iPLEDGE NON-COMPLIANCE ACTION POLICY

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1. **OVERVIEW**

The Isotretinoin Risk Management Program (iPLEDGE) 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 iPLEDGE.

2. **DEFINITION OF NON-COMPLIANCE**

For the purposes of the iPLEDGE Program, the definition of non-compliance is a stakeholder (Patient, Pharmacy, Prescriber, Designee or Wholesaler) who does not meet the requirements of the iPLEDGE program. Actions qualifying as non-compliant are specific to the category of stakeholder (e.g. Patient, Pharmacy, Prescriber, Designee or Wholesaler).

3. **PURPOSE OF POLICY**

As referenced in the FDA Approval Letter of October 22, 2010, one of the components for the isotretinoin Risk Evaluation and Mitigation Strategy (REMS) 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 restrictions for safe use under the iPLEDGE program”.

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

4. **NOTIFICATION OF RELATED PARTIES**

The iPLEDGE 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 confirmed acts of non-compliance with the iPLEDGE program requirements, which have been verified following the iPLEDGE investigative procedures, will result in a deviation report to the FDA:

- 15-day reportable events include:
  - Distribution or sale of any isotretinoin product to an unregistered and/or un-activated pharmacy or unregistered wholesaler
  - Sale/dispensing of any isotretinoin product by a pharmacy not registered and activated in iPLEDGE
  - Transfer of any isotretinoin product in any manner (Sale/Borrow/Loan) between pharmacies
- Deactivations of stakeholders, according to the criteria contained in this Policy
• Any confirmed non-compliant event that the IPMG deems reportable to the FDA

5. **POLICY COMPONENTS**

5.1 **Suspension**

- A suspension is a temporary, 30-day inactivation of a stakeholder from the iPLEDGE risk management program, pending implementation of a corrective action plan by the stakeholder.
  - A corrective action plan for a stakeholder in suspension must include the following:
    - A root cause analysis for each non-compliant event(s)
    - Remediation plan to prevent recurrence of each type of non-compliance
    - Implementation date for the remediation plan
  - 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 a Temporary Deactivation status.
  - If an acceptable corrective action plan is not received within 180 days from the effective date of the suspension, the stakeholder will be permanently deactivated.

- The suspension is removed and full privileges are restored upon successful implementation of the corrective action plan, which is verified by the project sponsors after monitoring the corrective action plan for the first 30 days after reinstatement.

- A suspended Pharmacy or Wholesaler will be permitted to retain in-house any isotretinoin inventory acquired prior to the effective date of the suspension. A suspended Pharmacy or Wholesaler may not purchase additional isotretinoin until the suspension is removed. A suspended Pharmacy may not dispense isotretinoin from its existing inventory. A suspended Wholesaler may not sell and/or distribute isotretinoin from its existing inventory.

- If a Pharmacy or Wholesaler in a 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-compliant activity and the effective date and expiration date of this status.

5.2 **Temporary Deactivation**

- A temporary deactivation is a temporary, 90-day inactivation of a pharmacy from the iPLEDGE risk management program, pending implementation of a corrective action plan by the stakeholder.
  - A corrective action plan for a stakeholder who is temporarily deactivated must include the following:
    - A root cause analysis for each non-compliant event(s)
    - Remediation plan to prevent recurrence of each type of non-compliance
    - Implementation date for the remediation plan
    - 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.
If a corrective action plan is not received within 90 days of the effective date of the Temporary Deactivation, on day 91 the stakeholder will be permanently deactivated.

If an acceptable corrective action plan is not received within 180 days from the effective date of the temporary deactivation, the stakeholder will be permanently deactivated.

- The temporary deactivation is removed and full privileges are restored upon successful implementation of the corrective action plan, which is verified by the project sponsors after monitoring the corrective action plan for the first 30 days after reinstatement.
- 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.
- 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.

5.3 Permanent Deactivation

A permanent deactivation is the stakeholder’s permanent removal from participation in iPLEDGE.

Deactivated Prescribers and Designees will no longer be able to interact with iPLEDGE for any existing or future patients, effectively removing the capability to provide isotretinoin as a therapy option for the Prescriber’s patient population.

- The Prescriber’s active iPLEDGE patient population will be contacted to inform them of the prescriber’s deactivation. Each active patient will be provided with instructions for transferring to another prescriber if desired.

- Deactivated Prescribers and Designees will be added to the program Watch List. Stakeholders on this list are monitored for any further iPLEDGE activity including patients in a deactivated Prescribers population who attempt to fill prescriptions without transferring to a new prescriber, and any attempt to re-register in iPLEDGE under a different iPLEDGE Prescriber ID.

Permanently deactivated Pharmacies and Wholesalers will be required to return all existing isotretinoin inventory as per the manufacturer’s instructions.

- 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-compliant activity and the effective date of the permanent deactivation.
5.4 Case Reconsideration
A stakeholder may request that the result of any investigation into non-complaint 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 during any such reconsideration. After reconsideration, a letter will be sent to the stakeholder either confirming that the original decision remains, or informing the stakeholder that the additional information or circumstances have altered the course of action being taken.

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

6. INFORMATION REQUIREMENTS
Once a non-compliant activity is reported and verified following the iPLEDGE investigative procedures, the stakeholder will be contacted and provided information regarding the non-compliant action or event. If the stakeholder does not respond to the notification of non-compliance within 30 days, the iPLEDGE program will consider the stakeholder to have agreed and consented to the findings and subsequent action taken.

7. INVESTIGATION AND ACTION IMPLEMENTATION
7.1 Investigation and Action for entities and prescribers not registered in iPLEDGE
When acts of non-compliance with the iPLEDGE program requirements are verified following iPLEDGE investigative procedures for entities and prescribers not registered in iPLEDGE, 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 iPLEDGE.

7.2 Non-compliance by Designees – Impact to Prescriber status
Verified 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 deactivation. A single designee deactivation will not impact the status of the associated Prescriber. However, if two designees of the same prescriber have been deactivated within 1 year, then the prescriber will be deactivated as well. If a designee is deactivated, the related prescriber will be consulted during the investigation of non-compliance, and will be notified of warnings or deactivation of the designee.

7.3 Non-compliance by Delegate – Impact to Prescriber status
Non-compliant 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

Verified non-compliance by a pharmacist will be accumulated at the pharmacy level, which may lead to pharmacy 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-compliant activity is categorized based on the type of response required following a verified occurrence of a non-compliant activity. The classifications are as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Description/Comments</th>
<th>Corrective Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notice of Non-Compliance</td>
<td>An action that demonstrates a lack of understanding of program requirements. Notices of non-Compliance are not accumulated for further action, but can be considered when assessing additional disciplinary action to be taken against a stakeholder when more serious non-compliance issues occur</td>
<td>Provide re-education and reinforcement of program requirements.</td>
</tr>
<tr>
<td>Warning</td>
<td>Failure to comply with one or more fundamental elements of the iPLEDGE risk management program, not to include failure leading to receipt of product by a non-qualified patient.</td>
<td>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. Stakeholder must comply with corrective action required by IPMG.</td>
</tr>
<tr>
<td>Category</td>
<td>Description/Comments</td>
<td>Corrective Action</td>
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<tr>
<td>Suspension</td>
<td>A defined number of Warnings accumulated over a specified period (number and time may vary by stakeholder) as provided in the table below, will result suspension.</td>
<td>Stakeholder must fulfill with corrective action requirements of the IPMG. Submission, acceptance and effectiveness of a corrective action plan is required prior to stakeholder reinstatement.</td>
</tr>
<tr>
<td>Temporary Deactivation</td>
<td>Failure to comply with the iPLEDGE risk management program leading to receipt of product by a non-qualified patient.</td>
<td>Stakeholder must fulfill with corrective action requirements of the IPMG. Submission, acceptance and effectiveness of a corrective action plan is required prior to stakeholder reinstatement.</td>
</tr>
<tr>
<td>Permanent Deactivation</td>
<td>An action that falls into one of the following categories: • Stakeholder fails to implement corrective action or no future program compliance can be expected.</td>
<td>No corrective action possible. Notice of Permanent Deactivation, including description of non-compliant activity to be sent to stakeholder and FDA.</td>
</tr>
</tbody>
</table>

9. **NON-COMPLIANCE ACTIVITY BY EACH STAKEHOLDER AND CATEGORY**

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

<table>
<thead>
<tr>
<th>Stakeholder and Category</th>
<th>Non-compliance activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber</td>
<td></td>
</tr>
<tr>
<td>Notice of Non-compliance</td>
<td>• A person other than the patient answers the Comprehension Questions on behalf of the patient. • A person provides significant assistance to patient in responding to the Comprehension Questions such that the answers do not reflect the patient’s</td>
</tr>
<tr>
<td>Stakeholder and Category</td>
<td>Non-compliance activity</td>
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</tr>
<tr>
<td></td>
<td>understanding of program requirements and patient responsibilities.</td>
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<tr>
<td></td>
<td>• Trends within prescriber’s patient population or prescriber activities that indicate a possible misunderstanding or incorrect interpretation of program requirements.</td>
</tr>
<tr>
<td><strong>Warning</strong></td>
<td>• Failure to provide iPLEDGE counseling to the patient, but indicating in iPLEDGE that such counseling has taken place.</td>
</tr>
<tr>
<td></td>
<td>• Issuing a prescription to a patient outside of the iPLEDGE System.</td>
</tr>
<tr>
<td></td>
<td>• Providing incorrect pregnancy test specimen collection dates which are subsequently corrected, and determined to not be an attempt to violate program requirements.</td>
</tr>
<tr>
<td></td>
<td><strong>Note</strong>: Intentional falsification of specimen collection dates or the entry of non-existent pregnancy tests will result in Permanent Deactivation.</td>
</tr>
<tr>
<td></td>
<td>• Incorrect Classification of Patient Type (e.g. FCBP vs. FnCBP), verified for a specific patient population which results in possible fetal exposure.</td>
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<tr>
<td></td>
<td>• Prescriber knew patient was obtaining isotretinoin outside the iPLEDGE program or instructed the patient to obtain isotretinoin outside the iPLEDGE program.</td>
</tr>
<tr>
<td></td>
<td>• Prescriber did not use a CLIA-certified laboratory for qualifying pregnancy tests.</td>
</tr>
<tr>
<td></td>
<td>• Prescriber instructed patient to enter different contraception methods from what she was using in order to access her contraception comprehension exam and obtain drug.</td>
</tr>
<tr>
<td></td>
<td><strong>Note</strong>: Intentional falsification of contraception methods will result in Permanent Deactivation if the action put the patient at risk.</td>
</tr>
<tr>
<td><strong>Warning Accumulation</strong></td>
<td>2 Warnings in 60 days = Permanent Deactivation</td>
</tr>
<tr>
<td><strong>Temporary Deactivation</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Permanent Deactivation</strong></td>
<td>• Prescriber dispensed medication directly to patient, regardless of patient status.</td>
</tr>
<tr>
<td></td>
<td>• Intentional falsification of pregnancy test results (including incorrect date of sample collection date).</td>
</tr>
<tr>
<td></td>
<td>• 2 Warnings in a 60 day period.</td>
</tr>
<tr>
<td></td>
<td>• Deactivation of two designees for the same prescriber within a 1 year period.</td>
</tr>
<tr>
<td><strong>Designee</strong></td>
<td>• A person other than the patient answers the Comprehension Questions on behalf of the patient.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• Trends within prescriber’s patient population or prescriber activities that indicate a possible misunderstanding or incorrect interpretation of program requirements.</td>
</tr>
<tr>
<td>Stakeholder and Category</td>
<td>Non-compliance activity</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------</td>
</tr>
</tbody>
</table>
| **Warning**              | • Failure to provide iPLEDGE counseling to the patient, but indicating in iPLEDGE that such counseling has taken place.  
• Issuing a prescription to a patient outside of the iPLEDGE System.  
• 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.  
• Incorrect Classification of Patient Type (e.g. FCBP vs. FnCBP), verified for a specific patient population which results in possible fetal exposure.  
• Designee did not use a CLIA-certified laboratory for qualifying pregnancy tests.  
• Designee instructed patient to enter different contraception methods from what she was using in order to access her contraception comprehension exam and obtain drug.  
  **Note:** Intentional falsification of contraception methods will result in Permanent Deactivation if the action put the patient at risk. |
| **Temporary Deactivation** | None |
| **Permanent Deactivation** | • Designee dispensed medication directly to Patient, regardless of patient status.  
• Intentional falsification of pregnancy test results (including incorrect date of sample collection date).  
• 2 Warnings in a 60 day period. |
| **Pharmacy** | (Note: a single store location is considered a pharmacy) |
| **Notice of Non-compliance** | • Did not train personnel, no evidence of training records  
• Sold or otherwise transferred drug to/from another pharmacy.  
• Did not write RMA Number on prescription.  
• Did not write “Do Not Dispense to Patient After” date on Bag Sticker  
• Pharmacy broke a blister pack. |
| **Warning** | • Did not check in iPLEDGE, dispensed medication  
• Dispensed multiple prescriptions without obtaining new authorization for each dose  
• Dispensed prescription after prescription window expired  
• Dispensed more than a 30-day supply  
• Obtained drug from unauthorized source (e.g. Internet, non-activated wholesaler)  
• Dispensed prescription while in a status other than activated. |
<table>
<thead>
<tr>
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</tr>
</thead>
</table>
| **Warning Accumulation and Suspension** | 2 Warnings in 60 days will result in Suspension from iPLEDGE for 30 days  
1 Warning while in Suspension will result in Permanent Deactivation  
2 Suspensions in 6 months will result in Permanent Deactivation |
| Temporary Deactivation | • Checked iPLEDGE, prescription denied, but dispensed prescription |
| Permanent Deactivation | • Refusal to return undistributed/unsold drug after not choosing to reactivate, or as otherwise requested.  
• 2 Suspensions in a 6 month period  
• 1 Warning while in a Suspended status |
| **Wholesaler** (note: a single site distributing isotretinoin is considered a wholesaler) | |
| Notice of Non-compliance | None |
| Warning | • Sold or shipped drug to a pharmacy not activated in iPLEDGE at time of shipment.  
• Sold or shipped drug to a wholesaler not activated in iPLEDGE at time of shipment.  
• Sold or shipped drug to a wholesaler without written consent from the manufacturer.  
**Warning Accumulation and Suspension**  
2 Warnings in 60 days will result in Suspension from iPLEDGE for 30 days  
1 Warning while in Suspension will result in Permanent Deactivation  
2 Suspensions in 6 months will result in Permanent Deactivation |
| Temporary Deactivation | • None |
| Permanent Deactivation | • Wholesaler not registered in iPLEDGE, and distributing drug.  
• Distribution of non-FDA approved isotretinoin products.  
• Refusal to return undistributed/unsold drug to the manufacturer after choosing not to re-register, or as otherwise requested.  
• 2 suspensions in a 6 month period.  
• 1 Warning while in a Suspended status |
| **Patient** | |
| Notice of Non-compliance | • Obtained isotretinoin from a source outside of the iPLEDGE program (includes Internet)  
• 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 iPLEDGE requirements, and possible termination of isotretinoin therapy.  
• Patient did not follow the labeling requirements for contraception.  
• Any other non-compliant activity related to patient behavior |
<p>| Warning | • None |</p>
<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Temporary Deactivation</td>
<td>• None</td>
</tr>
<tr>
<td>Permanent Deactivation</td>
<td>• None</td>
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</tbody>
</table>