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## Memorandum

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**Through:** Jana McAninch, Senior Medical Epidemiologist, DEPI II, OPE, OSE  
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**Date:** September 21, 2017

**Subject:** DEPI II Responses to the Transmucosal Immediate Release Fentanyl (TIRF) Industry Group (TRIG) Responses Dated March 31, 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 System (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 cases of accidental exposures to TIRFs in children using the Researched Abuse Diversion and Addiction-Related Surveillance System (RADARS) Poison Center Program and the FDA Adverse Event Reporting System (FAERS) data. FDA remains concerned that additional cases of accidental exposures in children may be missed. The Division of Epidemiology-II (DEPI) previously explored the possibility of using the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) emergency department (ED) data as a source to monitor accidental poisonings in children<sup>a</sup>. In a sample of approximately 60 hospitals that provided ED data from 2004-2015 there were only ten accidental pediatric poisonings from fentanyl; two of them were for TIRF products, and the rest were from fentanyl patches. Distinguishing between patches and TIRFs was possible from the ED medical notes (Appendix A Table 2); however, the case counts were not high enough to generate reliable national estimates. Because the NEISS-CADES data source was determined to be insufficient for continued monitoring of accidental pediatric poisonings due to the limited coverage of EDs, FDA asked the TRIG to conduct additional monitoring of accidental poisonings from EDs and death data from

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<sup>a</sup> Meyer, T. 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.

nationally-representative data sources or sources that covered multiple large geographic areas. Specifically, FDA requested that the TRIG:

1. *Explore opportunities to conduct surveillance in emergency departments (EDs) from a data source that is nationally-representative or covers multiple large geographic areas, and*
2. *Explore opportunities to conduct surveillance using mortality data from a data source that is nationally-representative or covers multiple large geographic areas.*

The FDA communicated this request to the TIRF industry group (TRIG) in a teleconference on March 3, 2017 and in a follow-up Information request (IR) on March 6, 2017. In addition to the request that the TRIG propose data sources to capture accidental TIRF poisonings in children, other requests were made to:

- provide additional details on the accidental childhood poisoning cases identified in poison center exposure calls,
- conduct a rigorous review of medical literature and lay media reports of adverse events,
- identify prescribers who prescribe TIRFs to patients who are not opioid tolerant or for non-cancer pain, and
- to evaluate TIRF-related adverse outcomes in patients who are not opioid tolerant (see 31MAR2017 TRIG response letter in Appendix B).

The Division of Risk Management (DRISK) requested that DEPI provide responses to the TRIG proposals in their 31MAR2017 communication for ED and death data sources. The primary purpose of this memo is to evaluate and respond to the TRIG's responses to FDA request for additional ED and mortality data for monitoring of unintentional pediatric poisonings. We also provide additional recommendations for the TRIG's proposed study of adverse events in patients who are not opioid tolerant (Appendix B) in response to DRISK's request to:

- *Evaluate TIRF-related adverse outcomes in patients who are opioid non-tolerant. For example, conduct an evaluation of events/outcomes in a population of patients using TIRFs without prior opioid exposure that would qualify them as opioid tolerant. The TRIG should develop and submit a concept paper or protocol for FDA review prior to conducting the study.*

DRISK will review the other TRIG responses, separately.

## Results

The TRIG identified six possible data sources to assess accidental childhood poisonings in EDs and three data sources to assess adverse outcomes in patients who are non opioid-tolerant (Table 1). Very brief proposals for the analysis were provided.

**Accidental childhood poisonings:** Within each data source, they will search for diagnosis codes from administrative claims for ICD-10 code T40.4X1; poisoning by other synthetic narcotics, accidental (unintentional). After identifying patients and dates of care, they will evaluate the medical notes associated with the ED visit, either using access to the electronic medical record (EMR) for the Humedica data source, or by contacting individual hospitals to abstract the ED charts for the other data sources. Text in the medical records may specify the fentanyl molecule and details that identify a TIRF product, such as noting a form like a lollipop or nasal spray. The TRIG claims that only a small percentage of hospitals will provide approval to access the charts. They estimate only 25% participation for the Premier data source, for example.

In a preliminary search of HealthCore data, 11 records were found with the T40.4X1 ICD-10 code, although the search time period was not specified. It was also not specified whether the 11 records were in children or for patients of all ages. The TRIG estimated that it would take 1-2 years to review these data, and they concluded that there are no ED data sources that will provide "meaningful numbers" of accidental poisonings of children by TIRFs. They were also concerned that the ED medical records would not have enough information with which to identify a TIRF, or a specific TIRF product. The TRIG did not know of any national mortality data sources available to identify TIRF products, as was requested by FDA.

**Adverse outcomes in non opioid-tolerant patients:** In the 31MAR2017 letter, the TRIG said that they would send a protocol for this study to FDA on or before 01AUG2017, but a protocol has not yet been received at the time of this review. The TRIG proposed to use Optum Clinformatics Data Mart, Truven Commerical/Medicare, and IMS PharMetrics as data sources, and they estimated that a study would take between 10-12 months. No other details of a proposed study were provided.

**Table 1. Proposed data sources to assess accidental poisonings of children related to transmucosal immediate release fentanyl products (TIRFs) as well as adverse outcomes from non opioid-tolerant patients using TIRFs**

Study Aim	Data Source	Brief Description*
Accidental childhood poisonings	Premier Healthcare Database	This is a large, US hospital-based database primarily from geographically diverse non-profit, nongovernmental, and community and teaching hospitals and health systems. Outpatient visits to EDs are captured for the primary diagnosis. Patients' hospital stays and outpatient visits to the hospitals are linked. Records are not limited to specific payers.
	HealthCore, Inc.	HealthCore Integrated Research Database is a longitudinal database of medical claims, pharmacy claims, and some electronic laboratory results from 2006 to 2016 from numerous Blue Cross and/or Blue Shield licensed plans. Inpatient and outpatient medical records can be requested from a subset of patients.
	Humedica (Optum)	The Optum longitudinal clinical database contains EHR data across various sources including inpatient visits, outpatient visits, medications, laboratory results, vital signs, and notes from physicians, pathologists, and radiologists. Text searches can be done in the EMR data source without the need for approvals and abstraction at each hospital.
	Practice Fusion	Practice Fusion is a large, real-time, cloud-based healthcare EHR database from 30,000 physician practices (family practice and specialists) that have three or less physicians in the practice. Pharmacy and laboratory data are also available from about 90% of US pharmacies and about 600 laboratories.
	Optum Data Mart	The Optum Clinformatics Data Mart contains administrative health claims for United Health managed care. Outpatient lab tests are available for a small subset of the population.
	IMS EMR Data (SDI database)	No information was provided.
Adverse outcomes in non opioid-tolerant patients	Truven Health Analytics' MarketScan Research Databases	Truven Health Analytics' MarketScan Research Databases contain commercial and supplemental Medicaid and Medicare claims for inpatient care, outpatient care, and prescription fills. Specialty pharmacy and mail-order prescription fills are included. Specialty databases link some claims to health risk assessment; dental, laboratory, and medical records. A separate hospital database allows for in-hospital research.
	Humedica (Optum)	The Optum longitudinal clinical database contains EHR data across various sources including inpatient visits,

		outpatient visits, medications, laboratory results, vital signs, and notes from physicians, pathologists, and radiologists. Text searches can be done in the EMR data source without the need for approvals and abstraction at each hospital.
	IMS Pharmedics Plus	IMS RWD Adjudicated Claims contain claims for prescriptions, inpatient care, and outpatient care from 2006 to present. The database is primarily made up of commercial PPO plans.

\*Descriptions are from the sponsors' submission

ED, emergency departments; EHR, electronic health record; EMR, electronic medical record; RADARS, Researched Abuse Diversion and Addiction-Related Surveillance System

## Discussion

While we agree with the TRIG that searching for accidental childhood poisonings using ED medical records may result in low numbers of cases of accidental poisonings in any one data source, the Agency does not want to rely solely on passive adverse event reports or poison center call data for case-finding, as both of these capture an unknown, and likely small proportion of actual cases. Additional data sources are needed to fully understand the effectiveness of the REMS in preventing accidental exposures in children; even small numbers of adverse outcomes related to TIRFs may indicate a need for revision of the REMS. Given that the TRIG is concerned about a low percent participation from hospitals contacted for ED records, DEPI will direct the TRIG to evaluate additional data sources that can link ED claims to EMRs. The TRIG can add integrated managed care systems, such as Kaiser Permanente, federal care systems like the system of military treatment facilities under the Department of Defense, or other large consortiums of hospitals. From our experience reviewing the NEISS-CADES ED data, the medical notes available with the ED records were able to clearly differentiate between a fentanyl patch and a TIRF product (Appendix A Table 2). DEPI agrees with the TRIG that the specific product may not be identifiable, except by dosage form; however, the dosage form is unique for some of the TIRF products so we may be able to identify a specific TIRF product by dosage form (Appendix A Table 1).

The sponsor could not identify any data source with the capability to capture TIRF-involved accidental deaths in children, but DEPI is aware of some possible options. First, a new de-identified data source has recently been developed by FDA and NCHS to identify specific drugs involved in death cases, based on all US death certificates.<sup>b,c</sup> This data source is publicly available and can be accessed by an analyst on-site at one of the Research Data Center locations after approval of a research proposal. The ability to identify drugs at the substance level (e.g., fentanyl), when they are mentioned on the death certificate, has already been shown.<sup>b,c</sup> The ability to identify a group of specific products in the data source, such as TIRFs, has not yet been shown, but there is access to text descriptors of the drug involved in the death that have been extracted from the raw text available in the death certificate. The extracted descriptors include any words that are immediately before or after the drug search term, helping to describe the search term (e.g., PRESCRIPTION, TABLET, PATCH) or surrounding phrases describing how the drug was involved in death (e.g., INGESTED)<sup>c</sup>. These terms could be mined to search for the dosage form of fentanyl mentioned on death certificates in a manner similar to the search of ED medical records for fentanyl dosage form. Medical examiner records are another possible source to search for accidental childhood poisonings from TIRF products, and these records may contain more details about the fentanyl products involved in death. Although there is not currently a comprehensive national database of medical examiner records, collaboration with state health departments, researchers who use medical examiner data, the National Association of Medical Examiners, and even law enforcement agencies may yield valuable information on deaths involving these products. In addition to death certificate and medical examiner data

<sup>b</sup> Trinidad JP, Warner M, Bastian BA, Minino AM, Hedegaard H. [Using Literal Text From the Death Certificate to Enhance Mortality Statistics: Characterizing Drug Involvement in Deaths](#). Natl Vital Stat Rep. 2016 Dec;65(9):1-15.

<sup>c</sup> Warner M, Trinidad JP, Bastian BA, Minino AM, Hedegaard H. [Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2010-2014](#). Natl Vital Stat Rep. 2016 Dec;65(10):1-15.

sources, some, if not all states also have child death investigation programs to search for root causes, criminal child neglect, etc. The TRIG should conduct a thorough investigation of using these and other data sources.

We await a protocol for the study of adverse outcomes in patients who are non opioid-tolerant. However, we have some concerns about the ability to accurately identify opioid tolerance and potential adverse outcomes of interest (e.g., overdose, death) in claims-based data sources. A study in claims data will first need to demonstrate adequate validity of any algorithms used to identify opioid tolerance and adverse outcomes. DRISK should specify which adverse outcomes are of primary interest in this study. Since death is a particular outcome of concern, the TRIG will need to select a data source that captures both in- and out-of-hospital deaths.

## Conclusion

While the TRIG was not optimistic about finding cases of accidental childhood poisonings due to TIRFs in ED medical records or in death data, the Agency is concerned about this outcome and would like to pursue additional cases. DEPI provides recommendations for additional data sources that the TRIG can use to capture cases of accidental childhood poisoning. We will await the submission of a protocol for the proposed study of adverse outcomes in non opioid-tolerant patients, but we do have concerns about using only administrative claims databases to conduct the study.

## Recommendations for the TRIG:

1. To address your concerns about whether emergency department (ED) medical records will contain enough information to identify TIRFs, we were able to clearly identify the form of fentanyl involved in accidental childhood poisonings from ED records in a small study. Therefore, we continue to believe that ED medical records are a valuable source of information in estimating the scope of accidental childhood poisonings involving TIRFs. We request that you pursue the evaluation of accidental childhood poisonings in ED medical records.
2. Given the concerns about low expected hospital response rates to requests for ED records, add additional data sources with access to electronic medical records without the need for hospital-specific requests for records, such as large integrated managed care systems, government hospitals, or other large consortiums of hospitals.
3. As an interim step to your evaluation of accidental childhood poisonings, provide the following information by February 2, 2018:
  - a. 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 for each study data source.
  - b. The number of patients ages 0-6 years with the ICD10-code T40.4X (or other relevant codes) from a nationally-representative data source (e.g., Healthcare Cost and Utilization Project/National Emergency Department Sample) during the same time frame.
  - c. A description of the IMS EMR SDI data source and any other new data sources selected.
  - d. Clarification about whether Practice Fusion data contains any ED records.
4. Based on the proportion of synthetic opioid accidental poisoning coded claims (T40.4X1) found to be TIRF poisonings after ED medical record evaluations, estimate the number of total US ED cases of accidental childhood TIRF poisonings in the US, stratified by age.
5. We agree that the CDC Wonder data would not be helpful for identifying childhood poisonings from TIRFs. Pursue more granular sources of data on drug-involved deaths. One recently-developed source has abstracted drug names and drug characteristics (e.g., PRESCRIPTION, TABLET, PATCH) or surrounding phrases describing how the drug was involved in death (e.g., INGESTED) from all US death certificates (Warner M. Natl Vital Stat Rep. 2016;65(10):1-15 and Trinidad JP. Natl Vital Stat Rep. 2016;65(9):1-15.). Public access to these Drug Induced Mortality (DIM) data (<https://www.cdc.gov/rdc/b1/datatype/dt1229.html>) is available through the National Center for Health

Statistics (NCHS) Research Data Center (RDC) restricted access data program. The process for data access is described on the RDC website (<https://www.cdc.gov/rdc/index.htm>). Another option is to obtain medical examiner records from multiple states, perhaps through the National Association of Medical Examiners. Also explore whether information from state investigations of child fatalities can be searched for TIRF-related deaths (<https://www.childwelfare.gov/topics/responding/fatalities/#state>). We remain very concerned about the possibility of accidental childhood poisonings resulting in death, and the TRIG must provide data with which to assess the effectiveness of the REMS in preventing these childhood poisonings.

6. We await your study protocol to assess adverse events in patients using TIRFs without sufficient opioid tolerance, but we have some initial concerns about the validity of opioid tolerance and adverse event algorithms using the claims data sources noted in the 31MAR2017 communication. The rate of TIRF use in apparently non opioid-tolerant patients in the annual REMS assessment report was alarming, but does raise questions about whether administrative claims data fully and accurately reflect patients' recent experience with opioids and their opioid tolerance status prior to receiving a TIRF. We therefore require further work to validate the opioid tolerance algorithms. Validation of non-opioid tolerance could be informed by a study of linked electronic medical records (see the 2013 Guidance for industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data). At the time that you submit your protocol for the study of adverse events in non opioid-tolerant patients, or shortly thereafter, provide information about the validity of algorithms used to determine opioid tolerance as well as all adverse events being evaluated. As capturing TIRF-involved deaths is of particular interest, any data sources will need to capture both in- and out-of-hospital deaths.

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

<b>Drug Name</b>	<b>Dosage Forms</b>	<b>NDA/ANDA</b>	<b>Applicant</b>	<b>Approval Date</b>
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 Pharmaceutical, 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 A Table 2. Details of cases of accidental exposure to fentanyl transdermal and transmucosal immediate release fentanyl (TIRF) products in children, NEISS-CADES 2004-2014**

Case Number	Year	Age	Drug Role	Form	Disposition	Comments
<b>Transmucosal fentanyl</b>						
1	2004	18 mths	Probable/Likely	Lollipop	Treated/Released	Ingested Mom's migraine medications; treated with 1mg Narcan in field
2	2006	2 yrs	Probable/Likely	Lollipop	Observation	Licked Grandma's fentanyl lollipop found in trash; observed
<b>Transdermal fentanyl</b>						
3	2005	9 mths	Probable/Likely	Patch	Treated/Released	Exposed to Father's fentanyl patch via skin contact; treated with IV Narcan
4	2006	2 yrs	Probable/Likely	Patch	Transferred to different hospital	Ingested Dad's fentanyl patch; treated with charcoal magcitrade
5	2008	20 mths	Probable/Likely	Patch	Treated/Released	Found Grandfather's fentanyl patch in toilet and put in mouth
6	2009	10 mths	Probable/Likely	Patch	Admitted	Got into Dad's fentanyl patches
7	2010	10 yrs	Probable/Likely	Patch	Admitted	Found with multiple of Grandma's fentanyl patches on body; treated with intubation, Ativan, Narcan, IV fluids, mannitol, and epinephrine
8	2011	17 mths	Possible/Suspect	Patch	Admitted	Possible contact with Mom's fentanyl patch when sitting with her, Narcan 800 mcg given
9	2013	19 mths	Possible/Suspect	Patch	Treated/Released	Grandma concerned that patient touched pair of scissors used to cut fentanyl patch; patient asymptomatic
10	2015	4 mths	Probable/Likely	Patch	Treated/Released	Found with Grandma's fentanyl patch on thigh after bath; given Zofran

\*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. NEISS-CADES collects data from a national stratified probability sample of about 60 hospitals with a minimum of six beds and a 24-hour ED in the US and its territories. Trained coders at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed adverse drug-related events (ADEs), to report up to two medications implicated in each ADE, and to record narrative descriptions of the incident. The drugs for which ADEs are recorded include prescription or over-the-counter medications, vaccines, vitamins, and herbal/dietary supplements. The NEISS-CADES dataset used for this analysis contained cases from 2004-2015. We searched for 'fentanyl' in the two free text and two standardized drug name fields in the data source. Cases were limited to patients ages <18 years and to ADE mechanisms of 'unintentional overdose' We screened several free text fields for details of the case to differentiate TIRFs, patches, and other forms of fentanyl.



**APPENDIX B: Letter from the Transmucosal Immediate Release Fentanyl (TIRF) Industry Group (TRIG) to FDA dated 31MAR2017**

## 31MAR2017 FDA Response

On 06MAR2017, the FDA provided a follow-up communication to the 03MAR2017 TRIG-FDA Teleconference requesting that the TRIG provide an update on the status of plans to provide the additional information within 4 weeks. Regarding the first two bullets under item 2c, more vigorous surveillance, FDA encouraged the TRIG to provide proposed data sources and rationale along with these updates. The TRIG assumes that these requests would be reported based on the current reporting period (e.g., no retrospective data would need to be collected). If the needed data analyses can be achieved within the current reporting cycle, then the TRIG will include the results in the next annual REMS Assessment Report. If more time is needed, the TRIG will submit a Supplemental Report.

The TRIG is committed to working with FDA on these initiatives; however, there are limitations to several of these analyses as cited below. It is unclear whether the results from these analyses will aid the FDA and the TRIG in determining if the TIRF REMS is effective in meeting its goals.

**FDA 48-Month FDA Acknowledgement Letter Comment**

Item 2c: *“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”*

**FDA Discussion Topics Provided on 01MAR2017 (noted in italics)**

*More vigorous surveillance:*

- *Explore opportunities to conduct surveillance in emergency departments from a data source that is nationally-representative or covers multiple large geographic areas*
  - **TRIG Response:** After review of multiple data sources, the TRIG was unable to identify any databases that could provide meaningful numbers of records.

The TRIG researched the following 6 data sources: Premier Healthcare Database, HealthCore, the Optum Clinformatics Data Mart, Humedica (Optum), Practice Fusion and IMS EMR Data (SDI database). A summary of the features of each data source is included as Attachment 1. The timeline needed for this type of study would range from 1-2 years. All datasets that were identified and researched to fulfill this request have similar limitations.

- All searches are only at the ICD code level. Specific ICD-10 codes to be searched are shown below and fall into the rubric of “accidental exposures to synthetic opioids”.

**T40.4X1** Poisoning by other synthetic narcotics, accidental (unintentional)

▶	<b><u>T40.4X1A</u></b> .....	initial encounter
▶	<b><u>T40.4X1D</u></b> .....	subsequent encounter
▶	<b><u>T40.4X1S</u></b> .....	sequela

- In order to determine whether an accidental exposure is related to a TIRF product, a chart review would be required. This can be done electronically by text searches in Humedica; for all other data sources, an abstractor must visit each hospital and abstract the relevant charts.
- Approvals to access data must be obtained at the hospital level. The database owners indicated that it will only be a small percentage of hospitals that will provide approval. For example, based on previous experience, Premier estimated that no more than 25% of hospitals would participate and the number of applicable records per hospital is unknown. Similarly, HealthCore only identified 11 records with the applicable ICD codes.

31MAR2017 FDA Response

- While initial feasibility for this approach was attempted, until the study is underway there is no way to foresee the amount of detail that will be available in a patients' chart or whether a specific TIRF product can be identified.
- *Explore opportunities to conduct surveillance using mortality data from a data source that is nationally-representative or covers multiple large geographic areas*
  - **TRIG Response:** The TRIG has researched the available mortality data, but has not identified any source that can identify specific TIRF products.

The CDC Wonder data is the most comprehensive database for mortality data based on the research conducted. Similar to the limitations referenced for the emergency department surveillance, the CDC Wonder Multiple Cause of Death files only provide data at an ICD code level (as noted above); the codes reflect accidental exposure to a synthetic opioid product and no reporting would be TIRF product specific.

- *Obtain more complete data on events from poison center exposure call data (from RADARS PC or other poison center data)*
  - **TRIG Response:** The TRIG proposes obtaining additional data through the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) Poison Center Program on each report of an accidental exposure to a TIRF product. Unlike the previous approaches, these data will potentially identify TIRF products.

Based on initial conversations with Rocky Mountain Poison and Drug Center (RMPDC), redacted notes from the RADARS Poison Center Program can be provided for all cases of accidental exposure to a TIRF product. The level of detail may vary between each Poison Center.

- *Conduct a rigorous review of medical literature and lay media reports (traditional and social media); include results in the annual REMS assessment report*
  - **TRIG Response:**

Traditional safety surveillance: The TRIG will use the aggregate line listing format already provided in the REMS Assessment Report to include literature as a separate line listing. This will include all literature cases identified by each TRIG member, removing any duplicate cases that are identified. (Currently, the line listing excludes literature cases and data obtained from Poison Control Centers.)

Social media surveillance: Two vendors with capabilities and experience in social media monitoring were identified: Epidemico and RMPDC. Each vendor has a similar approach to social media monitoring. The TRIG is currently working to obtain refined specifications from each vendor. The TRIG expects to begin monitoring 01JUL2017.

31MAR2017

Page 2 of 5

31MAR2017 FDA Response

**FDA 48-Month FDA Acknowledgement Letter Comment**

Item 3i. *“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.”*

**FDA Discussion Topics Provided on 01MAR2017 (noted in italics)**

*Utilize registered patients and prescribers to more effectively identify patient-related concerns:*

- *Explore potential prescriber-level interventions. For example, identify prescribers who prescribe TIRFs in patients who are not opioid-tolerant, or for pain not related to cancer, and send communications reiterating appropriate use.*
  - **TRIG Response:** The TRIG will reinforce the appropriate use of TIRF medicines (highlighting the approved indications) through a Dear Healthcare Provider Letter to all currently enrolled prescribers. Additionally, the TRIG will continue REMS education on the appropriate use of TIRF medicines and enrollment of prescribers, which includes attesting that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
  
- *Evaluate TIRF-related adverse outcomes in patients who are opioid non-tolerant. For example, conduct an evaluation of events/outcomes in a population of patients using TIRFs without prior opioid exposure that would qualify them as opioid-tolerant. The TRIG should develop and submit a concept paper or protocol for FDA review prior to conducting the study.*
  - **TRIG Response:** The TRIG will prepare a protocol for this analysis, and submit it to FDA on or before 01AUG2017. The TRIG has identified the following as possible data sources for this analysis and is continuing to perform feasibility: the Optum Clinformatics Data Mart, Truven Commercial/Medicare, and IMS PharMetrics. The database owners estimate that this type of analysis would take between 10-12 months. Brief descriptions of each data source are included as an attachment.

31MAR2017

Page 3 of 5

31MAR2017 FDA Response

### Attachment 1: Description of Potential Data Sources

**Premier:** The Premier Healthcare Database (PHD) is a large, U.S. hospital-based, service-level, all-payer database that contains information on inpatient discharges, primarily from geographically diverse non-profit, nongovernmental and community and teaching hospitals and health systems from rural and urban areas. Hospitals/healthcare systems submit administrative, healthcare utilization and financial data from patient encounters. Inpatient admissions include over 80 million\* visits with more than 5 million\* per year since 2011, representing approximately twenty percent of annual United States inpatient discharges across all regions of the US. Outpatient encounters include over 550 million\* outpatient visits, with more than 34 million visits per year since 2011. Outpatient visits to emergency departments, ambulatory surgery centers and alternate sites of care are captured for the primary diagnosis. The PHD contains data from over 147 million unique patients. Using a unique masked identifier, patients can be tracked in the same hospital across the inpatient and hospital-based outpatient settings, with the ability to assess hospital length of stay and readmissions to the same hospital.

**HealthCore:** HealthCore, Inc. (established 1996) is an independently operating, wholly owned subsidiary of WellPoint, Inc. WellPoint is among the largest health benefits company in terms of medical enrollment in the United States. By leveraging HealthCore's unique research environment, which comprises of a longitudinally integrated medical and pharmacy claims and electronic laboratory result database, with the ability to enrich the data with inpatient and outpatient medical records, national vital records for a portion of these lives, and access to a provider network with deep local market penetration. The HealthCore Integrated Research Database (HIRDSM) is owned and operated by HealthCore and includes automated computerized claims data and enrollment information from 2006 to 2016 for more than 50 million lives with at least medical enrollment, and over 30 million lives with medical and pharmacy enrollment information from numerous Blue Cross and/or Blue Shield (BCBS) licensed plans. The HIRD also contains diagnostic laboratory testing results from two large national laboratories for WellPoint-affiliated health plan members receiving outpatient laboratory services for a subset of patients.

**Humedica:** Optum's longitudinal clinical database is derived from multiple health care providers. EHR data are aggregated from across the continuum of care, both inpatient and ambulatory, to provide a comprehensive clinical overview that includes medications, lab results, vital signs, physician notes, diagnoses, procedures, demographics, hospitalizations, and outpatient visits. The data are certified as de-identified by an independent statistical expert. Humedica data files contain both structured (coded) and unstructured data, which are extracted from physician, pathology and radiology notes and clinical reports using proprietary software that conducts a context-sensitive search.

**Practice Fusion:** Practice Fusion is one of the nation's largest real-time, cloud-based healthcare electronic record databases of its kind, drawing on records from over 112,000 medical professionals seeing over 5 million patients a month on the Practice Fusion data entry platform. The data represents more than 30,000 physician practices (family practices and specialists) that have 3 or less physicians in the practice. Pharmacy data are provided by more than 90% of US pharmacies, and laboratory data are provided from more than 600 laboratories nationwide.

**Optum DataMart:** The Optum Clinformatics Data Mart (formerly called InVision Data Mart or LabRx) is a database of administrative health claims for members of a large, US national managed care company (United Health) affiliated with OptumInsight Life Sciences, Inc. ("Optum"). Administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion in Clinformatics 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. The Clinformatics Data Mart largely comprises commercial health plan data, but also contains historic claims for Managed Medicaid and Medicare + Choice members. The population is

31MAR2017

Page 4 of 5

31MAR2017 FDA Response

geographically diverse, spanning all 50 states, the District of Columbia, and Puerto Rico. The Clinformatics Data Mart also includes results for outpatient lab tests for a small subset of the total population. These data are processed by large, US national lab vendors under contract with the managed care organization.

**Truven:** Truven Health Analytics' MarketScan Research Databases are large fully-integrated patient-level datasets. The core databases - Commercial, Medicare Supplemental and Medicaid –represent inpatient, outpatient and pharmacy claim data for over 170 million patients since 1995. Longitudinal integrity is strong. Complete payment information is captured, including payments from both the benefit plan and patient. Specialty pharmacy and mail-order prescription fills are included. Specialty databases link claims to unique data sets such as productivity management; health risk assessment; dental, laboratory, and medical records; and hospital data at the de-identified patient level. A separate hospital database allows for in-hospital research.

**PharMetrics Plus:** IMS RWD Adjudicated Claims: USA [IMS PharMetrics Plus] includes complete, adjudicated plan level data including complete inventory of a patient's prescriptions, in-patient hospital, and outpatient medical claims via a collaboration with Health Intelligence Company (HIC), operating as Blue Health Intelligence. Data are available from 2006 to the present time. In addition, all 3-digit zip codes in the US are covered and reported, allowing more granular patient segmentation and comparisons by geography. The database consists primarily of commercial PPO plans and can thus under-represent the patients on Medicaid or Medicare relative to patients on commercial plans (i.e., > 65 population). The database includes ~150 million patients with a medical benefit, and a subset of over 95 million patients with both medical and pharmacy benefits. Data include diagnoses (ICD-9/10-CM), procedures (CPT, HCPCS, ICD-9/10-CM), and diagnostic & lab tests ordered (no lab values).

31MAR2017

Page 5 of 5

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