DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
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Elizabeth Planet
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The National Center on Addiction
And Substance Abuse at Columbia University
633 Third Avenue
New York, NY 10017-6706

Re: Docket Nos. FDA-2007-P-0009 and FDA-2009-P-0227

Dear Mr. Califano, Ms. Planet, and Ms. Schlinger:

This letter responds to two related citizen petitions from The National Center on Addiction and Substance Abuse at Columbia University (CASA) asking FDA to promulgate regulations intended to strengthen FDA regulation of opioids and other controlled prescription drugs[1] and to help minimize the risks of diversion and abuse of such drugs.

The first petition, submitted on October 25, 2007 (2007 Petition), asks that FDA promulgate regulations:

(1) requiring pharmaceutical companies manufacturing controlled drugs to demonstrate and certify in their application materials for FDA approval of new drugs that they have made every effort to formulate the drug in such a way that avoids or at least minimizes the drug's potential for both intentional and unintentional abuse without compromising its therapeutic effectiveness, and

(2) requiring pharmaceutical companies to include proactive risk management plans in all new applications for controlled drugs, demonstrating strong evidence of a prescription drug's safety, as well as concrete steps that will be taken to prevent the abuse of the drug while maintaining its maximum therapeutic effectiveness.

[1] For the purposes of this petition response, the term "controlled prescription drug" means a drug product containing a substance that is scheduled under the Controlled Substances Act (see 21 USC 802(6) and 21 USC 801 et seq) and that, under the terms of its approved drug application, can be dispensed only upon a prescription pursuant to section 503(b) of the Federal Food, Drug, and Cosmetic Act.

(2007 Petition at 1-2).[2]

CASA's second petition, submitted on May 15, 2009 (2009 Petition), asks that FDA promulgate a new regulation mandating classwide risk evaluation and mitigation strategies (REMS) for all opioid drugs (2009 Petition at 2). CASA asks that the regulation provide that every opioid drug be covered by a REMS containing the following elements:

(1) A timetable for submission of assessments at 18 months, 3 years, and 7 years after the strategy is approved.

(2) A medication guide, as provided for under part 208 of title 21, Code of Federal Regulations (or any successor regulations).

(3) A patient package insert.

(4) A communication plan, which may include:

   a. sending letters to health care providers;

   b. disseminating information about the elements of the REMS to encourage implementation by health care providers of components that apply to such health care providers, or to explain certain safety protocols (such as medical monitoring by periodic laboratory tests); or

   c. disseminating information to health care providers through professional societies about any serious risks of the drug and any protocol to assure safe use.

(5) Elements to assure safe use. The Secretary may require that:

   a. Health care providers who prescribe the drug have particular training or experience, or are specially certified;

   b. Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;

   c. The drug be dispensed to patients only in certain health care settings, such as hospitals;

   d. Each patient using the drug be subject to certain monitoring;

   e. Each patient using the drug be enrolled in a registry; or

   f. Other measures be taken to minimize risk of abuse, diversion or harm while preserving patient access and therapeutic efficacy.

[2] This petition was originally assigned docket number 2007-P-0429. The number was changed to FDA-2007-P-0009 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

(6) Formulation certification. Each opioid drug REMS shall include a certification that the drug has been formulated to minimize potential for abuse, both intentional and unintentional, to the extent possible without compromising the drug's therapeutic effectiveness.

(2009 Petition at pp. 2-3).

We have carefully considered the petitions. As explained below, they are denied. We agree that abuse and misuse of many controlled prescription drugs, particularly certain opioids, are pressing public health concerns. We do not agree, however, that we should impose the blanket requirements you propose for all such products, as the benefits and risks , as well as the appropriate response to such risks, can vary significantly from product to product. Instead, we intend to continue taking a more targeted approach, using the tools at our disposal to craft particularized responses that take into consideration the risks and benefits presented by individual controlled prescription drugs or, where we determine that a multi-product approach is appropriate, classes of such drugs. Accordingly, we do not think a rule requiring a REMS for all opioids is appropriate or warranted at this time, and we note that the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) does not require that FDA promulgate such a rule.[3] Similarly, we do not think it appropriate at this time to promulgate a rule requiring that each opioid REMS contain each of the elements you request, and we note that such a rule is not required to be promulgated under the Act. Finally, while we will continue to encourage sponsors to develop abuse-deterrent formulations of drugs with abuse potential and we will take appropriate regulatory action regarding such products on a case-by-case basis, we do not think it appropriate at this time to require sponsors to certify that drugs have been formulated to minimize the potential for abuse without compromising therapeutic effectiveness.

I. BACKGROUND

The CASA petitions ask that FDA promulgate regulations that would require RiskMAPs and abuse-deterrent formulations for all controlled prescription drugs, and REMS for all opioid drugs. Before discussing the merits of these requests, we briefly discuss our regulatory activities relating to these topics.

A. Risk Evaluation and Mitigation Strategies

The Food and Drug Administration Amendments Act (FDAAA) (Public Law 110-85) was signed into law on September 27, 2007. Section 901 of FDAAA created new section 505-1 of the FD&C Act (21 U.S.C. 355-1), authorizing the Secretary of Health and Human Services to require sponsors to submit a REMS (1) in connection with an

[3] For the reason discussed in Part II.A, we treat the 2007 Petition's request to promulgate a rule requiring RiskMAPs for all controlled prescription drugs as a request to promulgate a rule requiring REMS for such products.

application for a proposed new drug if the Secretary determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks or (2) for an approved drug if the Secretary becomes aware of new safety information and determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks (21 U.S.C. 355-1(a)(1)-(2)). A REMS may include a Medication Guide, a patient package insert, a communication plan to health care providers, and elements to assure safe use (e.g., required training for health care providers who prescribe the drug, restricting dispensing of the drug to pharmacies that are specially certified, or required patient monitoring) (21 U.S.C. 355-1(e)).

FDA has approved a number of REMS, including several for controlled prescription drugs.[4]

B. RiskMAPs

Before FDAAA was enacted, FDA approved a small number of products with risk minimization action plans (RiskMAPs). A RiskMAP is a strategic safety program designed to minimize the risks of a product while preserving its benefits. As FDA explained in a 2005 guidance document,[5] routine risk minimization measures, particularly FDA-approved product labeling and adverse event monitoring and reporting, are sufficient to minimize risks and preserve benefits for the majority of products (RiskMAP Guidance at 3-5). For some products, however, FDA determined that a RiskMAP was warranted (RiskMAP Guidance at 6-7). FDA specifically recommended that "sponsors of Schedule II controlled substances, including Schedule II extended release or high concentration opiate drug products, consider developing RiskMAPs" (RiskMAP Guidance at 7). FDA emphasized, however, that "RiskMAPs [should] be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients," and that "[d]ecisions to develop, submit, or implement a RiskMAP are always made on a case-by-case basis" (RiskMAP Guidance at 5-6).

Now that FDAAA has authorized FDA to require REMS, FDA does not intend to approve new RiskMAPs (with certain exceptions not relevant here).[6] Instead, FDA

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[4] A list of approved REMS is available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

[5] See the guidance for industry on *Development and Use of Risk Minimization Action Plans* (March 2005) (RiskMAP Guidance), available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf.

[6] See the draft guidance for industry on *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* (September 2009) at pages 3-4 (REMS Draft Guidance), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf.

anticipates that a product that would previously have been approved with a RiskMAP will be approved with a REMS if the statutory requirements for a REMS are met.[7]

C. Extended-Release and Long-Acting Opioid REMS

After a thorough public process,[8] on July 9, 2012, FDA approved a REMS for all extended-release (ER) and long-acting (LA) opioid analgesics.[9] This new REMS requires sponsors of ER/LA opioids to make available training for health care professionals on proper prescribing practices and also to distribute educational materials to prescribers and patients on the safe use of these medications. The prescriber training will provide instruction on safe prescribing practices for ER/LA opioids, will be provided through accredited continuing education (CE) providers, and will be supported by educational grants funded by the sponsors ER/LA opioid analgesics.[10] The educational materials include a Patient Counseling Document (PCD) that the prescriber may use to facilitate a discussion of the risks associated with ER/LA opioids at the time of prescribing,[11] as well as a product-specific Medication Guide[12] that must be provided to the patient each time an ER/LA opioid is dispensed.[13]

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[7] REMS Draft Guidance at 3.

[8] FDA announced its intention to use its REMS authority to ensure that the benefits of ER and LA opioid analgesics outweighed their risks on April 20, 2009. Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting, 74 FR 17967 (April 20, 2009).

FDA received numerous comments and held several meetings concerning the proper design and scope of the REMS. These meetings included a stakeholders meeting on February 10, 2009, an industry meeting on March 3, 2009, a second stakeholders meeting on May 4-5, 2009, a public meeting on May 27-28, 2009, a meeting with an industry working group on December 4, 2009, and a Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on July 22-23, 2010. More information about these meetings can be found at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm (Q&A #12).

[9] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm (announcing the ER/LA REMS), http://www.er-la-opioidrems.com/IwgUI/rems/home.action (describing the REMS for healthcare professionals and patients and providing educational materials), http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf (the official ER/LA REMS document, approved July 9, 2012 and updated in August 2012), and http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251735.htm (listing all ER/LA opioid products required to have a REMS).

[10] See http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf for additional information about prescriber training.

[11] See http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action for additional information about educational materials for prescribers and patients.

[12] A Medication Guide (MedGuide) is FDA-approved patient labeling that is provided to patients when a prescription drug product is dispensed. See 21 CFR part 208. FDA may require a MedGuide if it determines that the drug product poses a serious and significant public health concern requiring distribution of FDA-approved patient information and that patient labeling is needed for patients' safe and effective use of the product (21 CFR 208.1(a) and (b)). A Medication Guide will be required if FDA determines that one

D. Abuse-Deterrent Formulations of Controlled Prescription Drugs

FDA has consistently encouraged the development of drug products that have the potential for abuse to have mechanisms designed to deter abuse. FDA works with sponsors interested in developing such drugs on a product-by-product basis. If the applicable statutory and regulatory requirements are met, FDA will grant fast track designation to such products upon the sponsor's request.[14] FDA will also assign priority review timelines to new drug applications (NDAs) for these products if applicable standards are met.[15]

FDA has also consulted with advisory committees in connection with the development, evaluation, and labeling of abuse-deterrent opioids. For instance, joint meetings of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee have been held concerning Purdue's new formulation of OxyContin (oxycodone hydrochloride controlled-release) tablets as well as Acura Pharmaceuticals, Inc.'s NDA for Acurox (oxycodone HCl and niacin).[16] Another joint meeting of these committees was held in October 2010 to discuss, among other things, how sponsors should design and conduct postmarketing epidemiological or observational

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of the following circumstances exists: (1) the drug product is one for which patient labeling could help prevent serious adverse effects; (2) the drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or continue to use, the product; or (3) the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

[13] http://www.er-la-opioidrems.com/IwgUI/rems/products.action.

[14] The FDA's fast track programs are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. FDA determines whether a product qualifies for Fast Track designation by applying standards contained in section 506 of the Food Drug and Cosmetic Act (see 21 U.S.C. 356) and elaborated upon in the guidance for industry on *Fast Track Drug Development Programs — Designation, Development, and Application Review* (Jan. 2006), (Fast Track Guidance) available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079736.pdf.

[15] As set forth in FDA's Manual of Policies and Procedures (MAPP 6020.3), FDA will designate a new drug application for priority review if it determines that the proposed product has potential to provide a safe and effective therapy where no satisfactory alternative exists or a significant improvement over marketed products in treating, preventing, or diagnosing a disease. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/ucm082000.pdf.

[16] Summary meeting minutes of the September 24, 2009, joint meeting concerning reformulated OxyContin are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM187629.pdf. Summary meeting minutes of the April 22, 2010, joint meeting concerning Acurox are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220274.pdf.

studies to evaluate whether and to what extent products designed to reduce the likelihood and incidence of abuse actually do so.[17]

FDA has also published two draft guidances relevant to the development of abuse-deterrent formulations of controlled prescription drugs. *Assessment of Abuse Potential of Drugs* discusses, among other things, the design and implementation of clinical studies that may be used to help assess whether a proposed abuse-deterrent formulation can be expected to reduce a product's abuse potential relative to an appropriate comparator product.[18] *Abuse-Deterrent Opioids – Evaluation and Labeling* describes FDA's recommendations regarding the data that should be provided to demonstrate that a formulation has abuse-deterrent properties and how those data will be evaluated by the agency.[19]

FDA makes regulatory decisions regarding abuse-deterrent formulations on a case-by-case basis. For example, FDA recently announced regulatory decisions for OxyContin and Opana ER. The sponsors of both OxyContin (oxycodone hydrochloride) Controlled-Release Tablets and Opana ER (oxymorphone hydrochloride) Extended-Release Tablets reformulated these products with the intention of deterring manipulation for purposes of abuse or misuse. In the case of OxyContin, FDA determined that the original product poses an increased potential for abuse by certain routes of administration compared to the reformulated product. FDA concluded that the benefits of original OxyContin, which lacks abuse-deterrent properties, no longer outweigh its risks, and that original OxyContin was withdrawn from sale for safety or effectiveness reasons.[20] FDA also

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[17] Summary meeting minutes are available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM236242.pdf. The products at issue were Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) capsules and reformulated OxyContin, but the knowledge gained and expertise developed in connection with those products should help facilitate the development and evaluation of other potentially abuse-deterrent formulations of controlled prescription drugs.

[18] See the draft guidance for industry on *Assessment of Abuse Potential of Drugs* (Abuse Potential Guidance) (Jan. 2010) at pages 8-9, 12-16, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

[19] See the draft guidance for industry on *Abuse-Deterrent Opioids - Evaluation and Labeling* (Jan. 2013) (Abuse-Deterrent Opioids draft guidance), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. This draft guidance was produced following mandates in the White House prescription drug abuse plan, *Epidemic: Responding to America's Prescription Drug Abuse Crisis* (2011), available at http://www.whitehouse.gov /sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf, and the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. Law 112-144 (section 1122(c)).

[20] See Determination that the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness, 78 Fed. Reg. 23,273 (April 18, 2013).

approved product labeling describing certain abuse-deterrent properties of the reformulated product.[21] In the case of Opana ER, FDA determined that there is insufficient evidence that original Opana ER poses an increased risk of abuse compared to reformulated Opana ER. Based on the totality of the data and information available to the Agency, FDA determined that the original product's benefits continue to outweigh its risks. Accordingly, FDA concluded that original Opana ER was not withdrawn from sale for safety or effectiveness reasons.[22]

In sum, FDA has devoted significant effort to developing the regulatory science of evaluating abuse-deterrent drugs, continues to explore ways in which it could further encourage sponsors to develop drug products with the potential to deter abuse, and takes appropriate regulatory actions regarding potentially abuse-deterrent products on a case-by-case basis.

II. DISCUSSION

In Part A we address CASA's requests that we promulgate a rule requiring REMS for all controlled prescription drug products.[23] In Part B we address CASA's requests that we promulgate a rule requiring sponsors of controlled prescription drug products to certify that their products have been formulated to avoid or minimize abuse to the extent possible without compromising the products' therapeutic effectiveness.

A. RiskMAPs and REMS

The 2009 Petition's requests (1) through (5) ask that FDA promulgate a rule requiring a REMS with certain specified elements for all prescription opioid medications (2009 Petition at 2-3, 11). The 2007 Petition's request (2) asks that FDA promulgate a rule requiring pharmaceutical companies to include proactive RiskMAPs in all new applications for controlled prescription drugs, demonstrating strong evidence of a prescription drug's safety, as well as concrete steps that will be taken to prevent the abuse of the drug while maintaining its maximum therapeutic effectiveness (2007 Petition at 2). Given that FDA does not intend to approve new RiskMAPs (except in limited circumstances not applicable here), we treat the 2007 Petition's request (2) as a request for a rule requiring REMS for such products.

We first address the 2009 Petition's requests (1) through (5), which call for FDA to promulgate a rule requiring a REMS with certain elements for each prescription opioid. As CASA notes (2009 Petition at 4-5), FDA has, thus far, only required REMS for certain opioids. As CASA also notes, the decision to include certain elements in a

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[21] See *FDA approves abuse-deterrent labeling for reformulated OxyContin*, available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm.

[22] See Letter Response from Dr. Janet Woodcock to Endo Pharmaceuticals, Inc., FDA-2012-P-0895 (May 10, 2013).

[23] As discussed in Part II.A, we treat the 2007 Petition's request to promulgate a rule requiring RiskMAPs for all controlled prescription drugs as a request to promulgate a rule requiring REMS for such products.

particular REMS (e.g., a Medication Guide, prescriber training, or some other element to assure safe use) is currently made on a case-by-case basis (2009 Petition at 4). CASA contends that promulgating a rule mandating a REMS with certain required elements for each prescription opioid would remove uncertainty for industry and would be more efficient than the current "piecemeal" approach (2009 Petition at 5).

We do not think the blanket approach proposed by the petitioner would be appropriate. FDA may only require a REMS for a particular drug if it determines that doing so is "necessary to ensure that the benefits of the drug outweigh the risks of the drug" (21 U.S.C. 505-1(a)(1) and (a)(2)(A)). FDA must make additional determinations regarding specific elements of a particular REMS.[24] That is, the authority both to impose a REMS and to require a specific REMS element is specific to the product in question. While all prescription opioids present at least some risk of abuse, it does not follow that each presents sufficient risk relative to benefits to justify a REMS, or that the appropriate risk mitigation strategy would necessarily be the same for each prescription opioid.

As the petitioner is aware, the adverse events associated with opioid medications (including addiction, overdose, and death) are not evenly distributed across all products. For some opioid medications (see examples below) FDA has concluded that REMS are necessary to ensure that the benefits of these products outweigh their risks. For others, however, FDA believes at this time that the routine risk minimization steps required for all prescription drug products (FDA-approved product labeling, adverse event monitoring and reporting) should be sufficient. While FDA could ultimately conclude that a REMS should be required for some or all of these products, it does not believe that an across-the-board requirement is justified at present.

Furthermore, for those opioids for which a REMS is necessary, the specific REMS elements imposed can and often should differ, because neither the risks posed by a particular drug (or class of drugs) nor the elements needed to mitigate those risks will necessarily be the same from product to product (or class to class). As the examples below illustrate, FDA has determined that the serious risks associated with different therapeutic categories of opioids require different risk mitigation strategies.

As discussed in Part I.C of this response, FDA determined that a REMS should be required for each ER/LA opioid product to ensure that the benefits of these drugs continue to outweigh the risks of adverse outcomes resulting from inappropriate prescribing, abuse, and misuse. ER/LA products are designed to release the opioid over a long period of time. Accordingly, a single dose often contains a large amount of opioid and the drug can take long time to be cleared out of the body. These characteristics make improper use of ER/LA products, including both accidental misuse and intentional abuse,

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[24] For example, to require a patient package insert as part of a particular REMS, the Secretary must determine "that such insert may help mitigate a serious risk of the drug," and to require a communication plan the Secretary must determine "that such plan may support implementation of an element of the strategy" (21 U.S.C. 505-1(e)(2)(B) and (e)(3)).

very dangerous. Also, this subset of opioids has played and continues to play a disproportionately large role in the problem of prescription opioid abuse. FDA determined that a classwide approach to ER/LA opioids is appropriate because the products in this class pose similar risks that should be addressed in similar ways, and because a classwide approach would minimize the burden on the healthcare system. FDA determined that a prescriber training program is necessary to mitigate the serious risks posed by each ER/LA product, and required the sponsors of ER/LA opioids to develop a single, shared system to implement the REMS. In addition, FDA determined that each of the ER/LA products poses a serious and significant public health concern requiring the distribution of a product-specific Medication Guide to patients each time the product is dispensed.

The REMS required for transmucosal immediate-release fentanyl (TIRF) products provide a different example of a classwide approach.[25] These products, approved to treat "breakthrough" pain in adult patients with cancer who are already taking around-the-clock opioid analgesics, pose heightened risks. The TIRF products are designed to deliver a potent opioid dose to the patient in a relatively short period of time. The indicated dose can be fatal to individuals who are not already taking an opioid product. Although TIRF products that entered the market prior to the enactment of FDAAA were approved with restrictions to assure safe use under Subpart H of FDA's regulations (see 21 CFR 314.520), postmarketing data showed disturbing trends of increasing numbers of non-opioid tolerant patients being prescribed TIRF products, increasing numbers of serious adverse events, and incorrect substitution of one TIRF product for another, despite specific labeling warning against such substitutions. Accordingly, after the enactment of FDAAA, the TIRF products approved under Subpart H were deemed to have a REMS and FDA required a REMS for post-FDAAA approvals. Each TIRF REMS created a similar restrictive distribution program designed to ensure that the prescribers, pharmacies, and patients who prescribe, dispense, distribute, and receive the drug are aware of the risks associated with the product and take appropriate precautions in light of those risks.[26] To reduce the burden to the healthcare system, a similar REMS for each product in the TIRF class was approved on December 28, 2011.

Thus, the different risks posed by the products necessitate different safety measures. For certain opioids, such as the ER/LA opioids, a REMS consisting of a Medication Guide and a prescriber training program may be sufficient. For others, such as the TIRF products, more restrictive measures included in a REMS were necessary to ensure safe

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[25] See http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM251595.pdf and http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm for a list of all approved REMS, including several REMS for transmucosal fentanyl products.

[26] The TIRF REMS establishes a restricted distribution program. Under this program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive the drug in an outpatient setting. See, for example, the ABSTRAL REMS for a detailed description of one such program.
http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM240001.pdf.

use.[27] In the future, for any other opioids, FDA may determine that a REMS is required and elements similar or the same as some of those included in the ER/LA or TIRF REMS are appropriate, or that some other elements not included in either should be included. The rule that CASA requests would restrict our flexibility to make a case by case determination as to whether the standard in the Act to require a REMS is met and on the appropriate REMS elements for any particular opioid drug product.

Accordingly, we agree with CASA that a classwide approach may be appropriate and efficient in certain instances, and, as just discussed, we have taken this approach for certain classes of opioid products. We think, however, that the class CASA would have us create — all opioids — is too broad, and the REMS elements CASA would have us impose are not sufficiently tailored to drug-specific risks.

Next, we address the 2007 Petition's request (2) for RiskMAPs as applied to all other (non-opioid) controlled prescription drugs. As discussed at the outset of this section, we treat this request as a request to promulgate a rule requiring a REMS (not a RiskMAP) for all such drugs. For the reasons discussed above in connection with opioids, we deny this request as well. We do not believe that all controlled prescription drugs pose such significant risks (relative to their benefits) that the standard in the statute for imposing a REMS would be met in every case. For many such products, FDA believes that the routine risk minimization steps (FDA-approved product labeling, adverse event monitoring and reporting) should be sufficient to address safety concerns. FDA does not believe that requiring a REMS for all non-opioid controlled prescription drug products is justified based on the information we have at this time.

We note that CASA does not offer targeted arguments or evidence in support of any of its requests. While CASA believes FDA should broaden its focus and require a blanket REMS for all prescription opioids (and RiskMAPs for all non-opioid controlled prescription drugs), the petitions do not offer detailed justifications for such an approach. CASA provides general information regarding the problems of drug abuse, but does not provide information to demonstrate that any controlled prescription drug or specific opioid presents sufficiently serious risks that a REMS should be required at all, much less that the *same* REMS elements should be required for *all* such products. Furthermore, CASA does not provide information to specifically justify inclusion of any of the REMS elements it believes should be mandated in each and every opioid REMS. Rather, CASA simply lists most of the possible REMS elements specified at section 505-1 of the FD&C Act and states without elaboration that each should be required in each case (2009 Petition at 3, 5, 11). Finally, CASA does not offer any reasons for why it would be necessary or advantageous for FDA to promulgate a rule to require REMS for all controlled prescription drugs or, specifically, all prescription opioids, as opposed to simply requiring REMS directly under the authority of section 505-1 of the FD&C Act.

[27] See footnote 16.

FDA may ultimately determine that REMS are necessary for some or all other opioids, or for some other non-opioid controlled prescription drug products. FDA may further determine that some of these future REMS should be implemented on a classwide basis. Likewise, FDA will monitor the ER/LA opioid REMS approved in July 2012, and may make adjustments to the required elements or add or remove elements as appropriate, consistent with all applicable statutory and regulatory requirements. But for the reasons given, FDA does not agree that it should promulgate a rule requiring a REMS for all opioids, or for all other controlled prescription drugs, or that every REMS imposed must necessarily include the elements requested by the petitioner.[28] Accordingly, the 2007 Petition's request (2) and the 2009 Petition's requests (1) through (5) are denied.

B. Formulation Certification

The 2007 Petition asks that FDA promulgate a regulation requiring each sponsor of a new controlled prescription drug to demonstrate and certify in its application materials that it has made every effort to formulate the drug in such a way that avoids or at least minimizes the drug's potential for both intentional and unintentional abuse without compromising its therapeutic effectiveness (2007 Petition at 1). The 2009 Petition further requests that FDA promulgate a regulation which requires that each REMS for opioid drugs include a requirement that the sponsor certify that it has formulated the drug to "minimize potential for abuse, both intentional and unintentional, to the extent possible without compromising the drug's therapeutic effectiveness" (2009 Petition at 3). CASA states that the formulation of an opioid can affect its potential for abuse (2009 Petition at 5). CASA specifically notes that antagonists may be added to opioids in an effort to reduce a product's abuse potential (2009 Petition at 6).

We consider the petitions' formulation certification requests together. While we support and encourage development of abuse-deterrent formulations of prescription opioids, we do not think that a rule requiring either certification requirement proposed by CASA is appropriate.

First, as discussed above, the benefits and risks of controlled prescription drugs, including opioids, vary from product to product. We assess the benefit-risk profile of each product candidate, including whether a REMS is necessary for the particular product (or class of products), as part of our normal drug review process. CASA's request, however, is not product-specific; rather, CASA asks that FDA impose a blanket formulation certification requirement.

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[28] Taken together, the petitions request REMS for all opioids and RiskMAPs for all non-opioid controlled prescription drug products. As discussed above, we treat the petitioner's request that we promulgate a rule requiring RiskMAPs for all controlled prescription drug opioids as if it were a request that we require REMS for all such products, because FDA now requires REMS where before FDAAA we would have requested RiskMAPs. Even in the absence of such authority, however, we would still deny CASA's request for a blanket rule requiring RiskMAPs for all controlled prescription drugs for the same reasons (explained in the text) that we will not promulgate a rule requiring REMS for all such products.

Second, although abuse of controlled prescription drugs is a major public health problem, such abuse is not distributed evenly across all such drugs. For many controlled prescription drugs, FDA believes that routine risk minimization steps (adverse event reporting, prominent warnings on labeling) are sufficient. For others, including the opioids which are the subject of the ER/LA and TIRF REMS discussed in Part II.A above, FDA determined that a REMS was necessary but did not also seek formulation changes.

Third, as FDA notes in the Abuse-Deterrent Opioids draft guidance, the science of abuse deterrence is relatively new. Both the drug and formulation technologies involved and the clinical, epidemiological and statistical methods for evaluating those technologies are rapidly evolving. Accordingly, FDA has said that it will take a flexible, adaptive approach to the evaluation and labeling of these products. Imposing an across-the-board certification requirement would be inconsistent with this flexible approach.

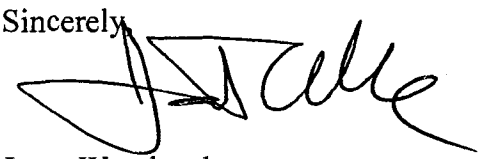
The foregoing reasons apply to both the 2007 Petition's request (1) and the 2009 Petition's request (6). With regard to the latter request, which asks that FDA impose a formulation certification requirement as a REMS element for every opioid, FDA reiterates that it may only require a REMS for a particular drug if a REMS is necessary to ensure that the benefits of the drug outweigh its risks. As discussed in Part II.A, these determinations must be made on a product-by-product basis (although where the products in question are sufficiently related FDA may adopt a classwide approach). Accordingly, just as we do not believe it would be appropriate at this time to require a REMS for every opioid, or to require that each such REMS have all of the same elements, we likewise do not agree with the petitioner that it would be appropriate to impose a formulation certification requirement in every instance. Necessarily, then, we do not think a regulation imposing such a requirement at this time would be appropriate or warranted.

In summary, while we will continue to encourage the development of abuse-deterrent formulations of prescription opioids and other controlled prescription drugs, and we will continue to take appropriate regulatory actions regarding potentially abuse-deterrent products on a case-by-case basis, we do not think it appropriate at this time to issue the specific requested rules imposing formulation certification requirements on all sponsors of such products.

III. CONCLUSION

As explained above, the 2007 and 2009 Petitions are denied.

Sincerely,



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