

**POLICY AND PROCEDURES**

**OFFICE OF THE CENTER DIRECTOR**

**Tracking of Significant Safety issues in Marketed Drugs --  
Use of the DARRTS Tracked Safety Issues**

**Table of Contents**

**PURPOSE .....1**  
**BACKGROUND .....1**  
**POLICY .....2**  
**RESPONSIBILITIES AND PROCEDURES .....2**  
**REFERENCES.....4**  
**DEFINITIONS .....4**  
**EFFECTIVE DATE.....6**  
**CHANGE CONTROL TABLE.....7**

**PURPOSE**

This MAPP describes the policies and procedures for all Office of New Drug (OND) and Office of Surveillance and Epidemiology (OSE) staff when tracking significant safety issues related to marketed prescription and over-the-counter drugs<sup>1</sup> in a Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) Tracked Safety Issue (TSI).

Specifically, this MAPP outlines:

- The role of OND in tracking significant postmarket safety issues
- The role of OSE in tracking significant postmarket safety issues
- For what issues a DARRTS TSI and workplan should be created

This MAPP focuses primarily on significant postmarket safety issues being evaluated by OSE and OND. However, other Center for Drug Evaluation and Research (CDER) Offices may be involved. The processes described in this MAPP are intended to ensure that significant postmarket safety issues are tracked consistently.

**BACKGROUND**

For marketed drugs, both OND and OSE receive and analyze safety information. Establishment of policies and procedures to delineate responsibilities between OND and OSE regarding the tracking of significant postmarket safety issues is essential.

<sup>1</sup> “Drugs” refers to drug and therapeutic biologic products regulated by CDER.

---

**POLICY**

- Significant postmarket safety issues will be tracked to ensure timely evaluation and management with the same accountability as that of premarket efficacy, safety, and quality issues.
- The DDS and SRPM in each OND review division, Team Leaders in the OSE divisions, and the OSE Safety Regulatory Project Management staff will ensure that significant postmarket safety issues are tracked as described in this MAPP.
- A DARRTS TSI may be shared by two or more OND divisions when they will be managing a significant postmarket safety issue in the same way. When a significant postmarket safety issue common to two or more OND divisions is being managed differently in the involved divisions (e.g., because the indications dictate different regulatory responses), each division should create its own DARRTS TSI for the issue.
- A multidisciplinary Safety Issue Team (SIT) will be established when a significant safety issue is identified. Generally, the SIT uses a safety issue workplan to manage the evaluation of the safety issue for which the DARRTS TSI has been created.

---

**RESPONSIBILITIES AND PROCEDURES**

- **Creation of a DARRTS TSI by the OND SRPM**

The OND SRPM, with concurrence from the OND DDS, creates a DARRTS TSI for tracked postmarket safety issues that have been identified by OND staff or by staff in other offices (excluding OSE).

- The OND SRPM notifies the OSE SRPM assigned to the OND division that a new DARRTS TSI has been created.
- For a significant safety issue that was identified during the evaluation of an NDA or BLA that will require a REMS or postmarketing requirement (PMR) for an observational epidemiological study or clinical trial, the DARRTS TSI should be created at the time of drug approval. The approval letter that describes the REMS and/or PMR(s) should be checked into the DARRTS TSI to provide background information. However, it is not necessary to check in all the supporting reviews and correspondence that led to the REMS and/or PMRs.
- For a significant safety issue that is identified in the postmarketing period, the DARRTS TSI should be created at the time that the determination is made that the safety issue should be tracked, and prior to the SIT planning meeting.

**Creation of a DARRTS TSI by the OSE SRPM for a Tracked Safety Issue**

- The OSE SRPM creates a DARRTS TSI for an OSE-identified tracked safety issue. OSE-identified tracked safety issues are communicated by OSE staff to the OSE SRPM as specified in OSE procedures.

- 
- The OSE SRPM notifies the relevant OND SRPM(s) that a new DARRTS TSI has been created.
  - When an OSE-identified tracked safety issue does not involve OND because it involves only a generic drug (e.g., a medication error related to the name and/or packaging of an ANDA), the OSE SRPM will create the DARRTS TSI. The OSE SRPM will notify the Office of Generic Drugs (OGD) contact that a DARRTS TSI has been created.
  - When an OSE-identified tracked safety issue involves only an unapproved drug product, the OSE SRPM will create the DARRTS TSI. The OSE SRPM will notify the Office of Compliance (OC) contact and the relevant OND DDS and SRPM that a DARRTS TSI has been created.
  - **Creation of a DARRTS Safety Issue Workplan**
    - When a DARRTS TSI is created, a safety issue workplan is automatically generated; this includes base activities and can be modified with supplemental activities that describe the expected evaluation process for the significant safety issue.
  - **Managing DARRTS Tracked Safety Issues**

Generally the OND SRPM will be responsible for managing the DARRTS TSI and workplan as described below, regardless of who created the application.

DARRTS TSI management activities include, but are not limited to, the following:

- Entering the names of reviewers assigned to the SIT into the DARRTS TSI on the “Pool Designations” list and keeping the list current. The OSE SRPM will be responsible for entering and maintaining the list of OSE members.
- Maintaining the Safety Issue workplan with input from the SIT.
- Notifying the drug product sponsors in writing that a DARRTS TSI has been created.
- Ensuring that safety issue-related communications (e.g., forms, reviews, and correspondence) are entered into the DARRTS TSI by the relevant SIT members.
- Uploading supporting documents (e.g., regulatory submissions, medical literature).
- Changing application status. The SIT will decide as a group when to close the DARRTS TSI. However, the SRPM responsible for managing the application may change the status from active to ongoing without consulting the SIT.

There are some areas related to the safety of marketed drugs, as described in the Memorandum of Agreement between OND and OSE, for which OSE will be taking the regulatory lead, including medication errors. Once OSE assumes regulatory lead for these areas, the OSE SRPM will be responsible for managing the affected DARRTS TSIs and workplans.

The OSE SRPM will manage the DARRTS TSI and workplans created for significant postmarket safety issues identified by OSE that primarily involve OGD or OC.

- **Using DARRTS as a System of Record by CDER Personnel**

---

DARRTS is not yet the system of record for all CDER applications. For the time being, the following guidelines apply with regard to document sign-off:

- Documents related to a DARRTS TSI involving NDA and ANDA products
  - Are signed off and archived in DFS by the author and appropriate managers. A copy of the DFS-generated signed-off document is checked into the relevant DARRTS TSI (the document is not signed a second time in DARRTS) by the author, and a signature comment is entered indicating that the review has already been signed off in DFS.
- Documents related to a DARRTS TSI involving BLA products
  - Are signed off and archived in the Central Document Room (CDR) by the author and appropriate managers. An electronic copy of the signed document (such as a scanned pdf file) is checked into the relevant DARRTS TSI (the document is not signed a second time in DARRTS) by the author, and a signature comment is entered indicating that the review has already been signed off in the CDR.
- Documents related to a DARRTS TSI involving an IND (e.g., studies for a new indication of a marketed product) or involving products without a marketing application (e.g., monograph non-prescription products, unapproved marketed prescription products)
  - Are signed by the author and appropriate managers and archived in the DARRTS TSI.
- All CDER personnel are responsible for checking their communications (e.g., signed-off copies of NDA, ANDA, and BLA postmarket safety-related documents) into the relevant DARRTS TSI. A signature comment is entered indicating that the review has already been signed off in DFS (for NDAs and ANDAs) or the CDR (for BLAs).
- All CDER personnel are responsible for checking in and signing off their documents in DARRTS that relate to INDs or products without a marketing application (e.g., monograph nonprescription products, unapproved marketed prescription products).

---

## REFERENCES

DARRTS Safety Issue Business Rules, dated January 2009

<http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm026566.html>

Memorandum of Agreement between the Office of New Drugs and the Office of Surveillance and Epidemiology, CDER, effective June 16, 2008

---

## DEFINITIONS

**Document Archiving, Reporting, and Regulatory Tracking System (DARRTS):** A CDER information technology (IT) platform intended to replace many of CDER's core tracking systems, including components of the Center-wide Oracle-based Management Information System (COMIS), the Division File System (DFS), and CDER Standard Letters and Forms (CSL). DARRTS is currently the archival system of record for all investigational new drug applications (INDs), Emergency Use Applications, drug master files, and TSIs. Ultimately, it will be the archival system of record for new drug applications (NDAs), biologics license applications (BLAs), and abbreviated new drug applications (ANDAs) as well.

---

**DARRTS Tracked Safety Issue (TSI):** An FDA-generated application created for the purpose of tracking and archiving regulatory activities associated with a significant safety issue related to a marketed prescription or over-the-counter drug.<sup>2</sup>

**Safety Issue Team (SIT):** A multidisciplinary team that includes staff from OND and OSE, with other CDER offices as needed, that is charged with evaluating and managing a significant postmarket safety issue in accordance with a workplan established by the group.

**Significant Safety Issue:** A significant safety issue generally includes safety issues that have the potential to lead to

- Withdrawal of an approved drug from the market
- Withdrawal of an approved indication
- Limitations on a use in a specific population or subpopulation in the postmarket setting
- Additions or modifications to the Warnings, Precautions, or Contraindications sections of the labeling, or the Medication Guide or other required Patient Package Insert, including safety labeling changes required under the Food and Drug Administration Amendments Act (FDAAA)
- The establishment of or changes to the proprietary name/container label/labeling/packaging to reduce the likelihood of medication errors
- The establishment or modification of a risk evaluation and mitigation strategy (REMS)
- The requirement that a sponsor conduct a safety-related postmarket clinical trial or observational epidemiological study
- The conduct of a safety-related observational epidemiological study by the FDA

**Tracked Safety Issue:** A significant safety issue associated with a marketed drug that requires follow-up and triggers the creation of a DARRTS TSI.

It may not always be possible from the outset to determine whether a safety issue will become a significant safety issue. Therefore the following types of safety issues should generally be tracked in a DARRTS TSI:

- Safety issues identified by OSE staff from their internal work of monitoring the Adverse Event Reporting System (AERS) and other sources of postmarketing adverse event data for which an OSE team leader has decided that a review should be written and that requires the input of an organization outside of OSE.
- Safety issues identified by OND staff (or submitted to them by a sponsor) that require the input of an organization outside of the OND division and its co-locates (e.g., OSE, another OND division, another CDER office, another FDA Center, or regulatory briefing, Drug Safety Oversight Board meeting, or advisory committee meeting) for their evaluation.

Modifications to the Warnings, Precautions, or Contraindications sections of the labeling made for editorial purposes (e.g., associated with conversion of labeling to Physician Labeling Rule format), or additions made to those sections to make a label consistent with other drugs in the class, do not require a DARRTS TSI.

---

<sup>2</sup> Significant safety issues related to marketed unapproved drugs may be tracked in a TSI as well.

---

**Tracked Safety Issue Status:** A designation in the DARRTS TSI that indicates where the significant safety issue stands in activity. When a DARRTS TSI is created, it automatically has an “Active” status. The OND Deputy Director for Safety (DDS) and Safety Regulatory Project Manager (SRPM), along with input from the OSE staff assigned to the significant safety issue, determine when the status needs to be changed. A form must be submitted into the DARRTS TSI to change the status. The status categories are described below.

- **ACTIVE** – An issue for which there are activities pending (e.g., submissions or reviews are being evaluated, responses from sponsors are pending and expected within a few months, or regulatory actions are being contemplated, requested, or required).
- **ONGOING** – An issue has not been resolved; however, the awaited data are expected to take months or years to be submitted. For example, a REMS assessment is awaited or an epidemiological study or clinical trial is being conducted before a regulatory decision will be made.

**CLOSED** –

- An evaluation is completed and a decision has been made NOT to take a regulatory action AND all relevant submissions have reviews entered into the DARRTS TSI.
- OR
- A decision has been made that some regulatory action is necessary, the regulatory action is complete (e.g., the reviewing division has approved a labeling supplement), AND all relevant submissions have reviews entered into the DARRTS TSI.

When a TSI is closed, a comment should be included in the Application Comment field to note whether regulatory action was taken or not, as follows:

CLOSED – No regulatory action taken/necessary/indicated

CLOSED – Regulatory action taken

If a previously **CLOSED** issue is reevaluated and deemed to need tracking again, the application status should be changed to “ACTIVE,” and the new documents (e.g., reviews, letters) should be entered into the existing DARRTS TSI (rather than opening a new DARRTS TSI).

- **CANCELLED** – An issue was mistakenly entered into the system.

---

**EFFECTIVE DATE**

This MAPP is effective upon date of publication.

---

**CHANGE CONTROL TABLE**

Effective Date	Revision Number	Revisions
6/8/09	Initial	n/a
12/20/11	Rev. 1	Renumbered from 6700.4 to 4121.2 Rev. 1, to reflect change in ownership from OSE to OCD.