Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee
August 3, 2018

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland

Topic: The committees discussed results from assessments of the transmucosal immediate-release fentanyl (TIRF) medicines' risk evaluation and mitigation strategy (REMS), approved in December 2011. The TIRF REMS requires that healthcare providers who prescribe TIRF medicines for outpatient use are specially certified, that pharmacies that dispense TIRF medicines for inpatient and outpatient use are specially certified, and that completion of the prescriber-patient agreement form occurs prior to dispensing TIRF medicines for outpatient use. The Agency sought the committees' assessment as to whether this REMS with elements to assure safe use (ETASU) assured safe use, was not unduly burdensome to patient access to the drugs, and to the extent practicable, minimized the burden to the healthcare delivery system. The Agency also sought the committees' input on any possible modifications to the TIRF REMS goals and requirements, as well as input on the adequacy of the evaluations conducted in the REMS assessments to determine whether the TIRF REMS goals are being met.

These summary minutes for the August 3, 2018 joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration were approved on September 7, 2018.

I certify that I attended the August 3, 2018 joint meeting of the DSaRM and AADPAC of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Yinghua S. Wang, PharmD, MPH
Acting Designated Federal Officer
DSaRM

/s/
Brian T. Bateman, MD, MSc
Acting Chairperson
DSaRM

Summary Minutes of the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee
August 3, 2018

The Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on August 3, 2018, at the FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and the Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Industry Group (TRIG). The meeting was called to order by Brian Bateman, MD, MSc (Acting Chairperson). The conflict of interest statement was read into the record by Yinghua Wang, PharmD, MPH (Acting Designated Federal Officer). There were approximately 100 people in attendance. There was one Open Public Hearing (OPH) presentation.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committees discussed results from assessments of the transmucosal immediate-release fentanyl (TIRF) medicines' risk evaluation and mitigation strategy (REMS), approved in December 2011. The TIRF REMS requires that healthcare providers who prescribe TIRF medicines for outpatient use are specially certified, that pharmacies that dispense TIRF medicines for inpatient and outpatient use are specially certified, and that completion of the prescriber-patient agreement form occurs prior to dispensing TIRF medicines for outpatient use. The Agency sought the committees' assessment as to whether this REMS with elements to assure safe use (ETASU) assured safe use, was not unduly burdensome to patient access to the drugs, and to the extent practicable, minimized the burden to the healthcare delivery system. The Agency also sought the committees' input on any possible modifications to the TIRF REMS goals and requirements, as well as input on the adequacy of the evaluations conducted in the REMS assessments to determine whether the TIRF REMS goals are being met.

Attendance:

Drug Safety and Risk Management Advisory Committee Members Present (Voting):
Laurel A. Habel, MPH, PhD; Martin Kulldorff, PhD; Steve B. Meisel, PharmD, CPPS; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting):
Kelly Besco, PharmD, FISMP, CPPS; Denise M. Boudreau, PhD, RPh; Sonia Hernandez-Diaz, MD, MPH, DrPH; Marie R. Griffin, MD, MPH; Suzanne B. Robotti; Anne-Michelle Ruha, MD, FACMT; Soko Setoguchi, MD, DrPh

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting): Linda Scarazzini, MD, RPh

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Brian T. Bateman, MD, MSc (Acting Chairperson); Raeford E. Brown, Jr., MD, FAAP; Basavana G. Goudra, MD, FRCA, FCARSCI; Ronald S. Litman, DO, ML; Mary Ellen McCann, MD, MPH (via telephone)

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): W. Joseph Herring, MD, PhD (Industry Representative)

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Abigail B. Shoben, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP; Lonnie Zeltzer, MD

Temporary Members (Voting): Cynthia L. Arfken, PhD; Paul Brand, PharmD, AE-C; David Craig, PharmD, BCPS; Michael O. Fry, PharmD, RPh; Jennifer G. Higgins, PhD (Acting Consumer Representative); Elizabeth Joniak-Grant, PhD (Patient Representative); Joanna G. Katzman, MD, MSPH; Lewis S. Nelson, MD; Friedhelm Sandbrink, MD; Margaret Warner, PhD

FDA Participants (Non-Voting): Doris Auth, PharmD, Sharon Hertz, MD; Cynthia LaCivita, PharmD; Claudia Manzo, PharmD; Judith A. Racoosin, MD, MPH; Judy Staffa, PhD, RPh

Acting Designated Federal Officer (Non-Voting): Yinghua S. Wang, PharmD, MPH

Open Public Hearing Speaker: Stephanie Fox-Rawlings, PhD (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee	**Brian Bateman, MD, MSc** Acting Chairperson, DSaRM
Conflict of Interest Statement	**Yinghua S. Wang, PharmD, MPH** Acting Designated Federal Officer, DSaRM
FDA Opening Remarks	**Sharon Hertz, MD** Director Division of Anesthesia, Analgesia and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
FDA PRESENTATIONS	
Approval History of TIRF Medicines	**Elizabeth Kilgore, MD, MS** Medical Officer DAAAP, ODE-II, OND, CDER, FDA

FDA PRESENTATIONS (CONT.)

REMS Authority and TIRF REMS	**Cynthia LaCivita, PharmD** Director Division of Risk Management (DRISK) Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) CDER, FDA
INDUSTRY PRESENTATIONS	**TIRF REMS Industry Group (TRIG)**
Introduction	**Stephen Sherman, JD, MBA** Senior Vice President Regulatory Affairs and Clinical Development Insys Therapeutics
Breakthrough Cancer Pain and the Public Health Impact of the TIRF Medicines	**Joseph Pergolizzi, MD** Senior Partner Naples Anesthesia and Pain Associates, Inc.
Overview of TIRF REMS Access Program	**Kyle Irwin, MBA** Associate Director, REMS Operations Teva Pharmaceuticals
REMS Evaluation Results	**Annette Stemhagen, DrPH, FISPE** Senior Vice President, Chief Science Officer United BioSource Corporation
RADARS Data	**Richard C. Dart, MD, PhD** Executive Director, RADARS® System Denver Health and Hospital Authority University of Colorado School of Medicine
Effectiveness of the TIRF REMS Access Program	**Dean Mariano, DO** Senior Director Clinical Development & Medical Affairs Insys Therapeutics
Planned Changes and Proposed Action Items	**Stephen Sherman, JD, MBA**
Conclusions	**Stephen Sherman, JD, MBA**
Clarifying Questions	

BREAK

FDA PRESENTATIONS

FDA Review of the TIRF REMS Assessment	**Doris Auth, PharmD** Associate Director DRISK, OMEPRM, OSE, CDER, FDA
FDA Review of the Epidemiologic and Surveillance Data	**Rose Radin, PhD, MPH** Epidemiologist, Division of Epidemiology II (DEPI-II) Office of Pharmacovigilance and Epidemiology OSE, CDER, FDA
Concluding Remarks	**Doris Auth, PharmD**

Clarifying Questions

LUNCH

Yale University-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI) Presentation

Characterization of Potentially Unsafe Prescribing of Opioid Analgesics Requiring Prior Opioid Tolerance	**Molly Moore Jeffery, PhD** Scientific Director of Emergency Medicine Research Research Associate, Department of Health Sciences Research Mayo Clinic

Centers for Medicare & Medicaid Services (CMS) Presentation

Effect of TIRF-REMS on Transmucosal Fentanyl Prescribing	**William Fleischman, MD, MHS** Medical Officer Center for Program Integrity, CMS

Clarifying questions

OPEN PUBLIC HEARING

Charge to the Committees	**Claudia Manzo, PharmD** Director OMEPRM, OSE, CDER, FDA

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committees:

1. **DISCUSSION:** The intent of the Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) is to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

   Objective 1: Ensuring prescribing and dispensing TIRFs only to appropriate patients (e.g., opioid tolerant patients).

   a. Discuss whether the following strategies will inform if this objective is being met:

      i. Further validation of claims-based algorithm through EMR/chart study
      ii. Linked claims-based outcomes studies in patients prescribed TIRF medicines, comparing opioid non-tolerant patients to opioid tolerant patients

   b. Discuss other strategies the TIRF REMS Industry Group (TRIG) should undertake to inform this objective.

   Committee Discussion*: The committees agreed that based on the data available, TIRF medications are being prescribed to patients who are non-cancer patients and who are not opioid tolerant. The committee members noted the need to understand this phenomenon better, including whether this is product-specific or a class effect, information on the diagnosis of non-cancer patients, and more contemporaneous medical record access to notes. The committee members agreed that additional outcomes studies using claims data are needed to understand the risks of TIRF medicines in opioid tolerant versus non-tolerant patients. One member recommended a registry for patients taking TIRF medicines because of the size of the patient population and dangerous nature of these products; however, another member noted that a registry may make patients nervous and needs to be handled carefully. It was noted that fatal overdoses are rare as an outcome, and one member suggested that data from Western Europe may be helpful, as the products are prescribed more there. Other strategies suggested for the TRIG include strengthening the REMS education component with more rigorous knowledge tests for prescribers and pharmacists, and to amend the patient-prescriber agreement form (PPAF) with an attestation to include that the patient is opioid tolerant. Please see the transcript for details of the Committees' discussion.*

   Objective 2: Preventing inappropriate conversion between TIRF medicines.

   c. Discuss whether the following strategy will inform if this objective is being met:

      i. Further study to obtain dosing instructions for TIRFs dispensed to estimate the number of inappropriate conversions

   d. Discuss other strategies the TRIG should undertake to inform this objective.

***Committee Discussion**: The committee members noted that no further study is needed as the data suggested dosing conversions occurred, and that conversion guidance for prescribers are available on labels and other online sources. Suggestions from committee members include to enforce compliance and to educate providers on safe conversion. Please see the transcript for details of the Committees' discussion.*

Objective 3: Preventing accidental exposure to children and others for whom it was not prescribed.

e. Discuss whether the addition of multiple approaches to identify these rare events will inform if this objective is being met.

f. Discuss other strategies the TRIG should undertake to inform the objective.

***Committee Discussion**: The committee members noted that the data showed accidental exposure to children is rare, but still problematic thus more data sources should be used to better define the frequency of poisoning in children. Suggestions to minimize the TIRF exposure to children include to educate parents, to dispose unused medication appropriately, and to co-prescribe naloxone in households with children. Please see the transcript for details of the Committees' discussion.*

Objective 4: Educating prescribers, pharmacists and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

g. Discuss whether the prescriber, patient, and pharmacy survey results, as well as the requirement for re-certification of prescribers and pharmacists, are sufficient to inform this objective.

h. Discuss other strategies the TRIG should undertake to inform the objective.

***Committee Discussion**: The committee members noted that there is knowledge attrition over time, thus more rigorous education (longer than 30 minutes) and repeated education could help. Other suggestions include just-in-time education, checklists, and system approaches for the providers. One committee member suggested having a small subset of pharmacies certified as TIRF-specialized pharmacies. One committee member noted the need to ensure knowledge is conveyed to patients. Committee members noted that better response rate to survey is needed. Please see the transcript for details of the Committees' discussion.*

2. **DISCUSSION:** The goal of the TIRF REMS is to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors. Considering the substantial limitations of the surveillance data, discuss the significance of findings suggestive of increasing rates of adverse events, despite decreasing use of TIRF medicines.

***Committee Discussion**: The committee members noted a number of plausible explanations for the findings suggestive of increasing rates of adverse events, including a shift of patient*

population to high risk patients, more awareness of fentanyl and adverse effects leading to surveillance bias, and changes in the specific TIRF medicine being used that might have different risk profiles. The committee members also noted that the number of events are small and the estimates of risk are unstable due to sparse data, and therefore it is a challenge to come to any conclusion. Please see the transcript for details of the Committees' discussion.

3. **DISCUSSION:** The REMS assessment data indicate the outpatient use of TIRF medicines has decreased approximately 75% since 2010.

    a. Discuss any factors that may have resulted in the decrease in use of TIRF medicines.

    b. Discuss whether the TIRF REMS may be creating unnecessary barriers to access to these products for patients who could benefit from them, and if so, what can be done to reduce these barriers.

    c. Discuss whether there are additional mechanisms to reduce burden to the healthcare system associated with the TIRF REMS.

    ***Committee Discussion**: The committee members noted multiple explanations that could lead to the decrease in TIRF prescribing, including more appropriate use, changes in pharmacy benefits, cost considerations, cheaper alternative opioids, and stigma to fentanyl. The committees agreed that there are barriers, which are reasonable given the risks associated with TIRF medicines. Some members voiced concerns about the decrease in REMS certified prescribers and noted the need to better evaluate the reasons for the decline. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** The TIRF REMS requires that prescribers and pharmacists are educated on the risks and safe use of TIRF medicines prior to prescribing and dispensing, and that patients sign a form acknowledging that they have been made aware of the risks and methods for safe use.

    a. Given the limitations of the assessment data and the limited use of these products, discuss whether the goals and objectives of the TIRF REMS are still appropriate.
    b. If you believe the goals and objectives remain appropriate, discuss whether you believe the TIRF REMS is adequately designed (i.e., ensuring prescribers, pharmacists and patients are educated) to achieve these goals and objectives.

    ***Committee Discussion**: Most committee members agreed that the goals and objectives of the TIRF REMS are appropriate. Some members suggested strengthening the REMS to ensure TIRF medicines are used for cancer breakthrough pain only while others noted that patients with non-cancer breakthrough pain should be able to get them too. The committee members also recommended improving approaches to education and ensuring providers and patients have knowledge of TIRF REMS in practice. Please see the transcript for details of the Committees' discussion.*

The meeting was adjourned at approximately 4:55 PM.