DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Edward J. Markey
United States Senate
Washington, D.C. 20510-2107

NOV 28 2016

Dear Senator Markey:

Thank you for your letter of October 11, 2016, regarding the off-label prescribing of Subsys. The Food and Drug Administration (FDA or the Agency) is deeply concerned about the growing epidemic of opioid misuse, opioid use disorders and overdose in the United States. In response to this crisis, the Agency has developed a comprehensive action plan to take concrete steps toward reducing the impact of opioid misuse on American families and communities. As part of this plan, the Agency is enhancing safety labeling; requiring new data; and seeking to improve treatment of both substance use disorders and pain. We have also taken other actions, including seeking advice from the National Academy of Science Engineering and Medicine on how to balance both the needs of patients with pain and the need to address opioid misuse. FDA is committed to taking all of these steps transparently and in close cooperation with its sister agencies and stakeholders.

We have restated your questions below in bold, followed by our response.

1. **How is off-label prescribing of Subsys – for example, for neck and back pain – consistent with the FDA's warning accompanying the drug, which states: "SUBSYS is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain"?**

   The language you have identified is from the Indication and Usage section of the approved labeling for Subsys. The full text of the approved labeling is designed to give healthcare professionals the information they need to prescribe drugs appropriately, and is available at: *www.accessdata.fda.gov/drugsatfda_docs/label/2014/202788s009s011s012lbl.pdf.* Prescribing Subsys for neck and back pain that is unrelated to cancer is prescribing it for a use that is not consistent with the conditions set forth in the approved labeling.

2. **How is off-label prescribing of Subsys – for example, for neck and back pain – consistent with the TIRF-REMS, which restricts the use of "TIRF medicines. . . to manage breakthrough pain in adults with cancer who are routinely taking other opioid pain medicines around-the-clock for pain"?[1]**

[1] *www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm284717.htm*

The transmucosal immediate-release fentanyl (TIRF) products, including Subsys, are indicated for the management of breakthrough pain in adult cancer patients who are already receiving, and who are tolerant to, around-the-clock opioid therapy. TIRFs are subject to a REMS program called the TIRF REMS Access Program (TIRF REMS). The TIRF REMS does not affirmatively restrict off-label prescribing, but rather seeks to mitigate risks associated with TIRF products by ensuring that prescribers and pharmacists are educated before prescribing and dispensing these products. The TIRF education program emphasizes appropriate patient selection and warns of the risk of life-threatening respiratory depression at any dose in opioid non-tolerant patients.

The TIRF REMS was established in December 2011 and all drugs in this class (currently nine products) are subject to it. The goals of the TIRF REMS are to mitigate the risk of misuse, substance use disorder, overdose, and serious complications due to medication errors by meeting the following objectives:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, substance use disorder, and overdose of TIRF medicines.

The aspects of the REMS program aimed at ensuring that TIRF products are prescribed and dispensed only to appropriate patients are focused on educating prescribers and pharmacists. Healthcare providers who want to prescribe TIRF products for outpatient use must become certified by completing the training and a knowledge assessment, and enrolling in the TIRF REMS Program. Pharmacies that want to dispense TIRF products must also become certified by enrolling and ensuring that all pharmacy staff have completed the TIRF REMS training. Only pharmacies that are certified in the TIRF REMS program can receive the drug, and certified pharmacies are required to confirm that prescribers are enrolled in the TIRF REMS program prior to dispensing a TIRF product to patients.

The TIRF REMS education program for prescribers and pharmacists and the TIRF REMS Prescriber Enrollment Form includes extensive information on appropriate patient selection. This includes information on the approved indication and the contraindications that are specified in the approved prescribing information, including that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain; that TIRF medicines are contraindicated for use in opioid non-tolerant patients; that fatal overdose can occur at any dose; and that TIRF medicines must not be used to treat any contraindicated conditions described in the full approved prescribing information , such as acute or postoperative pain, including headache/migraine. A prescriber wishing to enroll in the TIRF REMS program must attest to understanding all of this information as a condition of enrollment.

The TIRF REMS program does not require pharmacists to verify that a patient meets the description in the FDA-approved indication . Instead, the pharmacist verifies that the prescriber has been enrolled in the TIRF REMS program and has received the training discussed above. Prescribers are required to re-enroll every two years. Additionally prescribers and patients are required to complete a Patient-Prescriber Agreement Form for every patient who begins treatment with a TIRF product. The Patient-Prescriber Agreement Form is a tool that covers key safety points with patients.

Information about the TIRF REMS, including the related materials required for enrollment in the program and specific requirements for prescribers, patients, and pharmacies is available on our website, at *www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60.*

3. a. Has Insys submitted its required assessment of the TIRF-REMS for Subsys?[2] If so, please provide a copy of Insys' assessment. If not, why not?

Insys has met its requirement to submit assessments of the TIRF REMS per the timetable for submission of assessments included in the TIRF REMS document. The TIRF REMS assessment is a shared assessment of the TIRF REMS Program which provides aggregate information on all of the TIRF products; it does not include product-specific information. There is no separate assessment specific to Subsys.

b. If Insys has submitted its assessment of the TIRF-REMS, has the FDA completed its review of the assessment? [3] If so, please provide a copy of the FDA's review. If not, why not?

The TIRF REMS assessment includes information on program utilization (including the number of prescribers, pharmacists and patients participating in the TIRF REMS program), dispensing activity, program infrastructure and performance (the ability of the program to ensure processes are in place and functioning prior to dispensing a prescription for a TIRF medicine), program non-compliance, safety surveillance, and periodic surveys of patients, healthcare providers, and pharmacists.

The TIRF REMS sponsors have submitted five REMS assessments to date, the last of which was received December 30, 2015. The first of these assessments, was due at six months post-approval of the REMS, and served only to update the Agency on the implementation of the program (e.g., numbers of prescribers and pharmacies that have become certified). Each of the annual REMS assessments following the 6-month assessment demonstrated that compliance with the REMS requirements were being followed. This includes the requirement for prescribers and dispensers of TIRF medicines to become certified, including completion of the TIRF education program, enrollment into the program and attesting to their understanding of the risks and agreement to adhere to the requirements of the program, and the requirement for patients to be counseled on the risks and safe use of TIRF medicines. In

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[2] *www.accessdata. fda.gov/drugsatfda docs/nda/2012/2027880riglsOOOApprov.pdf.*
[3] *www.fda.gov/downloads/ AboutFDA/Transparency/Basics/UCM328784.pdf.*

addition, data from patient, prescriber, and pharmacist knowledge surveys showed an overall high understanding of the risks, safe use, and safe storage of TIRF medicines.

Obtaining data demonstrating that patients are opioid tolerant before receiving a prescription for a TIRF medicine, that inappropriate switches between TIRF products are not being made, and that accidental exposure to children and others for whom a TIRF was not prescribed has been challenging. This is partially related to the lack of availability of databases that can adequately capture these metrics in the small population of patients receiving TIRF medicines, and partially related to the ability of the initial databases used by the TIRF REMS sponsors to inform these metrics. The Agency has provided the TIRF sponsors recommendations on methods to better capture these metrics.

The most recent assessment, received in December 2015, covered the period between October 29, 2014 to October 29, 2015. FDA continues to evaluate the most recent assessment and whether any REMS modifications are necessary based upon data submitted in this assessment. The next TIRF assessment is due December 2016.

4. Is the FDA taking any steps in response to Insys' pattern of aggressive and illegal off-label marketing of Subsys? If so, what is the FDA doing? If not, why not?

FDA is extremely concerned about the current opioid epidemic and has taken a number of steps this year to address this epidemic as part of our Opioids Action Plan. We are aware of recent reports in the news media regarding Insys's activities in marketing Subsys; as your letter points out, a number of Federal and state investigations and enforcement actions have also already been initiated. FDA takes allegations of conduct that may indicate violations of the FD&C Act extremely seriously. As a matter of policy, however, we do not confirm or deny the existence of any pending investigation or speculate about any potential future compliance action.

As an overall matter, FDA continues to monitor the marketing and distribution of all opioids and is committed to addressing potential violations of FD&C Act requirements. As part of this work, the Office of Prescription Drug Promotion (OPDP) in FDA's Center for Drug Evaluation and Research conducts proactive surveillance of promotional activities for prescription drugs, including opioids, to identify evidence that a drug's manufacturer or distributor has failed to satisfy requirements for the lawful distribution of the drugs they address. This program includes regular surveillance through a variety of channels, such as examination of promotional labeling and advertising submitted to the Agency at time of first use pursuant to post-approval reporting requirements, online surveillance, in-person surveillance activities at major medical meetings, and review of complaints sent to FDA. In addition, FDA, particularly through its Office of Criminal Investigations, also works with federal, state, local, and international law enforcement partners, using customary law enforcement methods and techniques to investigate potential violations of the FD&C Act and other statutes related to drugs and other FDA-regulated products.[4]

[4] *www.fda.gov/ICECI/CriminalInvestigations/ucm123062.htm*

It is important to remember that federal efforts to ensure that pharmaceutical companies comply with applicable laws in their activities with regard to sale of prescription drugs, including opioids, are not confined to FDA. If concerns arise that a firm is distributing misbranded drugs or otherwise committing a violation of the FD&C Act, for example, FDA works with the Department of Justice to investigate and pursue judicial enforcement actions, when appropriate. FDA employees, including scientists, compliance personnel, and attorneys often provide support for such actions. Furthermore, the FD&C Act is not the only law that is potentially relevant to allegations of illegal activity by pharmaceutical companies. Federal fraud and abuse laws such as the False Claims Act and the Anti-Kickback Statute may often be implicated, and FDA is not the agency charged with interpretation or enforcement of those laws. Thus, depending on the circumstances, multiple federal agencies, including the Department of Justice (DOJ), the HHS' Office of the Inspector General (OIG), and the Centers for Medicare and Medicaid Services (CMS) may independently investigate allegations of illegal activity by pharmaceutical companies.

FDA will continue to use its tools to monitor the marketing and distribution of Subsys as well as other prescription drug products and to address potential violations of FD&C Act requirements. We encourage anyone with knowledge of prescription drug promotion that may be misleading or raise other regulatory concerns to contact the FDA through our Bad Ad Program at *BadAd@fda.gov* or 855-RX-BADAD.

As you recognized in your letter, on November 9 - 10, 2016, the Agency held a two-day public hearing on manufacturer communications regarding unapproved uses of approved or cleared medical products. We urge you to submit this letter and any other information you deem appropriate to the public docket by January 9, 2017. Submit electronic comments to *www.regulations.gov*. Submit written comments to the Division of Docket's Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments must be identified with the docket number FDA-2016-N-1149. The *Federal Register* notice includes additional details regarding the scope of the public meeting and topics on which the agency particularly seeks input. The notice is available at *https://federalregister.gov/a/2016-21062*. Additional information, including links to the archived webcast of the hearing, can be found at *www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm489499.htm* .

Thank you, again, for contacting us regarding your concerns. Please let us know if there are any further questions.

Sincerely,

Dayle Cristinzio
Acting Associate Commissioner
For Legislation