TIRF REMS
NON-COMPLIANCE PROTOCOL

Version 8.0

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1. Background

Opioids remain the mainstay of treatment of moderate to severe pain, especially for opioid-tolerant patients experiencing breakthrough cancer pain (BTCP). Transmucosal immediate release fentanyl (TIRF) medicines are short-acting opioid products that have a rapid onset and relatively short duration of action and are designed for the treatment of episodes of BTCP in opioid-tolerant patients with chronic cancer pain.

On December 28, 2011, the Food and Drug Administration (FDA) approved a single, shared Risk Evaluation and Mitigation Strategy (REMS) for TIRF products. The shared system strategy, called the TIRF REMS, is used by all sponsors of TIRF products and is designed to ensure access to important medications for appropriate patients.

The goals of the TIRF REMS are to:

1. Mitigate the risk of overdose by:
    a. Requiring documentation of opioid tolerance with every TIRF prescription for outpatient use.
    b. Requiring inpatient pharmacies to develop policies and procedures to verify opioid tolerance in inpatients who require TIRF medicines while hospitalized.
    c. Educating prescribers, pharmacists, and patients that the safe use of TIRF medicines requires patients to be opioid-tolerant throughout treatment.
2. Mitigate the risk of accidental exposure by educating prescribers, and pharmacists and patients about proper storage and disposal of TIRF medicines.
3. Assess safe use and trends in accidental exposure, misuse, abuse, addiction, and overdose by enrolling all patients who receive a TIRF medicine for outpatient use in a registry.

Compliance with the TIRF REMS ("program") is necessary in accordance with the appropriate use of TIRF products and proper patient selection. The TIRF REMS includes a continuous evaluation process of compliance to the program. Any deviation from program procedures is evidence of non-compliance and may result in corrective measures, such as a warning, suspension or program deactivation.

2. Goals and Objectives

The goal of the Non-compliance Protocol is to ensure that a system is in place to identify and investigate stakeholder non-compliance with the TIRF REMS by monitoring possible program deviations detected through program reporting and spontaneous events identified by the program.

Suspected non-compliance is defined as an instance when it is believed that a stakeholder is not following a program requirement. Suspected non-compliance scenarios may be detected through standard program reports, spontaneous reports identified via the program's call center or vendor/sponsor reported events. A suspected non-compliant event is deemed compliant in the event the information presented on a stakeholder scenario does not clearly identify or support

that a program deviation has occurred and/or no evidence of the program goals not being met are present.

A confirmed non-compliant event occurs when the information presented clearly indicates that a program deviation has occurred and/or evidence of the program goals not being met through stakeholder actions is identified. Confirmation of a non-compliant stakeholder act will typically occur after further investigation has been completed and supportive data has been reviewed and presented to the TIRF REMS Non-Compliance Review Team.

The objectives of this Non-compliance Protocol are to:

- Describe the purpose and activities of the TIRF REMS Non-Compliance Review Team
- Describe the purpose and activities of the TIRF REMS Non-Compliance Working Group
- Describe the process to identify program non-compliance
- Outline an index of possible scenarios of non-compliance
- Identify data sources to review for suspected non-compliant events
- Describe suggested actions taken once non-compliance is confirmed
- Describe the process to monitor program deviations and occurrences of non-compliance

3. Non-Compliance Review Team and Working Group Responsibility

A TIRF REMS Non-Compliance Review Team ("Review Team") will be created composed of membership from the TRIG Sponsors. The Review Team will be responsible for review, escalation, and decision-making of all non-compliance cases, and ensure corrective measures are applied when necessary.

The responsibilities of the Review Team may not be delegated or transferred to other parties without prior consent of the TRIG sponsors. If the need arises, the Review Team shall have the authority to consult external advisors, experts, or consultants, in order to effectively assess and process cases of program non-compliance. If it is determined that a program modification may be warranted due to cases of non-compliance, the Review Team may need to consult with the FDA for their review and approval of any changes impacting the approved TIRF REMS. Any proposed program modifications must be approved by the TRIG prior to implementation. The Review Team will meet regularly to discuss all issues of non-compliance and/or program modifications, at a frequency interval defined by the TRIG sponsors. The Review Team will consist of members with expertise from the following specialties:

1. Regulatory Affairs
2. REMS Specialist
3. Project Management
6. Drug Safety

Additionally, the Review Team may be supplemented with additional members from the following specialties, if a specific need arises:

1. Legal
2. Quality Assurance
3. Commercial
4. IT

Legal would be requested to participate in the Review Team if there is a concern, threat, or pending of legal action related to a non-compliance activity. Quality Assurance would be requested to participate if the non-compliance activity is related to a quality issue. Commercial would be requested to participate if the non-compliance activity is related to a commercialization issue. IT would be requested to participate if the non-compliance activity is related to a technical issue.

A TIRF REMS Non-Compliance Working Group ("Working Group") will be created from program staff and will be responsible for collecting data and preparing reports for the Review Team, in compliance with Privacy Health Information (PHI) regulations. The Working Group will consist of program agents who have been working with and/or trained on the TRIG Non-compliance Protocol, as well as have background necessary to evaluate data and make objective decisions on instances of non-compliance, based on the data available.

The functions of the Working Group will be to:

1. Review reports, call center logs, TIRF REMS system data, or audit report data to identify potential incidences of non-compliance
2. Conduct further investigation as needed to clarify the potential incident and identify the root cause of deviation
3. Evaluate compliance with the TIRF REMS stakeholder requirements
4. Respond to identified events of non-compliance in accordance with the established business rules. Propose solutions and actions for confirmed non-compliance events that are not addressed by such business rules.
5. Prepare reports for review and approval by the Review Team

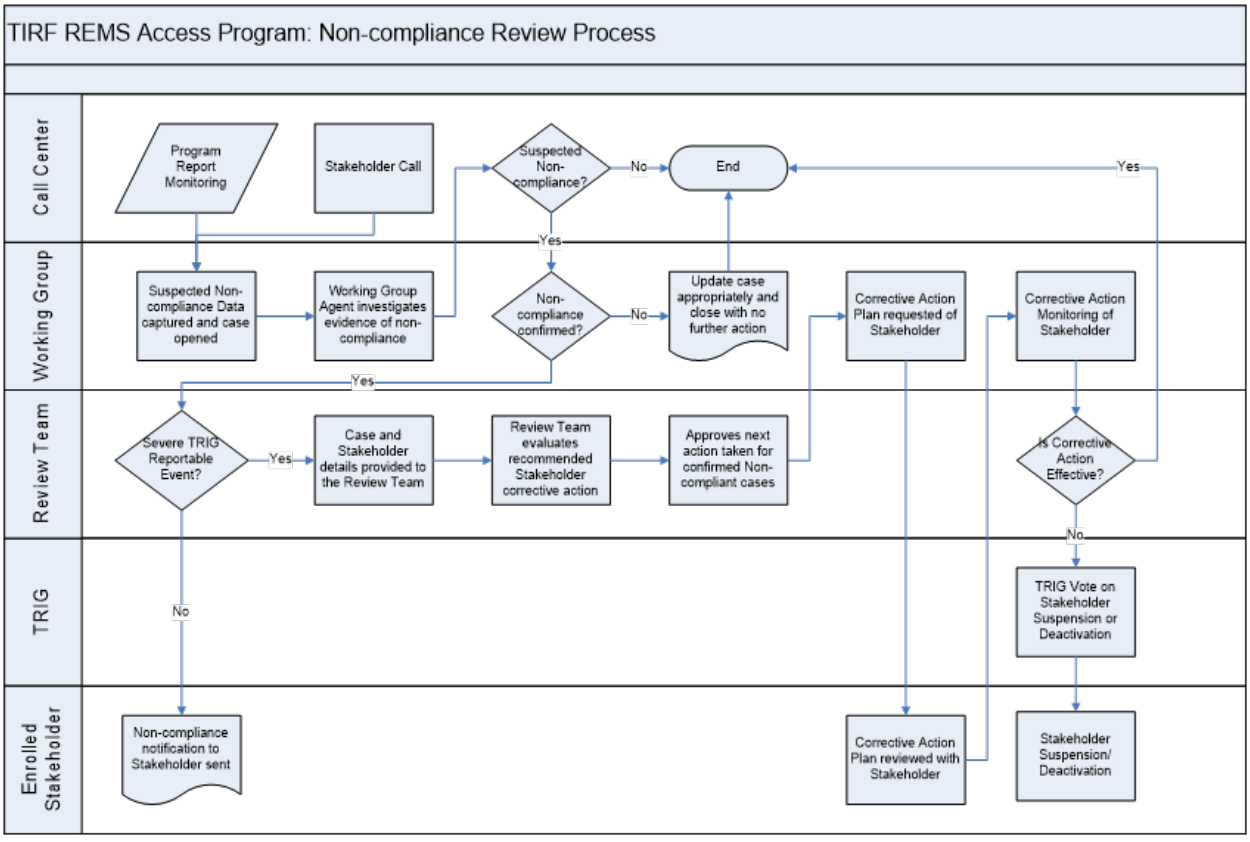
When a possible non-compliant event is identified, the event will be referred to the Working Group. The Working Group will perform an initial investigation to determine if the event should be considered a suspected non-compliance case. If the Working Group determines that there is no suspected non-compliance, the process ends. Suspected non-compliance cases are further investigated to confirm if non-compliance exists. Both the initial and subsequent investigations may include communications with the stakeholder(s) involved to collect information regarding the case. If non-compliance is confirmed, the case will be presented to the Review Team during the next regularly scheduled Review Team meeting. An ad-hoc Review Team meeting may be schedule if the Working Group determines the case warrants immediate review. If the case does not require stakeholder corrective action, the Working Group notifies the stakeholder of the confirmed non-compliance by mail. If the case requires a stakeholder corrective action, the Review Team must evaluate and approve the recommended action for the case. Once approved, the Working Group notifies the stakeholder by mail including the request for corrective action. See Section 4 for a description of the timing requirements for corrective actions. Once the

corrective action is implemented, the Working Group will monitor the stakeholder to determine if the corrective action is effective. If the corrective action is ineffective, the case will be referred to the TRIG Program Managers to vote on stakeholder suspension or deactivation.

Ongoing Review Team responsibilities include:

- Attend all regularly scheduled Review Team meetings to review, assess and make decisions on any non-compliance issues needing attention including any issue that the Working Group could not handle because it was beyond the scope of the business rules used by the Working Group.
- Identify if an audit of a stakeholder is required
- Determine if any report or communication should be made to the FDA outside of regular TIRF REMS assessment reports.
- Determine if changes to this protocol need to be made and make such changes.

The following process flow outlines the interactions between the Working Group, the Review Team and the program stakeholders to monitor, review and act upon corrective actions for non-compliant scenarios identified.



Identification and Investigation Process of Non-Compliant Events

Identification Process

Call center staff in the TIRF REMS or TRIG sponsor companies will refer cases of potential non-compliance to the Working Group.

Investigation Process

If an instance of potential non-compliance is identified, further investigation will be conducted. This may include:

- Review case details to determine if evidence of non-compliance exists
- Make attempt(s) to contact relevant stakeholder to validate data/information and solicit further information
- Conduct further investigation of TIRF REMS databases

For instances of potential non-compliance that are not described in Section 5, a suggested course of action will be presented to the Review Team. The Working Group will consult with the Review Team if proprietary or commercially sensitive information arises that would not ordinarily be shared among TRIG representatives.

4. Corrective Actions for Instances of Non-Compliance

Corrective actions resulting from non-compliance will be determined according to the severity of the action. The stakeholders in this Non-compliance Protocol include prescribers, patients, distributors, and pharmacies. The primary elements for corrective action include; warnings, suspension, and deactivation based on the requirements of the TIRF REMS. If a prescriber, pharmacy or distributor is suspended or deactivated, information will be made available through the program to assist associated stakeholders (e.g. – patients of a suspended prescriber) in finding alternative access to product.

Each non-compliant event will be categorized based on the level of severity of the event. A non-compliant case may include multiple non-compliant events. These events may be investigated as a single investigation of all identified deviations from program requirements. The total number of events in a case will remain visible as separate events and evaluated with further non-compliance by the stakeholder. The event classifications are as follows:

Minor

A minor event is defined as a first-time event within an enrollment period with minimal patient risk and where other measures are in place to prevent the risk occurring. Re-education is required to inform the stakeholder of program requirements. An investigation will be conducted by program staff to identify the root cause of the event. Program staff will also work with the stakeholder to create and implement a corrective and preventative action plan. The corrective

and preventative action plan must be received within 15 business days. It must be deemed acceptable and implemented within 90 days of receipt or the stakeholder will be suspended. Once the corrective and preventative action plan is implemented, the stakeholder will be monitored for compliance with the plan of action and provided with a written warning for their files. Two or more minor non-compliance events within the same enrollment period demonstrates a lack of understanding of the REMS requirements and is considered a moderate event. Additionally, three or more minor events in successive enrollment periods is considered a moderate event.

Moderate

A moderate event is defined as an event that has associated patient risk, or repeated minor events within the same enrollment period. Examples of a moderate event include a pharmacy that dispenses drug after receiving a reject, or a prescriber who fails to provide Patient Enrollment Forms in multiple non-compliance events. An investigation will be conducted by program staff to identify the root cause of the event. This level of offense will result in a suspension from the program and possible deactivation. Program staff will work with the stakeholder to create and implement a corrective and preventative action plan. The corrective and preventative action plan must be received within 10 business days. It must be deemed acceptable and implemented within 90 days of receipt or the stakeholder will be deactivated. Once the corrective and preventative action plan is implemented, the enrollment will be reinstated, and the stakeholder will be monitored for compliance with the plan of action. Two or more moderate non-compliance events within the same enrollment period is considered a serious event. Additionally, three or more moderate events in successive enrollment periods is considered a serious event.

Serious

A serious event is defined as an event that results in serious or significant injury or potential risk to a patient irrespective of the number of previous non-compliance occurrences or continued non-compliant events after retraining has occurred and within the same enrollment period. An example of a serious event is a prescriber who no longer has the ability to prescribe Schedule II narcotics. This level of offense will result in a deactivation from the program for a two-year period. During the two-year period, deactivated prescribers will not be able to participate in the TIRF REMS for any existing or future patients, effectively barring their ability to provide TIRF medicines as a therapy for their patients. Following the two-year period, the stakeholder can reinstate their enrollment in the TIRF REMS by going through the enrollment process, provided that the previous non-compliance issues have been resolved.

A stakeholder may request that the result of any investigation into non-compliance be reconsidered. Only verifiable, additional information or extenuating circumstances will be considered as grounds to reinstate enrollment. Requests for reinstatement must be in writing and will be evaluated by the Review Team for final determination.

Detailed business rules will outline the process, timeline and corrective action plan for each level of program non-compliance. Non-compliant closed-system pharmacies must, at a minimum, be issued a Warning, and be asked to satisfactorily complete a corrective and preventative action

(CAPA) plan. Pharmacies with non-compliance or audit deviations will be assigned a unique identifier code that will be used consistently so that they can be tracked in assessment reports for non-compliance events.

The Review Groups will determine whether a suspended pharmacy or distributor will be permitted to keep an inventory of TIRF medicines already acquired prior to suspension. Pharmacies may not dispense TIRF medicines from such existing inventory during the suspension and distributors may not sell and/or distribute TIRF medicines. If a suspended outpatient pharmacy or distributor is part of a larger entity, the parent entity will be notified of the noncompliant activity and resultant suspension.

Deactivated pharmacies and distributors will be required to return all existing TIRF medicine inventory. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

5. Evaluation Process

5.1. Index of Non-Compliance Scenarios

Stakeholder	Scenario		Monitoring	Severity	Corrective Action
	#	Non-Compliance Activity	Tool		Corrective Action Level
Pharmacy	1	A TIRF medicine was dispensed by an outpatient pharmacy without obtaining authorization to dispense from the TIRF REMS to verify that the prescriber and the patient are enrolled, and the patient is opioid tolerant.	Audit or Spontaneous event reported	Moderate	Suspension with request for a CAPA
	2	Dispensing activity for enrolled outpatient pharmacies during reporting period not matching distributor shipment data for that pharmacy.	Audit or Sponsor reported	Moderate	Suspension with request for a CAPA
	3	Pharmacy is dispensing TIRF medicine while suspended or deactivated from the TIRF REMS.	Audit or Spontaneous event reported	Serious	Deactivation
	4	Pharmacy no longer has a valid DEA.	Audit or Spontaneous event reported	Serious	Deactivation
	5	Authorized Inpatient Pharmacy does not comply with the requirements of the TIRF REMS.	Audit or Spontaneous event reported	Moderate	Suspension with request for a CAPA
	6	Inpatient Pharmacy dispenses for outpatient use.	Audit or Spontaneous event reported	Moderate	Suspension with request for a CAPA
	7	Pharmacy sold, loaned or transferred TIRF medicine inventory to another pharmacy, institution, distributor or prescriber.	Audit or spontaneous event reported	Moderate	Suspension with request for a CAPA
	8	Outpatient pharmacy did not establish processes and procedures to assess the patient's medication use for a change in opioid tolerance.	Spontaneous event reported	Moderate	Suspension with request for a CAPA
	9	Inpatient pharmacy did not establish processes and procedures to verify the patient is opioid tolerant.	Spontaneous event reported	Moderate	Suspension with request for a CAPA
	10	Pharmacy did not train all relevant staff involved in dispensing of TIRF medicines on the risks associated with TIRF medicines and the requirements of the REMS program using the Pharmacy Education.	Spontaneous event reported	Moderate	Suspension with request for a CAPA
	11	Pharmacy does not have a process to detect/assess an inappropriate conversion between TIRF products.	Audit or spontaneous event reported	Moderate	Suspension with a request for a CAPA
Wholesaler/ Distributor	1	Wholesaler/Distributor is suspended or deactivated from the TIRF REMS and is purchasing or distributing TIRF medicines.	Sponsor reported	Serious	Deactivation
	2	Wholesaler/Distributor fills an order for TIRF medicines for a non-enrolled stakeholder.	Audit or Spontaneous event reported	Moderate	Suspension with request for a CAPA

Prescriber	1	Prescriber is prescribing TIRF medicines while suspended or deactivated from the TIRF REMS.	Audit or Spontaneous event reported	Serious	Deactivation
	2	Prescriber submits inaccurate or false opioid tolerance information for a patient.	Audit or Spontaneous event reported	Serious	Deactivation
	3	Prescriber no longer has a valid, schedule II DEA.	Audit or Spontaneous event reported	Serious	Deactivation
	4	Prescribed TIRF medicines to an opioid non-tolerant individual.	Audit or Spontaneous event reported	Serious	Deactivation
	5	Inappropriate conversions between TIRF products.	Audit or Spontaneous event reported	Moderate	Suspension
Patient	1	The Patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction	Audit or Spontaneous event reported	N/A	Suspected patient non-compliance will be reported to the patient's prescriber for further intervention.
All Stakeholders	1	ENROLLMENT MONITORING ONLY: Monitor stakeholders who are not enrolled in TIRF and are associated with non-compliance cases.	Program Reports	N/A	N/A

Stakeholder	Scenario		Monitoring	Severity	Corrective Action
	#	Non-Compliance Activity	Tool		Corrective Action Level
Pharmacy	1	A TIRF medicine was dispensed by an outpatient pharmacy without obtaining authorization to dispense from the TIRF REMS to verify that the prescriber and the patient are enrolled, and the patient is opioid tolerant.	Audit or Spontaneous event reported	Moderate	Suspension with request for a CAPA
	2	Dispensing activity for enrolled outpatient pharmacies during reporting period not matching distributor shipment data for that pharmacy.	Audit or Sponsor reported	Moderate	Suspension with request for a CAPA
	3	Pharmacy is dispensing TIRF medicine while suspended or deactivated from the TIRF REMS.	Audit or Spontaneous event reported	Serious	Deactivation
	4	Pharmacy no longer has a valid DEA.	Audit or Spontaneous event reported	Serious	Deactivation
	5	Authorized Inpatient Pharmacy does not comply with the requirements of the TIRF REMS.	Audit or Spontaneous event reported	Moderate	Suspension with request for a CAPA
	6	Inpatient Pharmacy dispenses for outpatient use.	Audit or Spontaneous event reported	Moderate	Suspension with request for a CAPA
	7	Pharmacy sold, loaned or transferred TIRF medicine inventory to another pharmacy, institution, distributor or prescriber.	Audit or spontaneous event reported	Moderate	Suspension with request for a CAPA
	8	Outpatient pharmacy did not establish processes and procedures to assess the patient's medication use for a change in opioid tolerance.	Spontaneous event reported	Moderate	Suspension with request for a CAPA
	9	Inpatient pharmacy did not establish processes and procedures to verify the patient is opioid tolerant.	Spontaneous event reported	Moderate	Suspension with request for a CAPA
	10	Pharmacy did not train all relevant staff involved in dispensing of TIRF medicines on the risks associated with TIRF medicines and the requirements of the REMS program using the Pharmacy Education.	Spontaneous event reported	Moderate	Suspension with request for a CAPA
	11	Pharmacy does not have a process to detect/assess an inappropriate conversion between TIRF products.	Audit or spontaneous event reported	Moderate	Suspension with a request for a CAPA
Wholesaler/ Distributor	1	Wholesaler/Distributor is suspended or deactivated from the TIRF REMS and is purchasing or distributing TIRF medicines.	Sponsor reported	Serious	Deactivation
	2	Wholesaler/Distributor fills an order for TIRF medicines for a non-enrolled stakeholder.	Audit or Spontaneous event reported	Moderate	Suspension with request for a CAPA

Prescriber	1	Prescriber is prescribing TIRF medicines while suspended or deactivated from the TIRF REMS.	Audit or Spontaneous event reported	Serious	Deactivation
	2	Prescriber submits inaccurate or false opioid tolerance information for a patient.	Audit or Spontaneous event reported	Serious	Deactivation
	3	Prescriber no longer has a valid, schedule II DEA.	Audit or Spontaneous event reported	Serious	Deactivation
	4	Prescribed TIRF medicines to an opioid non-tolerant individual.	Audit or Spontaneous event reported	Serious	Deactivation
	5	Inappropriate conversions between TIRF products.	Audit or Spontaneous event reported	Moderate	Suspension
Patient	1	The Patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction	Audit or Spontaneous event reported	N/A	Suspected patient non-compliance will be reported to the patient's prescriber for further intervention.
All Stakeholders	1	ENROLLMENT MONITORING ONLY: Monitor stakeholders who are not enrolled in TIRF and are associated with non-compliance cases.	Program Reports	N/A	N/A

5.2. Reference – Severity

Severity Guideline	
Level of Severity	**Definition**
Minor	A first-time event within an enrollment period where re-education is required to inform the stakeholder of program requirements
Moderate	An event that has associated patient risk, or repeated events within the same enrollment period
Serious	An event that results in serious or significant injury or potential risk to a patient irrespective of the number of previous non-compliance occurrences or continued non-compliant events after retraining has occurred and within the same enrollment period.

5.3 Reference – Corrective Action

Corrective Action Guideline	
Action	**Measure**
Warning	Minor violation that demonstrates a misunderstanding of the program requirements
	Warnings are intended to re-educate stakeholders
	Patient warnings will be sent to a patient's prescriber
Suspension	Temporary deactivation from the program
	A suspended pharmacy or distributor may keep existing TIRF inventory but may not purchase or acquire additional TIRF medicines
	Pharmacies may not dispense TIRF medicines from existing inventory and distributors may not sell/distribute TIRF medicines during suspension
	If the pharmacy or distributor is part of a larger entity that entity will be notified of the suspension
	Moderate violation that has potential risk to patients
Deactivation	Deactivations may result from multiple failures to comply with the program elements and/or non-compliance where there is no feasible corrective action
	Bars stakeholder to provide TIRF medicines as a therapy for their patients
	Pharmacies and distributors must return all existing TIRF medicine
	Patient deactivation will be sent to a patient's prescriber. Patients may only be reinstated into the program by a request from their prescriber
	Serious violation resulting in risk to the patient, or continued non-compliance events

5.4 Reference – Monitoring Frequency Guidelines

Monitoring Frequency Guideline	
Report Category	**Frequency**
Existing Reports	Bi-Monthly
Report Does Not Exist	Cost/Timeline TBD - Report request will be handled via the Change Management Process
Sponsor Reported	During every Non-Compliance Review Team Meeting and as needed
KAB Surveys	12 and 24 months from the date of the REMS approval and as needed thereafter
Escalation Log	During every Quality Management Workstream meeting and as needed

6 Non-Compliance Assessment Reporting

Confirmed non-compliance events will be included in FDA assessment reports.