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.

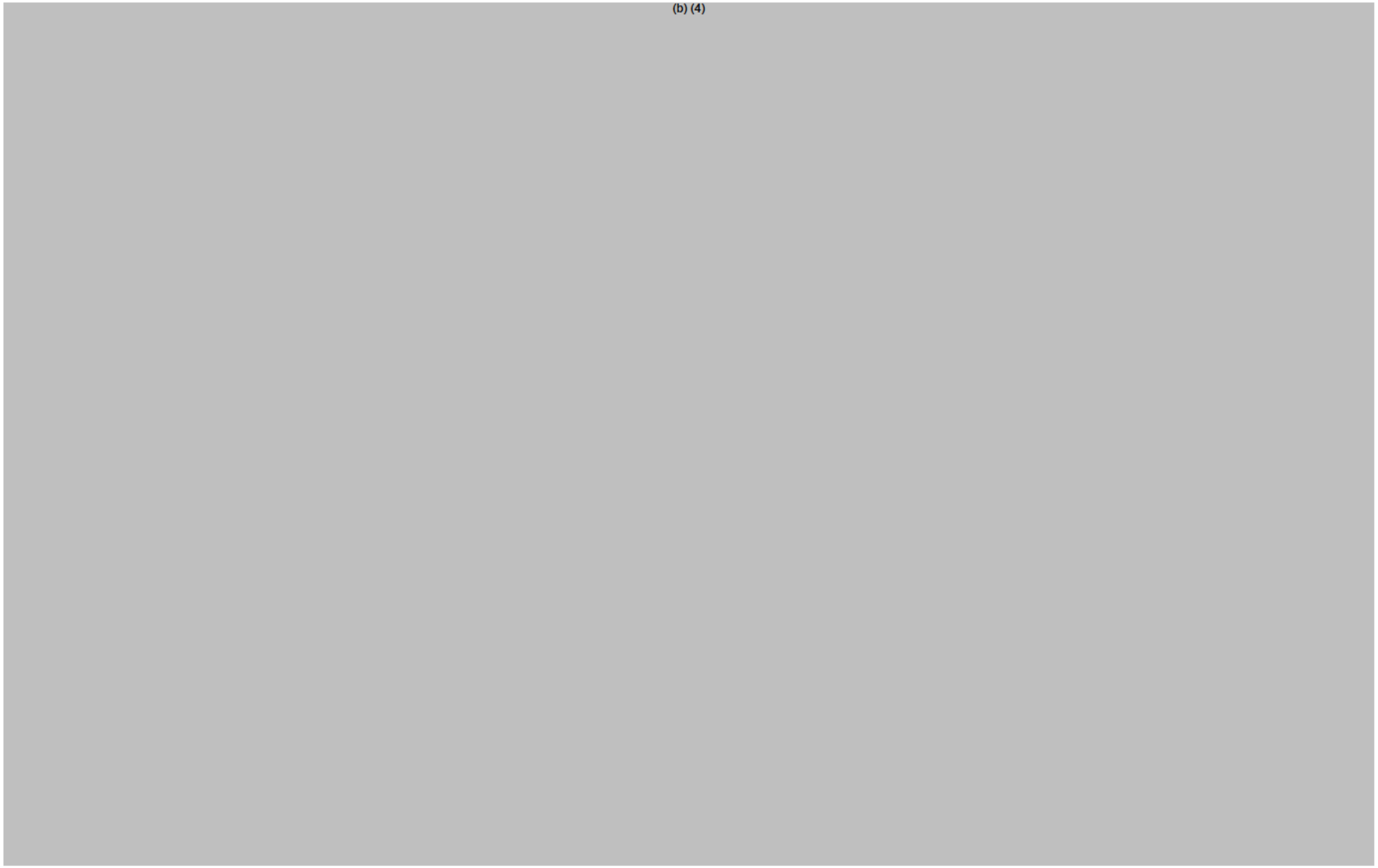
"2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. ~~opioid pain medications. I understand that before I can take any TIRF medicine, I must be opioid tolerant.~~ If I am not taking around-the-clock opioid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

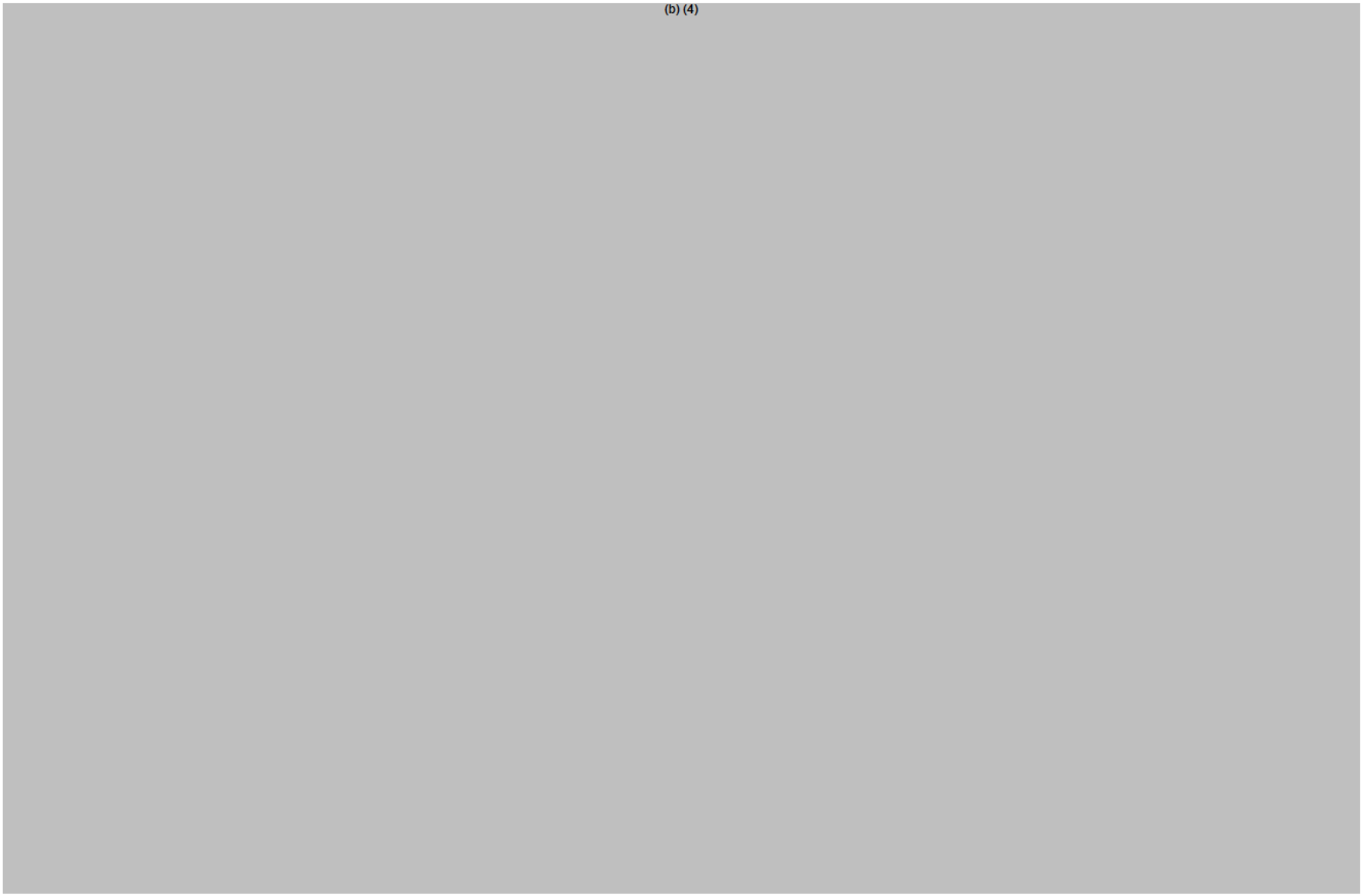
TIRF REMS Access – Prescriber - Fax Enrollment Process Flow



TIRF REMS Access - Chain Outpatient Pharmacy - Fax Enrollment Process Flow

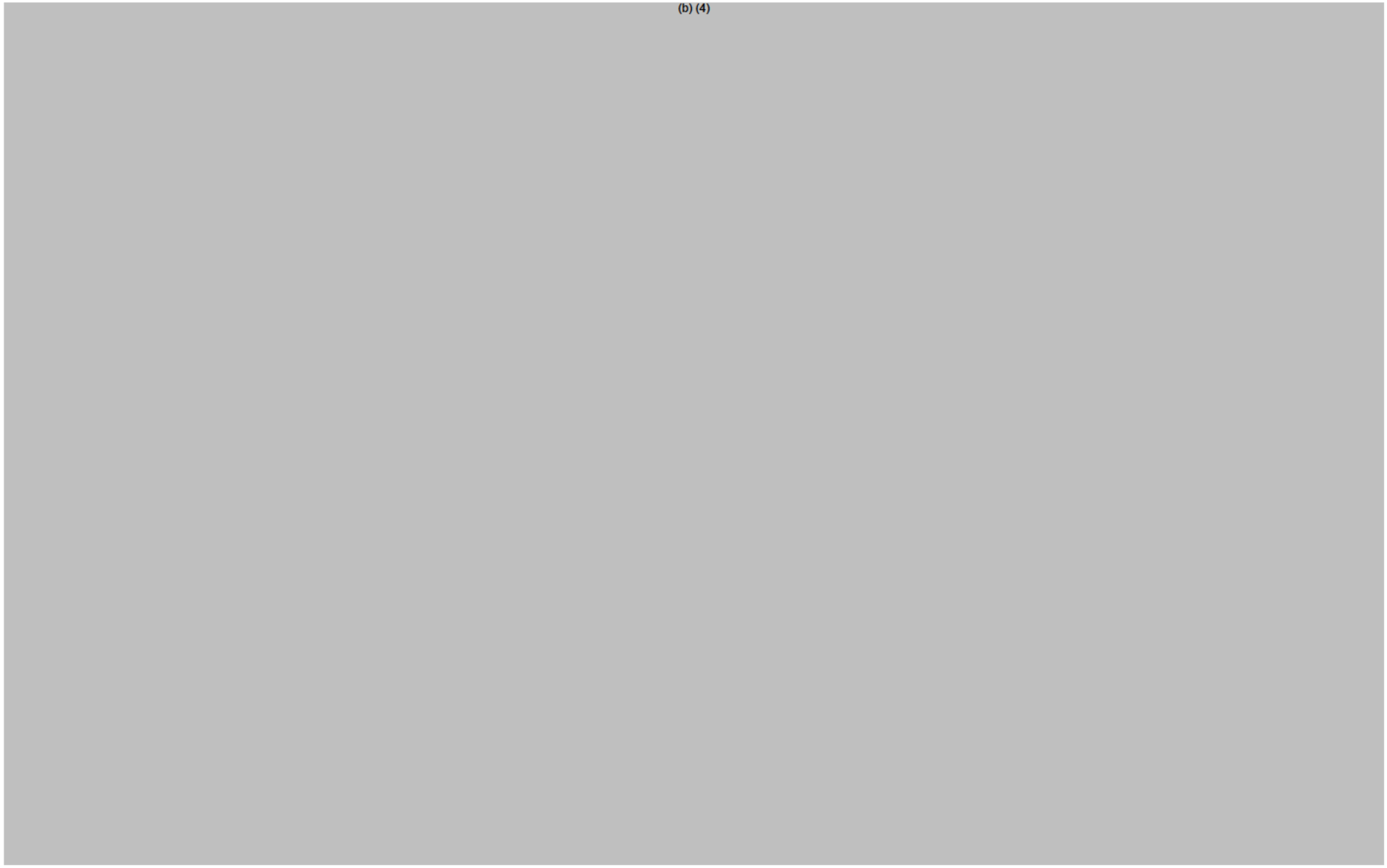
(b) (4)

TIRF REMS Access - Independent Outpatient Pharmacy - Fax Enrollment Process Flow



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

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



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MARK A LIBERATORE
05/07/2013