DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Chief Scientific Officer
Mylan Laboratories Inc.
P.O. Box 4310
781 Chestnut Ridge Road
Morgantown, WV 26504-4310

Re: Docket No. FDA-2006-P-0016

Dear Sir or Madam:

This letter responds to the citizen petition submitted on behalf of Mylan Laboratories Inc. by John P. O'Donnell, Ph.D., Chief Scientific Officer, received on July 24, 2006 (the Petition).[1] The Petition requests that the Food and Drug Administration (FDA or Agency) determine whether a risk management program (RMP) is necessary for fentanyl transdermal systems (fentanyl patches). If so, you request that FDA develop and adopt a single, unified RMP for all fentanyl patches based on input provided by all sponsors of approved marketing applications for these products. You also request that FDA adopt a unified, comprehensive RMP for all fentanyl drug products with the participation of all sponsors of these products.[2] We have carefully considered the Petition and other relevant information. For the reasons stated below, the Petition is granted in part and denied in part.

I. BACKGROUND

A. Fentanyl

Fentanyl is a potent opioid analgesic classified in Schedule II under the Controlled Substances Act.[3] There are eight approved new drug applications (NDAs) for currently-marketed fentanyl drug products.[4] The approved NDAs cover six different dosage forms and a variety of

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[1] The Petition was originally assigned docket number 2006P-0290. The number was changed to FDA-2006-P-0016 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] We have also received a citizen petition raising issues related to the safety of reservoir and matrix patches (2005P-0441). This response does not address that citizen petition, to which a response will be issued separately.

[3] 21 U.S.C. 812.

[4] Innovar (NDA 016049) and Ionsys (NDA 021338) are also fentanyl drug products with approved NDAs, but they are no longer marketed at this time. Accordingly, they are not included for purposes of this response. In addition,

indications.[5] Each NDA and its associated dosage form and approved indication(s) are described in the chart below.

Drug product (current sponsor)	NDA no. (yr. approved)	Dosage form or route of administration	Summary of indication(s)
Sublimaze (Akorn Manufacturing)	16-619 (1968)	Injectable/injection	Analgesia during anesthesia; narcotic analgesic supplement during anesthesia; anesthetic agent with oxygen in high risk patients
Duragesic (Alza Corporation)[6]	19-813 (1990)	Transdermal patch	Management of persistent, moderate-to-severe chronic pain in opioid-tolerant patients
Actiq (Cephalon, Inc.)	20-747 (1998)	Oral transmucosal	Management of breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain
Fentora (Cephalon, Inc.)	21-947 (2006)	Oral transmucosal	Management of breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain
Onsolis (Meda Pharmaceuticals, Inc.)	22-266 (2009)	Oral transmucosal	Management of breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain
Abstral (ProStrakan, Inc.)	22-510 (2011)	Sublingual tablets	Management of breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain
Lazanda (Archimedes	22-569 (2011)	Nasal spray	Management of breakthrough pain in cancer patients who are already receiving and who

there are two other NDAs for injectable fentanyl products that were approved under FDA's "paper NDA" policy and are not included in the description of NDAs above. These NDAs are Baxter Healthcare's injectable fentanyl citrate (NDA 19101) and Hospira's injectable fentanyl citrate (NDA 19115). For background information about the "paper NDA" policy, see pages 6-8 of the Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA's transition to Regulations.gov).

[5] A number of approved fentanyl analogues (e.g. alfentanil, sufentanil, and remifentanil) also exist but will not be discussed in this response.

[6] Duragesic is manufactured by Alza Corporation and distributed by Janssen Pharmaceutical Products, L.P., both subsidiaries of Johnson & Johnson.

Drug product (current sponsor)	NDA no. (yr. approved)	Dosage form or route of administration	Summary of indication(s)
Development Ltd.)			are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain
Subsys (Insys Therapeutics Inc.)	202788 (2012)	Sublingual spray	Management of breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain

Duragesic is the only fentanyl NDA approved in a transdermal patch dosage form. Petitioner and other companies are sponsors of generic fentanyl patches. There are seven approved abbreviated new drug applications (ANDAs) for fentanyl patches for which Duragesic is the reference listed drug. They include:[7]

- ANDA 76-258 (Mylan Technologies, Inc.), approved in January 2005
- ANDA 77-051 (Lavipharm Laboratories, Inc.), approved in August 2006
- ANDA 76-709 (Watson Pharmaceuticals, Inc.), approved in August 2007
- ANDA 77-062 (Actavis Elizabeth LLC), approved in August 2007
- ANDA 77-449 (Aveva Drug Delivery Systems), approved in October 2008
- ANDA 77-775 (Noven Pharmaceuticals, Inc.), approved in October 2009
- ANDA 77-154 (Mallinckrodt, Inc.), approved in February 2011

There are also generic versions of the fentanyl drug products Sublimaze, Actiq, and Fentora. See FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) for additional information regarding these generic products.

B. Risk Minimization Action Plans

Before the passage of the Food and Drug Administration Amendments Act in 2007 (described in the next section), FDA approved a few products with risk minimization action plans (RiskMAPs). A RiskMAP is a strategic safety program designed to meet certain goals and objectives in minimizing the risks of a product while preserving its benefits. As FDA explained in a 2005 guidance for industry,[8] routine risk minimization measures, particularly product labeling, are sufficient to minimize risks and preserve benefits for the majority of products.[9] For some products, however, FDA believed a RiskMAP would be warranted.[10] The Agency

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[7] In addition, Sandoz markets an authorized generic version of Duragesic based on the Alza NDA.

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

[9] RiskMAP Guidance at 3-5.

[10] RiskMAP Guidance at 6.

specifically recommended that "sponsors of Schedule II controlled substances, including Schedule II extended-release [ER] or high-concentration opiate drug products, consider developing RiskMAPs...."[11] FDA recommended, however, that "RiskMAPs 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."[12]

C. Risk Evaluation and Mitigation Strategies

1. Food and Drug Administration Amendments Act

On September 27, 2007, the Food and Drug Administration Amendments Act of 2007 (FDAAA) was enacted. Title IX, Subtitle A, section 901 of FDAAA created new section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1), which authorizes FDA to require persons submitting certain applications to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) as part of such application if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.

Section 505-1 also authorizes FDA to require holders of covered applications approved without a REMS to submit a proposed REMS if the Agency becomes aware of new safety information as defined in section 505-1(b)(3) and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

If FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks, FDA will then decide which elements of a REMS are necessary and will approve the REMS once it has determined that the proposed REMS will ensure that the benefits of the drug outweigh the risks, and that the other relevant statutory criteria in section 505-1 are met.

Section 505-1 also sets forth the requirements for applicants for generic versions of drug products that have a REMS. Section 505-1(i) provides that a drug that is the subject of an ANDA under section 505(j) of the FD&C Act (21 U.S.C. 355(j)) is subject to certain elements of the REMS for the applicable listed drug. These elements are: (A) a Medication Guide or patient package insert, if required under section 505-1(e) for the applicable listed drug and (B) elements to assure safe use, if required under section 505-1(f) for the listed drug.

Section 505-1(i) states that an ANDA drug and the listed drug shall use a single, shared system under section 505-1(f), unless the Secretary waives the requirement under certain circumstances.

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[11] RiskMAP Guidance at 7.

[12] RiskMAP Guidance at 5-6.

Section 505-1(i) also requires that for an applicable listed drug for which a drug is approved under section 505(j), FDA shall undertake any communication plan to health care providers required under section 505-1(e)(3) for the applicable listed drug, and FDA shall inform the responsible person for the ANDA drug if the REMS for the applicable listed drug is modified.

Now that FDAAA has authorized FDA to require sponsors to submit REMS, FDA does not plan to request new RiskMAPs (except in the case of generic drug products for which the reference listed drug has a RiskMAP).[13] Instead, 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.[14]

2. Class-wide REMS for Long-Acting and Extended-Release Opioids

On April 20, 2009, FDA announced that it intended to use its REMS authority to mitigate risks associated with long-acting (LA) and extended-release (ER) opioids, including inappropriate prescribing, abuse, misuse, and overdose.[15] These drugs included innovator and generic products formulated with certain active ingredients, including certain products formulated with fentanyl. FDA requested and received numerous comments concerning the design and scope of the REMS. We also held several meetings on the proposed REMS, including 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, 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, and another meeting with an industry working group on May 16, 2011.[16]

On April 19, 2011, FDA announced that a REMS would be required for all ER and LA opioid drug products.[17] In a letter, we directed the sponsors of these products to submit a proposed

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[13] See the Draft Guidance for Industry *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.

[14] REMS Draft Guidance at 3.

[15] Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting, 74 FR 17967 (April 20, 2009).

[16] More information about the REMS for LA and ER opioids, including transcripts and/or minutes of the meetings discussed in the text, can be found at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

[17] FDA Acts to Reduce Harm from Opioid Drugs, April 19, 2011, available at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm251830.htm.

REMS within 120 days of the date of the letter.[18] On July 9, 2012, FDA approved the REMS for LA/ER opioid analgesics.[19] The central component of the LA/ER opioid analgesics REMS is an education program for prescribers (e.g., physicians, nurse practitioners, and physician assistants) that would include information on LA/ER opioid analgesics, patient selection, initiating therapy, modifying dosing, discontinuing use of LA/ER analgesics, monitoring patients, and counseling caregivers about the safe use of these drugs. FDA expects that sponsors will meet this obligation by providing educational grants to accredited, independent continuing education (CE) providers to offer training, at no or nominal cost to the health care professionals.

3. REMS for Transmucosal Immediate-Release Fentanyl Drug Products

On December 28, 2011, FDA approved a single, shared system REMS for the entire class of transmucosal, immediate-release fentanyl (TIRF) drug products. These drug products contain fentanyl and are used to manage breakthrough pain[20] in adults with cancer who are routinely taking other pain medicines around the clock for pain. To use TIRF drug products safely, these patients must be opioid-tolerant based on concurrent regular use of another opioid medication.[21] The REMS requires prescribers, pharmacies, distributors, and outpatients to enroll in the REMS program--called the TIRF REMS Access Program by the sponsors--to prescribe, dispense, or receive all drugs in the TIRF class to reduce the risk of misuse, abuse, addiction, and overdose.[22]

The TIRF REMS was developed with input from the TIRF REMS Industry Group (TRIG), which was comprised of the sponsors of TIRF drug products. Of the fentanyl products identified in

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[18] FDA's actions concerning the ER/LA opioid analgesics REMS were taken in connection with the White House's comprehensive action plan to address the national prescription drug abuse epidemic. See *Epidemic: Responding to America's Prescription Drug Abuse Crisis*, available at http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan_0.pdf. The letter sent to opioid manufacturers outlining opioid REMS implementation can be found at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM251595.pdf. See also FDA Acts to Reduce Harm from Opioid Drugs, April 19, 2011, available at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm251830.htm.

[19] Additional information is available on FDA's Web site at: http://www.fda.gov/drugs/drugsafety/InformationByDrugClass/ucm163647.htm.

[20] Breakthrough pain is pain that comes on suddenly for short periods of time and is not alleviated by a patient's normal pain management plan.

[21] Questions and Answers: FDA approves a class Risk Evaluation and Mitigation Strategy (REMS) for transmucosal immediate-release fentanyl (TIRF) medicines, available at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm284717.htm.

[22] Questions and Answers: FDA approves a class Risk Evaluation and Mitigation Strategy (REMS) for transmucosal immediate-release fentanyl (TIRF) medicines, available at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm284717.htm.

Section A, Actiq, Fentora, Onsolis, Abstral, Lazanda, Subsys and generic versions of these products, are all subject to the TIRF REMS.

II. DISCUSSION

In the Petition, you request that FDA determine whether an RMP is necessary for fentanyl patches and assert that an RMP for fentanyl patches may provide additional safeguards to ensure this form of pain medication is used safely and in accordance with the labeling (Petition at 1).[23] If an RMP is determined to be necessary, you request that FDA develop and adopt a single, unified RMP for all fentanyl patches based on input by all sponsors of approved marketing applications for these products (Petition at 1). You also request that FDA adopt a unified, comprehensive RMP for all fentanyl drug products (which would include all dosage forms) with the participation of all sponsors of these products (Petition at 2). You state that "in the absence of a single, unified Risk Management Program, individual fentanyl users and prescribing physicians would be exposed to multiple separate educational messages if each manufacturer developed and adopted its own Risk Management Program for fentanyl transdermal patches" (Petition at 4). You also assert that if FDA determines that an RMP should be implemented for fentanyl, the RMP should encompass all dosage forms of fentanyl rather than just the oral transmucosal and patch dosage forms (Petition at 5).

We discuss your requests below.

A. Single, Unified RMP for Fentanyl Patches Involving All Sponsors

Since the date of submission of your Petition, the regulatory landscape relevant to whether a RMP is necessary for fentanyl patches has been changed by the passage of FDAAA and approval of the class-wide LA/ ER opioid REMS. As noted above, FDAAA authorized FDA to require a sponsor to submit a REMS if it determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks.[24] FDA has required a REMS for LA/ER opioid analgesic drug products, which include Duragesic and approved generic equivalents.[25] Therefore, your request that FDA determine whether an RMP is necessary for fentanyl patches is moot and is denied.

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[23] You state that Mylan provided FDA with a conceptual outline of an RMP for fentanyl patches at FDA's request during a September 7, 2005, meeting. We note that it was Mylan who initiated the presentation of the RMP outline to FDA.

[24] See 21 U.S.C. 355-1(a) and the Draft Guidance for Industry *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.

[25] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251735.htm.

However, we anticipate that the new class-wide LA/ER opioid analgesic REMS will provide the "additional safeguards" you request to help assure "that this form of pain medication is used safely and in accordance with FDA-approved labeling" (Petition at 1). The LA/ER opioid analgesics REMS requires that prescriber education be made available to educate doctors about proper prescribing practices. The REMS also requires companies to make available FDA-approved patient education materials, including a Medication Guide that uses consumer friendly language to explain safe use and disposal of LA/ER opioid analgesics.[26]

With respect to your request for a single unified RMP for all fentanyl patches based on input from all sponsors with approved marketing applications for these products, the class-wide LA/ER opioid analgesics REMS addresses this request. The development of the LA/ER opioid analgesic REMS involved several public meetings as well as meetings with manufacturers of LA/ER opioid products. Since notifying the sponsors of LA/ER opioid drugs that they were required to submit a REMS, FDA has had numerous meetings with the sponsors that market these products on the required REMS to discuss the REMS and FDA's development of the content of the Blueprint for prescriber education.[27] We also solicited written comments through a docket and received over 2,000 comments. We believe the class-wide REMS for LA/ER opioid analgesic drug products addresses your concerns that individual fentanyl users and prescribing physicians would be exposed to multiple separate education messages, because all manufacturers of fentanyl patches will be subject to the same REMS requirements and will develop educational materials for prescribers based on the same FDA-approved content. Therefore, to the extent that your Petition requests a single unified RMP based on input from all sponsors with approved applications for transdermal fentanyl drug products, the request is granted in part.

B. Comprehensive RMP for All Dosage Forms of Fentanyl

You also request that FDA adopt a unified, comprehensive RMP for all fentanyl drug products with the participation of all sponsors of these products (Petition at 1).

As discussed above, your request that FDA determine whether an RMP is necessary for fentanyl is moot. Most fentanyl drug products are currently subject to a REMS. All LA/ER opioids, including Duragesic and approved generic fentanyl patches, are subject to the class-wide LA/ER Opioid REMS. Actiq, Fentora, Onsolis, Abstral, Lazanda, and Subsys are all transmucosal, immediate-release fentanyl drug products that are subject to the TIRF REMS. Accordingly, the only approved fentanyl drug products on the market not currently subject to a REMS are injectable forms of fentanyl.

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[26] FDA Introduces New Safety Measures for Extended-Release and Long-Acting Opioid Medications, available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310870.htm.

[27] See Meetings with Industry and Stakeholders at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm305245.htm.

We do not believe that it would be appropriate for all fentanyl dosage forms to be covered by the same REMS. As discussed above, REMS are required when elements beyond the approved labeling are necessary for the benefits of a drug (or class of drugs) to outweigh the risks. REMS have specific goals with respect to the mitigation of the risks posed by a particular drug (or class of drugs), and impose specific requirements authorized by section 505-1 of the FD&C Act to mitigate those risks.

For example, the LA/ER opioid analgesics pose different risks than IR drug products. IR opioid analgesics work for shorter periods of time. ER opioid analgesics are designed to provide a longer period of drug release so that they can be taken less frequently, and LA opioid analgesics have a longer period of action because of the inherent characteristics of the drug substance, which stays longer in the body, and not because of the special design features of the finished product. The amount of opioid analgesic contained in an ER tablet can be much greater than the amount of opioid analgesic contained in an IR tablet, because ER tablets are designed to release the opioid analgesic over a longer period of time. While improper use of any opioid can result in serious side effects, including overdose and death, this risk is magnified with ER/LA opioid analgesics. Thus, after concluding that there was a disproportionate safety problem associated with ER/LA opioid analgesics, FDA required a REMS specific to ER/LA opioid analgesics.

With regard to TIRFs, the decision to approach risk management for this subset of opioids differently from the ER/LA opioids resulted from the distinctive properties of these IR opioids when compared to other opioid drug products. The unique risk of TIRFs is that, unlike any other IR opioid, they are indicated only for opioid-tolerant cancer patients, due to the substantial risk of overdose and death when used in persons who are not opioid-tolerant. The pharmacokinetic profile of TIRFs is intended to provide a relatively fast peak plasma level and not a sustained level. Efficacy and safety have only been demonstrated in the opioid-tolerant cancer patient population; most of the doses can be expected to result in an overdose in a person who is not opioid-tolerant.

At the time of approval of the first TIRF products, FDA considered that although the TIRF products had been found to be safe and effective when used in an opioid-tolerant population for breakthrough cancer pain, their approval required a RiskMAP because of the potential for harm given the increased possibility of improper patient selection, improper use, or unsafe storage. Following approval, initial postmarket data showed that a large proportion of TIRF product usage was off label. Fortunately, most of this off label use was in opioid-tolerant patients. As we continued to review postmarket data, however, we found that, over time, even with the initial RiskMAP in place, use in non-opioid tolerant patients continued and serious adverse events were documented as a result. As additional TIRF products were approved, the FDA determined that to stop the upward trend of serious adverse events in non-opioid tolerant patients, a single, shared TIRF REMS Access Program should be developed. To the extent that the risk of serious adverse

events, including overdose and death, is greater for the TIRF products as a class than for the ER/LA opioid analgesics as a class, the TIRF REMS was designed to address these greater risks.

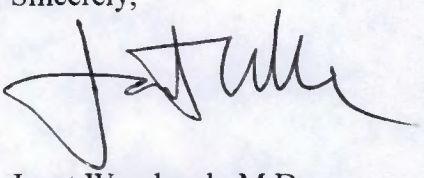
Although you assert that the RMP could include attributes addressing issues unique to each dosage form, we believe that attempting to address the different risks described above in one REMS would cause confusion and defeat the alleged simplicity of having a single REMS. This is why different REMS apply to different classes of fentanyl drug products (e.g., TIRF products, such as Actiq and generics, and LA/ER opioids, such as Duragesic and generics). Specifically, a single REMS for all fentanyl transdermal patches permits enhanced prescriber and patient education, risk and safety monitoring, and comparisons among the innovator and generic patches.

For the reasons discussed above, we deny your request for a comprehensive REMS encompassing all fentanyl dosage forms. Because we are denying your request, we need not address your request that it involve all sponsors of these products. In any case, development of the ER/LA opioid REMS and the TIRF REMS has already included participation by sponsors of these products.

III. CONCLUSION

For the reasons stated above, we grant your Petition in part and deny your Petition in part.

Sincerely,



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