_____

Memorandum

To:	Doris Auth, Associate Director
	Igor Cerny, REMS Assessment Reviewer
	Division of Risk Management, Office of Surveillance and Epidemiology (OSE)
	Judith Racoosin, Deputy Director for Safety
	Sharon Hertz, Division Director
	Division of Anesthesia, Analgesia, and Addiction Products, Office of New Drugs
From:	Tamra Meyer, Reviewer, Division of Epidemiology II (DEPI II), Office of Pharmacovigilance and Epidemiology (OPE), OSE
Through:	Jana McAninch, Senior Medical Epidemiologist, DEPI II, OPE, OSE
	Judy Staffa, Associate Director for Public Health Initiatives, OSE
Date:	November 15, 2017
Subject:	DEPI II Responses to the Transmucosal Immediate Release Fentanyl (TIRF) Industry Group (TRIG) Responses Dated October 16, 2017

Background

Transmucosal immediate-release fentanyl (TIRF) products are indicated for management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. All six brand and three generic TIRF products (Appendix A Table 1) are subject to a shared-system Risk Evaluation and Mitigation Strategy (REMS) that was approved on 12/28/2011 and launched on 3/12/2012. The goals of the REMS are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

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, abuse, addiction, and overdose of TIRF medicines.

The TIRF REMS Industry Group (TRIG) submits annual REMS assessment reports that include descriptions of accidental exposures to TIRFs in children, use of TIRFs by patients without appropriate opioid tolerance, and other events of interest to FDA. FDA remains very concerned about accidental childhood exposures, appropriate opioid tolerance prior to TIRF exposure, and adverse events, such as overdose, especially in patients who are not opioid-tolerant prior to exposure. The FDA and the TRIG have had several teleconferences and written communications about these concerns, and FDA has provided several recommendations for further actions to understand the extent of these safety concerns. The communications about i) accidental childhood exposures, ii) opioid non-tolerance, and iii) adverse events in opioid non-tolerant patients from the 11/1/2016-11/1/2017 period are listed here (other issues discussed in the communications are not described):

1. **11/10/2016**: 48 Month REMS Assessment Acknowledgement Letter (RAAL) from FDA to TRIG communicating the need for:
   a. investigation of continued high levels of opioid non-tolerance in patients (42% of patients) and inappropriate conversion between TIRFs (17-21% of patients) at the individual-product level;
   b. additional surveillance of accidental TIRF poisonings in children; and
   c. other data sources to track adverse outcomes.

2. __3/1/2017__: Written FDA Meeting Agenda for 3/3/2017 teleconference with TRIG requesting:
    a. more vigorous surveillance for accidental childhood poisonings due to TIRFs;
    b. exploration of prescriber-level interventions to reduce prescriptions in opioid non-tolerant patients or for pain not related to cancer; and
    c. evaluation of adverse events in patients receiving TIRFs who are not opioid-tolerant.
3. __3/3/2017__: Teleconference to follow-up with TRIG about requests made in 11/10/2016 48-month RAAL. TRIG to provide:
    a. information on opioid non-tolerance by product and
    b. description of databases to explore accidental poisonings in children.
4. __3/7/2017__: Written follow-up to the 3/3/2017 teleconference from FDA to TRIG to provide instruction on the opioid non-tolerant analysis.
5. __3/10/2017__: Written communication (email only) from TRIG to FDA about the opioid non-tolerant analysis. They expressed concerns that the analysis requested for product-specific dispensing to opioid non-tolerant patients will not accurately reflect the dispensing of specific TIRF products to opioid non-tolerant patients.
6. __3/21/2017__: Written FDA response to 3/10/2017 communication from TRIG to provide additional requests for the opioid non-tolerant analysis.
7. __3/31/2017__: Written response from TRIG to FDA's requests from the 3/3/2017 teleconference. The response describes:
    a. lack of viable data sources to evaluate accidental poisonings in children,
    b. a plan to provide more details from poison center calls for accidental exposures to TIRFs,
    c. a plan to conduct review of medical literature and lay media reports/social media, and
    d. a general plan to conduct a study of adverse events in non opioid-tolerant compared to opioid-tolerant patients using TIRFs (protocol promised by 8/1/2017).
8. __9/27/2017__: Written FDA Meeting Agenda for 10/2/2017 teleconference and DEPI responses to the 3/31/2017 written TRIG communication providing additional guidance on:
    a. evaluation of childhood poisonings from TIRFs,
    b. validity of the opioid tolerance algorithm, and
    c. adverse events in opioid non-tolerant patients.
9. __10/2/2017:__ Teleconference with TRIG. We discussed:
    a. opioid tolerance data concerns,
    b. increasing trends for significant outcomes/AEs for TIRFs over time with some trends greater than those observed for other opioids, and
    c. that TRIG must find databases to assess accidental childhood poisonings.
10. __10/16/2017:__ Written communication from TRIG to FDA responding to our requests in the 10/2/2017 teleconference. The communication discussed plans for:
    a. validation of the opioid tolerance algorithm,
    b. a study to assess the risk of adverse events in non opioid-tolerant versus opioid-tolerant patients using TIRF products, and
    c. analyzing accidental childhood poisonings in electronic health records and mortality data.

Refer to the relevant DEPI and DRISK reviews for in-depth reasoning to support the requests and recommendations in the string of communications, above:
1. DRISK review of the 48-month REMS Assessment Report (9/28/2016),[a]
2. DEPI Memo assessing a possible source for emergency department visits due to accidental TIRF poisonings (4/14/2017),[b]
3. DEPI review of the 48-month REMS Assessment Report (5/2/2017),[c]

---

[a] Cerny I and Harris S: Review of the fifth (48 month, October 29, 2014 to October 28, 2015) Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for Transmucosal Immediate Release Fentanyl (TIRF) Agents
[b] Meyer T. Epidemiology: Review of NEISS-CADES Data on Pediatric Emergency Department Visits Related to Accidental Exposure to Transmucosal Immediate Release Fentanyl. In DARRTS
[c] Coyle DT and Pham T. Subject: Epidemiologic Review of 48-Month TIRF Product REMS Assessment Supplemental Report. In DARRTS 5/2/2017, Ref ID: 4091934.

4. DEPI review of the 60-month REMS Assessment Report (8/4/2017),[d] and
5. DEPI Memo responding to the TRIG's 3/31/2017 written communication outlining plans for assessment of opioid non-tolerance and accidental childhood poisonings (9/21/2017).[e]

The purpose of this memo is to explain the proposed responses from DEPI to the October 16, 2017 communication from the TRIG (Appendix B) that responded to requests from an October 2, 2017 teleconference between the FDA and TRIG.

During the October 2, 2017 teleconference, FDA and TRIG discussed:
1. *Opioid tolerance data concerns—only 44.6% to 65.4% appear to be opioid-tolerant*
2. *That surveillance indicates increasing trends in significant outcomes/adverse events for TIRFs over time; some of these increases appear greater than those observed for other opioids.*
3. *A need to explore opportunities to conduct surveillance in emergency departments (EDs) from a data source that is nationally-representative or covers multiple large geographic areas, and*
4. *A need to explore opportunities to conduct surveillance using mortality data from a data source that is nationally-representative or covers multiple large geographic areas.*

FDA asked for TRIG to respond to the concerns discussed in the teleconference, specifically,
1. *A plan for validation of the opioid tolerance algorithm,*
2. *A proposal for an analysis to evaluate adverse events in non-opioid tolerant patients,*
3. *A proposal for analyses to evaluate accidental childhood poisonings, and*
4. *Recommendations for REMS modifications (*DRISK will review these TRIG responses, separately).

Results
1. **Plan for validation of the opioid tolerance algorithm:** First, the TRIG proposed to explore why different versions of an algorithm to assess opioid tolerance produced different results. In an analysis previously conducted using a different algorithm from Insys, there was a higher proportion of opioid tolerance among TIRF users (77%) than in analyses conducted by the TRIG using their current opioid tolerance algorithm (44.6-65.4% opioid tolerance). The TRIG plans to investigate the difference in these algorithms before conducting the validation study.

    The TRIG proposed two possible data sources for the validation study; the Henry Ford Health System (HFHS) and Optum's Clinformatics claims data and integrated claims-electronic medical record (EMR) data. As we mentioned in our call with the TRIG on October 2, FDA is currently conducting an assessment in Optum's claims-EMR data of possible sources of opioid exposure that are not captured in claims data, alone, so we focused our review on the merits of the HFHS data source. Briefly, the HFHS is a closed healthcare system serving Detroit, Michigan and the surrounding metropolitan area. According to the TRIG communication, the HFHS has both claims data, EMR data, and a tumor registry. The TRIG commented that outpatient prescription records are available for Henry Ford Medical Group patients with Health Alliance Plan coverage.

2. **Proposal for analysis to evaluate adverse events in non-opioid tolerant patients:** The TRIG was asked to evaluate safety concerns in patients using TIRFs without sufficient opioid tolerance in the March 1, 2017 agenda prior to the March 3, 2017 teleconference. The TRIG responded in their March 31, 2017 communication that they would provide a protocol for this study by August 1, 2017. In the March 31 communication, they identified three possible data sources for the study, Optum Clinformatics Data Mart, Truven Commercial/Medicare, and IMS PharMetrics data. In a September 27, 2017 FDA communication to the TRIG prior to the October 2, 2017 teleconference, FDA communicated that:
    i.   we are still waiting for their study protocol,

---

[d] Meyer T. Subject: Review of Surveillance Data from the 60-month REMS Assessment Report for TIRF Products. In DARRTS 8/4/2017, Ref ID 4135176.
[e] Meyer T. Subject: DEPI II Responses to the Transmucosal Immediate Release Fentanyl (TIRF) Industry Group (TRIG) Responses Dated March 31, 2017.

     ii.   validation of the opioid tolerance algorithm is needed, and

     iii.   any data source for the study must capture both in- and out-of-hospital death.

We have yet to receive a protocol for this study, and the October 16, 2017 communication from the TRIG contains only two paragraphs about the proposed study. They propose to compare the rates of abuse, misuse, overdose, death, hospitalizations, and other health care encounters in patients receiving TIRFs who did and did not have evidence of sufficient opioid tolerance. They will match patients based on propensity scores to control for confounding based on important covariates. The target data source is Optum (both Clinformatics claims data and Optum claims-Humedica data).

3.   **Proposal for analyses to evaluate accidental childhood poisonings**: The TRIG proposes to evaluate the frequency of TIRF poisonings in children treated in the ED or inpatient hospital settings in Optum claims-Humedica data. The TRIG claims that this data source covers 20% of the US population. Initial case identification will be based on relevant ICD-9 and 10 codes indicating an accidental poisoning by a synthetic opioid product or codes identifying administration of naloxone. Subsequent searches of the EMR will be used to try to identify TIRF exposure and the clinical course of the patient. Cases will be extrapolated to national estimates. The TRIG will provide a protocol once FDA agrees to the data source and the approach.

The TRIG will also attempt to evaluate accidental childhood poisonings from TIRFs that result in death from the Drug Induced Mortality (DIM) data and other data sources like Child Welfare and Medical Examiner data, per FDA request on September 27, 2017. The TRIG will pursue analysis in the DIM data by limiting the deaths to those with an underlying cause of death due to drug overdose and then using the literal text to search for TIRFs. They will submit a protocol for the DIM data analysis by February 2, 2018. Investigations of the other data streams are underway.

Discussion

1.   **Plan for validation of the opioid tolerance algorithm:** There was no description of the "Insys algorithm" or the differences between the "Insys algorithm" and the algorithm used by the TRIG for recent calculations of opioid tolerance in the 48-month REMS Assessment Report. Instead, the TRIG said that they would explore the differences in the algorithms before moving forward with a validation study. DEPI recommends that the TRIG explain the differences in the two algorithms in a subsequent communication with a **short deadline for response, such as two weeks**. The difference in opioid tolerance results from these two algorithms only highlights the need for algorithm validation. DEPI is concerned about holding up the validation of claims-based opioid-tolerance algorithms any longer. The TRIG must move forward with the validation study without delay, even if it means validating both algorithms.

FDA has already started an investigation into sources of opioid tolerance in Optum EMR data in patients who appeared to get TIRFs but were not opioid-tolerant, as we communicated in our October 2, 2017 teleconference. Therefore, the TRIG should focus on an alternate data source for the main validation study, and they can do a smaller portability assessment of the validated algorithm in Optum if they end up using Optum data for their assessment of adverse events in non opioid-tolerant TIRF patients.

The HFHS appears to be a reasonable data source to conduct the validation of opioid tolerance algorithm(s), given that the data source includes EMR data to search for other sources of opioid tolerance. The availability of a linked tumor registry could also provide valuable information on the proportion of patients getting TIRFs for non-cancer indications. However, since the validation of the algorithm can only be done among patients with evidence of a prescription fill for a TIRF, it is only the subset of patients in the Henry Ford Medical Group with Health Alliance Plan coverage and a prescription for a TIRF that will be part of the validation study. The TRIG provided a comparison of age, sex, and race

between the patients in HFHS as compared to 2012 US Census to try to show that this validation data source will be representative of the US population, but the relevant target population is US patients using TIRFs. DEPI recommends that the TRIG provide the number of patients who filled a prescription for a TIRF during the proposed validation period to estimate sample size. In addition, DEPI proposes that the TRIG provide demographic and clinical characteristics of the TIRF users in the HFHS compared to TIRF users in the US so that we can determine whether the HFHS is likely to be representative of the target population. The TRIG may want to provide the TIRF user counts and comparisons of demographic and clinical characteristics to US TIRF users for an alternate data source in case there are insufficient TIRF users in HFHS. DEPI recommends that the TRIG submit the number of TIRF users in HFHS and comparison demographic and clinical characteristics to US TIRF users by **February 2, 2018**.

2. **Proposal for analysis to evaluate adverse events in non-opioid tolerant patients:**
There are insufficient details in the two paragraphs provided with which to evaluate the proposed study of adverse events in opioid non-tolerant versus opioid-tolerant TIRF users in Optum data. The TRIG needs to submit a more thorough protocol as they proposed to send by August 1, 2017. We reiterate our September 27, 2017 comment that the Optum data, alone, are unlikely to be useful because we require an assessment of both in- and out-of-hospital death from overdose. The TRIG can pursue the safety outcomes of misuse and abuse for their own purposes, but DEPI is more concerned about the overdose and death outcomes. We recommend that the TRIG focus on the outcome of fatal and nonfatal overdose, propose a data source with access to both in- and out-of-hospital death, and submit a protocol for this study with a **short deadline for response**. Four weeks is likely to be sufficient time to submit a protocol draft, but since the TRIG is to submit other responses by February 2, 2018, the protocol could be submitted with the **February 2, 2018** responses to streamline efforts to respond to the various submissions.

3. **Proposal for analyses to evaluate accidental childhood poisonings**: DEPI agrees with the general outline for assessment of accidental poisonings in children, provided that there appear to be a reasonable number of patients ages 0 to 6 years with codes for accidental poisoning by a synthetic opioid. We request that the TRIG submit a protocol for this study and submit counts of patients ages 0-6 with a code for accidental poisoning by a synthetic opioid product **by February 2, 2018**.

Recommendations to send to the TRIG:

1. **Validation of opioid tolerance algorithm:**
    i. Within two weeks from receipt of this communication, submit a detailed explanation of the differences between the "Insys algorithm" for opioid tolerance and the current TRIG algorithm for opioid tolerance.
    ii. The TRIG must move forward with the validation study, without delay. If necessary to avoid any further delay, validate both algorithms.
    iii. A full validation study in Optum data is not necessary since, as we discussed in the October 2 call, FDA has already initiated a similar investigation of opioid tolerance validation in Optum. Instead, you could do a smaller portability assessment of the algorithm in Optum if that is the data source that you plan to use for the study of adverse events in opioid non-tolerant patients. The full validation should be done in a different data source.
    iv. The HFHS data source appears to be reasonable. The linked tumor registry has the added advantage of facilitating an analysis of the proportion of patients prescribed TIRFs who have evidence of cancer at the time of TIRF initiation. FDA would be very interested in this information, as it would help provide additional context for the data you are submitting on TIRF use in opioid non-tolerant patients. To help us further assess the suitability of the data source, by February 2, 2018 please:

        i.   provide the number of patients using TIRFs during the proposed validation study period in HFHS and

        ii.   compare the demographic and clinical characteristics of the TIRF users in HFHS to a geographically diverse sample of US patients who receive TIRFs, such as from a large nationwide claims database.

     v.   If the number of TIRF recipients in HFHS is insufficient for a robust analysis, provide counts as well as demographic and clinical characteristics of TIRF recipients in an alternate data source.

2. **Adverse events in non-opioid tolerant patients:**

     i.   Of the outcomes proposed, fatal and nonfatal overdose are of most concern to the FDA. We are unaware of any claims-based algorithms that have performed acceptably for misuse or abuse.

     ii.   The brief outline for the study of adverse events in opioid non-tolerant vs opioid tolerant patients appears appropriate except that the data source does not appear to have both in- and out-of-hospital deaths with which to assess risk of overdose. Ensure that the data source(s) that you choose can be linked to out-of-hospital death and include this information in your protocol.

     iii.   Submit your protocol for the study of fatal and non-fatal overdose in opioid non-tolerant versus opioid tolerant patients starting TIRFs by February 2, 2018.

3. **Childhood poisonings:**

     i.   We agree with your outline for assessment of accidental poisonings in children in Optum-Humedica data provided that the sample size is sufficient for estimating the incidence of accidental poisonings from TIRFs with a reasonable level of precision. Provide a protocol for this study, along with the counts of children ages 0-6 years with evidence of a claim for poisoning by a synthetic opioid, by February 2, 2018. Include in your protocol discussion of sample size and precision of estimates.

     ii.   We agree with your plan for assessing the DIM data for cases of deaths due to accidental poisoning. We look forward to your protocol by February 2, 2018.

     iii.   We look forward to hearing more about your outreach to assess the feasibility of other sources of data for accidental TIRF poisonings in children.

APPENDIX A: TABLES

Appendix A Table 1: Transmucosal Immediate-release Fentanyl (TIRF) Product Descriptions and Approval Dates

Drug Name	Dosage Forms	NDA/ANDA	Applicant	Approval Date
Abstral	Sublingual Tablet	NDA 022510	Sentynl Therapeutics, Inc.	1/7/2011
Actiq	Oral Transmucosal Lozenge ("lollipop")	NDA 020747	Cephalon, Inc.	11/4/1998
Fentora	Buccal Tablet	NDA 021947	Cephalon, Inc.	9/25/2006
Lazanda	Nasal Spray	NDA 022569	DepoMed, Inc.	6/30/2011
Onsolis	Buccal Soluble Film	NDA 022266	BioDelivery Sciences International, Inc.	7/16/2009
Subsys	Sublingual Spray	NDA 202788	Insys Therapeutics, Inc.	1/4/2012
fentanyl citrate	Oral Transmucosal Lozenge ("lollipop")	ANDA 78907	Mallinckrodt, Inc.	10/30/2009
fentanyl citrate	Oral Transmucosal Lozenge ("lollipop")	ANDA 077312	Par Pharmaceuitcal, Inc.	10/30/2009
fentanyl citrate	Oral Transmucosal Lozenge ("lollipop")	ANDA 079075	Watson Laboratories, Inc.	1/7/2011

*Table reproduced from Meyer, TE. Review of NEISS-CADES Data on Pediatric Emergency Department Visits Related to Accidental Exposure to Transmucosal Immediate Release Fentanyl. Dated April 14, 2017. DARRTS Reference ID: 4084489.

APPENDIX B: Letter from the Transmucosal Immediate Release Fentanyl (TIRF) Industry Group (TRIG) to FDA dated 16OCT2017

02OCT2017 FDA Teleconference Follow-up

This correspondence is in follow-up to the TRIG-FDA teleconference held on 02OCT2017. The TRIG met with the FDA to discuss the below four topics:

1. *Opioid tolerance data concerns - only 44.6% to 65.4% appear to be opioid-tolerant [June 15, 2017 submissions]*
2. *Surveillance appears to indicate increasing trends in significant outcomes/AEs for TIRFs over time; some of these trends appear greater than those observed for other opioids.*
3. *TRIG unable to find databases that can provide ED EMR data and death certificate data of sufficient Ns for TIRFs*
4. *Programmatic issues (PPAFs, unaddressed non-compliance; Rx Processing times)*

The discussion on item #3 was based on a previously submitted response on 31MAR2017. Written feedback from FDA was provided on 27SEP2017.

As follow-up to that discussion, the FDA requested a response from TRIG focusing on:

1. *Plan for validation of the opioid tolerance algorithm*
2. *Proposal for an analysis to evaluate to adverse events in non opioid-tolerant patients*
3. *Proposal for analyses to evaluate accidental childhood poisoning*
4. *Recommendations for REMS modifications*

Lastly, the FDA requested the contact information for a TRIG Sponsor to serve as the point of contact for ongoing discussions.

1. Plan for Validation of the Opioid Tolerance Algorithm

Based on an analysis previously conducted by Insys, the proportion of patients who were opioid-tolerant was substantially higher (77%). Therefore, the TRIG will further investigate the difference between the algorithm used in the TRIG analyses and that used by Insys before proceeding with the validation study.

The TRIG has investigated several data options for the validation study and has narrowed the selection to the below two choices. Further discussions with each of these data source companies are ongoing and TRIG will notify the FDA which option was selected following resolution of the above referenced algorithm comparison.

Option 1. The Henry Ford Health System (HFHS)

The TRIG will validate the opioid tolerance definition used in the analyses presented in the 48-month Supplemental Report and the product specific reports submitted on 15JUN2017 within the Henry Ford Health System (HFHS). The HFHS is a vertically integrated (closed) healthcare system serving Detroit, Michigan and the surrounding metropolitan area. HFHS maintains multiple, centralized databases that include encounter and claims data, comprehensive Electronic Medical Records (EMR), and a population-based tumor registry that contributes to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The medical record is completely integrated into an EHR interface in real time, and therefore provides a true "gold standard" for validation studies. The population to be included in the validation study will not be a subset of patients; all eligible patients have EMR/medical records. Outpatient prescription medication data are available for all Henry Ford Medical Group (HFMG) patients with Health Alliance Plan (HAP) coverage.

Representativeness of the HFHS Population

As Table 1 illustrates, the HFHS patient population is similar to the US population in age distribution; they have slightly more females, a greater African American population than the US as a whole and correspondingly a somewhat smaller white population, and a much smaller Hispanic population. HFHS is

FDA_7407

02OCT2017 FDA Teleconference Follow-up

generally accepted as being representative of the US population as evidenced in many peer-reviewed articles.

Table 1. Comparison of Demographic Characteristics of Patients in the HFHS System and the 2012 US Census Data

Demographic Characteristic	HFHS	2012 US Census Data
Female	54.0%	50.8%
≥65 years of age	14.8%	13.7%
<18 years of age	24.8%	23.5%
< 5 years of age	4.2%	6.4%
White, not Hispanic	51.9%	63.0%
African American	34.5%	13.1%
Hispanic	0.6%	16.9%

Option 2. Optum's Clinformatics Claims Data and Integrated Claims-EMR Data
The TRIG will validate the opioid tolerance definition used in the analyses presented in the 48-month Supplemental Report and the product specific reports submitted on 15JUN2017 within Optum's Clinformatics Claims Data and Integrated Claims-EMR Data. The purpose of this study is to validate the FDA's algorithm for opioid tolerance which was developed to assess the appropriate prescribing and dispensing of TIRF products to only those deemed to be opioid-tolerant.

Two datasets from Optum will be used for this analysis:

Dataset 1: The Optum Clinformatics Data Mart (formerly called InVision Data Mart or LabRx) is a database of administrative health claims for over 80 million members of a large, US national managed care company (United Health). Administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion in the Data Mart. Claims are included for the time periods that patients have both pharmacy and medical coverage to enable users to evaluate the complete health care experience. These data will provide a robust dataset that may be stratified by important variables (e.g., cancer/non-cancer, duration of TIRF therapy, those with opioid-related disorders, prior and concomitant medication use, or duration of opioid use).

Dataset 2: Integrated Optum Claims – Humedica Database. This large integrated pharmacy, medical claims and EMR database has a subset of about 10 million lives annually. It offers pharmacy and medical claims and EMR structured data as well as structured fields extracted from the unstructured EMR notes fields using Optum's advanced natural language processing (NLP) algorithms.

Of particular relevance for this study, Optum has significant experience with opioid-related research. Therefore, the opioid-related data points they have created as structured fields from information found in

16OCT2017 v1.0 FINAL   Page 2 of 5

FDA_7408

02OCT2017 FDA Teleconference Follow-up

the unstructured text are extensive and will provide significant efficiencies to the development of analytic datasets required to conduct this study.

The analysis will first use Dataset 1, the Optum claims dataset that includes all TIRF users. Using the FDA algorithm, the percentage of TIRF patients who received a prescription for an opioid analgesic product in the defined time period prior to their TIRF prescription with a daily dose or equianalgesic dose consistent with the TIRF REMS Access program definition of opioid tolerance will be calculated.

The analysis will then be replicated using the Optum/Humedica subset (Dataset 2) and will include additional opioid-related variables extracted from the EMR data toward developing a sense of "truth" regarding a patient's opioid tolerance. Various metrics will be explored from the EMR data.

The analysis will also estimate the sensitivity and specificity, positive and negative predictive value of each analysis, and for any potential new algorithm, in the event that the validation exercise uncovers potential updates to the algorithm.

2. **An Analysis to Evaluate Adverse Events in Non Opioid-Tolerant Patients**
A retrospective database study will be conducted to evaluate risks of adverse outcomes in a cohort of patients who initiated a TIRF product but did not meet a validated definition of the labeled requirement of opioid tolerance (see Item 1 above for the description of a proposed study to validate existing algorithms). Patients will qualify for the study cohort if they were prescribed an initial TIRF product in routine clinical practice for any indication. Stratifications will be performed in the analysis phase to determine if adverse event risks differ according to subpopulations of interest. Adverse event rates in the non opioid-tolerant TIRF population will be compared to rates in a comparator population of patients who initiated a TIRF and met a validated definition of opioid tolerance.

Outcomes of interest will include abuse, misuse, overdose and death. Rates of hospitalizations and other health care encounters in the period following the TIRF initiation will be evaluated. Confounding will be controlled through a combination of methods, including a propensity score matching algorithm for selection of a control population who is closely balanced to the non opioid-tolerant TIRF initiators with respect to important covariates. The databases targeted for this study include the Optum Clinformatics claims data and the integrated Optum claims-Humedica database.

3. **Analyses to Evaluate Accidental Childhood Poisoning**

a. *Humedica EMR Database*
The Humedica EMR database will be used to evaluate the frequency of TIRF poisonings in children who are treated in emergency department or inpatient hospital settings. The Optum Electronic Health Record (EHR) data (Humedica) is a combined electronic medical record database from approximately 60 integrated delivery systems across the US with a 2017 census of approximately 70 million patients (or approximately 20% of the US population). The study would be a case finding project, with most of the effort devoted to comprehensive case identification and screening for the TIRF product subset. The initial 'potential' case identification will use relevant ICD-9/10 codes indicating accidental poisoning by a synthetic opioid product (T40.4X1: T40.4X1A- Initial Encounter, T40.4X1D- Subsequent Encounter, T40.4X1S- Sequela) as well as codes identifying administration of naloxone.

With access to the full-text notes for the patients identified, we will develop narrative summaries of each case that describes the patient and the history leading to the TIRF exposure along with the clinical course of the patient. The cases could be extrapolated to national estimates, accounting for differences in the

16OCT2017 v1.0 FINAL   Page 3 of 5

02OCT2017 FDA Teleconference Follow-up

EHR database relative to the US as a whole. Information on the exposure to TIRF would arise from the written patient record of each case, representing the patient care notes (including patient history) and would not depend on prescription or dispensing records, an important feature that provides the flexibility needed to identify inadvertent or unintentional exposure to medications that might have been prescribed to a different person (even one who is not included in the data source, such as a friend or relative).

A protocol for this study will be provided after FDA agreement on the approach and specific data source.

b. *Drug Induced Mortality Data (DIM)*

To evaluate accidental childhood TIRF poisoning that resulted in death, the Drug Induced Mortality (DIM) data will be evaluated. The DIM Restricted Variable Database was created using the National Vital Statistics System mortality files from 2010-2014 (or more current data if available), which were linked to electronic files containing literal text information from death certificates. To create the DIM dataset, among deaths with an underlying cause of death of drug overdose, the literal text in three fields of the death certificate which include: the cause of death, significant conditions contributing to death, and a description of how the injury occurred, were searched to identify drug mentions. Search term lists were developed using existing drug classification systems as well as from manual review of the literal text. The search term list was then used to identify the specific drugs involved in overdose deaths to create this database.

A protocol for this analysis will be submitted in the 02FEB2018 submission.

Note: The TRIG is in the process of investigating the other data sources referenced by the FDA in their 27SEP2017 communication (i.e., Child Welfare and Medical Examiner data). Although the publicly available data are imprecise in identifying TIRF product exposure, efforts are underway to contact researchers to determine if there are more granular data available.

c. *Other data requested by FDA*

As per the 27SEP2017 FDA communication, the below information will be provided on 02FEB2018:

- The number of unique patients ages 0-6 years with the ICD-10 code T40.4X1 (or other relevant codes to identify accidental drug poisoning or overdose related to fentanyl) during the reporting period from the Humedica EMR database

- The number of patients ages 0-6 years with the ICD10-code T40.4X (or other relevant codes) from a nationally-representative data source, National Emergency Department Sample (NEDS) from the AHRQ Healthcare Cost and Utilization Project.

4. **Recommendations for REMS Modifications**
   a. *PPAFs and Unaddressed Non-compliance*

The FDA noted in the 48-Month Assessment Report FDA Acknowledgement Letter and during the 02OCT2017 teleconference that it is concerning that the TRIG's criteria of an individual prescriber non-compliance with PPAF requirements needs to involve at least "5 or more patients enrolled by the prescriber without a complete Patient-Prescriber Agreement Form (PPAF) on file, with each patient having greater than 10 working days lapse from initial enrollment date" and that this may potentially lead to an under-reporting of PPAF non-compliance. The TRIG will reduce the PPAF threshold to flag prescribers for non-compliance based on patients without a PPAF from 5 to 3 patients. The TRIG evaluated the incidents of non-compliance and has determined that the threshold can be lowered to 3 without a large impact to patient access.

16OCT2017 v1.0 FINAL   Page 4 of 5

FDA_7410

02OCT2017 FDA Teleconference Follow-up

The Corrective Action Guidelines within the Non-compliance Protocol will be modified to remove the second level of Notices, Warnings and Suspensions, thereby reducing the number of non-compliant events that can occur prior to deactivation of a non-compliant stakeholder, including prescribers. Once non-compliance has been confirmed, the revised non-compliant event schedule will include the following actions.

- A first offense of non-compliance will result in a Notice

- A second offense of non-compliance will result in a Warning

- A third offense of non-compliance will result in a Suspension

- A fourth offense of non-compliance will result in a Deactivation

As a result of both changes, a stakeholder, including prescribers, will be deactivated from the program upon four non-compliant events.

A redlined and clean versions of the Non-compliance Protocol are provided. This change will become effective subsequent to FDA approval.

b. Prescription Processing Times

The TRIG plans to conduct an analysis of prescription processing times for prescriptions that encounter at least one REMS-related rejection over the period October 29, 2014 – October 28, 2017 to evaluate trends over time. In addition to this analysis, TRIG will expand the reporting of these data to FDA to show a more holistic view of overall REMS rejections, which will put into context the overall processing time for all rejected TIRF prescriptions.

The updated metrics will be included in the 02FEB2018 submission.

c. Other Proposed REMS Modification

TRIG proposes to modify the PPAF to add a statement above the prescriber's signature line that states that by signing the PPAF, the prescriber confirms that the patient is opioid-tolerant, as defined in the attestation language of the PPAF.

A redlined and clean versions of the PPAF showing the proposed modification are provided.

5. TRIG Sponsor Contact Information

Brian Kilmartin (Teva) will serve as the point of contact for FDA for future discussions related to these topics. His contact information is included below.

Brian Kilmartin, RPh
Manager, REMS Operations
Phone: 1-610-727-6625
Email: Brian.Kilmartin@tevapharm.com

FDA_7411

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMRA E MEYER
11/15/2017

JANA K MCANINCH
11/15/2017

JUDY A STAFFA
11/15/2017

FDA_7412