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Food and Drug Administration

Center for Drug Evaluation and Research

Date: **July 25, 2018**

To: **Members of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee**

Subject: **Addendum to the FDA briefing information to summarize TIRF REMS issues relevant to the August 3, 2018 meeting**

In 2010, the FDA determined that a REMS would be necessary to mitigate the potential for harm associated with the transmuscosal immediate-release fentanyl (TIRF) products. The main safety concern with these products is use in opioid non-tolerant patients because of potential for life-threatening respiratory depression in patients not taking chronic opioids. For this reason, these products are contraindicated in the management of postoperative pain, as well as in headache, migraine, dental pain, or use in the emergency room. In order to take these products safely, patients must be opioid tolerant.

The TIRF REMS was approved on December 28, 2011 and includes all members of the TIRF class. The intent of the REMS was to ensure that prescribers and dispensers were knowledgeable about the risks; that the TIRF medicines were prescribed to appropriate patients (i.e., those patients who are opioid tolerant); and that patients were counseled about the risks and safe use of the drugs.

The goal of the TIRF REMS is 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; and
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

The TIRF REMS requires that prescribers and pharmacists are educated on the safety 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 safe use. The committees will be asked to discuss whether the TIRF REMS is adequately designed to achieve its goals and objectives, whether the approaches to obtain additional data related to the goal and objectives will result in useful information, and whether the TIRF REMS creates unnecessary barriers to patient access and whether there are ways to decrease burdens on the healthcare delivery system of complying with the TIRF REMS.

Assessment data are collected from TIRF REMS utilization statistics; dispensing activity by enrolled pharmacies; the non-compliance plan; safety surveillance from multiple sources; and annual knowledge, attitude, and behavior (KAB) surveys of patients, prescribers, and pharmacies.

From an operations perspective, the TIRF REMS program appears to be functioning as intended to ensure that prescribers and pharmacists receive training on the risks and the safe use of TIRF medicines prior to prescribing or dispensing, and to ensure that patients are informed of the risks and safe use of TIRF medicines before taking them. Surveys of prescribers, pharmacists and patients, despite their limitations, suggest that they are knowledgeable about these risks. However, the results of some of the assessments either suggest concerning safety findings, or have not yet provided the information necessary to determine whether the TIRF REMS is meeting its goals and objectives. Below is a summary of these concerns and assessment gaps.

Mitigating the risk of misuse, abuse, addiction, and overdose

Aggregate data from several data streams suggest that the prescription-adjusted rates of abuse of TIRF medicines increased from the pre-to-post REMS period. Also, surveillance data are suggestive of increases in the prescription-adjusted rates of intentional misuse, unintentional therapeutic errors, and ED visits/hospitalizations, although these estimates were imprecise. For all outcomes, drawing conclusions based on the evaluated data sources was difficult due to the limited number of events and the relatively low utilization of TIRF medicines. Considering the substantial limitations of surveillance data, we would like the committees to discuss the findings of potential increasing rates of events with decreasing use of TIRF medicines.

Prescribing and dispensing TIRF medicines to appropriate patients, including use in only in opioid- tolerant patients

Analyses conducted by the application holders indicate use of TIRF medicines in opioid-tolerant patients was approximately 58%. It is unclear whether use of TIRF medicines in opioid non-tolerant patients has increased, decreased or remained stable since the implementation of the REMS. It is also unclear whether this estimate of use in opioid-tolerant patients is valid, as it is based on administrative claims data only. The application holders have committed to submitting a study protocol to validate the claims-based algorithm later this year; FDA has also commissioned a study to validate the claims-based algorithm, and results will be presented during the meeting.

Additional work is required to understand the implications of prescribing TIRF medicines to opioid non-tolerant patients. It is still unclear, based on the assessment data submitted, whether use of TIRF medicines in opioid non-tolerant patients has led to poorer patient outcomes. Spontaneous adverse event reports of death and overdose lack sufficient information to determine if these events occurred as a result of the use of a TIRF medicine in patients who

are opioid non-tolerant. The application holders have been asked to conduct a study of fatal and nonfatal overdose with a comparison of opioid-tolerant to opioid non-tolerant patients.

We would like the committees to discuss if a claims-based study of the algorithm and claims-based outcomes studies in patients prescribed TIRF medicines can likely inform whether this objective is being met.

Mitigating the serious complications due to medication errors by preventing inappropriate conversion between TIRF medicines

In previous assessments, the TRIG used data from the TIRF REMS database to describe trends in switching between TIRF medicines among patients dispensed a TIRF medicine. This initial evaluation was intended to be exploratory in nature to determine whether switching between TIRF medicines was a common occurrence. The analysis revealed that conversion from one TIRF medicine to another is not uncommon, occurring in approximately 20% of patients. However, analyses based on data with greater clinical granularity than allowed in administrative claims data, particularly with regard to dose, are needed to determine the appropriateness of TIRF medicine switching.

We would like the committees to discuss whether other strategies, such as conducting a chart review within an integrated healthcare system – one that captures patient encounters across inpatient and outpatient settings, as well as accessing prescription drug data with prescriber dosing instructions- could better inform whether this objective is being met.

Preventing accidental exposure to children and others for whom it was not prescribed

The data on accidental TIRF exposures among children in previous assessment reports have been sparse, yet not reassuring. FDA has provided examples of databases that could be used to more broadly study accidental TIRF poisonings in children. The TRIG has proposed to evaluate TIRF poisonings in children by using claims data linked to electronic medical record data, as well as the Drug Involved Mortality database. We would like the committees to discuss if any of these approaches will likely inform whether this objective is being met.

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

Surveys of prescribers, pharmacists and patients, despite their limitations, suggest that they are knowledgeable about the key risk messages related to accidental exposure and the potential for misuse, abuse, addiction, and overdose of TIRF medicines. All groups were less aware of the need to only prescribe and dispense TIRF medicines to appropriate patients (opioid-tolerant).

We would like the committees to discuss whether the survey results, as well as the requirement for re-certification of prescribers and pharmacists, are sufficient to inform this objective.

MEMORANDUM

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Date: July 24, 2018

Subject: Progress on New Assessments of the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) as of June 6, 2018

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1 INTRODUCTION

Transmucosal immediate-release fentanyl (TIRF) medicines are indicated for management of breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid analgesic therapy for their underlying persistent cancer pain. Most TIRF medicines are approved for patients ages 18 years and older; Actiq and its associated generic products are approved for ages 16 years and older. All six brand and three generic TIRF medicines (Appendix 4.1) 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.

FDA remains highly concerned about accidental childhood poisonings, appropriate opioid tolerance prior to TIRF medicines exposure, intentional misuse and abuse, and overdose, especially in patients who are not opioid-tolerant prior to exposure. The TIRF REMS Industry Group (TRIG) submits annual REMS assessment reports; the Division of Epidemiology II (DEPI) reviews the safety surveillance data. This review is an addendum to the DEPI review of surveillance data from the TIRF REMS 72-month Assessment Report.

The purpose of this memorandum is to explain the TRIG's progress on fulfilling FDA's recommendations to conduct further evaluation of:

- **The claims-based algorithm for assessing opioid tolerance in people who are starting treatment with TIRF medicines,**
- **The risk of overdose in people who are starting treatment with TIRF medicines and who are opioid non-tolerant, versus opioid tolerant, and**
- **The extent of accidental poisoning in children.**

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS REVIEWED

TRIG response to FDA Information Request. February 9, 2018.

72-month TIRF REMS Assessment Report. February 28, 2018:

- Appendix 12.7: Comparison of the 2015 vs. 2016 and 2017 analyses: Percentage of opioid tolerant patients
- Appendix 12.8: Counts of transmucosal immediate-release fentanyl users in the Henry Ford Health System and in PharMetrics Plus
- Appendix 12.10: CDC Research Data Center Proposal to Access Drug Induced Mortality Data

TRIG response to FDA Information Request. April 6, 2018.

TRIG response to FDA Information Request. June 6, 2018.

2.2 REVIEW CRITERIA

The documents reviewed explained progress on designing additional evaluations of the specific safety concerns listed above, and these study designs were expected to follow sound epidemiologic principles.

3 RESULTS AND DISCUSSION

Algorithm for opioid tolerance and study of overdose in opioid non-tolerant versus opioid tolerant patients

In the 60-month REMS Assessment, the TRIG found 58% opioid tolerance among TIRF medicine initiators in an analysis of the IQVIA Longitudinal Prescription Database, 2012 – 2015. As the REMS aims to ensure that TIRF medicines are used only in opioid tolerant patients, the estimated 58% opioid tolerance was concerning to FDA. The apparent high prevalence of opioid non-tolerance in patients starting treatment with TIRF medicines raised concerns about these patients' risk of overdose from these potent opioids. Thus, in March 2017 FDA began a dialogue with the TRIG about how to investigate overdose among opioid non-tolerant patients initiating TIRF medicines.

Another possibility related to this finding was that the estimated 58% opioid tolerance could be an under-estimate if there were substantial prior opioid exposures, e.g., from inpatient and specialty pharmacy settings, which the claims-based algorithm failed to capture. Adding to our questions about the validity of the opioid tolerance algorithm used in the 60-month and 72-month REMS assessments, the TRIG stated that a Sponsor's alternative algorithm found 77% opioid tolerance, also using the IQVIA Longitudinal Prescription Database. In October 2017, FDA asked the TRIG to validate their opioid tolerance algorithm. We have suggested that the TRIG could validate multiple versions of the algorithm, however, the TRIG examined differences in the two algorithms (Appendix 4.2.1). In their report, they concluded that the largest difference between the two algorithms, and the likely source of the higher percentage of opioid tolerant patients reported in the Sponsor's analysis, was its use of a less specific definition of opioid tolerance that did not take minimum daily dose into account. DEPI agrees with the report findings that the 77% estimated prevalence of opioid tolerance was inflated by basing its definition only on the prior seven days' supply of opioid, with no regard to minimum daily dose. Also, the study should validate the opioid tolerance algorithm that incorporates moiety-specific thresholds for minimum opioid daily dose, as defined in the TIRF REMS Access Program.

The TRIG initially proposed to validate the algorithm among patients administered inpatient TIRF medicines in a communication on 2/28/2018 but subsequently agreed to include both inpatient and outpatient settings. Over 50% of the proposed study population received outpatient dispensings. The TRIG submitted the validation study protocol to FDA and the local institutional review board (IRB) on 6/29/18. The study is expected to start this summer, pending IRB approval and FDA final review, and the final report is expected 10/31/2018.

As part of the ongoing dialogue about assessing risk for overdose in opioid non-tolerant patients versus opioid tolerant patients starting treatment with TIRF medicines, in October 2017 FDA asked the TRIG to submit a protocol to study fatal and non-fatal overdoses among opioid non-tolerant versus opioid tolerant patients initiating TIRF medicines. At that time, FDA communicated a sense of urgency for undertaking this evaluation; however, by March 2018, FDA had seen little progress. To facilitate more rapid study development, in March and April DEPI

requested submission of specific deliverables and set milestone dates between June and September 2018 for submitting quantitative feasibility data and a protocol for the study of overdose. This entailed developing studies in parallel to accelerate progress. In response, the TRIG has submitted these deliverables during June and July, demonstrating that it has identified valid data sources and has begun calculating quantitative feasibility data to inform a full study protocol. The full study protocol is expected 9/30/2018. A potential remaining area of disagreement between FDA and TRIG is how many different databases must be used in the study to compare overdose incidence precisely. The TRIG has recommended using at most three of the four, but it has not submitted all the quantitative feasibility data needed to estimate expected statistical precision. It may be that the surest way to accrue enough patients to is to include all four databases in the overdose study

Assessment of accidental poisoning in children

Preventing accidental childhood poisonings involving TIRF medicines is one of the primary goals of the TIRF REMS, yet evaluating the effectiveness of the REMS is challenging for this rare outcome. Therefore, FDA recommended the TRIG complement their surveillance of data from poison control centers and spontaneous reports, with data from electronic medical records (EMR), emergency department (ED) and other healthcare claims, and death certificates. FDA expects the additional data sources would better capture accidental TIRF poisonings that produce the most severe outcomes in children.

The TRIG initiated feasibility assessments to identify accidental poisonings in children age 0 – 6 years in three, complementary databases.

1. Optum® Humedica® database of healthcare claims linked to EMR; available data 2015 – 2017.
2. Nationwide Emergency Department Sample (NEDS), a nationally-representative database of medical claims from ED visits with claims coded with International Classification of Diseases version 10 (ICD-10) available data October – December 2015.
3. Drug Involved Mortality (DIM) database contains variables mined from the literal text of death certificates to codify mentions of drugs related to the death. Data are available from 2010 – 2014.

In conclusion, the TRIG continues to make progress toward assessing additional sources that may capture more severe TIRF medicine poisonings among children 0 – 6 years. FDA has requested specific interim deliverables and due dates to facilitate rapid progress. Even with these additional data, accidental TIRF medicine poisonings may be too rare to determine changes in observed rates of accidental childhood TIRF poisonings over time. The rationale for investigating additional data is to have the best chance of uncovering any fatal poisonings involving TIRF medicines in children, an important safety concern.

4. APPENDICES

4.1 APPENDIX: 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 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.

4.2 DETAILED PROGRESS OF THE STUDY OF OVERDOSE IN OPIOID NON-TOLERANT VERSUS OPIOID-TOLERANT PATIENTS INITIATING TREATMENT WITH TIRF MEDICINES

In the 60-month REMS Assessment, the TRIG found 58% opioid tolerance among TIRF medicine initiators in an analysis of the IQVIA Longitudinal Pharmacy Claims Database, 2012 – 2015. As the REMS aims to ensure that TIRF medicines are used only in opioid tolerant patients, the estimated 58% opioid tolerance was concerning. The apparent high prevalence of opioid non-tolerance in patients starting treatment with TIRF medicines raised concerns about these patients' risk of overdose from these potent opioids. Thus, in March 2017 FDA began a dialogue with the TRIG about how to investigate overdose among opioid non-tolerant patients initiating TIRF medicines.

This section describes the progress on obtaining additional safety surveillance data by presenting a chronological summary of communications between FDA and the TRIG, organized by research topic and by data source.

4.2.1 Comparison of Algorithms for Opioid Tolerance

4.2.1.1 FDA and TRIG Communications from October – November 2017: Summary

FDA held a teleconference with the TRIG on 10/2/2017, asking the TRIG to address concerns about the low prevalence of opioid tolerance among patients receiving TIRF medicines by validating the opioid tolerance algorithm and writing a proposal for analyzing overdose among non-opioid tolerant patients. The TRIG's written response on 10/16/2017 proposed to explore why different versions of an algorithm to assess opioid tolerance produced different results. It noted an analysis previously conducted, using a different algorithm from Insys, that found a higher proportion of opioid tolerance among TIRF users (77%) than in analyses conducted by the TRIG using their current opioid tolerance algorithm (58% opioid tolerance). The TRIG stated its plan to investigate the difference between these algorithms before conducting the validation study. FDA responded in November 2017 by requesting a two-week turn-around for the results of the comparison.

4.2.1.2 TRIG Summary of Differences in Algorithms Used to Analyze Opioid Tolerance

The 72-month TIRF REMS Assessment report presented the comparison of the 2015 analysis (which showed 77% opioid tolerance among patients receiving TIRF medicines), with the 2016 and 2017 analyses (2016: 58% opioid tolerance among patients receiving TIRF medicines, 2017: 45-65% opioid tolerance, depending on the TIRF medicine).[1] The report compared the analyses by component:

- Data source
- Study, index, and look-back periods

[1] Appendix 12.7, 72-month TIRF REMS Assessment Report, submitted February 28, 2018.

- Definition of index medication and index date
- Inclusion criteria
- Exclusion criteria
- Definition of opioid tolerance
- Opioid tolerance calculation

The report concluded that the largest difference between the two algorithms, and the likely source of the higher percentage of opioid tolerant patients reported in the 2015 analysis, was the use of a less specific definition of opioid tolerance in 2015 that did not take minimum daily dose into account.

- 2015 definition of opioid tolerance (showing 77% opioid tolerance): a patient was considered to be on an opioid "around-the-clock" if they had enough days' supply of opioid medicines for the seven days prior to their TIRF prescription. The algorithm considered 37 opioid medicines in oral liquid, oral solid, or transdermal dosage form.
- 2016/2017 definition of opioid tolerance (showing 58% opioid tolerance): per the TIRF REMS Access program, patients were considered opioid tolerant if, for the seven days prior to the initial TIRF prescription, they took at least:
    - 60 mg oral morphine/day
    - 25 mcg transdermal fentanyl/hour
    - 30 mg oral oxycodone/day
    - 8 mg oral hydromorphone/day
    - 25 mg oral oxymorphone/day

    Or an equianalgesic dose of another oral opioid: The algorithm considered 37 opioid medicines in oral liquid, oral solid, or transdermal dosage form.

4.2.1.3 DEPI Comment on Algorithms Used to Analyze Opioid Tolerance

DEPI agrees with the report findings that the 77% estimated prevalence of opioid tolerance was inflated by basing its definition only on the prior seven days' supply of opioid, with no regard to minimum daily dose. In contrast, the analyses that estimated 58% opioid tolerance used the TIRF REMS Access Program's definition for opioid tolerance, and so their methods are appropriate to use in the opioid tolerance validation study. DEPI has requested that the TRIG move forward with validating the definition that includes average daily dose in addition to any other algorithms that the TRIG will validate.

4.2.2 Validation Study of Opioid Tolerance Algorithm

4.2.2.1 Summary of the Feasibility Information for Conducting the Validation Study Submitted February 28, 2018

FDA asked the TRIG to validate their 2016/2017 opioid tolerance algorithm in October 2017, and the TRIG proposed to conduct a validation study of the opioid tolerance algorithm by using Henry Ford Health System (HFHS) data on health care claims, tumor pathology reports, and electronic medical records. HFHS is a closed-system health plan in Detroit, MI and the surrounding area, and data are available from 01/01/2012 – 01/01/2018. The TRIG provided the

distribution of age, sex, and race in patients with inpatient TIRF administration in HFHS and among patients with inpatient or outpatient TIRF claims in PharMetrics Plus data.

There were 126 patients with one or more inpatient administrations of a TIRF product in the HFHS data. The TRIG, however, did not provide the distribution of clinical characteristics, which the FDA had requested to understand how representative the HFHS study population was compared to a nationwide sample of patients receiving TIRF medicines.

4.2.2.2 *DEPI Comment on the Feasibility of the Validation Study*

DEPI had expected that HFHS data would include data from outpatient and inpatient dispensings of TIRF medicines, based on a 10/2/2017 teleconference with the TRIG concerning its proposal to use HFHS data to validate opioid tolerance. However, the feasibility information provided by the TRIG on 2/28/2018 lacked data on outpatient dispensings, indicating that the TRIG intended to validate opioid tolerance by using a population consisting only of patients administered TIRF medicines in a hospital. This approach was deemed insufficient given the need to evaluate the REMS' effectiveness at preventing inappropriate prescribing to opioid non-tolerant patients in both inpatient and outpatient settings, and we suspected that algorithm validity in the inpatient setting would not generalize to the outpatient setting.

Therefore, we recommended that the TRIG include outpatient pharmacy claims in the validation study and analyze initial TIRF claims for inpatient administrations separately from outpatient dispensings. We instructed the TRIG that if these data were not available in sufficient numbers for HFHS patients, to select a suitable data source that has sufficient outpatient dispensings of TIRF medicines and to submit the validation study protocol by 6/29/2018 and to include specific descriptive information about the study population. FDA also asked the TRIG to submit the final validation study results in a brief report by 8/31/2018.

4.2.2.3 TRIG Communication from June 6, 2018: Summary

On June 6 of this year, the TRIG responded that they would submit the validation study protocol by June 29, 2018. (This was submitted on time, but FDA has not yet had time to complete its formal review) However, TRIG indicated that they could not meet the August 31, 2018 deadline for submission of the final validation study results, and were instead targeting October 31, 2018. The TRIG stated that they need this extra time for review and approval of the study protocol by the Henry Ford Health System (HFHS) Institutional Review Board (IRB). This process generally takes 6 – 8 weeks, so that a protocol submitted by June 29 per FDA recommendation would be approved in mid-August at the earliest. Only then could trained study personnel conduct the medical record review to validate the opioid tolerance algorithm.

Furthermore, the TRIG stated, contrary to the feasibility information submitted on February 28, 2018, there were data on outpatient dispensings of TIRF medicines, in addition to inpatient TIRF administration. Whereas the 72-month report stated there were 126 patients with ≥1 inpatient TIRF administration, this communication reported that additional research of claims codes had yielded an estimated break-down of 66 outpatient, 48 inpatient, and 13 that were unable to be confirmed without medical records (127 total patients; additional research identified a new patient). Therefore, the validation study would include outpatient and inpatient dispensing.

4.2.2.4 : *DEPI Comment*

The TRIG requested extending the deadline for the validation study results from 8/31/2018, to 10/31/2018, to allow time for the IRB to review and approve the validation study protocol. Such an extension to 10/31/2018 is reasonable to FDA.

The TRIG informed FDA that data on outpatient TIRF dispensing were available for the validation study, as they had initially stated in a teleconference on 10/2/2017. An important limitation is that 127 patients is too small a sample size, considering that the validation study will stratify the population into the inpatient administrations and outpatient dispensings for analysis. This will likely produce imprecise estimates of algorithm accuracy.[2] Furthermore, apparently, prevalent users are included in the approximately 127 patients. However, a mitigating factor for these limitations is that FDA is expecting the results of a separate validation study of the opioid tolerance algorithm: the Yale University – Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI) is conducting a study using Optum's integrated claims and EMR data for opioid exposures that are not captured in EMR. Also, HFHS has offsetting strengths as a setting for the validation study, as it is a closed-system health plan with a diverse patient population.

4.2.3 Study of Fatal and Non-Fatal Overdose in Opioid Non-Tolerant Versus Opioid-Tolerant Patients Starting TIRF medicines

4.2.3.1 TRIG Communication About Overdose Study Dated February 9, 2018: Summary

FDA asked the TRIG to study the occurrence of fatal and non-fatal overdose among patients who are starting treatment with TIRF medicines; with a comparison of opioid non-tolerant to opioid tolerant TIRF initiators. The TRIG responded that it received a proposal from its contractor, Optum, for a data-linkage study using Optum-Humedica data from medical and prescription claims and health records, linked to the Social Security Administration Death Master File (DMF). The TRIG indicated that in Optum-Humedica data, from January 2012 to September 2017, 1,273 patients initiated a TIRF medicine after six months without a TIRF claim. The TRIG showed power calculations demonstrating that there would be sufficient statistical power to detect a relative risk of overdose ~5.00, assuming 50% of patients were opioid non-tolerant and 0.36% experience an overdose. The TRIG concluded there would be an insufficient number of cases to estimate the relative risk of overdose, barring a large effect size.

4.2.3.2 *DEPI Comment*

The TRIG proposed using DMF records linked to Optum-Humedica claims data to identify overdose deaths. However, DMF records the fact that a person died, not cause of death, making it inadequate for identifying fatal, out-of-hospital o p i o i d overdose cases. DEPI recommended that the TRIG replace the DMF with a data source that can identify out-of-hospital, fatal overdoses. While FDA understands that this may increase both the cost and time required for the study, understanding the risk of both fatal and non-fatal overdose is critically important to understanding the potential implications of prescribing TIRF medicines to opioid non-tolerant patients.

The TRIG's power calculations indicated that relying on healthcare claims data from Optum-Humedica would not yield enough cases to estimate the differential risk of overdose in opioid non-tolerant versus opioid-tolerant patients. Therefore, on 3/31/18, DEPI recommended to the

[2] Carnahan RM. Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative data: summary of findings and suggestions for future research. Phamacoepidemiol Drug Saf 2012;21(S1):90-90.

TRIG that the study incorporate additional claims data sources, and that the TRIG respond by 4/6/18 with a date when it would submit feasibility information for additional data sources. DEPI also advised that the TRIG must link any healthcare claims data to death-record data capable of identifying fatal opioid overdose, with the expectation that there will be few overdose cases given the low utilization of TIRF medicines. Furthermore, we requested that design considerations of the study be carefully planned and outlined in a protocol (e.g., controlling for concomitant medications, indication for use, and comorbid conditions). We requested the TRIG to send by 4/6/18 the date when they would submit the overdose study protocol.

We also noted that the TRIG presented power calculations (using Optum-Humedica data linked to the DMF) without disclosing the values of certain parameters that affect the determination of study feasibility (i.e., the values set for the significance level and false-discovery rate). When determining study feasibility, full transparency about the parameters used for the power calculations makes the assessment more credible. DEPI requested that the protocol report all parameters for the power calculations.

4.2.3.3 TRIG Communication About Overdose Study Dated April 6, 2018: Summary

The TRIG gave June 6, 2018 as the date when it could submit feasibility information for conducting the study on fatal and non-fatal overdoses with additional data sources.

The TRIG stated that moving forward with the protocol would depend on the findings of the feasibility study. The TRIG noted that protocol development also depended on FDA and TRIG reaching agreement on three critical design issues for studying overdose among opioid-tolerant and opioid-non-tolerant patients:

1. The suitability of the additional data sources for health care claims and death records, which were due to be submitted in two months.
2. The suitability of the proposed study population for the validation study of the opioid tolerance algorithm, i.e., Henry Ford Health System patients who are dispensed TIRF medicines.
3. The results of the validation study of the opioid tolerance algorithm.

The TRIG stated that, after it completed the feasibility study and reached agreement with FDA on these three issues, it would need approximately three more months to develop the protocol. Furthermore, the TRIG declined to make a firm commitment to this timeline citing that it was difficult for them to foresee how much time it would take to develop a protocol with multiple vendors who had not yet been identified. The TRIG also mentioned that "the timeline and complexity of activities for protocol development and statistical analysis" would be impacted by each vendor needing to conduct its own analyses separately before conducting a pooled analysis for final results.

4.2.3.4 DEPI Comment

DEPI noted that the TRIG originally had proposed to submit a protocol in August 2017 to study overdose risk by opioid tolerance status among patients receiving TIRF medicines. However, since that time, the TRIG only had provided feasibility information for a study in Optum-Humedica data, stating that it would be under-powered, and feasibility information for a validation study of opioid tolerance among HFHS patients who were administered a TIRF medicine in the hospital. To facilitate rapid study progress, DEPI requested specific deliverables and milestone dates, summarized below:

- *Submitting the opioid tolerance algorithm validation study protocol, and quantitative feasibility data and a protocol for the study of overdose by opioid tolerance status among TIRF initiators,between June and September 2018.*
  - *This entailed developing studies in parallel to accelerate progress.*
  - *Each data vendor for the overdose study should apply for National Death Index linkage as soon as possible, as obtaining those data could take several months.*
- *Providing validation study results expeditiously after study launch.*

In addition to facilitating study progress, the interim deliverables are expected to give FDA preliminary indicators of a potential safety signal in some of the data for the full overdose study. These preliminary feasibility analyses approximate (1) the extent of opioid non-tolerance among patients starting TIRF medicines, and (2) the risk of incurring medical claims for overdose among patients starting TIRF medicines without evidence of prior opioid tolerance. DEPI recommended some preliminary ICD-9 and ICD-10 codes suggestive of opioid overdose that we deemed acceptable for use for interim study reports and feasibility assessment while the TRIG identifies a validated claims-based algorithm for overdose and generates the data linkages needed to identify overdose deaths. If the preliminary feasibility data show frequent non-fatal opioid overdoses occurring in patients that appear to be opioid non-tolerant, there may be a need for a rapid regulatory response prior to the completion of the formal study. However, we emphasize that these quantitative feasibility data are primarily intended to inform a robust study design that uses a validated overdose algorithm and linkages to death records.

The urgent need for comparing overdose among patients starting TIRF medicines who are opioid non-tolerant versus opioid tolerant justifies the effort to draft a protocol for a claims-based study of overdose before the opioid tolerance algorithm is validated. The TRIG described plans to validate the opioid tolerance algorithm prior to writing the protocol for the study of overdose in opioid non-tolerant and tolerant patients, but we urged them to proceed with the protocol and plans for the study without delay because of the seriousness of the safety concern. It is possible that the validation study will find that the opioid tolerance algorithm has poor validity; such a finding would limit the inferences we could draw from claims-based studies of overdose in opioid non-tolerant patients versus opioid tolerant patients starting TIRF medicines.

DEPI has been making a concerted effort to provide timely feedback on the comparative study of overdose and the opioid tolerance validation study. We expect protocol development to be fast for this straightforward study. We do not foresee any delays from complicated analyses of vendor-specific data, as the analyses needed for protocol development are simple summations of patients receiving TIRF medicines and of patients with claims for opioid overdose.

4.2.3.5 TRIG Communication About Overdose Study Dated June 6, 2018: Summary

The TRIG indicated that it was working to submit the requested quantitative feasibility information and the full overdose study protocol by their respective due dates, 7/11/2018 and 9/30/2018.

Potential data sources evaluated for overdose study

The TRIG submitted a study feasibility report that evaluated 11 databases, including the original database of healthcare claims from Optum-Humedica. The report identified four databases that were suitable for inclusion in the study, based on the ability to link to state or national mortality data that contain cause of death and the estimated number of patients starting TIRF medicines (**Table 1**). The report used the number of patients with outpatient dispensings for TIRF medicines

to predict the number of patients in each group (opioid tolerant and non-opioid tolerant), using the following assumptions:

- 75% of TIRF users would be initiators.
- 50% of TIRF initiators would be non-opioid tolerant
- If needed, further assumptions could be made specific to the database, e.g., proportion of members in states with death-record linkage available, proportion of members with pharmacy and medical outpatient data available to study

The two claims databases that were feasible (based on the estimated number of patients starting TIRF medicines and the ability to link to cause-of-death data) each have a subset of data that can be linked to EMR data.

Table 1. Databases that met the criteria for studying overdose among patients starting TIRF medicines.

Database	Type of Data	Date Range	Patients starting TIRF medicines without opioid tolerance (estimated)
Optum® Clinformatics®	Pharmacy and Medical Claims; Subset of data have linked EMR (Integrated Optum Claims)	2012-2017	600
Allscripts Practice Fusion	Ambulatory care EMR	2015- 2017	689
IBM Watson Health™ MarketScan®	Pharmacy and Medical Claims	2010-2017	1478
IBM Watson Health™ Explorys®	EMR	2015- 2017	400

Source: Table 1 of Feasibility Assessment submitted by the TRIG, June 6, 2018.

Regarding other databases evaluated, Integrated Optum Claims is an EMR-linked subset of Optum Clinformatics® that could be added if EMR are needed. The other six databases were excluded due to the following reasons: no linkage to cause-of-death data (Optum Humedica, Health Verity EMR); limited number of patients using TIRF medicines (Henry Ford Medical Center); organization not interested in research collaboration (Kaiser Permanente); feasibility data incomplete as of report submission (Geisinger, GE Centricity [IQVIA]).

Options for pooling databases

Table 2. TRIG's options for databases to study overdose among patients starting TIRF medicines.

Option	Databases included	Non-opioid tolerant patients starting TIRF medicines, N
1) One claims database	MarketScan®	**1,478**
2) Pool two claims databases	MarketScan® + Clinformatics®	**2,078**
3) Pool one claims database with one EMR Database	MarketScan® + Allscripts Practice Fusion (APF)	**2,167**
4) Pool two claims databases with one EMR Database	MarketScan®+ Clinformatics® + APF	**2,767**
5) Pool two claims databases with one EMR Database:	MarketScan® + Clinformatics® + Explorys®	**2,478**

Source: Table 2 of Feasibility Assessment submitted by the TRIG, June 6, 2018.

The TRIG noted there is some overlap between the IBM Watson Health's MarketScan® (claims) and Explorys® (EMR) databases.

Estimated statistical precision

The feasibility information included a table, "Population Size and Precision Trade-offs," which presented the width of the confidence interval around an estimated cumulative incidence of overdose, given the parameters:

1) Number of opioid-tolerant patients initiating TIRF medicines (300, 600, 800, 900, 1200);

2) Cumulative incidence of overdose among these patients (0%, 1%, 2%, 3%, 4%, 5%, 10%, 33%, 50%).

The table calculated the "relative width," which it explained was the confidence interval width expressed as a percent of the cumulative incidence, per the following formula:

(upper 95% confidence limit – lower 95% confidence limit) / Estimated Cumulative Incidence

The TRIG explained that if the relative width was ≤ 0.666, this was "a reasonable benchmark for adequate precision." The rationale was, "The 66.6% is the same coverage of 1 standard deviation for a standard normal random variable and therefore a reasonable bench mark [sic] for adequate precision."

Conclusions by the TRIG

The TRIG's conclusion of the feasibility assessment using the MarketScan® database "appears to be the most reasonable database" for the safety study, noting it would measure an overdose incidence of 3% or higher with good precision.

It also noted that an updated feasibility assessment and database selection were pending the results of the quantitative feasibility assessment, expected July 11, 2018. The decision to include additional data was also expected to incorporate the results of the validation study.

4.2.3.6 : *DEPI Comment*

The TRIG submitted a feasibility assessment that identified four healthcare databases that can link to cause-of-death data and that together provide an estimated 3,167 patients in each group defined by opioid tolerance status. This may be an over-estimate as it does not take duplicate patients into account. Still, this is an improvement on the data submitted in February, which included only an estimated 600 patients from the Optum Clinformatics claims database.

The feasibility assessment's analysis of statistical precision had several important limitations:

- *It lacked a description of the methods used to estimate the potential confidence limits, or a reference to the published literature.*
- *For each population size, there were two estimates for relative width of the confidence interval around a 1% incidence.*
- *It lacked estimates of statistical precision for group N size > 1,200, i.e., of estimates that corresponded to the various database options #1 – 5 (see Table 2, above).*

Considering the weak evidence provided to predict statistical precision of the overdose study, and pending the quantitative feasibility information expected on July 11, it may be that the surest way to accrue enough patients to estimate overdose incidence precisely is to use all four databases in the overdose study.

The TRIG noted that the decision to include EMR data would be based on the validation study results. However, as the FDA had requested developing the overdose study's protocol before the validation study ends, DEPI recommends including the EMR database in the development of the overdose study protocol. Again, the surest way to compare overdose by opioid tolerance status validly and precisely may be to use all available sources of information on opioid tolerance. We anticipate receiving the full study protocol on September 30, 2018.

4.3 DETAILED PROGRESS OF THE ASSESSMENT OF ACCIDENTAL POISONING IN CHILDREN

FDA noted in its review of the 48-month REMS Assessment Acknowledgment Letter (November 2016) the very low number of poison control center calls for TIRF poisonings in children and asked for additional data sources on TIRF poisonings in children. The scarcity of poison control center calls could reflect either an actual low risk, or a failure to identify severe TIRF poisonings in children that are more likely to present to the emergency department (ED), or result in rapid death. In March 2017, FDA recommended the TRIG complement their surveillance of data from poison control centers, with data from electronic medical records (EMR), emergency department (ED) and other healthcare claims, and death certificates. These data sources would need to cover a large population, owing to the low utilization of TIRF medicines. FDA expected these additional data sources would better capture accidental TIRF poisonings that produced the most severe outcomes in children. FDA also expressed that we would consider other data sources on TIRF poisoning in children.

The TRIG and FDA have communicated about obtaining additional data on accidental poisoning in children from three data sources, Optum® Humedica® healthcare claims and electronic medical records (EMR), Nationwide Emergency Department Sample (NEDS) emergency department claims, and Drug Involved Mortality (DIM) database of information mined from the

literal text of death certificates. Because of the potential for severe harm to children from TIRF medicine poisoning, we encouraged the TRIG to seek any data it could find on these types of events, which are expected to be rare.

FDA had suggested in March 2017 that the TRIG search NEDS for medical claims with ICD-10 claim T40.4X1, signifying poisoning from synthetic opioids other than methadone. The results of this study would be a national projection of the ED encounters by children that generated the claim T40.4X1. This could be used to estimate the number of ED visits by children for poisonings with TIRF medicines if it were known what fraction of cases with these claims involved TIRF medicines. To estimate this fraction, FDA suggested the TRIG conduct a separate, complementary study to review EMR of pediatric patients with claim T40.4X1 and identify the poisonings that involved a TIRF medicine.

Also in March 2017, FDA had suggested they search DIM for TIRF mentions in children's death certificates. To uncover all TIRF poisonings in children, we needed to look for cases that may have caused death rapidly, obviating any poison control center call or medical claim. This was the rationale for searching DIM, although it was uncertain that the death certificate literal text would record a fatal overdose from a TIRF as such. Instead, the death certificate literal text may record it as fentanyl, thus under-ascertaining fatal TIRF poisonings.

Each sub-section below describes the progress on one data source.

4.3.1 Optum® Humedica®

4.3.1.1 TRIG Communication from February 9, 2018: Summary

The TRIG did not submit the requested protocol by 2/28/2018, but they provided the requested feasibility update from Optum's first pass at identifying possible accidental poisonings by TIRF medicines among children 0-6 years old, during 2015-2017, in claims data. Claims related to accidental poisoning by synthetic opioids, including TIRF medicines, were not ascertainable in ICD-9, but are now ascertainable using ICD-10 claim T40.4X1, *accidental poisoning by other synthetic narcotics* [*other* is used because accidental methadone poisonings use a separate code]. This search found records for 155 children age 0-6 with this code; the number of individuals in this age range would increase to 180 if the search were to add cases of adverse reactions and undetermined poisonings related to synthetic opioids other than methadone; to 1,582 if related to all opioids other than heroin, methadone, and opium; and potentially higher if they use codes to identify additional children who received naloxone in the ER or hospital. The TRIG expressed its concern that the expected number of TIRF-related poisonings was so small as to not provide useful information and that the cost to conduct the study would be onerous. The TRIG supported their concern about low yield of TIRF-related accidental poisonings in young children with the following statistics: 1 of 1,000 synthetic opioid prescriptions is for a TIRF; the 60-month REMS Assessment reported only three cases of accidental poisoning in people ages 0-18 years from spontaneous adverse event report data and three cases in people ages 0-19 years from RADARS Poison Center data.

4.3.1.2 : *DEPI Comment*

We agree with the TRIG's determination that searching medical records for TIRF-related poisonings would yield a limited number of cases in the Humedica data source. We also remain committed to quantifying the incidence of accidental TIRF poisonings in children, including more severe effects like ED visits and deaths. Over the past year we have given the TRIG several recommendations for achieving this, including (1) pooling multiple, large emergency department

data sources with access to electronic medical records; (2) using the DIM database to find fatal poisonings; and (3) studying EHR data linked to ICD-10 claims codes to enable projected estimates in representative data sets of ICD-10 claims codes. The TRIG's proposed use of DIM and NEDS suggests it is making some progress on the second and third areas.

It appears that the Humedica data will not yield enough poisoning cases to inform projected estimates in representative datasets of ICD-10 claims codes. Still, it could yield results that can be combined with results from other data streams, including DIM, and additional years of data that can be reported in future REMS Assessment Reports. We expect that accidental TIRF-related poisonings in children is a rare event, given the limited utilization of TIRF medicines, but the TIRF REMS is one of the most restrictive REMS programs that are being used for opioid analgesic products. Even small numbers of accidental poisonings in children may be sufficient to indicate the need for regulatory action to modify the REMS program. The TRIG has not yet fully explored the potential contribution of large electronic healthcare data sources to identifying cases of accidental TIRF-related poisonings so we recommend that they continue to pursue the study in Humedica. We also recommend that they pursue further studies in other large electronic healthcare data sources with linked EMR data to increase the number of cases, and that they make efforts to pool results from all data streams studied.

4.3.1.3 TRIG Response from June 6, 2018

"As requested by FDA, the TRIG will proceed with the planned study of accidental poisonings in Optum-Humedica without delay." [This was the entire response to FDA's recommendation.]

4.3.1.4 DEPI Comment

It would be appropriate to set expectations for receiving the study results, and January 31, 2019 is a reasonable timeframe for the TRIG to complete the study and report the results in time for DEPI to review it with the 84-month REMS Assessment report in 2019. We therefore requested this milestone date in our recommendations to the TRIG.

4.3.2 Nationwide Emergency Department Sample (NEDS)

4.3.2.1 TRIG Communication from February 9, 2018: Summary

As requested by FDA, the TRIG is working to get counts of accidental childhood poisonings using the Nationwide Emergency Department Sample (NEDS). According to the TRIG, NEDS contains data through 2015, so only ICD-9 codes are available. ICD-9 codes are less granular about the specific opioids involved in poisonings.

4.3.2.2 TRIG Communication from February 9, 2018: DEPI Comment

Current NEDS data availability includes ICD-10 codes from October – December 2015. When more recent years become available in NEDS, this will enable projected estimates in representative data sets of ICD-10 claims codes provided that the TRIG accrues sufficient numbers from reviewing ICD-10 claims codes against medical records to understand the proportion of the ICD-10 claims codes that appear to represent TIRF-related poisonings.

4.3.2.3 TRIG Communication from April 6, 2018: Summary

NEDS contains all-payer medical claims data from visits to U.S. hospital-owned emergency departments (EDs). The annual data sample provides national estimates for various diagnosis codes that year, with current availability 2006-2015. The sample's make-up varies by year, with data from 30 – 35 states included each year. The TRIG assessed the feasibility of using NEDS to

provide the number of ED visits nationwide for accidental poisonings from synthetic opioids in children, age 0 – 6 years, by using the ICD-10 code T40.4X per FDA's recommendation. FDA recommended this with the aim of obtaining a national estimate of accidental poisonings from TIRF medicines in children. Calculating this estimate would also require the proportion of T40.4X claims that implicate TIRF medicines in this age group. The TRIG's ongoing medical record review of cases with the T40.4X claim in Optum-Humedica aims to produce an estimate of the proportion of T40.4X claims that implicate TIRF poisonings; as the expected number of TIRF-related ED visits in children is quite small in this review, FDA recommended that the TRIG also review additional data sources. **Table 3** presents the frequencies of relevant ICD-10 and ICD-9 claims codes as sample counts and as national estimates. The coding system changed from ICD-9 to ICD-10 on 10/1/2015.

Table 3. Emergency Room (ER) Visits by Children Ages 0-6 Years With Evidence of a Claim for Poisoning by a Synthetic Opioid (2012-2015)

	Sample Counts	Projected National Counts
Number of ER visits by children ages 0-6 years with at least one medical claim with an ICD-9 diagnosis code (January 2012-September 2015) of:		
965.09 Poisoning by other opiates and related narcotics	1,099	5,028
E850.2 Accidental poisoning by other opiates and related narcotics	1,466	6,656
E935.2 Other opiates and related narcotics causing adverse effects in therapeutic use	370	1,678
E980.0 Poisoning by analgesics, antipyretics, and antirheumatics, undetermined whether accidentally or purposely inflicted	315	1,433
Number of ER visits by children ages 0-6 years with at least one medical claim with an ICD-10 diagnosis code (October-December 2015) of:		
T40.4X1 Poisoning by other synthetic narcotics, accidental	36	162
T40.4X4 Poisoning by other synthetic narcotics, undetermined	**	**
T40.4X5 Adverse effect of other synthetic narcotics	**	19
T40.2X1 Poisoning by other opioids, accidental (unintentional), non heroin, non opium	85	399
T40.601 Poisoning by unspecified narcotics, accidental (unintentional)	14	65
T40.691 Poisoning by other narcotics, accidental (unintentional)	**	14
Total number of unique ER visits by children ages 0-6 years with any of the above codes	**2,364**	**10,752**

Source: Table 1 of the letter from the TRIG to FDA dated 4/6/2018.

** Cell count is less than or equal to 10. Per HCUP Data Use Agreement, specific numbers cannot be reported. Note: Visits may be counted in more than one distinct diagnosis category. Overall unique visits are provided in the row titled 'Total number of unique ER visits by children ages 0-6 years with any of the above codes'.

HCUP Nationwide Emergency Department Sample (NEDS). Healthcare Cost and Utilization Project (HCUP). 2012-2015. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup- us.ahrq.gov/nedsoverview.jsp. Accessed February 26, 2018.

The TRIG noted that current NEDS availability of ICD-10 codes for only three months of data presents challenges to conducting a study of childhood TIRF poisonings in NEDS. The ICD-10 system is needed for distinguishing accidental poisonings due to synthetic opioids, while ICD-9 has lower specificity, i.e., identifying cases with code 965.09, *poisoning by other opiates and related narcotics*. The limited time with ICD-10 data would prevent analyses of the entire REMS period, including time trends.

4.3.2.4 TRIG Communication from April 6, 2018: DEPI Comment

As we noted previously, current NEDS data contain ICD-10 codes for three months, October – December 2015. We agree with the TRIG that there is little value in relying solely on currently available NEDS data to estimate national counts of ED visits for childhood accidental TIRF poisonings. The main limitations of available NEDS data are the scarcity of ICD-10 coded data, and the >2 years' lag time. However, when more recent years become available in NEDS, we expect it will be feasible to estimate national counts of ED visits for childhood accidental TIRF poisonings. This is one reason why we requested that the TRIG proceed with its medical record review in Optum-Humedica (and other data sources), without delay, in order to understand the rough proportion of cases identified via ICD-10 T40.4X codes that may be related to TIRF medicines to apply to ICD-10 codes in future updates of NEDs. We agree that assessment of ICD-9 codes is unlikely to be useful. We requested that the TRIG submit an update on current data availability in NEDS by 7/11/2018.

4.3.2.5 TRIG Communication from June 6, 2018: Summary

"The TRIG has communicated with the Healthcare Cost and Utilization Project (HCUP) Central Distributor to confirm when 2016 NEDS data will be released. It was confirmed that the HCUP Central Distributor does not have a release schedule for the data and that the website could be checked periodically to see when the data will be available (http://www.hcup-us.ahrq.gov/news/db_products.jsp). Since the 2015 NEDS was not released until December 2017, the TRIG estimates that the 2016 NEDS will not be available until December 2018." [This was the entire response to FDA's recommendation.]

4.3.2.6 TRIG Communication from June 6, 2018: DEPI Comment

The TRIG's response was satisfactory. DEPI verified that the web site displays the NEDS 2015 data with release date, December 2017. Using that schedule as a guide, DEPI recommends that the TRIG send another update regarding NEDS availability by January 31, 2019. If NEDS 2016 is released in December 2018, it will not be ready for analysis for the 84-month REMS Assessment report.

4.3.3 Drug Involved Mortality (DIM)

4.3.3.1 TRIG Communication from February 9, 2018: Summary

The TRIG is moving forward on other studies of accidental poisoning in children, as previously requested by the FDA. They propose to study fatal overdoses among children ages 0-6 years using the Drug Involved Mortality database.

4.3.3.2 TRIG Communication from February 9, 2018: DEPI Comments

The TRIG's proposed use of DIM suggests it is making some progress on using the DIM database to find fatal poisonings, per FDA's request.

4.3.3.3 TRIG Research Proposal from February 28, 2018: Summary

Per FDA's request, on 2/28/2018 the TRIG submitted a research proposal to identify fatal TIRF overdoses among children ages 0-6 years using the DIM database. The research proposal was included as an appendix to the 72-month REMS Assessment Report. The TRIG communication on April 6, 2018 included a request for FDA feedback on the research proposal.

STUDY METHODS

Setting and Study Population

The study will analyze death records for children age 0-6 years, U.S., 2011-2014 (or most recent year available).

Outcome

Briefly, DIM contains data on deaths in which drugs in some way contributed or were associated, including drug overdose. The variables describing the drug involvement were derived by using a software program that searched various text fields of the death certificate; also, standard variables encoding demographics, geography, etc., are included from final National Vital Statistics System-Mortality files. This method of identifying drugs mentioned in involvement with death was shown to have a 97% positive predictive value relative to manual review.

Statistical Analysis

The decedent will be the unit of analysis. Counts and percent of total will be presented for each year:

a) Total number of TIRF-related deaths,

i) cases with *prescription* among descriptors (n, % of total number of TIRF-related deaths),

ii) cases with *illicit* among descriptors (n, % of total number of TIRF-related deaths),

iii) cases lacking *prescription* and *illicit* among descriptors (n, % of total number of TIRF-related deaths)

b) Total number of fentanyl-related deaths, lacking any mention of TIRF products, and lacking the term *illicit* among the descriptors.

4.3.3.4 TRIG Research Proposal from February 28, 2018: DEPI Comments

FDA recommended this research study with the intention of utilizing all promising data sources to monitor fatal TIRF poisonings among children. The actual number of cases is expected to be small, and their capture in DIM is uncertain, but it is important to evaluate all potential sources of cases to understand if the REMS appears to be effective. There has been no evaluation of the accuracy of identifying prescription fentanyl exposures or illicit fentanyl exposures in DIM, to our knowledge. However, DIM has the general capability to identify such cases, and it is an efficient method to use.

One limitation is that the years in the research proposal do not cover all the years in the pre-period of the REMS. Also, it would help to see timing separated by pre- versus post- REMS implementation. Another limitation is that the investigators proposed only one descriptor each to identify pharmaceutical fentanyl and illicit fentanyl; we proposed additional descriptors. We also proposed additional variables where they could search for these descriptors, since they ignored many of the literal text fields. Finally, there was an error in the definition of the variable that negated drug involvement, and so we recommended a revision to the variable definition.

4.3.3.5 TRIG Research Proposal from February 28, 2018: Summary of Subsequent Communications and Comment

FDA made five specific, substantive recommendations for improving the research proposal and transmitted them to the TRIG on **May 2, 2018**, requesting a revised proposal by **June 6, 2018.** The TRIG submitted the revised proposal on **June 6, 2018**, noting that it was planning to move ahead with the study**.** DEPI reviewed the revised proposal and decided the revisions successfully addressed all DEPI's recommendations. DEPI will respond as soon as possible to request notification when the research proposal is approved by the National Center for Health Statistics Research Data Center.

The search for mentions of TIRF medicines involved in the fatal overdoses of children is an important component of the surveillance of TIRF poisonings among children because a pediatric fatal overdose may not generate any poison control center call or medical care. Thus, the DIM data may help the TRIG uncover cases of pediatric TIRF poisoning that would not be captured in the other datasets under investigation.