iPLEDGE NON-COMPLIANCE ACTION POLICY

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1. OVERVIEW

The iPLEDGE Risk Evaluation Mitigation Strategy (REMS) Program is a computer based restricted distribution program and pregnancy registry designed to support the public health goals that no woman who is already pregnant will initiate isotretinoin therapy and that no woman will become pregnant while on isotretinoin therapy for one month prior to, during, and for 30 days after the course of treatment. Compliance with the requirements of the iPLEDGE Program is necessary to achieve this public health goal, and potential fetal exposure is paramount when considering actions taken against a non-compliant stakeholder in the iPLEDGE Program.

2. DEFINITIONS

2.1. Non-Compliance- For the purposes of the iPLEDGE Program, the definition of Non-Compliance is a stakeholder (patient, pharmacy, prescriber, designee or wholesaler) that does not meet the requirements of the iPLEDGE Program. Actions qualifying as a Non-Compliance are specific to the category of stakeholder (e.g., patient, pharmacy, prescriber, designee or wholesaler).

2.2. Missing Risk Management Authorization--RMA Non-Compliance

2.2.1. "Suspected Non-Compliance"--This means that the iPLEDGE Program sponsors have received information via the iPLEDGE Program system or otherwise indicating that pharmacy X may have dispensed a prescription for patient Y in the past month even though the iPLEDGE Program system indicates that no RMA exists for that patient in the past month. Therefore, pharmacy X is suspected of Non-Compliance.

2.2.2. "Confirmed Non-Compliance"--pharmacy X is investigated, and has been found to have dispensed isotretinoin without an RMA. Once confirmed, a pharmacy would incur a Warning-level deviation per the iPLEDGE Program Non-Compliance Action Policy.

2.3. Isotretinoin Products Manufacturing Group ("IPMG")

3. PURPOSE OF POLICY

As referenced in the FDA Approval Letter of October 22, 2010, one of the components of the isotretinoin REMS Program is "implementation of a plan to monitor compliance, address deviations, and institute appropriate corrective actions to improve minimization of drug exposure during pregnancy and compliance with elements to assure safe use under the iPLEDGE Program".

This iPLEDGE Program Non-Compliance Action Policy sets forth the principles by which Non-Compliance by iPLEDGE Program stakeholders will be evaluated.

4. NOTIFICATION OF RELATED PARTIES

The iPLEDGE Program stakeholders involved in reported Non-Compliance will be contacted as part of the related investigation. Decisions and outcomes of investigations will be communicated to stakeholders via notification letters**. The following section**

identifies the confirmed acts of Non-Compliance with the iPLEDGE Program requirements that will result in a deviation report being sent to the FDA.

5. FDA REPORTABLE DEVIATION EVENTS

The following acts of Non-Compliance with the iPLEDGE Program requirements, if confirmed through the iPLEDGE Program investigative procedures, will result in a deviation report being provided to the FDA:

5.1. FDA Reportable Events

5.1.1. Distribution or sale of any isotretinoin product to an unregistered and/or un-activated pharmacy or unregistered wholesaler

5.1.2. Sale/dispensing of any isotretinoin product by a pharmacy not registered and activated in the iPLEDGE Program

5.1.3. Transfer of any isotretinoin product in any manner (sale/borrow/loan) between pharmacies

5.1.4. Permanent Deactivations of stakeholders, according to the criteria contained in this Policy (see Section 5.4)

5.1.5. Any other confirmed Non-Compliance event that the IPMG reasonably believes should be reported to the FDA pursuant to relevant laws and/or regulatory guidance

5.2. Suspension

5.2.1. A "Suspension" is a temporary, 30-day inactivation of a stakeholder from the iPLEDGE Program, pending implementation of a Corrective Action Plan by the stakeholder.

5.2.1.1. A Corrective Action Plan for a stakeholder in Suspension must include the following:

5.2.1.1.1. A root cause analysis for each Non-Compliance event(s)

5.2.1.1.2. Remediation plan to prevent recurrence of each type of Non-Compliance

5.2.1.1.3. Implementation date for the remediation plan

5.2.1.2. If a Corrective Action Plan is not received from a pharmacy within 30 days of the effective date of the Suspension, on day 31 the pharmacy will move to Temporary Deactivation status.

5.2.1.2.1. If an *acceptable* Corrective Action Plan is not received from the pharmacy within 180 days from the effective date of the Suspension, that pharmacy will be permanently deactivated.

5.2.1.3. For a wholesaler in Suspension, if an *acceptable* Corrective Action Plan is not received within 90 days from the initial Warning-level deviation, that wholesaler will be permanently deactivated.

5.2.2. The Suspension is removed and full privileges are restored upon successful implementation of the Corrective Action Plan, which is confirmed

by the iPLEDGE Program sponsors after monitoring the corrective action process for the first 30 days after reinstatement.

5.2.3. A suspended pharmacy or wholesaler will be permitted to retain in-house any isotretinoin inventory acquired prior to the effective date of the Suspension.

5.2.3.1. A suspended pharmacy or wholesaler may not purchase additional isotretinoin until the Suspension is removed.

5.2.3.2. A suspended pharmacy may not dispense isotretinoin from its existing inventory.

5.2.3.3. A suspended wholesaler may not sell and/or distribute isotretinoin to a pharmacy from its existing inventory.

5.2.4. If a pharmacy or wholesaler in suspended status is part of a larger entity (e.g., chain pharmacy or multi-site wholesaler) the parent entity will be notified of the Non-Compliance activity and the effective date and expiration date of this status.

5.3. Temporary Deactivation

5.3.1. A "Temporary Deactivation" is a 90-day deactivation of a pharmacy from the iPLEDGE Program.

5.3.1.1. A Corrective Action Plan for a pharmacy that is temporarily deactivated must occur within the 90-day Deactivation period and must include the following:

5.3.1.1.1. A root cause analysis for each Non-Compliance event(s)

5.3.1.1.2. Remediation plan to prevent recurrence of each type of Non-Compliance

5.3.1.1.3. Date of resumed operations under the acceptable Corrective Action Plan (must be at least 90 days from the effective date of Temporary Deactivation)

5.3.1.1.4. Documentation that any isotretinoin product in inventory was returned to the appropriate wholesaler/manufacturer or an affidavit that there was no isotretinoin product in inventory at the time of Temporary Deactivation to be returned.

5.3.1.2. If a Corrective Action Plan is not received within 90 days of the effective date of the Temporary Deactivation, on day 91 the pharmacy will be permanently deactivated.

5.3.1.3. If an *acceptable* Corrective Action Plan is not received within 180 days from the effective date of the Temporary Deactivation, the pharmacy will be permanently deactivated.

5.3.2. The Temporary Deactivation is removed and full privileges are restored upon acceptance of the Corrective Action Plan. Once operations are resumed, the iPLEDGE Program sponsors will monitor the corrective action process for the first 30 days.

5.3.3. A pharmacy in a status of Temporary Deactivation will be required to return any isotretinoin inventory already acquired prior to the Temporary Deactivation, and may not purchase or acquire additional isotretinoin until the Temporary Deactivation is removed, and may not dispense, sell and/or distribute isotretinoin from such existing inventory during the Temporary Deactivation.

5.3.4. If the pharmacy in a status of Temporary Deactivation is part of a larger entity (e.g. Chain pharmacy) the parent entity will be notified of non-compliant activity and effective date and expiration date of this status.

5.4. Permanent Deactivation

5.4.1. A "Permanent Deactivation" is the stakeholder's permanent removal from participation in the iPLEDGE Program

5.4.1.1. Permanently deactivated prescribers and designees will no longer be able to interact with the iPLEDGE Program for any existing or future patients, effectively removing the capability to provide isotretinoin as a therapy option for the prescriber's patient population.

5.4.1.2. The prescriber's active iPLEDGE Program patient population will be contacted to inform them of the prescriber's Permanent Deactivation. Each active patient will be provided with instructions for transferring to another prescriber if desired.

5.4.1.3. Permanently deactivated prescribers and designees will be added to the program Watch List. Stakeholders on this list are monitored for any further iPLEDGE Program activity including patients in a permanently deactivated prescriber's population who attempt to fill prescriptions without transferring to a new prescriber and any attempt to re-register in the iPLEDGE Program under a different iPLEDGE Program prescriber ID.

5.4.2. Permanently deactivated pharmacies and wholesalers will be required to return all existing isotretinoin inventory as per the manufacturer's instructions.

5.4.2.1. If the permanently deactivated pharmacy or wholesaler is part of a larger entity (e.g., Chain pharmacy or multi-site wholesaler), the parent entity will be notified of Non-Compliance activity and the effective date of the Permanent Deactivation.

5.5. Case Reconsideration

A stakeholder may request that the result of any investigation into Non-Compliance activity be reconsidered. However, only verifiable, additional information or extenuating circumstances will be considered as grounds for reversal of actions taken in accordance with this Policy.

The initial decision will stand while requests for reconsideration are pending. After reconsideration, a letter will be sent to the stakeholder either confirming that the original decision has been affirmed, or informing the stakeholder that the additional information or circumstances have altered the action being taken.

If reconsideration results in no change to the original action taken, the iPLEDGE Program will consider the case closed, and no response to any continued stakeholder inquiries will be provided.

6. INFORMATION REQUIREMENTS

Once a non-compliant activity is reported and confirmed following the iPLEDGE Program investigative procedures, the stakeholder will be contacted and provided information regarding the Non-Compliance action or event. If the stakeholder is uncooperative or does not respond to repeated contact attempts, the iPLEDGE Program will provide a deadline for stakeholder response. If the stakeholder still does not respond, the iPLEDGE Program may take additional action, up to and including Permanent Deactivation.

7. INVESTIGATION AND ACTION IMPLEMENTATION

7.1. Investigation and Action for entities and prescribers not registered in the iPLEDGE Program

When acts of Non-Compliance with the iPLEDGE Program requirements are confirmed following iPLEDGE Program investigative procedures for entities and prescribers not registered in the iPLEDGE Program, the education, communication, reporting, and actions taken will be the same as for a registered stakeholder. This includes a possible permanent bar to future participation in the iPLEDGE Program.

7.2. Non-Compliance by designees – Impact to prescriber status

The registered prescriber is responsible for all information entered, and activities performed, in the iPLEDGE Program by the office staff designee(s). Confirmed actions of Non-Compliance by a designee will be accumulated at the designee level working on behalf of a particular prescriber, which may lead to designee Permanent Deactivation. A single designee Permanent Deactivation will not impact the status of the associated prescriber. However, if two designees of the same prescriber have been permanently deactivated within 1 year, then the prescriber will be permanently deactivated as well. If a designee is permanently deactivated, the related prescriber will be consulted during the investigation of Non-Compliance, and will be notified of Warnings or Permanent Deactivation of the designee.

7.3. Non-Compliance by delegate – Impact to prescriber status

Non-Compliance actions of a delegate acting as a prescriber may impact the status of the prescriber who created the delegate relationship depending upon the involvement of the prescriber who created the delegate relationship. A prescriber always remains individually responsible.

If a delegate of the prescriber commits an act of Non-Compliance, the prescriber who established the delegate relationship will be notified.

7.4. Non-Compliance by pharmacists – Impact to pharmacy status

Confirmed Non-Compliance by a pharmacist will be accumulated at the pharmacy level, which may lead to pharmacy Permanent Deactivation. Warnings accumulated by

different pharmacists at the same pharmacy, will result in Suspension or Permanent Deactivation of the pharmacy. For purposes of this policy, the definition of "Same Pharmacy" is an entity that maintains the same NCPDP number under the same ownership or chain affiliation.

8. CATEGORIES OF ACTION AND CORRESPONDING REMEDIAL MEASURES, INCLUDING DEACTIVATION FOR NON-COMPLIANCE FOR ALL STAKEHOLDERS

Each Non-Compliance activity is categorized based on the type of response required following a confirmed occurrence of a Non-Compliance activity. The classifications are as follows in Table 1:

TABLE 1

Category	Description/Comments	Corrective Action
A. Notice of Non-Compliance	An action that demonstrates a lack of understanding of program requirements. Notices of Non-Compliance are not accumulated for further action (with the exception of 9.A.1.v. and 9.B.1.iv.), but can be considered when assessing additional disciplinary action to be taken against a stakeholder when more serious Non-Compliance issues occur.	Provide re-education and reinforcement of program requirements.
B. Warning	Failure to comply with one or more fundamental elements of the iPLEDGE Program. A defined number of Warnings accumulated over a specified period (number and time may vary by stakeholder) as provided in Table 2, will result in review for Suspension or Permanent Deactivation. Stakeholder response to any Warning issued may justify further action, including Permanent Deactivation without accumulation of other Warnings. Failure to submit a Corrective Action Plan by a wholesaler within 30 days of the confirmed date of the Warning-level deviation will result in a 2nd Warning-level deviation, therefore, triggering a	Each Warning will document the non-compliant action, provide a history of other Warnings received by the same stakeholder, and remind them that continued Non-Compliance (similar or otherwise) could lead to reporting to the FDA and/or Permanent Deactivation from the program. Submission and acceptance of a Corrective Action Plan are required for wholesalers who have received a Warning-level deviation.

Category	Description/Comments	Corrective Action
	30-day Suspension beginning on day 31. Failure to submit an *acceptable* Corrective Action Plan by a wholesaler within 90 days of the initial Warning-level deviation will result in Permanent Deactivation on day 91.	Stakeholder must comply with corrective action required by IPMG.
C. Suspension	A defined number of Warnings accumulated over a specified period (number and time may vary by stakeholder) as provided in Table 2, will result in Suspension. Failure to submit a Corrective Action Plan by a suspended pharmacy within 30 days of the effective date of Suspension will result in Temporary Deactivation on day 31. Failure to submit an *acceptable* Corrective Action Plan by a suspended pharmacy within 180 days of the effective date of Suspension will result in Permanent Deactivation on day 181.	Stakeholder must fulfill with corrective action requirements of the IPMG. Submission and acceptance of a Corrective Action Plan are required prior to stakeholder reinstatement.
D. Temporary Deactivation	Failure to comply with the iPLEDGE Program leading to receipt of product by a non-qualified patient. Failure to submit a Corrective Action Plan by a temporarily deactivated pharmacy within 90 days of the effective date of Temporary Deactivation will result in Permanent Deactivation on day 91. Failure to submit an *acceptable* Corrective Action Plan by a temporarily deactivated pharmacy within 180 days of the effective date of Temporary Deactivation will result in Permanent Deactivation on day 181.	Stakeholder must fulfill with corrective action requirements of the IPMG. Submission and acceptance of a Corrective Action Plan are required prior to stakeholder reinstatement.
E. Permanent Deactivation	An action that falls into one of the following categories: • Stakeholder fails to implement Corrective Action or the iPLEDGE Program sponsors determine that no	No corrective action possible. Notice of Permanent Deactivation, including description of non-

Category	Description/Comments	Corrective Action
	future program compliance can be expected.	compliant activity to be sent to stakeholder and FDA.

9. NON-COMPLIANCE ACTIVITY BY EACH STAKEHOLDER AND CATEGORY

The table below assigns the typical Non-Compliance activities into the response categories of this policy. This table is intended to provide guidance for action to be taken for respective Non-Compliance actions or inactions which are determined after an investigation. However, the specific circumstances of any act of Non-Compliance can be considered by the iPLEDGE Program sponsors to modify the action taken.

TABLE 2

Stakeholder and Category	Non-Compliance activity
A. Prescriber	
1. Notice of Non-Compliance	**i.** A person other than the patient answers the comprehension questions on behalf of the patient **ii.** A person provides significant assistance to patient in responding to the comprehension questions such that the answers do not reflect the patient's understanding of program requirements and patient responsibilities **iii.** Trends within prescriber's patient population or prescriber activities that indicate a possible misunderstanding or incorrect interpretation of program requirements **iv.** Prescriber wrote prescription for more than a 30-day supply **v.** Prescriber used an iPLEDGE ID other than their own when accessing the iPLEDGE Program **Note:** Subsequent Non-Compliance in this category (9.A.1.v.) within a 6 month period will result in a Warning-level deviation (9.A.2.xi.) **vi.** Prescriber failed to report a pregnancy case
2. Warning	**i.** Failure to provide iPLEDGE Program counseling to the patient, but indicating in the iPLEDGE Program system that such counseling has taken place **ii.** Issuing a prescription to a patient outside of the iPLEDGE Program system: prescriber issued a prescription while in a status other than activated **iii.** Providing incorrect pregnancy test specimen collection dates which are subsequently corrected, and determined to not be an attempt to violate program requirements **Note**: Intentional falsification of specimen collection dates or the entry of non-existent pregnancy tests will result in Permanent Deactivation **iv.** Incorrect Classification of patient Type (e.g., Female of Reproductive

Stakeholder and Category	Non-Compliance activity
	Potential (FRP) vs. Female of Non-Reproductive Potential (FNRP)), confirmed for a specific patient which results in possible fetal exposure **v.** Prescriber knew patient was obtaining isotretinoin outside the iPLEDGE Program or instructed the patient to obtain isotretinoin outside the iPLEDGE Program **vi.** Prescriber did not use a CLIA (Clinical Laboratory Improvement Amendments)-certified laboratory for qualifying pregnancy tests **vii.** Intentionally left blank—previously used subsection discontinued **viii.** Prescriber entered incorrect pregnancy test results which are subsequently corrected, and determined to not be an attempt to violate program requirements **ix.** Issuing a prescription to a patient outside of the iPLEDGE Program system: prescriber failed to register patient **x.** Prescriber knowingly allowed another stakeholder to access the iPLEDGE Program system using their iPLEDGE ID **xi.** Subsequent to receiving a Notice of Non-Compliance level deviation 9.A.1.v., prescriber used an iPLEDGE ID other than their own when accessing the iPLEDGE Program **Note:** Warning-level deviation will be issued if the subsequent Non-Compliance occurred within a 6 month period **xii.** Prescriber's designee performed activities in the iPLEDGE Program system that indicate lack of training and/or supervision (at the sponsors' discretion, repeated acts of Non-Compliance will result in Permanent Deactivation) **Warning Accumulation** • 2 Warnings in 60 days = Permanent Deactivation
3. Temporary Deactivation	**i.** Not applicable
4. Permanent Deactivation	**i.** Prescriber dispensed medication directly to patient, regardless of patient status **ii.** Intentional falsification of pregnancy test results (including incorrect sample collection date) **iii.** 2 Warnings in a 60-day period **iv.** Permanent Deactivation of two designees for the same prescriber within a rolling 12-month period **v.** Intentional falsification of patient classification type determined to be an attempt to violate program requirements **vi.** Intentional falsification of contraception methods. Prescriber instructed patient to enter different contraception methods from what she was using in order to match the prescriber's contraception choices thereby allowing her to complete her contraception comprehension exam and obtain drug **vii.** Intentional misuse of the Serious Medical Reasons Exemption process **viii.** Repeated acts of Non-Compliance where prescriber's designee(s) performed activities in the iPLEDGE Program system that indicate systemic

Stakeholder and Category	Non-Compliance activity
	lack of training and/or supervision **ix.** Prescriber fails to implement Corrective Action or the iPLEDGE Program sponsors determine that no future program compliance can be expected (e.g., refusal to provide requested documentation for an investigation)
B. Designee	
1. Notice of Non-Compliance	**i.** A person other than the patient answers the comprehension questions on behalf of the patient **ii.** A person provides significant assistance to the patient in responding to the comprehension questions such that the answers do not reflect the patient's understanding of program requirements and patient responsibilities **iii.** Trends within prescriber's patient population or prescriber activities that indicate a possible misunderstanding or incorrect interpretation of program requirements **iv.** Designee used an iPLEDGE ID other than their own when accessing the iPLEDGE Program **Note:** Subsequent Non-Compliance in this category (9.B.1.iv.) within a 6 month period will result in a Warning-level deviation (9.B.2.xi.)
2. Warning	**i.** Failure to provide iPLEDGE Program counseling to the patient, but indicating in the iPLEDGE Program system that such counseling has taken place **ii.** Issuing a prescription to a patient outside of the iPLEDGE Program system: designee issued a prescription while in a status other than activated **iii.** Providing incorrect pregnancy test specimen collection dates which are subsequently corrected, and determined to not be an attempt to violate program requirements **Note:** Intentional falsification of specimen collection dates or the entry of non-existent pregnancy tests will result in Permanent Deactivation **iv.** Incorrect Classification of patient Type (e.g., Female of Reproductive Potential (FRP) vs. Female of Non-Reproductive Potential (FNRP)), confirmed for a specific patient which results in possible fetal exposure **v.** Designee did not use a CLIA (Clinical Laboratory Improvement Amendments)-certified laboratory for qualifying pregnancy tests **vi.** Intentionally left blank—previously used subsection discontinued **vii.** Designee entered incorrect pregnancy test results which are subsequently corrected, and determined to not be an attempt to violate program requirements **viii.** Designee knew patient was obtaining isotretinoin outside the iPLEDGE Program or instructed the patient to obtain isotretinoin outside the iPLEDGE Program **ix.** Issuing a prescription to a patient outside of the iPLEDGE Program system: designee failed to register patient **x.** Designee knowingly allowed another stakeholder to access the iPLEDGE

Stakeholder and Category	Non-Compliance activity
	Program system using their iPLEDGE ID **xi.** Subsequent to receiving a Notice of Non-Compliance level deviation 9.B.1.iv. designee used an iPLEDGE ID other than their own when accessing the iPLEDGE Program **Note:** Warning-level deviation will be issued if the subsequent Non-Compliance occurred within a 6 month period **xii.** Designee registered as a prescriber **xiii.** Designee self-registered as a patient in the iPLEDGE Program **<u>Warning Accumulation</u>** • 2 Warnings in 60 days = Permanent Deactivation
3. Temporary Deactivation	**i.** Not applicable
4. Permanent Deactivation	**i.** Designee dispensed medication directly to patient, regardless of patient status **ii.** Intentional falsification of pregnancy test results (including incorrect sample collection date) **iii.** 2 Warnings in a 60-day period **iv.** Intentional falsification of patient classification type determined to be an attempt to violate program requirements **v.** Intentional falsification of contraception methods. Designee instructed patient to enter different contraception methods from what she was using in order to match the designee's contraception choices thereby allowing her to complete her contraception comprehension and obtain drug. **vi.** Designee fails to implement Corrective Action or the iPLEDGE Program sponsors determine that no future program compliance can be expected (e.g., refusal to provide requested documentation for an investigation) **vii.** Designee self-registered as a patient in the iPLEDGE Program and obtained isotretinoin without prescriber's knowledge
C. Pharmacy	**(note: a single store location is considered a pharmacy)**
1. Notice of Non-Compliance	**i.** Did not train personnel, no evidence of training records **ii.** Sold or otherwise transferred drug to/from another pharmacy **iii.** Did not document RMA Number **iv.** Did not document "Do Not Dispense to Patient After" date **v.** Pharmacy broke a blister pack **vi.** Pharmacy did not dispense medication and failed to reverse the RMA in the iPLEDGE Program system
2. Warning	**i.** Did not check in the iPLEDGE Program system, dispensed medication without obtaining an RMA **ii.** Dispensed multiple prescriptions without obtaining new authorization for each dose **iii.** Dispensed prescription after prescription window expired **iv.** Dispensed more than a 30-day supply **v.** Obtained drug from unauthorized source (e.g., Internet, non-activated wholesaler)

Stakeholder and Category	Non-Compliance activity
	vi. Dispensed prescription while in a status other than activated **vii.** Pharmacy knowingly used an iPLEDGE ID other than their own when accessing the iPLEDGE Program **viii.** Pharmacy knowingly allowed another stakeholder to access the iPLEDGE Program system using their iPLEDGE ID **<u>Warning Accumulation and Suspension</u>** • 2 Warnings in 60 days will result in Suspension from the iPLEDGE Program for 30 days • 1 Warning while in a Suspended status will result in Permanent Deactivation • 1 Warning while in a Temporary Deactivation status will result in Permanent Deactivation • 2 Suspensions in 6 months will result in Permanent Deactivation
3. Temporary Deactivation	**i.** Checked the iPLEDGE Program system, prescription denied, but dispensed prescription without an RMA **ii.** A Corrective Action Plan was not received within 30 days of the effective date of Suspension
4. Permanent Deactivation	**i.** Refusal to return undistributed/unsold drug after being placed in a Temporary Deactivation status or after not choosing to reactivate, or as otherwise requested **ii.** 2 Suspensions in a 6 month period **iii.** 1 Warning while in a Suspended status **iv.** A Corrective Action Plan was not received within 90 days of the effective date of the Temporary Deactivation **v.** An acceptable Corrective Action Plan was not received within 180 days of the effective date of the Temporary Deactivation **vi.** 1 Warning while in a Temporary Deactivation status **vii.** Pharmacy fails to implement Corrective Action or the iPLEDGE Program sponsors determine that no future program compliance can be expected (e.g., refusal to provide requested documentation for an investigation)
D. Wholesaler	**(note: a single site distributing isotretinoin is considered a wholesaler)**
1. Notice of Non-Compliance	**i.** Not applicable
2. Warning	Note: A Corrective Action Plan is required for all confirmed wholesaler Non-Compliance Warning-level deviations **i.** Sold or shipped drug to a pharmacy not activated in the iPLEDGE Program at time of shipment **ii.** Sold or shipped drug to a wholesaler not registered in the iPLEDGE Program at time of shipment **iii.** Sold or shipped drug to a wholesaler without written consent from the manufacturer **iv.** Sold or shipped drug directly to an entity other than a pharmacy or wholesaler (e.g., physician or patient)

Stakeholder and Category	Non-Compliance activity
	Note: A second Warning in this category (9.D.2.iv.) within 6 months of the approval of the Corrective Action Plan will result in Permanent Deactivation **v.** A Corrective Action Plan was not received within 30 days of the confirmed date of the Warning-level deviation **Note:** This triggers a 2nd Warning-level deviation resulting in a 30-day Suspension beginning on day 31 **vi.** Wholesaler package adulteration (re-packaging of product from original state) **Warning Accumulation and Suspension** • 2 Warnings in 60 days will result in Suspension from the iPLEDGE Program for 30 days • 1 Warning while in Suspension will result in Permanent Deactivation • 2 Suspensions in 6 months will result in Permanent Deactivation **Warning Accumulation for 9.D.2.iv.** • Sold or shipped drug directly to an entity other than a pharmacy or wholesaler (e.g., physician or patient) • 2 Warnings in 6 months will result in Permanent Deactivation
3. Temporary Deactivation	**i.** Not applicable
4. Permanent Deactivation	**i.** Wholesaler not registered in the iPLEDGE Program, and distributing drug **ii.** Distribution of non-FDA approved isotretinoin products **iii.** Refusal to return undistributed/unsold drug to the manufacturer after choosing not to re-register, or as otherwise requested **iv.** 2 Suspensions in a 6 month period **v.** 1 Warning while in a Suspended status **vi.** 2 Warnings relative to 9.D.2.iv. in a 6 month period **vii.** An acceptable Corrective Action Plan was not received within 90 days from the confirmed date of the initial Warning-level deviation **viii.** Wholesaler fails to implement Corrective Action or the iPLEDGE Program sponsors determine that no future program compliance can be expected (e.g., refusal to provide requested documentation for an investigation)
E. Patient	
1. Notice of Non-Compliance	**i.** Obtained isotretinoin from a source outside of the iPLEDGE Program (includes Internet). This will also generate a letter to the prescriber with a strong recommendation that this patient be re-evaluated regarding adherence to the iPLEDGE Program requirements, and possible termination of isotretinoin therapy. **ii.** Patient shared medication with another person. This will also generate a letter to the prescriber with a strong recommendation that this patient be re-evaluated regarding adherence to the iPLEDGE Program requirements, and possible termination of isotretinoin therapy. **iii.** Patient did not follow the labeling requirements for contraception. This

Stakeholder and Category	Non-Compliance activity
	will also generate a letter to the prescriber with a strong recommendation that this patient be re-evaluated regarding adherence to the iPLEDGE Program requirements, and possible termination of isotretinoin therapy. **iv.** Any other Non-Compliance activity related to patient behavior. This will also generate a letter to the prescriber with a strong recommendation that this patient be re-evaluated regarding adherence to the iPLEDGE Program requirements, and possible termination of isotretinoin therapy.
2. Warning	**i.** Not applicable
3. Temporary Deactivation	**i.** Not applicable
4. Permanent Deactivation	**i.** None

10. INVESTIGATIVE PROCESS FOR DISPENSING WITHOUT AN RMA (REFER TO SECTION 9.C.2.): DID NOT CHECK IN THE IPLEDGE PROGRAM SYSTEM, DISPENSED MEDICATION WITHOUT OBTAINING AN RMA)

10.1. Methodology

Pharmacies that meet the following criteria will be investigated:

10.1.1. Pharmacies identified in more than one month, in a four-month time period as suspected of dispensing without an RMA.

10.1.2. Pharmacies identified three or more times by different patients in a single month as having dispensed without an RMA.

It is important to note that all cases of suspected Non-Compliance are tracked.

10.2. Investigative Process

10.2.1. Collect data on pharmacies suspected of dispensing without an RMA.

10.2.2. The iPLEDGE Program team reviews suspected non-compliant pharmacies and determines if they have deliverable addresses and National Council for Prescription Drug Programs (NCPDP) numbers in order to begin communications.

10.2.3. Letters are sent to each suspected retail pharmacy store detailing the Non-Compliance. As appropriate, emails will also be sent to pharmacy chain organization headquarters.

10.2.4. Retail pharmacies will then have 5 days to investigate the suspected Non-Compliance and provide appropriate patient dispensation records.

10.2.5. If pharmacies respond within 5 days with dispensation records proving RMAs they are released from remediation. If after 5 days they have not

provided dispensation records, they are granted one additional day to provide dispensation records.

10.2.6. If after the additional day pharmacies cannot show proof of appropriate RMAs, a Warning-level deviation letter is sent.

10.2.7. A 7-day re-education period for pharmacy staff begins on the day the pharmacy receives the Warning-level deviation letter, during which time the staff should be re-educated on policies and procedures to ensure compliance to the iPLEDGE Program.

10.2.8. At the beginning of the 7-day re-education period the pharmacy has a grace period extending through the end of that calendar month, after which they are subject to additional infractions for dispensing without an RMA, as noted above.

Note: Any pharmacy that receives a Warning-level deviation for dispensing without an RMA will be afforded a 7-day re-education period starting the day they receive the letter, followed by a grace period extending through the end of that calendar month. After this grace period, they are subject to additional infractions for dispensing without an RMA.

11. MONITORING AND INVESTIGATION FOR PATIENT MISCLASSIFICATION (REFER TO SECTIONS 9.A.4.V. AND 9.B.4.IV.): INTENTIONAL FALSIFICATION OF PATIENT CLASSIFICATION TYPE DETERMINED TO BE AN ATTEMPT TO VIOLATE PROGRAM REQUIREMENTS

Patients in the iPLEDGE Program **must** be classified **correctly** into one of three categories: Female of Reproductive Potential (FRP), Female of Non-Reproductive Potential (FNRP), or male. Prescribers and designees who have a significantly higher percentage of a particular patient category (compared to the program average) or other anomalies may be investigated.

The iPLEDGE Program actively monitors patient classification data. Prescribers/designees may be investigated based upon these data.

Version	Effective Date	Posted Date	Description
1.0	7/16/2012	7/15/2012	Original version of NCAP
Addendum	1/1/2013	N/A	Updated to include information regarding the process for investigating pharmacies that are suspected of dispensing isotretinoin without obtaining an RMA (section 10)
2.0	3/1/2013	3/6/2013	Combined original NCAP and Addendum; reformatted to easily reference Non-Compliance deviations
3.0	4/30/2013	4/30/2013	Editorial changes for consistency; clarification on the grace period for pharmacies confirmed to have dispensed without an RMA (section 10)
4.0	9/1/2014	8/20/2014	Created consistency between Table 1 and Table 2; Updated Table 2 to include additional Non-Compliance deviations and clarify Non-Compliance deviations for prescriber, designee, pharmacy, wholesaler, and patient; Capitalized defined improper nouns; changed undefined improper nouns to lower case.
5.0	3/9/2015	2/26/2015	Updated Table 2 to include additional Non-Compliance activities including SMRE process; updated terminology to replace FCBP and FnCBP with FRP and FNRP, respectively; added wholesaler Corrective Action Plan requirements.
6.0	12/31/2015	12/21/2015	Updated Table 2 to include additional Non-Compliance activities including: wholesaler adulteration (re-packaging); included information regarding the process for monitoring and investigating stakeholders that are suspected of intentional falsification of patient classification type (section 11)
7.0	11/1/2016	10/24/2016	Updated Table 2 to include additional Non-Compliance activities including: prescriber Permanent Deactivation for designee(s) lack of training and/or supervision; stakeholder Permanent Deactivation if sponsors determine that no future program compliance can be expected
8.0	5/15/2017	5/1/2017	Updated Section 5.1 to remove 15-day reference; Updated Table 2 to include additional designee Non-Compliance activities including: Designee self-registered as a patient in the iPLEDGE Program and Designee self-registered as a patient in the iPLEDGE Program and obtained isotretinoin without prescriber's knowledge