POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

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

Table of Contents

PURPOSE

This MAPP describes the policy and procedures for developing and posting quarterly lists of potential signals of serious risks identified by the FDA Adverse Event Reporting System (FAERS), formerly 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, directed 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."

The 21st Century Cures Act (Cures Act) was enacted on December 13, 2016, with the goal

of advancing medical product innovation, as well as ensuring patient access to safe and effective treatments as soon as possible. Section 3075 of the Cures Act amended section 505(k)(5) of the FD&C Act to strike "bi-weekly screening," as required by FDAAA, and insert "screenings"; it also added the requirement that FDA make publicly available on its internet website the following:

(i) guidelines, developed with input from experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that detail best practices for drug safety surveillance using the Adverse Event Reporting System; and

(ii) criteria for public posting of adverse event signals.

FDA staff in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) regularly examine the FAERS database as part of routine safety monitoring.[1] When CDER staff identify a potential signal of a serious risk from FAERS data, it is entered as a safety issue into CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), as defined in CDER MAPP 4121.2, *Tracking of Significant Safety Issues in Marketed Drugs – Use of the DARRTS Tracked Safety Issue*.

Sponsors of an approved new drug application or biologics license application are notified at the time a Tracked Safety Issue (TSI) is opened. CDER will provide a second notification to the sponsor at least 72 hours before the time of the quarterly Web posting.

When a potential signal of a serious risk is identified from FAERS 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 FAERS data are entered as safety issues in DARRTs and are referred to as TSIs. On a quarterly basis, CDER will post all TSIs identified during that quarter on the FAERS Internet Web site.

2. Data from previous quarters will remain available on the FAERS Web site and will be updated quarterly. Updates to TSIs posted during previous quarters will continue

[1] CBER uses FAERS 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.

until CDER determines and communicates the initial action(s) regarding the DARRTS TSIs and CBER safety issues.

3. CDER will use DARRTS TSIs as the CDER source data for signals of serious risks to post. CBER staff will identify safety issues for CBER-regulated products in accordance with CBER SOPP 8420.

4. The FAERS 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.

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 FAERS Web site.

8. The Center Director provides final clearance for each quarterly FAERS signals posting as needed.

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 507B 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 507B 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 FAERS-identified signals from the source data

a. All safety issues identified by FAERS 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).

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 FAERS. These signals can be based on any of various analyses of FAERS data, including the daily review of FAERS 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 FAERS and identifies 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 FAERS 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 FAERS 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-FAERS source. However, FAERS data heavily contributed to the identification of the safety signal.
   3.1. Non-FAERS 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 FAERS 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. <u>Example 1</u>*: A single case report in the literature described product-associated hepatitis that resolved; FAERS contained many additional cases of severe liver toxicity associated with the product, some of which were fatal. The issue should be included.*
   3.3. <u>Example 2</u>*: A manufacturer reports possible bacterial contamination of a product; FAERS 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 FAERS 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-FAERS source; *AND* FAERS 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. <u>Example</u>*: 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 FAERS 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 FAERS 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.

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:
   - new quarterly postings
   - 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 CBER 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 route the draft final list for CDER clearance. CDER clearance may include OND, OGD, the Office of Pharmaceutical Quality (OPQ), the CDER Executive Operations Staff (EOS), the Office of Regulatory Policy (ORP), and OSE. The CDER Center Director will provide final CDER clearance, as needed. Once CDER clearance is obtained, the draft 921 posting is shared with Office of International Programs (OIP).

8. Communicate to stakeholders

The 921 Team Project Manager will inform the 921 Team Members when clearance is obtained and that the posting will be live in 5 business days. The CDER EOS will inform the Office of International Programs (OIP) that the posting will be live in 5 business days. The CDER EOS will notify the FDA Office of the Commissioner Executive Secretariat (FDA Exec Sec) and CDER Office of Communications (OCOMM), as needed.

The 921 Team Project Manager will alert the appropriate designee in OND (currently OND Safety Policy and Research Team) that a potential signal for a serious risk for a drug will appear on the Section 921 posting. The OND Safety Policy and Research Team will alert the OND Deputy Directors for Safety (DDSs) and Safety Regulatory Project Managers (SRPMs) as soon as possible (no more than 4 business hours) of notification of the posting.

The OND SRPM will send a notification to the sponsor of a new drug application or biologics license application informing the sponsor that the potential safety issue identified will appear on the Section 921 posting. The notification will occur not less than 72 hours (i.e., 3 business days) before the postings.

The OND SRPM will archive the notification in the FDA system of record. The 921 Team Project Manager will receive an automatic notification from the FDA system of record when the communication is archived. The OND DDSs and SRPMs will coordinate with other OND Division staff (e.g., Regulatory Project Managers) as needed to ensure that the notifications are issued and archived as required.

9. Post on FDA Web site

Within 5 business days of CDER clearance, and following a final review for accuracy by the 921 Team Project Manager, the CDER Web Team will be notified that the list has been reviewed for accuracy by the 921 Team Project Manager and the appropriate sponsor(s) have been notified. The CDER Web Team 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 Staff (RAS) will be responsible for drafting responses to inquiries regarding the posting from requestors outside CDER. RAS 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
https://www.congress.gov/bill/110th-congress/house-bill/3580

21st Century Cures Act (December 13, 2016)
https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf

CDER MAPP 4121.2 Tracking of Significant Safety Issues in Marketed Drugs – Use of the DARRTS Tracked Safety Issue, effective 12/20/2011.
https://www.fda.gov/media/76785/download

CBER SOPP 8420 FDAAA Section 921: Posting of Potential Signals of Serious Risk, effective November 1, 2011.
https://www.fda.gov/media/82363/download

DEFINITIONS

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

Drug(s) – a drug or therapeutic biological product regulated by the FDA. For the purposes of this document, "drug" refers to human drug and combination products, including drugs that are biological products, regulated by CDER or CBER. "Drugs" is also used to refer to compounded drugs and drug products that are labeled as homeopathic and marketed in the United States without the required FDA approval.

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 FAERS, potential signals of serious risks are normally based upon groups of reports, although a single FAERS 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 EOS, 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 Staff (RAS) 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 507B 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, CDER EOS		
9	Communicate to stakeholders	CDER EOS, OND, OGD		
10	Post live	Web Team		

ATTACHMENT B: Sample Posting

Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) 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 FAERS 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.