Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set # 2

Date:	July 24, 2013
Reviewers:	Kimberly Lehrfeld, Pharm.D., Risk Management Analyst Division of Risk Management
Team Leader:	Reema Mehta, Pharm.D., M.P.H. Division of Risk Management
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Drug Name(s):	See Table below
Therapeutic Class:	Opioid Agonist
Dosage and Route:	Transmucosal Immediate-Release Fentanyl (TIRF)

Drug Name	Dosage and Route	Application Type/Number	Supplement Number	Applicant/ Sponsor	TSI #
Abstral (fentanyl)	Sublingual tablet	NDA 22-510	S-005	Galena BioPharma	290
Actiq (fentanyl citrate)	Oral transmucosal lozenge	NDA 20-747	S-034	Cephalon, Inc.	290
Fentora (fentanyl citrate)	Buccal tablet	NDA 21-947	S-015	Cephalon, Inc.	290
Lazanda (fentanyl)	Nasal spray	NDA 22-569	S-007	Archimedes Pharma US Inc.	290
Onsolis (fentanyl)	Buccal soluble film	NDA 22-266	S-009	Meda Pharmaceuticals	290
Subsys (fentanyl)	Sublingual spray	NDA 202-788	S-003	Insys Therapy	290

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1 INTRODUCTION

This is interim review set #2 of the proposed modification of the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) submitted by the Transmucosal REMS Industry Group sponsors (TRIG) via email on March 11, 2013 and May 6, 2013.

1.1 BACKGROUND

TIRF medicines are short-acting fentanyl products indicated for the management of breakthrough pain in adults with cancer who are routinely taking other opioid pain medicines around-the-clock for pain.

The approved TIRF medicines include:

- Abstral (fentanyl) sublingual tablet,
- Actiq (fentanyl citrate) oral transmucosal lozenge
- Fentora (fentanyl citrate) buccal tablet,
- Lazanda (fentanyl) nasal spray,
- Onsolis (fentanyl) buccal soluble film,
- Subsys (fentanyl) sublingual spray, and
- Approved generic equivalents of these products

The TIRF medicines are approved under a single shared system REMS that has the following goals:

The goals of the TIRF REMS Access program 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 elements included in the program are Medication Guides for each individual TIRF medicine and the following Elements to Assure Safe Use (ETASU):

- Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified
- TIRF medicines will only be dispensed by pharmacies that are specially certified

- TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

The timetable for submission of TIRF REMS Access Program assessments is at 6 and 12 months from the date of the initial REMS approval, and annually thereafter.

1.2 REGULATORY HISTORY:

A single shared REMS program, the TIRF REMS Access Program, was approved on December 28, 2011.

On June 30, 2012, the TIRF REMS was modified for the following reasons:

- Modification of the REMS document to allow participation of Closed System Pharmacies and inclusion of a closed system enrollment form.
- Addition of information about Subsys (fentanyl sublingual spray), whose REMS was newly approved on January 4, 2012, to pharmacy enrollment forms, DHCP letters, the education program, and Attachment 1 of the REMS.

On June 28, 2012, FDA requested a modification to the TIRF REMS to incorporate information about the closed system pharmacies into the appended REMS materials. The TRIG was sent the following request via email:

I. Create the following document:

1. *TIRF REMS Program Overview for Closed System Pharmacies*

II. Modify the following documents:

1. REMS Document

   Minor modification on page 11 to add the new Overview to the list

2. FAQ

   Add the following or a similar question: What if our pharmacy's management system cannot communicate with the TIRF REMS Access program (e.g. does not electronically transmit claims information)? You will need to contact the TIRF REMS Access program at 1-866-822-1483 to see if you qualify to enroll as a "closed system pharmacy".

3. *Website*

   Please provide feedback and/or a proposal as to what closed system pharmacy information and/or which documents will be posted on the TIRF REMS Website (we note your e-mail to Kimberly Compton on 6/22/2012 that stated that the enrollment form will not be posted, given that a pharmacy needs to be validated as being a closed system pharmacy prior to their enrollment). For example, closed-system pharmacies that are seeking to enroll in the TIRF REMS should understand that

there is a mechanism for them to participate in the REMS; however, it also needs to be clear this mechanism is not an option for pharmacies that can process through their pharmacy management system.

4. Supporting Document
    - Update to include information and a section on 'Closed System Pharmacies'
    - Update your REMS Assessment Plan and TIRF REMS Access Non-Compliance Plan

On February 4, 2013, FDA provided questions for the TRIG and Interim Comments Set #1 (K Lehrfeld REMS Review, February 2, 2013)

On March 11, 2013, TRIG emailed FDA their response to FDA questions (Appendix1). In addition to the response to the FDA's questions, the email included the following documents.

Revised REMS materials	New REMS Material	Summaries of Changes Documents
• REMS Document • REMS Supporting Document (including the TIRF REMS Web Prototype Screen Capture as a separate document) • TIRF REMS Education Program • Knowledge Assessment • Patient Prescriber Agreement Form • Frequently Asked Questions (FAQ) • *Enrollment Forms (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy, Inpatient Pharmacy, Prescriber, Distributor) • *OverviewForms (*Independent Outpatient Pharmacy, Chain Outpatient	The TIRF REMS Prescription Authorization Request form	TIRF REMS Web Prototype Changes document Email contained a summary of global changes to the TIRF REMS materials (see Appendix 2)

Pharmacy, Closed System Outpatient Pharmacy, Inpatient Pharmacy, Patient and Caregiver, Prescriber)		

On April 16, 2013, FDA emailed an information request (IR) to the TRIG addressing the following issues.

1. Provide a rational for revising the existing text "fatal overdose" to "fatal respiratory depression" as proposed by the TRIG to the Patient Prescriber Agreement Form, prescriber attestation #2.
2. Provide a rational for using the term "generally" in the definitions for chain and independent outpatient pharmacies.
3. Clarification of the website prototype (pages 124 & 136), which appear to show both chain outpatient pharmacies and independent outpatient pharmacies can enroll pharmacy locations and maintain a list of multiple stores in their pharmacy profile.
4. Provide a summary of the process for stakeholder enrollment (pharmacy, prescriber) via fax. Specifically, the Agency asked the TRIG to identify how many prescribers who enrolled via fax did not complete enrollment due to the KA not being included with the enrollment from.
5. The Agency proposed revisions to patient attestation #2 and inclusion of the deleted attestation #3. We requested TRIG provide adequate rational for any proposed revisions if they do not agree with the revised proposal.

May 6, 2013, TRIG emailed the response to the IR (Appendix 3) and the following revised documents to the FDA.

Revised REMS materials	New REMS Material	Summaries of Changes Documents
• Patient Prescriber Agreement Form • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient Pharmacy Enrollment Form • REMS Supporting document (and appended TIRF REMS Web Prototype)	The TIRF REMS Prescription Authorization Request form	Email containing a summary of TRIG proposed revisions to the REMS documents (see Appendix 4) TIRF REMS Web Prototype Changes document (see Appendix 5)

2 MATERIALS REVIEWED

- March 11, 2013 submission, via email
- May 6, 2013 submission, via email

3 OTHER MATERIALS INFORMING THIS REVIEW

- DRISK TIRF REMS Review (K Lehrfeld February 1, 2013)
- Fentora DRISK Review (K. Lehrfeld February 21, 2013)

4 SUMMARY OF APPLICANT'S PROPOSED REMS MODIFICATION

4.1 REMS DOCUMENT AND REMS APPENDED MATERIALS

4.1.1 REMS document

1. TRIG revised the category for "Non-chain" Outpatient Pharmacies to "Independent" Outpatient Pharmacies in order to align with industry standard pharmacy terminology. The REMS document text and appended REMS material text was revised accordingly. In addition, the titles of the following REMS appended materials were revised.

FDA Proposed Title	TRIG Proposed New Title
Non-Chain Outpatient Pharmacy Enrollment Form	Independent Outpatient Pharmacy Enrollment Form
Non-Chain Outpatient Pharmacy Overview Document	Independent Outpatient Pharmacy Overview Document

Reviewer Comment: FDA agrees with this revision.

2. TRIG inserted the word "generally" into the definition of Chain and Independent Outpatient Pharmacies.

   On April 16, 2013, DRISK asked the TRIG to clarify how Chain and Independent pharmacies are categorized.

   In response, the TRIG supplied the following information (see Appendix 3, Question 2, for complete response):

   - There are four (4) chain outpatient pharmacy headquarters with less than 10 sub-stores enrolled in the TIRF REMS Access program.
   - There are three (3) independent outpatient pharmacies with more than 10 stores enrolled in the TIRF REMS Access program.
   - The difference (between chain and independent outpatient pharmacies) is the concept of enrollment. The chain outpatient pharmacy headquarters authorized pharmacy representative can add store locations and mark them as trained on the pharmacy dashboard as appropriate. Each independent outpatient pharmacy must

individually enroll and complete test transactions at the store level, regardless if the authorized pharmacist is the same across multiple stores.

Reviewer Comment: The TRIG is not using the number of pharmacies to determine chain and independent classifications. The classification is determined by the authorized pharmacy representative responsible for enrollment and training of the associated pharmacies. If the authorized pharmacy representative agrees to take responsibility for assuring and documenting the training of all associated pharmacy's employees, they can enroll as a chain. However, if the pharmacist-in-charge at individual stores will have the responsibility to ensure and document training, each pharmacy will enroll separately as an independent pharmacy.

Therefore, FDA proposes the following pharmacy definitions:

- **Outpatient Pharmacies**
    i. **Chain Outpatient Pharmacy**: Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of pharmacy staff within all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chains stores) in TIRF REMS Access.
    ii. **Independent Outpatient Pharmacy**: Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location.
    iii. **Closed System Outpatient Pharmacy**: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information.
- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

3. The following documents were revised to reflect the changes to these definitions:
    - FAQ document
    - Independent Outpatient Pharmacy Overview
    - Chain Outpatient Pharmacy Overview

4. TRIG agreed to remove the DHCP letter from the TIRF REMS Access Program Website.
5. During the clearance of the REMS document, Office of Chief Counsel (OCC) advised revising the following statement in the Implementation System section (II.B.C.3.1)

of the REMS document as noted below. Furthermore, they recommended moving the language to the TIRF REMS Supporting document.

TIRF Sponsors will ensure that wholesalers/distributors who ~~take title to or direct the sale or disposition of TIRF medicines to persons other than a consumer or patient~~ distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

4.1.2 Patient Prescriber Agreement Form (PPAF)

1. On March 11, 2013, the TRIG agreed with the revised prescriber attestation #1 - #3 as indicated below:

    1. ~~My patient is currently using around the clock opioid medication and has been for at least one (1) week.~~ I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
    2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
    3. ~~My patient is opioid tolerant~~. I understand that p~~P~~atients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

2. TRIG proposed changing "overdose" to "fatal respiratory depression" in the prescriber attestation #2 below.

    2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal ~~overdose~~ respiratory depression can occur at any dose.

    The Sponsor provided no explanation for this revision. On April 16, 2013, FDA sent an IR requesting the TRIG's rationale for the change. On May 6, 2013, TRIG responded that "Fatal respiratory depression is consistent with the label/ boxed warning for all TIRF medicines."

Reviewer Comment:
FDA recommends using fatal overdose for the following reasons:

- *All TIRF products boxed warning contains both terms fatal overdose and fatal respiratory depression.*

- *The REMS goal is to mitigate the risk of overdose, not fatal respiratory depression.*
- *Respiratory depression is one symptom of overdose, therefore overdose I sa more appropriate term to use in this attestation.*

3. On March 11, 2013, the TRIG proposed modifying the patient attestation below.

    2) ~~I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around the clock, for my constant pain, then I must also stop taking my TIRF medicine.~~ I understand that before I can take any TIRF medicine, I must be opioid tolerant. My prescriber has discussed with me whether I am opioid tolerant.

The TRIG provided no explanation for this revision. On April 16, 2013, FDA sent an IR to request the TRIG's rationale for the change and proposed the following revisions.

2) I understand that TIRF medications should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. ~~opioid pain medications. I understand that before I can take any TIRF medicine, I must be opioid tolerant.~~ If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines. ~~whether I am opioid tolerant~~.

3) ~~I understand that if I stop taking another opioid pain medicine that I have been taking regularly , around the clock, for my constant pain, then I must also stop taking my TIRF medicine.~~ I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.

On April 16, 2013, TRIG agreed with the above proposal, via email.

4.1.3 Prescriber Enrollment Form

Addition of a field for Knowledge Assessment Authorization Number

Upon review of pharmacy and prescriber enrollment forms, it was noted that the form did not provide instruction for submission of the Knowledge Assessment quiz if it was completed on paper. In addition, it did not include a field for enrolled healthcare providers to indicate their Knowledge Assessment online training authorization number. On February 4, 2013, FDA proposed revisions to address these 2 issues.

On March 11, 2013, TRIG provided feedback that

(1) the Knowledge Assessment (KA) authorization number is not a searchable field in the TIRF REMS Access database and website.

(2) It is not required for the KA to be completed prior to the receipt of the enrollment form. Rather, stakeholders are notified upon receipt of the enrollment form if the

KA is not complete. As a result, adding the training authorization number to the form could result in stakeholder confusion and potential delays in enrollment.

In response to the TRIG's indication that when enrolling via fax, the stakeholder can attest to completing the KA prior to actually completing the KA, FDA requested a summary of the process for stakeholder enrollment via fax. In addition the following clarifications were requested and responses were received May 6, 2013 (see Appendix 3 for full responses):

1. Have incomplete prescriber enrollments results due to a prescriber's ability to sign the enrollment form before completing the Education Program and Knowledge Assessment? If so, how many?

   RESPONSE: A total of 567 prescribers submitted a signed TIRF REMS Access enrollment form prior to completing the Knowledge Assessment. 485 (85.5%) of these prescribers are currently enrolled in the TIRF REMS Access program.

2. If the knowledge assessment authorization number is not searchable within the TRIF REMS Access database, how is the TIRF able to identify which stakeholders have completed the assessment online after receipt of an enrollment form?

   RESPONSE: In clarification, although the Knowledge Assessment code is searchable, current TIRF REMS Access Call Center work instructions were created based on best practices and ease of database navigation.

3. Once the enrollment form is received and a stakeholder is notified of the need to complete the assessment, how does the TRIG track if it is completed?

   RESPONSE: The TIRF REMS Access database programmatically tracks the lifecycle of the enrollment from submission to completion regardless if the stakeholder completes the Knowledge Assessment via fax or web. The stakeholder is not enrolled until all steps are completed.

4. The comment provided by the TRIG indicated that "…it is not required for the KA to be completed prior to the receipt of the enrollment form" is contradictory to the first attestation statement on the enrollment form which states "I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment…" Provide further clarification by what was meant by the TRIG's comment.

   RESPONSE: To clarify TRIGs comment, stakeholders are not enrolled until all steps of the enrollment process are completed, including the Knowledge Assessment (KA). If the enrollment form is received prior to the KA, it will be processed but the stakeholder enrollment will be incomplete until a complete KA is received.

Reviewer Comment: Although FDA has concerns about the TRIGs process for processing faxed enrollment, which does not including a search for the Knowledge Assessment Authorization Number, the need for this may be minimized by agreed upon

revisions to the stakeholder enrollment forms. These revisions include adding the following statement to the Prescriber and Pharmacy Enrollment forms.

> To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3, 4 and 5 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

FDA will reassess stakeholder enrollment statistic in future TIRF REMS Access Program Assessments in order to determine if the frequency of KA not being submitted with faxed enrollments is decreasing.

4.1.4 TIRF REMS Frequently Asked Questions (FAQ) document

TRIG removed all reference to the transition from individual TIRF REMS programs to the shared system TIRF REMS Access Program. Furthermore, they added a section titled *"How long is my enrollment effective in the TIRF REMS Access program?"* which describes the reenrollment process to the following sections:

- outpatient pharmacies
- inpatient pharmacies
- prescribers
- distributor (wholesaler)

> **How long is my enrollment effective in TIRF REMS Access?**
> Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
>
> Independent outpatient pharmacies and chain outpatient pharmacies may re-enroll online or by fax. Closed system outpatient pharmacies may re-enroll by fax only.
>
> For re-enrollment online, go to the "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:
>
> - Add to, update, or delete your registration information on file.
> - Review the TIRF REMS Access Education Program.
> - Take the TIRF REMS Access Knowledge Assessment.
> - Submit your enrollment form by providing your attestation and signature.
>
> For re-enrollment by fax, review the TIRF REMS Access program Education Materials and submit a new TIRF REMS Access Enrollment Form and

Knowledge Assessment to the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Reviewer Comment: FDA agrees with these revisions.

4.1.5 Closed System Outpatient Pharmacy Overview

1. TRIG agreed with revisions to improve clarity and flow of stakeholder overview documents that are appended to the TIRF REMS. They revised the overview documents for Prescribers, Inpatient Pharmacies and Independent and Chain Outpatient Pharmacies to follow the same format.

Reviewer comment: FDA agrees with these revisions.

2. The closed pharmacy overview document was revised to indicate during prescription verification a DEA number will be required, if applicable, in order to validate a prescription. This was necessary due to a newly instituted process for enrolling a small number of closed system prescribers who do not require an individual DEA number in order to prescriber CII medicines. This process allows enrollment of these closed system prescribers and validation of a prescription written by these prescribers with only an NPI number. However, the affected prescribers can only enroll via fax.

Reviewer comment: FDA agrees with these revisions.

3. TRIG provided additional minor edits to the stakeholder overview documents which do not impact the goals of the REMS or operations.

Reviewer comment: FDA agrees with these revisions.

4.1.6 Education Program

An efficacy supplement (S-005) which includes new recommendations for safely switching from Actiq (fentanyl oral transmucosal lozenge) to Subsys (fentanyl sublingual spray) is currently under review by the Agency. Accordingly, slides 15 and 19 of the TIRF REMS Education Program were revised to reflect this change.

4.1.7 TIRF REMS Knowledge Assessment

An efficacy supplement (S-005) which included new recommendations for safely switching from Actiq (fentanyl oral transmucosal lozenge) to Subsys (fentanyl sublingual spray) is currently under review by the Agency. Accordingly, the following question in the TIRF REMS Knowledge Assessment was revised to reflect this change.

> **Question 11:** Conversion between specific ~~only two~~ TIRF medicines has been established and is described in the Prescribing Information for which ~~two~~ products? *Select one option.*

A. Lazanda to Actiq
B. Actiq to Fentora
C. ~~Abstral to Fentora~~ Actiq to Subsys
D. ~~Fentora to Actiq~~ Both B & C

4.2 REMS SUPPORTING DOCUMENT

1. As requested by FDA, the REMS Supporting Document was updated to add a specific section, "Closed System Pharmacies".

Reviewer Comment: FDA agrees with this revision.

2. As requested by FDA, the REMS Supporting document REMS Assessment Plan and TIRF REMS Access Non-Compliance Plan was revised to include references and information pertaining to closed system pharmacies.

Reviewer Comment: The Second REMS Assessment submitted on December 21, 2012 is currently under review. Therefore, the TRIG's proposed changes to the REMS Assessment plan and any future changes will be reviewed under separate cover.

3. On March 11, 2103, TRIG submitted the TIRF REMS Prescription Authorization Request Form for closed system outpatient pharmacies at the FDA request.

Reviewer Comment: FDA recommends this form be added to the TIRF REMS Supporting document as an appended material.

4. On May 1, 2013, Abstral ownership transitioned from ProStrakan to Galena BioPharma. In order to support this transition, the REMS Supporting document (Table 1 on page 4) was updated to reflect Galena as the new Applicant/Sponsor.

5. TRIG submitted the Website Protocol changes (see Appendix 5)

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the TRIF REMS Access Program proposal be sent to the TRIG. Please request that the TRIG respond to these comments as soon as possible to facilitate further review for this submission.

The comments below are based on DRISK's preliminary review of the REMS modification proposal for TIRF products. Appended to this review is the REMS modification proposal and the following REMS materials including our track changes (see Attachment 1 – 12).

1. REMS Document
2. Patient Prescriber Agreement Form
3. TIRF REMS Access Program Education Program

4. Website "Resources for Pharmacists" page 165
5. Website "Registration Identifier Question 2" pages 50-53

The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

6 COMMENTS FOR THE APPLICANT

6.1 REMS DOCUMENT (ATTACHMENT 1)

1. Revise the REMS document to reflect the following pharmacy definitions:

   - **Outpatient Pharmacies**

     i. **Chain Outpatient Pharmacy**: Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of pharmacy staff within all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chains stores) in TIRF REMS Access.

     ii. **Independent Outpatient Pharmacy**: Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location.

     iii. **Closed System Outpatient Pharmacy**: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information.

2. The following documents were revised to reflect the changes to these definitions:

   - FAQ document (Attachment 2)
   - Independent Outpatient Pharmacy Overview (Attachment 3)
   - Chain Outpatient Pharmacy Overview (Attachment 4)

3. Revise the following statement in the REMS document, Implementation System.

   TIRF Sponsors will ensure that wholesalers/distributors who ~~take title to or direct the sale or disposition of TIRF medicines to persons other than a consumer or patient~~ distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

6.2 PATIENT PRESCRIBER AGREEMENT FORM (ATTACHMENT 5)

Revise the prescriber attestation #2 (see below) to replace "respiratory depression" with "overdose". FDA recommends this for the following reasons:

- All TIRF products boxed warning contains both terms fatal overdose and fatal respiratory depression.
- Respiratory depression is one symptom of overdose, therefore overdose is more appropriate term to use in this attestation.
- The REMS goal is to mitigate the risk of overdose

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose ~~respiratory depression~~ can occur at any dose.

6.3 TIRF REMS EDUCATION PROGRAM (ATTACHMENT 6)

An efficacy supplement (S-005) which includes new recommendations for safely switching from Actiq (fentanyl oral transmucosal lozenge) to Subsys (fentanyl sublingual spray) is currently under review by the Agency. Accordingly, slides 15 and 19 of the TIRF REMS Education Program were revised to reflect this change.

6.4 TIRF REMS KNOWLEDGE ASSESSMENT (ATTACHMENT 7)

An efficacy supplement (S-005) which includes new recommendations for safely switching from Actiq (fentanyl oral transmucosal lozenge) to Subsys (fentanyl sublingual spray) is currently under review by the Agency. Accordingly, the following question in the TIRF REMS Knowledge Assessment was revised to reflect this change.

Question 11: Conversion between specific ~~only two~~ TIRF medicines has been established and is described in the Prescribing Information for which ~~two~~ products? *Select one option.*

A. Lazanda to Actiq
B. Actiq to Fentora
C. ~~Abstral to Fentora~~ Actiq to Subsys
D. ~~Fentora to Actiq~~ Both B & C

6.5 REMS SUPPORTING DOCUMENT (ATTACHMENT 8)

1. Add the *TIRF REMS Prescription Authorization Request Form* which closed system pharmacies utilize for requesting prescription verification via fax to the TIRF REMS Supporting document as an appended material.

2. The following underlined text was moved from the TIRF REMS document to the TIRF REMS Supporting document.

C. IMPLEMENTATION SYSTEM

The Implementation System includes the following:

a. Wholesaler/Distributor Enrollment and Fulfillment

- TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program before they are allowed to distribute TIRF medicines.

- For the purpose of the TIRF REMS Access program, the term distributor refers to wholesaler, distributor, and/or chain outpatient pharmacy distributor who take title to or direct sale or disposition of TIRF medicines to persons other than a consumer or patient.

3. The REMS Supporting Document and appended Web Prototype must be consistent with all changes made to the REMS document and REMS appended materials.

6.6 GENERAL COMMENTS

Resubmission Instructions

1) 1 PDF file that includes the REMS document + all appended materials*

   *The materials below should be appended to the REMS document (in the following order):

   1. TIRF REMS Access Prescriber Program Overview
   2. TIRF REMS Access Education Program
   3. Knowledge Assessment
   4. Prescriber Enrollment Form
   5. Patient-Prescriber Agreement Form
   6. TIRF REMS Access Patient and Caregiver Overview
   7. Frequently Asked Questions (FAQs)
   8. Dear Healthcare Provider Letter
   9. TIRF REMS Access Website
   10. Independent Outpatient Pharmacy Overview
   11. Chain Outpatient Pharmacy Overview
   12. Closed System Outpatient Pharmacy Overview
   13. Inpatient Pharmacy Overview
   14. Independent Outpatient Pharmacy Enrollment Form
   15. Chain Outpatient Pharmacy Enrollment Form
   16. Closed System Outpatient Pharmacy Enrollment Form
   17. Inpatient Pharmacy Enrollment Form
   18. Outpatient Pharmacy Letter
   19. Inpatient Pharmacy Letter
   20. Dear Distributor Letter
   21. Distributor Enrollment Form

2) 1 PDF file that includes the REMS Supporting Document

3) Individual Word files for the REMS document, REMS document and appended materials, the REMS Supporting Document. If you have files that were not created in Word, the individual file may be submitted in PDF (e.g. website)

4) The only PDF files that are required to be submitted, are those listed in 1) and 2) above. Individual PDF files of the Word files described in 1) are optional. The PDF files should include the final design format of all REMS materials.

APPENDICES:

1. Response to FDA questions, received March 11, 2013
2. TRIG email, received March 11, 2013
3. TRIG IR response, received May 6, 2013
4. TRIG email, received May 6, 2013
5. Web Prototype Changes, received May 6, 2013

ATTACHMENTS:

1. REMS Document, redlined
2. FAQ document, redlined
3. Independent Outpatient Pharmacy Overview, redlined
4. Chain Outpatient Pharmacy Overview, redlined
5. Patient Prescriber Agreement Form, redlined
6. TIRF REMS Access Program Education Program, redlined
7. TIRF REMS Access Program Knowledge Assessment, redlined
8. TIRF REMS Supporting document, redlined

Appendix 1: Response to FDA questions, received March 11, 2013

Responses to FDA Modification 2 General Comments to TIRF REMS Assess Program 04Mar 2013

1. **Submit the form which will be used by Closed System Outpatient Pharmacies to validate prescriptions by completing and faxing to the TIRF REMS Access Program.**

   We have attached to this email the TIRF REMS Access Prescription Authorization Request form used by closed system outpatient pharmacies to validate prescriptions via fax.

2. **Submit the script used by TIRF REMS Access program call center staff when validating prescriptions for Closed System Outpatient Pharmacies.**

   The call center agents adhere to a work instruction when validating prescriptions for closed system outpatient pharmacies. The process is outlined below:

   1.) REMS agent requests the closed system pharmacy NPI number or DEA number used to register in the TIRF REMS Access program.
   2.) REMS agent uses the number provided to search for the pharmacy in the TIRF REMS Access database and confirms they are a closed system outpatient pharmacy.
   3.) If confirmed, the REMS agent collects the following information:

Dispensing Pharmacy DEA	Patient Date of Birth	Rx Date of Service
Dispensing Pharmacy NPI	Patient First Name	Rx Number
Dispensing Pharmacy Phone #	Patient Last Name	Rx NDC #
Dispensing Pharmacy Fax #	Patient Zip Code	Days Supply
Prescriber DEA or NPI	Prescriber Last Name	Quantity for Dispense

   4.) This information is used to validate the prescription with the TIRF REMS Access program using the same REMS edits and business rules in the claim adjudication process as used for chain outpatient and independent outpatient pharmacies.
   - If validated, the system will provide the REMS Agent an *Authorization Number* which is provided to the closed system caller
   - If not validated, a rejection reason and information regarding how to resolve the rejection is provided to the closed system caller for follow-up or trouble-shooting

3. **What are the call center hours of operation?**

   Monday – Friday: 8am - 8pm ET

4. **Is validation of a Closed System Outpatient Pharmacy's TIRF prescription possible on weekends or on weekdays when the call center is not operational?**

   No, validation of closed system prescriptions can only be obtained during TIRF REMS Access program call center hours of operation of Monday – Friday, 8am-8pm ET.

   Have there been any complaints from Closed System Outpatient Pharmacies due to them not being able to dispense TIRF prescriptions when the call center is not operational?

   No complaints have been received since the implementation of the closed system outpatient pharmacy solution.

5. **Currently Closed System Outpatient Pharmacies can only validate TIRF prescriptions via phone or fax. Are there plans to provide these pharmacies with an online interface for performing the validation?**

   The current prescription authorization volume and absence of complaints does not warrant a change to the current process. Therefore we are not pursuing an online solution at this time. We will continue to monitor and assess the need for an alternate solution as appropriate.

Appendix 4: TRIG email, May 6, 2013

From: Servello, Diane L [mailto:Diane.Servello@covidien.com]
Sent: Monday, May 06, 2013 4:20 PM
To: Liberatore, Mark
Cc: Willene Brondum (wbrondum@insysrx.com); Jenkins, Darrell
Subject: RE: Follow-up: TIRF REMS Modification 2

Hi Mark:

This e-mail provides the TRIG's response to your April 16, 2012 questions concerning TIRF REMS Modification 2. Our responses to your questions are included in the attached PDF file ("*FDA Inquiry to REMS Modification 2 on April 16, 2013 – TRIG Response – Final").*

We are also submitting revised documents in two zip files (clean and redline versions). These documents have been revised to reflect the following:

- PPAF – revised patient attestations #2 and #3 per TRIG's response to FDA's question, 5b.
- To support Abstral's transition from ProStrakan to Galena BioPharma which took effect May 1st, the following REMS Modification 2 document were updated
    - Supporting Document – updated Applicant/Sponsor name for Abstral in Table 1 on page 4
    - Chain Outpatient Pharmacy Enrollment Form – added additional Abstral NDC numbers on page 4
    - Independent Outpatient Pharmacy Enrollment Form – added additional Abstral NDC numbers on page 3
    - Web Prototype - added additional Abstral NDC numbers on pages 89 and 100.

Due to size restrictions, I will be sending the zip files containing the revised documents in two separate e-mails immediately after this e-mail. (You will receive a total to three e-mails for this response.)

Please let me know if you require any additional information.

Best regards,

Diane Servello

Diane Servello

Sr. Director, Regulatory Affairs - API/Specialty Generics/Regulatory Operations

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Fax: 314-654-6496

e-mail: diane.servello@covidien.com

Appendix 2: TRIG email, March 11, 2013

From: Servello, Diane L [mailto:Diane.Servello@covidien.com]
Sent: Monday, March 11, 2013 11:01 AM
To: Liberatore, Mark
Cc: Jenkins, Darrell; wbrondum@insysrx.com
Subject: Response to 2/4/2013 email - TIRF REMS Modification 2

Dear Mark:

Please find our response enclosed, addressing the Agency's e-mail dated February 4, 2013 concerning Modification 2 of the TIRF REMS. We have enclosed two zip files. One file contains red-lined versions of each document and the other file contains "clean" versions. The red-lined versions have been annotated to show the revisions made. We have also enclosed a Word document providing responses to the questions in your February 4, 2013 e-mail. Another Word document is enclosed for the Closed System Rx Authorization form.

The following "global" changes have been made throughout the documents and are not annotated:

- For all occurrences of "FENTORA® (fentanyl citrate) buccal tablet", the product name was changed to "FENTORA® (fentanyl buccal tablet)"
- Changed the location of parenthesis in the Onsolis trade name from 'Onsolis® (fentanyl) buccal soluble film' to 'Onsolis® (fentanyl buccal soluble film)'.
- Replaced the ™ symbol after Subsys with ®.
- Changed location of parenthesis in Subsys trade name from 'Subsys™ (fentanyl) sublingual spray' to 'Subsys™ (fentanyl sublingual spray).
- Add new Subsys NDCs

  20482-001-10
  20482-002-10
  20482-004-10
  20482-006-10
  20482-008-10
  20482-001-01
  20482-002-01
  20482-004-01
  20482-006-01
  20482-008-01

- Changed the following Subsys NDCs:

  Replaced 20482-012-30 with 20482-012-15

  Replaced 20482-016-30 with 20482-016-15

- Changed “Non-chain Outpatient Patient Pharmacy” to “Independent Outpatient Pharmacy” to align with industry standard pharmacy terminology.

- Changed “Closed-system Pharmacy” to “Closed System Outpatient Pharmacy”

- Changed “Chain Pharmacy” to “Chain Outpatient Pharmacy”

- Revised definitions for chain, independent and closed system outpatient pharmacies to align with industry standard pharmacy terminology to prevent confusion upon determining pharmacy type when enrolling in TIRF REMS Access.

- Removed language only pertinent to transition of individual REMS programs to TIRF REMS.

- Language revisions made throughout documents to clarify processes.

Please let me know if you have any questions or concerns.

Best regards,

Diane

Diane Servello

Sr. Director, Regulatory Affairs - API/Specialty Generics/Regulatory Operations

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1. **Provide a rationale for revising the existing text "fatal overdose" to "fatal respiratory depression" as proposed by the TRIG to the Patient Prescriber Agreement Form, Prescriber attestation #2.**

   "2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal ~~overdose~~ respiratory depression can occur at any dose."

   RESPONSE: Fatal respiratory depression is consistent with the label/ boxed warning for all TIRF medicines.

2. **The revised definitions for outpatient pharmacies as proposed by the TRIG have been updated to align with industry standards to prevent confusion. Provide a response to the following:**

   2a. How is the term "generally", which is included in the definitions for chain outpatient pharmacies and independent outpatient pharmacies, used to determine the appropriate category designation?

   RESPONSE: There is no industry standard number of stores for chain vs. independent pharmacies. The definitions allow for flexibility of pharmacies to define their pharmacy type for managing the enrollment process in the TIRF REMS Access program.

   2b. Chain outpatient pharmacy: How many pharmacies with less than 10 stores under the same ownership has the TRIG enrolled as a chain pharmacy? Describe what criteria was used to enroll these pharmacies as a chain outpatient pharmacy.

   RESPONSE: There are four (4) chain outpatient pharmacy headquarters with less than 10 sub-stores enrolled in the TIRF REMS Access program. The pharmacies are enrolled as chain outpatient pharmacies due to their request to have a single authorized pharmacy representative responsible for managing enrollment and training for all stores.

   2c. Independent outpatient pharmacy: How many pharmacies with more than 10 stores under the same ownership has the TRIG enrolled as an independent pharmacy? Describe what criteria was used to enroll these pharmacies as an independent outpatient pharmacy.

   RESPONSE: There are three (3) independent outpatient pharmacies with more than 10 stores enrolled in the TIRF REMS Access program. The pharmacies are enrolled as independent outpatient pharmacies due to their request to have an authorized pharmacy representative from each store responsible for managing enrollment and training of each individual store.

3. **From the website prototype (pages 124 & 136), it appears both chain outpatient pharmacies and independent outpatient pharmacies can enroll pharmacy locations and maintain a list of multiple stores in their pharmacy profile. Provide a rationale for the following:**

   3d. Any differences between the lists managed for independent outpatient pharmacies as compared to chain outpatient pharmacies

   RESPONSE: The difference is the concept of enrollment. The chain outpatient pharmacy headquarters authorized pharmacy representative can add store locations and mark them as trained on the pharmacy dashboard as appropriate. Each independent outpatient pharmacy must individually enroll and complete test transactions at the store level, regardless if the authorized pharmacist is the same across multiple stores.

Chain outpatient pharmacy headquarters manages the training status of each individual store for which they have taken responsibility whereas the authorized pharmacist for the independent outpatient pharmacy has the ability to manage the enrollment process (enrollment form, training, knowledge assessment, test transactions) for other independent pharmacies for which they are the authorized pharmacist.

3e. Why are separate enrollment forms for chain and independent outpatient pharmacies necessary if both entities can enroll multiple pharmacy locations?

RESPONSE: The forms identify the pharmacy type for enrollment purposes. They differ in that the chain enrollment form allows enrollment for multiple pharmacy store locations under one chain enrollment. The independent outpatient pharmacy enrollment form only allows one store to be enrolled per form. Both enrollment forms contain the same 14 acknowledgement statements and Terms and Conditions.

4. Provide a summary of the process for stakeholder enrollment (pharmacy, prescriber) via fax. The summary should include a flowchart of the process and a description of each step within the process. Additionally, provide a response to the following:

RESPONSE: Refer to prescriber, independent outpatient pharmacy, chain outpatient pharmacy, inpatient pharmacy and closed system outpatient pharmacy fax enrollment flows in the Appendix beginning on page 4.

4f. Have incomplete prescriber enrollments resulted from a prescriber's ability to sign the enrollment form before completing the Education Program and Knowledge Assessment? If so, how many?

RESPONSE: Enrollment is not deemed as complete until all enrollment requirements are met. A total of 567 prescribers submitted a signed TIRF REMS Access enrollment form prior to completing the Knowledge Assessment. 485 (85.5%) of these prescribers are currently enrolled in the TIRF REMS Access program. The TIRF REMS Access database tracks the completion of each step and upon processing, immediately notifies the stakeholder of ALL outstanding requirements (i.e.; missing signature, missing address, knowledge assessment) via the incomplete correspondence letter.

4g. If the knowledge assessment authorization number is not searchable within the TIRF REMS Access database, how is the TRIG able to identify which stakeholders have completed the assessment online after receipt of an enrollment form?

RESPONSE: In clarification, although the Knowledge Assessment code is searchable, current TIRF REMS Access Call Center work instructions were created based on best practices and ease of database navigation. Upon receipt of a faxed enrollment form, the TIRF REMS Access Call Center Agent conducts a search of the TIRF REMS Access database to locate the stakeholder record. Fields used to search the TIRF REMS Access database include: name, city, state, zip code, phone number, fax number and stakeholder identifiers (DEA, NPI, state license number, NCPDP, Medicaid ID, chain ID, enrollment ID). Once the stakeholder has been identified in the TIRF REMS database, the Knowledge Assessment code will be visible if the Knowledge Assessment has been completed.

4h. Once the enrollment form is received and a stakeholder is notified of the need to complete the assessment, how does the TRIG track if it is completed?

RESPONSE: The TIRF REMS Access database programmatically tracks the lifecycle of the enrollment from submission to completion regardless if the stakeholder completes the Knowledge Assessment via fax or web. The stakeholder is not enrolled until all steps are completed.

4i. The comment provided by the TRIG indicated that "…it is not required for the KA to be completed prior to the receipt of the enrollment form" is contradictory to the first attestation statement on the enrollment form which states "I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment…" Provide further clarification by what was meant by the TRIG's comment.

RESPONSE: To clarify TRIGs comment, stakeholders are not enrolled until all steps of the enrollment process are completed, including the Knowledge Assessment (KA). If the enrollment form is received prior to the KA, it will be processed but the stakeholder enrollment will be incomplete until a complete KA is received.

5. Patient attestation on the Patient Prescriber Agreement Form

5a. The patient attestation on the Patient Prescriber Agreement Form was revised by the TRIG. Provide a rationale for the revision to the attestation statement.

RESPONSE: TRIG's rationale for this proposed change was an attempt to adapt the following language from the TIRF Medication Guides to the language of the PPAF.

"Do not use [TIRF] unless you are regularly using another opioid pain medicine around-the-clock for your cancer pain and your body is used to these medicines (this means you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant."

5b. The Agency proposes the following revisions to Attestation #2 and inclusion of the deleted attestation as attestation #3.

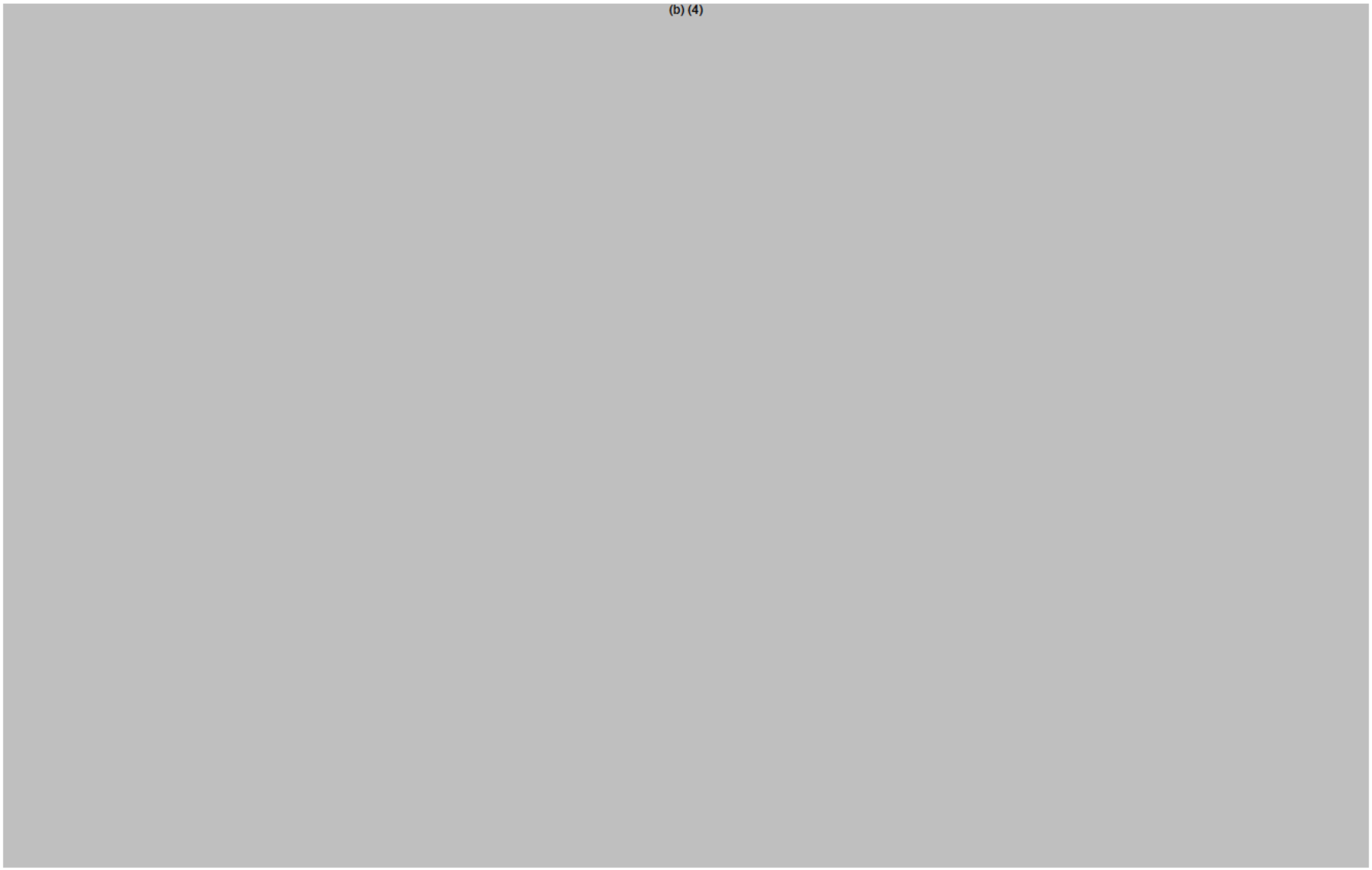
"2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. ~~opioid pain medications. I understand that before I can take any TIRF medicine, I must be opioid tolerant.~~ If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines. ~~whether I am opioid tolerant~~."

"3. ~~I understand that if I stop taking another opioid pain medicine that I have been taking regularly , around the clock, for my constant pain, then I must also stop taking my TIRF medicine.~~ I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine."

RESPONSE: TRIG agrees with the Agency's recommendation. The PPAF has been updated. A redlined and clean version of the revised PPAF is attached in the FDA Inquiry to Modification 2 Response email sent to the FDA on May 6, 2013.

APPENDIX – TIRF REMS Access Process Flows

TIRF REMS Access – Prescriber - Fax Enrollment Process Flow



TIRF REMS Access - Chain Outpatient Pharmacy - Fax Enrollment Process Flow
(b) (4)

TIRF REMS Access - Independent Outpatient Pharmacy - Fax Enrollment Process Flow
(b) (4)

TIRF REMS Access - Inpatient Pharmacy - Fax Enrollment Process Flow

(b) (4)

TIRF REMS Access – Closed System Outpatient Pharmacy - Enrollment Process Flow

(b) (4)

Appendix 5: Web Prototype Changes, May 6, 2013

Prototype Page #	Section	Modification
9	(b) (4)	
12		
16		
17		
18		
19		
22		
23		
27		
28		
29		

(b) (4)

47

(b) (4)

51

62

63

64

69

71

(b) (4)

74

78

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82

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85

86

87

88

89

(b) (4)

91

92

93

94

96

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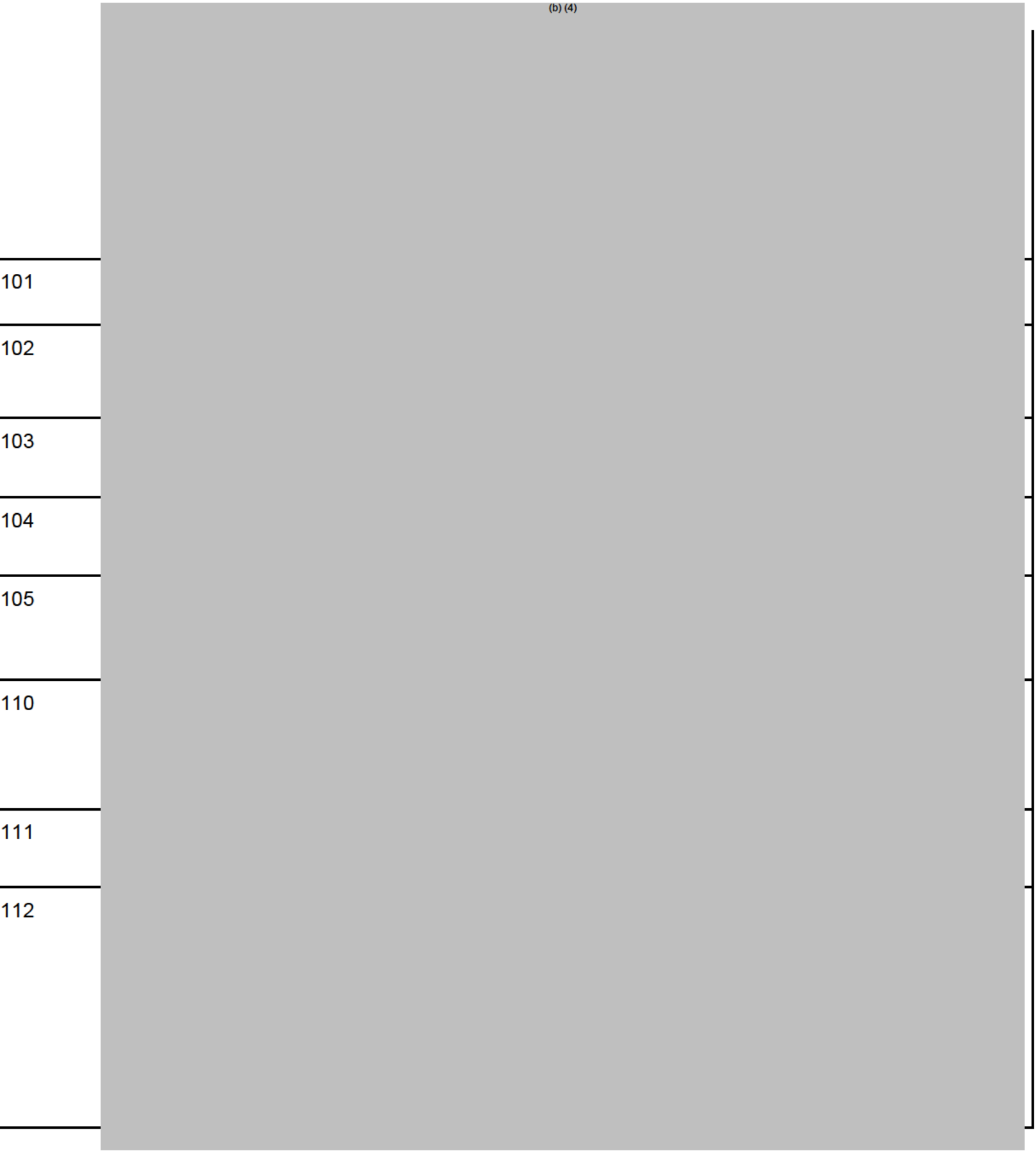
100

(b) (4)



113	(b) (4)
114	
117	
121	
123	
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126	
128	
129	
133	
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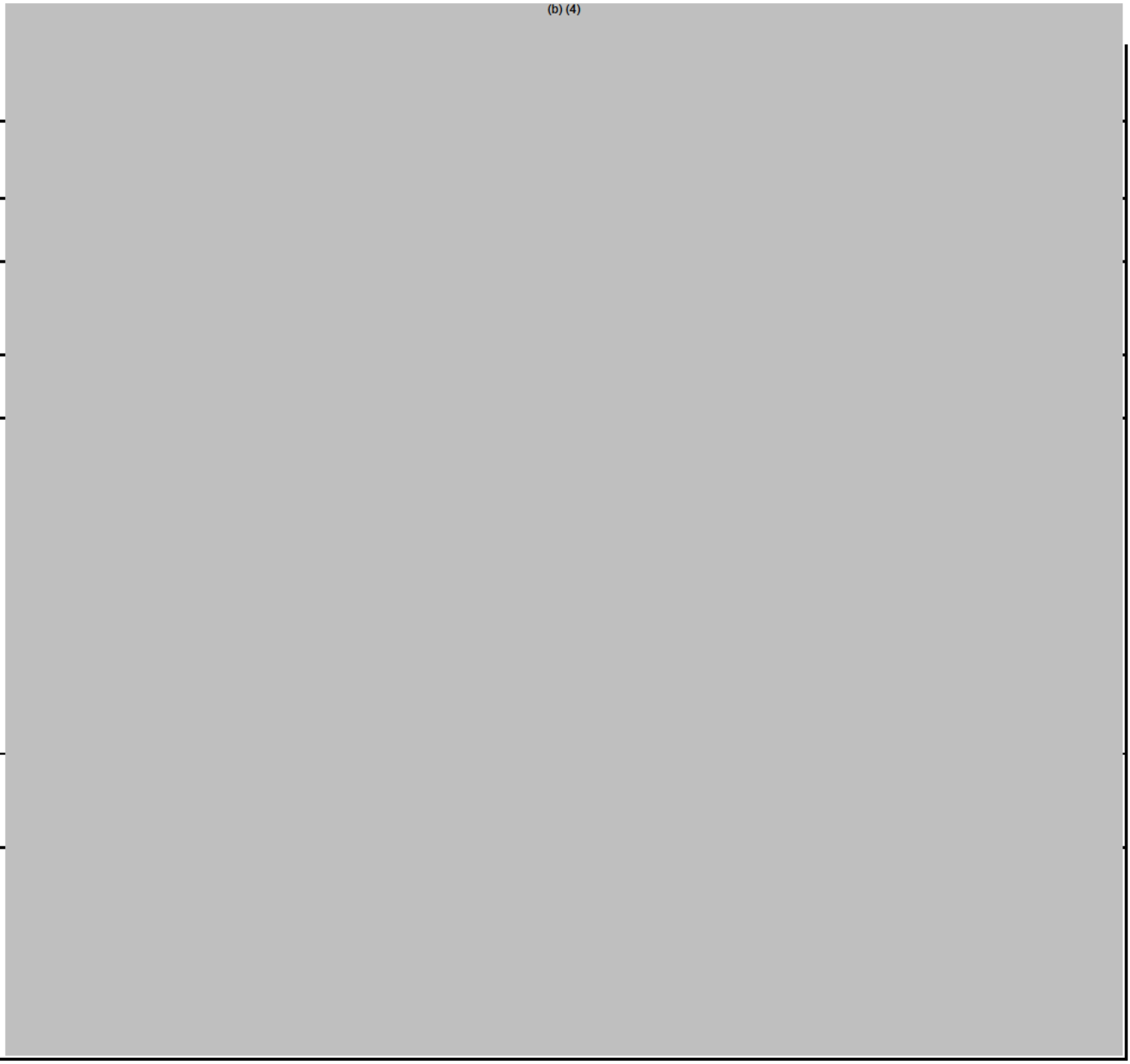
136	
137	
138	

(b) (4)



Initial REMS approval: 12/2011

Most recent modification: XXXXXX

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF)
RISK EVALUATION AND MITIGATION STRATEGY (REMS)

FOLLOWING THIS PAGE, FDA_6571 TO FDA_6681 WITHHELD IN FULL AS B(4)/CCI (PROPOSED/DRAFT REMS WEB MATERIALS)

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

/s/

KIMBERLY LEHRFELD
08/23/2013

CLAUDIA B MANZO
08/23/2013
concur