katz:

This letter responds to your citizen petition received on May 27, 2009, and submitted on behalf of the participants at the Tufts Health Care Institute Programs' meeting on Opioid Risk Management held on November 9-10, 2006 (Petition). In your Petition, you request that the Food and Drug Administration (FDA or Agency):

1. Publish a Guidance for Industry that will outline the approval requirements for safe and effective tamper-deterrent or abuse-deterrent formulations of opioid analgesics.

2. Grant fast track status to INDs [(investigational new drug applications)] for abuse-deterrent formulations (ADFs) of opioid analgesics.

3. Assign priority review timelines to NDAs [(new drug applications)] for ADFs of opioid analgesics.

4. Develop and publish guidelines for clear meaningful labeling for these products.

5. Devote sufficient and appropriate budgetary, personnel and management resources to accomplish the above.

6. Propose legislative remedies to provide incentives for the pharmaceutical industry to develop ADFs for opioid analgesics; such remedies may include, but are not limited to, exclusivity and/or tax credits

(Petition at 1). We have carefully reviewed the Petition and attachments. As discussed below, the Petition is granted in part and denied in part.

## I. BACKGROUND

### A. Opioid Analgesics

Opioid analgesics (e.g., hydrocodone, oxycodone, morphine, and fentanyl) play a vital role in treating both chronic and acute pain. The Institute of Medicine reports that millions of Americans are living with chronic pain, including those suffering from back pain, neuropathic pain, and pain associated with cancer, with an annual economic cost of approximately $600

billion in health care expenses and lost productivity.[1] Millions more suffer from acute pain following common medical procedures performed every day across the country, such as dental and orthopedic procedures. Although FDA is working to support the efficient development of safer, non-opioid alternatives for treating pain, opioids are currently an indispensable component of the pain treatment armamentarium and will remain so for some time to come.

Unfortunately, the abuse and misuse of opioid medications has become a public health crisis. A comprehensive approach is needed to address this crisis — one that involves Federal agencies, state governments, professional medical organizations, academic institutions, and other stakeholders. FDA, as one part of the response to this crisis, is working to improve the safe use of opioids.

### B. FDA's Actions on Opioid Analgesics With Abuse-Deterrent Properties

FDA strongly supports the development of opioid medications with meaningful abuse-deterrent properties.[2] Although this field holds great promise, it is relatively new. Currently available abuse-deterrent formulations are expected to provide improvements over existing formulations, but their impact on the abuse epidemic may be limited. For example, even though some abuse-deterrent technologies have been demonstrated to deter some forms of abuse (e.g., injection or intranasal) to varying degrees in controlled settings, as yet no marketed opioid formulation has been demonstrated to deter the simplest and most common form of abuse — swallowing a number of intact tablets or capsules. Further, all currently available formulations designed to deter abuse can be defeated with sufficient time, equipment, and expertise. These limitations may be impossible to completely overcome as these products must release the opioids they contain to have their intended therapeutic effects.

FDA believes abuse-deterrent technologies can and will improve substantially and can make a real impact in the fight against prescription opioid abuse. FDA hopes that as the market for opioid medications transitions to abuse-deterrent formulations, abuse rates will decrease and the most significant consequences of that abuse (addiction, overdose, and death) will diminish. To that end, fostering the development and iterative improvement of abuse-deterrent formulations of opioid medications is a top priority. FDA's work in support of this priority has included the following:

- Established an Opioids Taskforce to coordinate and support FDA work on abuse-deterrent formulations of opioids.

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[1] Institute of Medicine, 2011, Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, Washington, DC: National Academies Press, at 3, available at http://books.nap.edu/openbook.php?record_id=13172.

[2] We have defined *abuse-deterrent properties* to mean those properties shown to meaningfully *reduce* abuse, even if they do not fully *prevent* abuse.

- Consulted with advisory committees in connection with the development, evaluation and labeling of opioids with abuse-deterrent technologies. For example, in October 2010, a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held to discuss, among other things, how sponsors should design and conduct postmarket epidemiological or observational studies to evaluate whether and to what extent products designed to reduce the likelihood and incidence of abuse actually do so.

- Met and worked with sponsors seeking approval of potentially abuse-deterrent formulations and reviewed applications for approval. Also met and worked with sponsors seeking inclusion of language in product labeling regarding the products' purportedly abuse-deterrent properties.

- Determined that the original formulation of OxyContin posed an increased potential for abuse by certain routes of administration compared to reformulated OxyContin. Based on the totality of the data and information available, FDA concluded that the benefits of original OxyContin no longer outweighed its risks. The agency determined that original OxyContin was withdrawn for reasons of safety and effectiveness, and accordingly will not accept abbreviated new drug applications (ANDAs) that refer to original OxyContin.

- Conducted or supported research on opioid formulations designed to deter abuse. This includes development of in vitro testing methodologies to assess purportedly abuse-deterrent opioid formulations.

- Sought public comment on innovative packaging, storage, and disposal systems that could help deter prescription opioid abuse.

- Hosted a public meeting on October 30-31, 2014, to discuss the development, assessment, and regulation of abuse-deterrent formulations of opioid medications. The meeting focused on scientific and technical issues related to the development and in vitro assessment of these products, as well as FDA's approach towards assessing the benefits and risks of all opioid medications, including those with abuse-deterrent properties.

- Issued draft guidance to assist industry on the submission of an assessment of abuse potential for drug products that have the potential for abuse and which may need to be scheduled under the Controlled Substances Act (*Draft Guidance for Industry: Assessment of Abuse Potential for Drugs*) and issued guidance to assist industry in developing and assessing abuse-deterrent opioid formulations (*Guidance for Industry: Abuse-Deterrent Opioids — Evaluation and Labeling*).

## II. DISCUSSION

You state that "the development of opioid analgesics with abuse-deterrent properties is a public health priority" (Petition at 10). You also note that the development of opioids with abuse-deterrent properties "is formidable, and producers need to overcome technical, scientific, regulatory as well as economic hurdles" (Id.). You propose a number of actions to promote the development of these products. Although FDA agrees that the development of opioid analgesics with abuse-deterrent properties is a high priority, we do not agree that every aspect of your request is appropriate or necessary to further the development of these products. Accordingly, we grant your request in part and deny in part.

### A. Guidance for Industry on the Development and Labeling of Opioid Analgesics With Abuse-Deterrent Properties

You state that one of the major barriers to the development of opioids with abuse-deterrent properties is the lack of clear guidance from FDA in this area (See Petition at 14). Specifically, you note "the absence of clear direction from the Agency on standards for chemical and physical integrity of a formulation, requirements for human abuse liability testing, identification of specific criteria that can result in specific labeling claims, and requirements for demonstrating abuse deterrence in the post marketing environment, all of which could be put in place to develop the evidence for more explicit labeling claims of abuse deterrence" (Petition at 14-15).[3] In your Petition, you specifically request that FDA provide comprehensive and detailed Guidance for Industry in the following areas:

- CMC [(Chemistry, Manufacturing and Controls)] standards for classification of products based on extractability and degree of physical tamper-residence.
- Preclinical studies if any that are required to support the safety of the ADFs by various routes of abuse.
- Human clinical pharmacology studies that are required for approval: specifically, requirements to assess the effects of ethanol on the safety and abuse deterrent claim for each active constituent of ADFs.
- Human abuse liability studies that are required for all 'abuse-deterrent' opioid formulations, and to support each specific claim related to abuse deterrence.

[3] The first page of your Petition requests that FDA publish a guidance that "will outline the approval requirements for safe and effective tamper-deterrent or abuse-deterrent formulations of opioid analgesics" (Petition at 1). However, the remainder of your Petition and the attached "Background Paper for FDA Guidance Document" focuses on the studies and data necessary to support abuse-deterrent labeling claims. Therefore, we interpret your request to mean that you seek a comprehensive guidance document to address the evaluation and labeling of abuse-deterrent opioid products rather than the approval of such products.

- The specific requirements for satisfying 21 CFR § 300.50 when an antagonist component is added to the opioid drug product to deter IV abuse.

- Clinical trials (efficacy) if and when they are required for a formulation whose active pharmaceutical ingredient (API) is 'bioequivalent' to the reference listed drug.

- Safety requirements if and when they are required for a formulation whose API is 'bioequivalent' to the reference listed drug.

- Epidemiological studies if and when they are needed to address public health concerns related to maintaining benefit (analgesia/access), or reducing adverse consequences that could affect patients, non-patients (abusing populations) and individuals subjected to inadvertent exposure (e.g., accidental use by children), monitoring direct Health Care costs (e.g., cost of addiction treatment) or indirect expenses (e.g., cost of abuse-related diseases).

(Petition at 15-16).

Since the time that the Petition was submitted, FDA has issued guidances related to your requests. In January 2013, the Agency issued the draft guidance for industry, *Abuse-Deterrent Opioids — Evaluation and Labeling*. Today, we issued the final version of that guidance (Evaluation and Labeling Guidance).[4] The Evaluation and Labeling Guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given opioid product has abuse-deterrent properties, how those studies will be evaluated, and what labeling claims may be approved based on the results of those studies. This guidance stresses that abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. It identifies the following categories of studies that should be addressed by sponsors: laboratory-based, in-vitro manipulation and extraction studies; pharmacokinetic studies; clinical abuse potential studies; and post-marketing studies. Important general considerations for the design of these studies include the use of appropriate positive controls and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study. Also, the guidance explains that the labeling language regarding abuse deterrence should describe the product's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter.

In addition, in January 2010, the Agency issued the *Draft Guidance for Industry: Assessment of Abuse Potential for Drugs* (Draft Abuse Potential Guidance).[5] This draft guidance provides information on studies that should be performed in support of an application for a drug product with potential for abuse. Although the focus of this draft guidance is not on abuse-deterrent opioid products, the draft guidance is intended to assist sponsors developing products with the

[4] A copy of the guidance is available on FDA's Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[5] *Draft Guidance for Industry: Assessment of Abuse Potential for Drugs* (Jan. 2010), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

potential for abuse, which would include abuse-deterrent opioids.[6] As noted in the Draft Abuse Potential Guidance, for all drug products with the potential for abuse that may need to be scheduled under the Controlled Substances Act, the applicant must submit as a section in the NDA an assessment of abuse potential, which includes all pertinent preclinical, pharmacological, chemistry, biochemical, human laboratory, and clinical studies; drug formulation data; and a proposal for scheduling. See 21 CFR 314.50(d)(5)(vii).

These guidances address some of the issues that you request be included in a comprehensive guidance document. First, you state that a comprehensive guidance should include CMC standards for classification of products based on extractability and degree of physical tamper resistance (Petition at 15). Although the guidances do not set CMC standards for classification of products based on extractability and degree of physical tamper resistance, the Draft Abuse Potential Guidance provides recommendations about the type of CMC data that should be included as part of the abuse potential assessment and notes that in addition to the CMC data, "the abuse potential assessment should include an evaluation of the physicochemical properties of the drug substance and product" because "[i]nformation on extractability and solubility of a drug is relevant to the drug's abuse potential and should be addressed."[7]

Second, you ask that such a guidance address preclinical studies, human clinical pharmacology studies, human abuse liability studies, and epidemiological studies. The Evaluation and Labeling Guidance contains extensive discussion on the design and evaluation methods for these categories of studies.

You specifically request that any guidance include "human clinical pharmacology studies that are required for approval: specifically, requirements to assess the effects of ethanol on the safety and abuse-deterrent claims for each active constituent of ADF" (Petition at 15). The Evaluation and Labeling Guidance discusses how laboratory manipulation and extraction studies should consider the ways in which patients may alter the formulation to change the rate or amount of drug released, particularly in instances where the product is taken with alcohol.[8] The guidance also instructs sponsors to provide data on the effects that alcohol may have on the pharmacokinetic parameters of the formulation.[9]

With respect to epidemiological studies, you request that the guidance include information regarding "epidemiological studies if and when they are needed to address public health concerns related to maintaining benefit (analgesia/access), or reducing adverse consequences that could affect patients, non-patients (abusing populations) and individuals subjected to inadvertent exposure (e.g., accidental use by children), monitoring direct Health Care costs (e.g., cost of addiction treatment) or indirect expenses (e.g., cost of abuse-related diseases)" (Petition at 16). The Evaluation and Labeling Guidance states that the goal of postmarket studies "is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful

[6] The Draft Abuse Potential Guidance has a section on abuse-deterrent formulations. Id. at 8-9.
[7] Id.
[8] Supra, note 4, at 6.
[9] Id., at 9.

reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death."[10] The guidance provides "recommended guidelines for designing postmarket epidemiologic studies that are capable of detecting a change in the occurrence of abuse as a result of a drug product's abuse-deterrent properties."[11]

Next, you ask that FDA guidance on abuse-deterrent formulations of opioid products include "specific requirements for satisfying 21 CFR § 300.50 when an antagonist component is added to the opioid drug product to deter IV abuse" (Petition at 16). Although neither the Draft Abuse Potential Guidance nor the Evaluation and Labeling Guidance specifically references 21 CFR 300.50, the guidances provide assistance to sponsors developing products with an antagonist. Also, the Evaluation and Labeling Guidance provides information on the appropriate studies to be conducted and the study outcomes that would be expected when assessing products containing an antagonist.[12]

Finally, you request that FDA guidance on abuse-deterrent formulations of opioid products provide information on "clinical trials (efficacy) if and when they are required for a formulation whose active pharmaceutical ingredient (API) is 'bioequivalent' to the reference listed drug" and on "safety requirements if and when they are required for a formulation whose API is 'bioequivalent' to the reference listed drug" (Petition at 15). To the extent that your request is for guidance on comparative bioavailability information submitted as part of an NDA, the Evaluation and Labeling Guidance focuses on the evaluation and labeling of opioids with abuse-deterrent properties and not on the requirements for approval of a new formulation. Thus, the guidance does not include recommendations on the types of studies or safety information that should be submitted in support of a new formulation in an NDA. To the extent that you are requesting guidance regarding generic formulations of abuse-deterrent products, neither the Evaluation and Labeling Guidance nor the Draft Abuse Potential Guidance addresses generic formulations as they are outside of the scope of these guidances. However, FDA intends to issue a separate guidance or guidances that will focus on generic versions of abuse-deterrent opioids.

In sum, your request is granted to the extent that the Evaluation and Labeling Guidance and/or the Draft Abuse Potential Guidance addresses the topics on which you request FDA issue a guidance. To the extent that these guidances do not address the points you request be included in a comprehensive guidance document, your request is denied. However, as noted above, we intend to issue additional guidances that will focus on generic versions of abuse-deterrent opioids. As the field of abuse-deterrent products develops, we will continue to evaluate whether providing additional guidance on other topics is appropriate.

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[10] Id., at 18.

[11] Id. However, the Evaluation and Labeling Guidance does not provide a discussion on epidemiological studies that are focused on monitoring patient access to drugs or health care costs.

[12] Supra, note 4 at 6, 8-9, and 12-13.

### B. Incentives for Development of Opioid Analgesics With Abuse-Deterrent Properties

In addition to requesting clearer guidance on the evaluation and labeling of opioid products with abuse-deterrent properties, you request that FDA "provide incentives" to industry to facilitate development of these products (Petition at 16). You claim that the lack of incentives "limits the ability of pharmaceutical companies to justify resource allocation for these complicated programs" (Petition at 16). For the reasons set forth below, your request is granted in part and denied in part.[13]

#### 1. Request to Grant Fast-Track Status and Assign Priority Review Timelines

You ask that FDA grant fast-track status to IND applications for opioids with abuse-deterrent properties and assign priority review timelines to NDAs for such products (Petition at 1 and 17).

*Fast track* is a process designated to facilitate the development, and to expedite the review of, drugs to treat serious or life-threatening diseases or conditions that have an unmet medical need (Section 506(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356(b)). A drug that receives fast-track designation is eligible for some or all of the following: (1) more frequent interactions with FDA; (2) eligibility for accelerated approval and priority review, if relevant criteria are met; and (3) rolling review, whereby a sponsor can submit portions of a marketing application before the sponsor submits the complete application.[14]

An application for a drug will receive *priority review* designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition.[15] If an application is given a priority review designation, FDA's goal is to take action on the marketing application within 6 months of receipt (compared to 10 months under standard review).[16]

FDA has consistently stated that opioid analgesics with potentially abuse-deterrent properties can and should be granted both fast-track status and priority review so long as FDA determines that

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[13] You include a single statement that FDA should promulgate "standards for meaningful labeling that could result in reimbursement for approved formulations that are designed to reduce abuse, and thus more widespread adoption by the prescribing community" (Petition at 17). FDA does not handle issues concerning reimbursements for medical expenses.

[14] FDA guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, at 9-10.

[15] Id., at 24.

[16] Id., at 25.

the applicable criteria are met.[17] FDA will continue to apply this policy. Accordingly, to this extent, your requests are granted.

### 2. Request for Proposed Legislation to Provide Further Incentives for the Development of Opioids With Abuse-Deterrent Properties

You ask that FDA propose legislation to provide incentives for the development of opioids with abuse-deterrent properties (Petition at 1 and 17-18). For example, you request that FDA propose statutory changes that would extend the 3-year exclusivity provided under the Hatch-Waxman Amendments for NDAs submitted under section 505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)) for reformulated versions of opioids with abuse-deterrent properties (Petition at 17).[18] You also request that FDA propose tax credits for sponsors that conduct certain studies required for approval of opioids with abuse-deterrent properties, similar to the provisions in the Orphan Drug Act.[19]

We believe that your requests would be more appropriately directed to Congress, which proposes and enacts legislation. Accordingly, this request is denied.

## C. Sufficient Internal Resources Devoted to Your Requested Actions

Finally, you ask that FDA allocate sufficient internal resources to respond to your requested actions (Petition at 18).

As mentioned above, FDA agrees that development of abuse-deterrent opioid products is a top priority as evidenced by the various efforts that FDA has undertaken to further the development of opioid products with abuse-deterrent properties (See section I.B above). For example, FDA staff has devoted substantial time and effort to develop the guidances mentioned previously, and FDA staff continue to use various existing mechanisms (e.g., fast-track and priority review) to expedite the development and review of new opioid drug products with abuse-deterrent properties. FDA also intends to develop draft guidance that will focus on generic versions of abuse-deterrent opioids. Thus, to the extent that your request is for sufficient resources to address the development and issuance of relevant guidance or to grant fast-track status and priority review timelines to opioids with abuse-deterrent properties, your request is granted. To the extent that your request is for sufficient resources to respond to your other requested actions, which have been denied, this aspect of your request is also denied.

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[17] See, e.g., letter response from Dr. Janet Woodcock to Center for Lawful Access and Abuse Deterrence, FDA-2013-P-0703 (Oct. 25, 2013), available at http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0703-0004.

[18] The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Amendments, provides up to 3 years of market exclusivity for conducting clinical trials, other than bioavailability studies, to support changes to a product already on the market (Section 505(c)(3)(E)(iii) of the FD&C Act).

[19] The Orphan Drug Act of 1983 provides sponsors incentives to develop drugs for the prevention, diagnosis, or treatment of rare diseases. One such incentive is a tax credit of 50 percent of qualified clinical testing expenses for a designated orphan product.

## III. CONCLUSION

For the reasons discussed above, the Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock
Director
Center for Drug Evaluation and Research

cc: Rosemarie Curran, Tufts Health Care Institute
Andrea G. Barthwell, Human Resources Development Institute, Inc.
Michael C. Barnes, Center for Lawful Access and Abuse Deterrence
Robert Bianchi
Daniel Jedzinak, Coalition to End Needless Death on Our Roadways
William K. Schmidt, NorthStar Consulting, LLC
Edward J. Cone
Donald A. Cooper
Paul Scott O'Neill, Friends of the DEA