

POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

**FDA Posting of Potential Signals of Serious Risks
Identified by the Adverse Event Reporting System**

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PURPOSE

This MAPP describes the policy and procedures for developing and posting quarterly lists of potential signals of serious risks identified by the Adverse Event Reporting System (AERS).

BACKGROUND

Title IX, Section 921 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (121 Stat. 962) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to add subsection (k)(5) to section 505 (21 U.S.C. 355), requiring quarterly posting on the AERS Web site of potential signals of serious risks.

This section in FDAAA, among other things, directs the Food and Drug Administration (FDA) to "conduct regular, bi-weekly screening of the Adverse Event Reporting System [AERS] database and post a quarterly report on the AERS Web site of any new safety information or potential signal of a serious risk identified by AERS within the last quarter."

FDA staff in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) regularly examine the AERS database as part of

routine safety monitoring.¹ When CDER staff identify a potential signal of a serious risk from AERS data, it is entered as a safety issue into CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), as defined in CDER MAPP 6700.4, *Tracking of Significant Safety Issues in Marketed Drugs – Use of the DARRTS Tracked Safety Issue*.

Sponsors are notified at the time a Tracked Safety Issue (TSI) is opened. CDER does not provide a second notification to the sponsor at the time of the quarterly Web posting.

When a potential signal of a serious risk is identified from AERS data and entered into DARRTS as a TSI, FDA will post it in the required report for the quarter in which it was first identified. Typically, the appearance of a product and issue on this quarterly posting represents the sharing of information with the public at a very early stage of FDA's evaluation of the potential issue. As a result, FDA may not yet be able to determine or communicate what type of regulatory action, if any, is appropriate for the issue

FDA communicates product risks to the public using methods such as FDA's Drug Safety Communications Web page. As FDA completes its evaluation of each potential safety issue, one or more public communications may be issued as appropriate.

POLICY

1. Potential signals of serious risks identified through review of AERS data will be posted on the AERS Internet Web site quarterly. These postings will include all potential safety signals identified during the quarter.
2. Data from previous quarters will remain available on the AERS Web site and will be updated quarterly. Updates to information in the previously posted quarters will continue until CDER has determined and communicated the initial action(s) regarding the DARRTS TSIs and CBER safety issues.
3. DARRTS TSIs will be used as the CDER source data for signals of serious risks. Safety issues for CBER-regulated products will be identified by CBER staff, in accordance with CBER SOPP 8420.
4. The AERS signals lists will be posted on the FDA Web site no later than 90 days following the last day of a quarterly report period (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm>).
5. The appearance of a drug on each quarterly list does not mean that FDA has concluded that the drug has the listed risk. It also does not mean that FDA has identified a causal relationship between the drug and the listed risk.

¹ CBER uses AERS to monitor adverse events for products other than vaccines. Vaccine adverse events are included in the Vaccine Adverse Event Reporting System (VAERS) and are not addressed in this MAPP.

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6. The most recent quarterly report will be highlighted so that it can be easily located and distinguished from previously posted quarterly reports.
 7. The 921 Team will work collaboratively, be responsible for identifying the potential signals of serious risks and safety issues in the previous quarter, and prepare the potential signals list for posting on the AERS Web site.
 8. The Center Director provides final clearance for each quarterly AERS signals posting.
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PROCEDURES

1. Generate lists of potential signals for possible inclusion in the quarterly report and distribute to 921 Team

The 921 Team Project Manager will provide the source data for each quarterly posting by:

- a. Identifying the dates of the quarter.
- b. Using the DARRTS TSI 502A report, generate the list of TSIs opened during the relevant quarter *no earlier* than 15 days after the last date of the quarter (to allow CDER staff sufficient time to complete data entry in DARRTS), and *no later* than 30 days after the last date of the quarter.
- c. Requesting the draft list of potential signals for posting from the designated contact in CBER's Office of Biostatistics and Epidemiology during the same time interval as the DARRTS TSI 502A report.
- d. Distributing the DARRTS report by email to the 921 Team for review and preliminary determination of which potential safety issues listed in the source data will be included in the quarterly posting (refer to the inclusion and exclusion criteria below), and providing due date within 2 weeks for comments.

2. Determine the AERS-identified signals from the source data

- a. All safety issues identified by AERS during a quarter will be included in the posting, regardless of whether the evaluation of the issue has been completed at the time of the posting, and regardless of whether an action is planned or has been taken.
- b. The 921 Team Members will review the list of TSIs from the source data, share the list with relevant staff from their respective organizations, and compile information to help determine inclusion or exclusion of issues relevant to their divisions or offices (see step **3. Utilize inclusion and exclusion criteria**, below). The information will be returned to the 921 Team Project Manager by the requested due date (within 2 weeks).

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- c. The 921 Team Project Manager will collect and incorporate the list of potential signals for posting from the designated contact in CBER.
 - d. The 921 Team Project Manager will consolidate information received from 921 Team Members to determine whether there are outstanding questions that warrant discussion about including an issue. A 921 Team Meeting, including relevant subject matter experts, may be scheduled to review outstanding questions.
 - e. If a 921 Team Meeting is needed, the Members will discuss each outstanding issue, consider the **inclusion** and **exclusion** criteria listed below, and make final decisions regarding inclusion or exclusion for the next quarterly posting. The 921 Team may hold a face-to-face meeting or use alternative communication methods, such as email or telephone conference.
 - f. The 921 Team's review should result in a final decision on the listed issues. However, if further communication and research within CDER or CBER is required to determine whether the issues meet the inclusion criteria, 921 Team Members may be assigned to research one or more of the remaining issues that need further evaluation.
 - g. The 921 Team Members will establish a timeline for completion of tasks necessary for the quarterly posting. A sample Timeline Checklist is included as ATTACHMENT A. The posting should be available to the public no later than 90 days following the last day of the quarter.
 - h. The 921 Team Project Manager will note any action items, 921 Team Member assignments, and timelines determined at the 921 Team Meeting. The 921 Team Project Manager will distribute these notes to the 921 Team.

3. Utilize inclusion and exclusion criteria

INCLUDE safety issues in the quarterly posting when one or more of the following apply:

1. The safety issue was clearly identified as a potential signal due to one or more reports in AERS. These signals can be based on any of various analyses of AERS data, including the daily review of AERS reports, a review of summaries in the Periodic reports, generation of safety signals using data mining, or overviews of drug profiles, such as new drug postmarketing safety summary reviews and required pediatric reviews.
 - 1.1. *Example 1:* A safety evaluator has been monitoring case reports of seizures with Drug X and initiates an Office of Surveillance and Epidemiology (OSE)-identified safety issue.
 - 1.2. *Example 2:* Stevens Johnson syndrome and hemolytic anemia are identified during the review of the AERS data for a new drug postmarketing safety summary review.
2. The safety issue was identified by a sponsor who submits a labeling supplement that requests additions or changes to the safety sections of labeling, or responds to an FDA

request or requirement for safety-related labeling changes, and AERS data had contributed to or identified the safety signal.

3. The original source was one or more case reports or safety findings from a non-AERS source. However, AERS data heavily contributed to the identification of the safety signal.
 - 3.1. Non-AERS sources may include other databases, literature, a study, a media report, a citizen petition, a foreign regulatory agency, the World Health Organization (WHO), or another major health organization. Because review of AERS data may not have been the initial trigger for the safety issue, the 921 Team needs to consider whether to include such issues on a case-by-case basis.
 - 3.2. *Example 1:* A single case report in the literature described product-associated hepatitis that resolved; AERS contained many additional cases of severe liver toxicity associated with the product, some of which were fatal. The issue should be included.
 - 3.3. *Example 2:* A manufacturer reports possible bacterial contamination of a product; AERS contains numerous reports of patient infection with the contaminating organism. The issue should be included.

EXCLUDE safety issues from the quarterly posting when one or more of the following apply:

1. The safety issue was identified by a sponsor who submitted a labeling supplement, requesting additions or changes to the safety sections of the labeling where the issue was not identified by AERS prior to the sponsor's submission.
2. The safety issue originated from findings from a clinical trial, epidemiologic study, registry, scientific literature, or any other non-AERS source; AND AERS data did not heavily contribute.
3. The safety issue originated from a foreign regulatory agency, WHO, or another major health organization where the issue was already considered by this source to be a safety signal prior to FDA becoming aware of the issue.
 - 3.1. *Example:* The WHO Signal is published and includes the new issue of suicide and Drug X, based on spontaneous reports. This previously had not been identified by AERS as a potential signal.

4. Establish Web site content for the new quarterly posting and previous postings

- a. The 921 Team Project Manager will create a three-column table for the new quarterly posting. See example in ATTACHMENT B: Sample Posting.

Points to consider in creating the three-column table are as follows:

Column 1: Product Name: Active Ingredient (Trade) or Product Class

If only generic versions of a product are available, do not include a trade name. If the safety issue relates specifically to one dosage form, include the product's dosage form descriptor (e.g., injection, oral use).

Column 2: Potential Signal of Serious Risk/New Safety Information

The safety issue should be clearly described in one or a few words, and be easily understandable to health care providers. It is acceptable for the description of the safety issue to vary from the original DARRTS entry terms, as long as the safety issue is accurately described. If the safety issue applies to a specific population, identify the population.

Column 3: Additional Information Available (as of Month DD, 20YY)

The *as of* date is the date that additional information was updated, not the dates of the relevant quarter.

The information in Column 3 should describe FDA actions already taken, actions FDA is considering taking that have been communicated to the public, or the fact that FDA is not taking an action. See the 921 posting on the FDA Web site: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm>.

Use FDA information sources and Web site links where possible. It is acceptable to provide information from non-FDA sources if FDA otherwise routinely refers to that source or site, or if FDA is working on the particular issue with the non-FDA organization.

It is acceptable to provide references or use Web site links to medical journal articles if the article addresses the safety issue and the author is from FDA or the product's manufacturer.

- b. The 921 Team Project Manager will identify issues from previous quarterly postings that require updates on the AERS Web site. Once a safety issue has been updated to include an initial FDA action, no further updates will be posted. For the purpose of this MAPP an initial FDA action includes:
- Any modifications to safety sections of labeling
 - Market suspension or recall
 - An FDA decision not to take action

FDA may issue a Drug Safety Communication in conjunction with one of the actions above. However, a Drug Safety Communication by itself, without any of the above criteria, will not be considered an action for purposes of the 921 posting. Updates will continue until an FDA action has been taken.

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- c. The 921 Team Project Manager will distribute early drafts of the following to the 921 Team Members. Comments are due back in 5 business days:
 - o new quarterly postings
 - o updates of previous quarterly postings
 - d. The 921 Team Members will review the early drafts, share the drafts with relevant staff from their respective organizations, and provide additional information. Any other comments and concerns from staff will also be forwarded to the Project Manager by the due date.
- 5. Distribute the draft final lists to OSE, Office of New Drugs (OND), Office of Generic Drugs (OGD), and CBER staff for corrections or comments**
- a. The 921 Team Members will distribute the new and updated quarterly draft postings to staff in their respective organizations by email, requesting corrections or comments in 1 week.
 - b. The 921 Team Members will evaluate and resolve any comments within their organization and forward the revised lists to the Project Manager.
 - c. The 921 Team Project Manager will consolidate the received comments and distribute the resultant draft postings to the 921 Team by email, along with an explanation of any unresolved issues.
 - d. The 921 Team Members will discuss, evaluate, and resolve any final issues as needed, preferably by email. Final Web site content for clearance should be established no later than 2 weeks after the Project Manager distributes the consolidated draft postings.

6. Distribute final lists to the CDER Web Team for placement on a developmental Web site

The new and updated lists will be forwarded to the CDER Division of Information Services Web Project Manager (Web Team) for placement on a developmental Web site. The 921 Team Project Manager will review the content of the developmental Web site, and provide any corrections to the CDER Web Team prior to the live posting.

7. Obtain clearance

- a. The 921 Team Project Manager will first obtain OSE clearance of the draft list. CBER provides clearance only if there are CBER products included in the new posting.
- b. The 921 Team Project Manager will send the OSE- and CBER-cleared list to the CDER Division of Executive Operations (CDER Exec Sec).

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- c. CDER Exec Sec will route the draft final list through clearance after OSE and CBER clearance is obtained by the 921 Team Project Manager. CDER clearance would normally include the Office Directors in OND and the Office of Pharmaceutical Science (OPS), followed by the Director, Office of Regulatory Policy (ORP). The CDER Center Director will provide final CDER clearance. Once OSE, CBER, and OND clearance is obtained, the draft 921 posting is shared with Office of International Programs (OIP).

8. Communicate to stakeholders

Clearance by the CDER Center Director will trigger the posting time clock. Once clearance is obtained, CDER Exec Sec will inform the 921 Team Members, FDA Office of the Commissioner Executive Secretariat (FDA Exec Sec), FDA Press Office, CDER Office of Communications (OCOMM), and Office of International Programs (OIP) that the posting will be live in 2 business days.

9. Post on FDA Web site

Within 2 business days of CDER Center Director clearance, and following a final review for accuracy by the 921 Team Project Manager, the CDER Web Team will be notified that the Center Director cleared the list, it has been reviewed for accuracy by the 921 Team Project Manager, and will be directed to move the Section 921 posting from the developmental Web site to the FDA Web site.

10. Respond to questions related to the FDA Web site posting

OSE's Regulatory Affairs and Policy Team (RAPT) will be responsible for drafting responses to inquiries regarding the posting from requestors outside CDER. RAPT will screen all requests and work with CDER staff as needed when formulating responses. The OSE Office Director will clear the responses. Responses will be distributed to requestors using appropriate CDER processes; for example, press requests will be distributed by the Press Office.

REFERENCES

Food and Drug Administration Amendments Act of 2007

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/default.htm>

CDER MAPP 6700.4 Tracking of Significant Safety Issues in Marketed Drugs – Use of the DARRTS Tracked Safety Issue, effective 06/08/2009.

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM164967.pdf>

CBER SOPP 8420 FDAAA Section 921: Posting of Potential Signals of Serious Risk, effective November 1, 2011.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm277126.htm>

DEFINITIONS

Adverse Event Reporting System (AERS) - AERS is a computerized information database designed to support FDA's postmarketing safety surveillance program for all approved drug and therapeutic biological products. FDA uses AERS to monitor for new adverse events and medication errors that might occur with these marketed products.

Drug – a drug or therapeutic biological product regulated by the FDA.

New Safety Information - As defined in section 505-1(b)(3) of the FD&C Act, new safety information includes information derived from a clinical trial, an adverse event report, a postapproval study, or peer-reviewed biomedical literature, data derived from the postmarketing risk identification and analysis system under section 505(k), or other scientific data deemed appropriate about (1) a serious risk or unexpected serious risk associated with use of a drug since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug, or (2) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy

If derived from AERS, potential signals of serious risks are normally based upon groups of reports, although a single AERS report could lead to further evaluation of a potential safety issue. Potential signals are typically at the earliest stages of identification, when it is known that the issue needs to be evaluated further, but it is not known whether a regulatory action will be needed.

Initial action – The first FDA action related to the posted safety issue. For the purposes of this MAPP, initial action includes a modification to any safety section of the labeling, a market suspension or recall, or an FDA decision not to take action. Once an initial action is taken, the safety issue will not be updated in subsequent quarters. If a Drug Safety Communication is disseminated on the safety issue without an action, the safety issue will continue to be updated until an initial action has occurred.

921 Team - The 921 Team will be composed of staff from OSE, OND, OGD, CDER Exec Sec, OCOMM, and the Office of Biostatistics and Epidemiology (OBE) in CBER.

921 Team Project Manager - The 921 Team will be led by a member of the Regulatory Affairs and Policy Team (RAPT) from OSE.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

ATTACHMENTS

ATTACHMENT A: SAMPLE TIMELINE CHECKLIST

Task		Assigned To	Due Date	Completion Date
1	Run DARRTS 502A report, request CBER list, and distribute to 921 Team	921 Project Manager		
2	Schedule 921 Team Meeting, if needed	921 Team		
3	Complete initial review of safety issues for posting	921 Team		
4	Prepare chart content for new and previous quarters	921 Team and Project Manager		
5	Research publicly available additional information for Column 3	921 Team and Project Manager		
6	Distribute draft final lists to OSE, OND, OGD, and CBER/OBE staffs	921 Team		
7	Distribute final lists to Web Team for developmental Web site	921 Project Manager		
8	Obtain clearance	921 Project Manager, CBER, Exec Sec		
9	Communicate to stakeholders	Exec Sec, OND, OGD		
10	Post live	Web Team		

ATTACHMENT B: Sample Posting**Potential Signals of Serious Risks/New Safety Information Identified from the Adverse Event Reporting System (AERS) Between Month-Month 20YY**

Product Name: Active Ingredient (Trade) or Product Class	Potential Signal of Serious Risk/New Safety Information	Additional Information (as of Month DD, 20YY)
Trazodone	Prolongation of the electrocardiogram QT interval	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Stingacillin (Wonderdrug) eye drops	Corneal damage	FDA is continuing to evaluate this issue to determine the need for any regulatory action.
Valsartan (Diovan)	Hemolytic anemia	FDA decided that no action is necessary at this time based on available information. FDA is continuing to monitor the issue.
Mefloquine HCl (Lariam)	Psychiatric events	FDA is reevaluating the adequacy of current labeling, which already addresses psychiatric events under Warnings. Lariam labeling
Leukotriene receptor antagonists	Suicidal behavior and suicide	FDA issued an Early Communication on this topic in March 20YY and an update in January 20YY .
Temsirolimus (Torisel)	Labeling confusion resulting in incorrect dose	The FDA/CDER medication error division works closely with the Institute for Safe Medication Practices (ISMP) on some issues. Both FDA and ISMP have been evaluating this issue. The ISMP discussion of the issue is available on the Facts & Comparisons Web site (external link).
Lapatinib (Tykerb)	Hepatotoxicity	Information on hepatotoxicity was added to the Tykerb labeling in July 20YY; see Boxed Warning, Warnings and Precautions, Adverse Reactions. Tykerb labeling
Terbinafine (Lamisil) oral use	Psychiatric events	This issue was identified during a review of terbinafine adverse events as required by the Best Pharmaceuticals for Children Act. Information from a review of the AERS database was presented at a November 20YY advisory committee meeting . FDA is continuing to evaluate this issue in all age groups to determine the need for any regulatory action.