DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202788
MF 27320

REMS ASSESSMENT ACKNOWLEDGMENT

Insys Development Co.
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1333 South Spectrum Blvd., Suite 100
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Attention: Stephen Sherman
Sr. Vice President, Regulatory Affairs

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SUBSYS (fentanyl) sublingual spray.

We also refer to your December 29, 2015, submission containing your assessment of the Transmucosal Immediate-Release Fentanyl (TIRF) Products risk evaluation and mitigation strategy (REMS).

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete with the following comments:

1. After review of the 48 month (5th overall) REMS assessment report for the Transmucosal Immediate-Release Fentanyl (TIRF) Products REMS, we conclude that it is not possible to determine whether the overarching goal of the REMS - to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors is being met.
   a. The first objective (prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients) is not being achieved. In the TIRF REMS Industry Group's (TRIG's) assessment of opioid tolerance, approximately 42% of patients prescribed TIRF products were not opioid tolerant. It is important that the TRIG further investigate this issue.

   b. It is not possible to determine if the second objective (preventing inappropriate conversion between TIRF medicines) is being met. Though no instances of inappropriate conversions were submitted as a spontaneous report, the persistency analysis provided indicates that the number of patients who may be exposed to inappropriate conversion between TIRF medicines may be as high as 17.1-20.5% of patients receiving TIRF medicines. Further assessment of these findings is also warranted.

c. It is also not possible to determine if the third objective (preventing accidental exposure to children and others for whom it was not prescribed) is being met. The case reports for this metric remain quite low thus challenging the ability to assess the impact of the REMS on this objective, particularly since the case reports do not provide enough information to conduct a root cause analysis (RCA).

d. The fourth objective (educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines) is partially being met. Overall, patients, prescribers, and pharmacists seem to have an adequate understanding of most of the key risk messages related to preventing inappropriate conversion, accidental exposure, and the potential for misuse, abuse, addiction, and overdose of TIRF medicines; however, all groups had a lower awareness of the need to only prescribe and dispense TIRF medicines to appropriate patients.

2. In order to address the deficiencies outlined in 1a, b, c, and d, we have the following comments:

a. Regarding the assessment of opioid tolerance submitted in the 48 month assessment, approximately 42% of patients prescribed TIRF products were not opioid tolerant. The TRIG needs to further investigate this concerning finding. A timeline for a plan to further evaluate this finding should be submitted with the February 17, 2017, submission of the 60 month REMS assessment survey results. At a minimum, further evaluation of this finding will include product-specific assessment of opioid tolerance that each member sponsor will submit only to their NDA or ANDA. Additional details regarding this evaluation will be communicated in a separate letter.

b. Regarding the persistency analysis submitted by the TRIG, these data indicate that the number of patients who may be exposed to "inappropriate conversion between TIRF medicines" is not insignificant. Thus these TIRF product switches need to be further assessed by the TRIG and a protocol developed to assess the starting doses of the TIRF products that existing TIRF patients switch to in order to ascertain what proportion of these switches are conducted as per products' labeling. In addition, if the data system used has outcome data, this would be informative as to whether or not any switch marked as "inappropriate" resulted in any adverse sequelae. Limitations of the databases and/or approaches used are to be included in the protocol. Please submit this protocol with the February 17, 2017, submission of the 60 month REMS assessment survey results; if additional time for protocol development is needed, please request an extension.

c. We would like to schedule a meeting to discuss opportunities for obtaining additional data on accidental exposure to children and others for whom TIRF products are not prescribed, as well as to discuss possible ways to address the low

awareness of the need to prescribe and dispense TIRF medicines to appropriate patients.

3. Additional comments on the 48 month assessment:

a. In the FDA's 36-month REMS Assessment Acknowledgement Letter (date August 3, 2015), the TRIG was asked to "Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues."

In the 48 month assessment report, the TRIG responded that: "Based on…analysis, there is no barrier to patient access and further outreach is unwarranted." The TRIG states that 516 prescribers (8.6%) chose to not re-enroll and that these prescribers had an average of no more than four prescriptions total over the course of the reporting period. However, the reasons why these prescribers withdrew from the program are unknown as are the reasons why 1,134 prescribers had their enrollment expire this reporting period and remain expired. Additionally, the reasons why 412 pharmacies chose not to re-enroll are not presented.

It is therefore important that the TRIG proceed with conducting an "…outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons… (w)e are concerned about potential patient access issues." Submit a timeline for the plan to conduct this outreach in the February 17, 2017, submission of the 60 month REMS assessment survey results.

b. There continues to be a steady increase in mean and median prescription processing times during this reporting period versus the previous periods. The TRIG was previously asked to investigate this finding, but did not do so, instead stating that this finding may be due to a lower number of prescriptions with at least one initial REMS-related rejection this reporting (1,735) period as compared to the 36-month report (3,738). These differences cited by the TRIG do not appear to be so large as to account for some sort of number skewing induced by a small sample size. The TRIG needs to investigate and identify the causes of these increasing delays in prescription processing as these are potential indicators of access barriers.

c. The TRIG Protocol for Corrective Actions for Instances of Non-Compliance contains few concrete criteria or decision trees as to how to deal with episodes of non-compliance. Thus it is unclear to us what types of non-compliance actions would reliably lead to suspension or deactivation. The TRIG should add

increased specificity to the Non-Compliance Review Team (NCRT) protocol as well as to the Supporting Document of the REMS.

In addition, it is concerning that the TRIG's criteria for an incident of an individual prescriber non-compliance with Patient-Prescriber Agreement Form (PPAF) requirements needs to involve at least "5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date." These criteria would appear to potentially lead to an under-reporting of PPAF non-compliance. The TRIG should explore mechanisms to capture lower levels of non-compliance.

d. Regarding the three instances where a non-closed system pharmacy dispensed a TIRF product after a TIRF REMS rejection, all three reports were brought to the attention of the TRIG only after the pharmacy contacted the REMS. The TRIG should develop a more active mechanism by which to identify and prevent such occurrences.

e. Although results for both governmental (Veteran's Health Administration and Department of Defense) and closed-pharmacy systems appear to have improved from the 36-month audit, they continue to be unsatisfactory. The 36-month REMS Assessment Acknowledgement Letter requested that the TRIG "Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report." The TRIG has issued the following response: "The TRIG has determined that the current prescription authorization volume for closed-system pharmacies is less than 1% of all TIRF prescriptions and due to the absence of complaints with the current process, no changes are warranted at this time." An absence of complaints does not necessarily mean that a closed pharmacy system process is functioning optimally. These audits are likely one of the best sources of information regarding the performance of these closed-system pharmacies in meeting the REMS requirements. If the TRIG does not favor a novel authorization process for all of the closed-system pharmacies solely due to the poor performance of the governmental entities, the TRIG should propose an outreach to these programs to improve compliance. In addition, the TRIG should be sure to include both governmental entities in the 60-month audit so that their performance in the REMS can continue to be monitored.

Lastly, the TRIG presents the process times for prescriptions that have experienced at least one REMS-related rejection. However, data on the overall processing time of a prescription that does not meet with any rejections is unclear. Given that one of the pieces of information solicited during the closed-system audits is "Date and time of each prescription transaction," this is an excellent opportunity for the TRIG to assess prescription processing times for prescriptions that do not experience any REMS-related rejections. The TRIG should add this component to their closed-system audits.

f. For the Inpatient Pharmacy audits, six inpatient pharmacies either did not respond to the audit request or decided not to participate. In the current inpatient pharmacy enrollment form, the pharmacy only agrees to have their training audited. We are considering revisions to this enrollment form to allow for process audits so as to increase the potential pool of inpatient pharmacies in the audit and will communicate any required modifications during the review of the next REMS assessment.

g. The TRIG reports a number of instances where prescribers were either unaware of requirements to submit a PPAF or chose not to do so. It is important that the TRIG investigate mechanisms to reinforce to prescribers the necessity of timely completion of PPAFs.

h. For subsequent submissions of Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) data that contain CII opioid comparators, expand the CII immediate-release opioid category to include oxycodone/acetaminophen, oxycodone/aspirin, and oxycodone/ibuprofen.

i. The Agency has increasing concerns about the use of RADARS data to assess some of the outcomes outlined in the TIRF REMS. Given the limitations of RADARS, the Agency believes that additional data sources that can track adverse outcomes of interest associated with the TIRF products are necessary, and the TRIG must study intermediate objectives more closely related to the REMS intervention. The FDA proposes a meeting with the TRIG to discuss and explore new approaches to assessing this REMS with the goal of gathering useful information to better understand the impact of the REMS and to improve the program going forward.

4. We refer to the July 21, 2016, FDA electronic communication in which comments on the patient, prescriber, and pharmacist surveys were conveyed based upon the 48 month REMS assessment results. We acknowledge the subsequent agreement between the Agency and the TRIG that the survey results for the 60 month TIRF REMS assessment will be submitted to the Agency on February 17, 2017.

If you have any questions, call Mark Liberatore, PharmD; Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

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