

SOPP 8420: FDAAA Section 921: Posting of Potential Signals of Serious Risk

Version: 3

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I. Purpose

This SOPP describes the policy and procedures for Center for Biologics Evaluation and Research (CBER) staff in developing and posting quarterly lists of potential signals of serious risks identified by the FDA Adverse Event Reporting System (FAERS) in response to the Food and Drug Administration Amendments Act of 2007 (FDAAA), Title IX, Section 921.

II. Scope

A. This SOPP applies to all marketed drugs and biologics used for therapeutic purposes which are regulated by CBER and included in Section 921 of FDAAA. Vaccines are exempt as noted below.

B. Please refer to *MAPP 6700.9: FDA Posting of Potential Signals of Serious Risks Identified by the Adverse Event Reporting System* for information on products regulated by the Center for Drug Evaluation and Research (CDER).

III. Background

- A. Title IX, Section 921 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and subsequently amended by the 21st Century Cures Act in 2016, directed FDA to conduct screenings of the Adverse Event Reporting System [AERS] database¹ and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by AERS within the last quarter.
- B. FDA also communicates product risks to the public using other methods, such as FDA Safety Notifications (see references), Public Health Advisories, and product labeling. As FDA completes its evaluation of each potential safety issue, one or more of these methods as well as additional public communications may be issued as appropriate.

IV. Definitions

- A. **FDA Adverse Event Reporting System (FAERS)** – FAERS is a computerized information database designed to support the FDA’s postmarketing safety surveillance program for all approved drug and biologic products used for therapeutic purposes. The FDA uses FAERS to monitor for new adverse events and medication errors that might occur with these marketed products.
- B. **Potential Signal of a Serious Risk** - New safety information as defined in FDAAA [section 505-1(b)(3)] includes, among other things, information derived from Adverse Event (AE) reports about a serious risk associated with use of a drug that FDA has become aware of since the drug was approved or, for drugs that have Risk Evaluation and Mitigation Strategies (REMS), since the REMS was required or last assessed. “Potential” signals are typically at the earliest stages of identification, where it is known that the issue needs to be evaluated further, but it is not known if a regulatory action will be needed. Drug refers to drug and biologic products regulated by the FDA.

V. Policy

- A. Medical Officers (MOs) in the Office of Biostatistics and Pharmacovigilance (OBPV)/Division of Pharmacovigilance (DPV) regularly examine the FAERS database as part of routine safety monitoring. Staff screen FAERS reports as they are received and routinely analyze aggregated FAERS data to detect possible safety issues. DPV MOs also review periodic safety reports submitted by applicants (Periodic Adverse Event Reports (PAERs), Periodic Safety Update Reports (PSURs), or Periodic Benefit-Risk Evaluation Reports (PBRER)), and postmarketing study data to identify possible safety issues.

¹ FDAAA referred to the “Adverse Event Reporting System [AERS]”. This system was renamed “FDA Adverse Event Reporting System [FAERS]” in 2012. FAERS will be used to refer to this system elsewhere throughout this SOPP

- CBER uses FAERS to monitor adverse events for products other than vaccines. Vaccine adverse events that are included in the Vaccine Adverse Event Reporting System (VAERS) are exempted from this Internet posting requirement.
- B.** When a possible safety issue is identified from FAERS data, OBPV/DPV and the applicable Product Office will discuss the issue at regularly scheduled or ad-hoc Safety Assessment Meetings. Safety issues that are determined by the DPV Division Director and the Office Director (or designee) of the responsible Product Office to meet the criteria for potential signals of a serious risk (see section VII.C.2-6) are communicated to the applicant and posted on the Internet. FDA will post potential signals of a serious risk in the report for the quarter in which it is first identified. Typically, the appearance of a product and signal on this quarterly posting represents the sharing of information at a very early stage of FDA's evaluation of the potential issue; usually FDA is not yet able to determine what type of action, if any, is appropriate for the issue.
- The appearance of a product on a quarterly list means that FDA has identified a potential signal with the product or its use. It does not mean that FDA has concluded that the product has the listed risk, or that FDA has verified a causal relationship between the product and the risk.
 - Applicants will be notified no later than 72 hours before internet posting of a potential signal of a serious risk.
- C.** Potential signals of serious risks are normally based upon groups of FAERS reports, although a single FAERS report could lead to further evaluation of a potential safety issue.
- D.** New potential signals of a serious risk will be posted on the FAERS Internet Web site four (4) times per year (i.e., quarterly) and will include the signals identified during each quarter. New potential signals will be posted on the Internet no later than 90 days following the last day of an inclusive quarter.
- All potential signals that are identified by FAERS during an inclusive quarter will be posted whether or not FDA has completed its evaluation of the issue. If FDA has completed its evaluation prior to the time of the posting, the signal will be included regardless of whether or not an action has been taken or is planned (e.g., include the issue even when it is decided that no action is necessary at that time).
- E.** Data from previous quarters will remain available on the FAERS Web site. Information in the previously posted quarters will be updated until the FDA has determined the initial action(s) regarding the safety issues.
1. Initial FDA actions can include: modifications to safety sections of labeling, market suspension or recall, or an FDA decision not to take action.

2. An FDA Safety Notification is a public communication about a product safety issue that is disseminated on FDA's website or via other means. These notifications typically include a more detailed evaluation of the safety issue than the Section 921 postings discussed in this SOPP. FDA Safety Notifications may be issued in conjunction with one of the actions above. However, an FDA Safety Notification *per se*, without any of the above actions, will not be considered an action for purposes of the Section 921 posting, and the issue will continue to be updated until an action has occurred.

VI. Responsibilities

- A. **CBER Center Director** - Concurs with recommendation for posting if CBER's Safety Working Group (SWG) determines that Center Director review is necessary
- B. **CBER Safety Working Group (SWG)** - Reviews draft Internet posting for compliance with FDAAA and provides concurrence
- C. **Office of Communication, Outreach, and Development (OCOD)/Electronic Disclosure Branch (EDB)** - Provides web/disclosure clearance of draft potential signals
- D. **Product Office** (Office of Blood Research and Review [OBRR], Office of Tissues and Advanced Therapies [OTAT], or Office of Vaccines Research and Review [OVRR])
 1. **Office Director or designee** - Provides concurrence on recommendations for internet posting
 2. **Clinical Medical Officer (MO), Clinical Review Branch Chief, and/or Clinical Division Director, or other designated personnel**
 - a. Participates in preliminary assessment of safety issues at Safety Assessment Meetings
 - b. Participates in discussion of proposed internet postings of potential signals of serious risks at Safety Working Group meetings
 3. **Regulatory Project Manager (RPM)** - Notifies the product sponsor of newly identified safety issues and upcoming postings
- E. **Office of Biostatistics and Pharmacovigilance (OBPV)**
 1. **Office Director** - Provides concurrence on recommendations for Internet posting
 2. **Division of Pharmacovigilance (DPV) Director** - Provides concurrence on recommendations for Internet posting

3. Branch Chief

- a. Assigns each DPV Medical Officer a portfolio of products for FAERS review
- b. Provides concurrence on safety issues as appropriate
- c. Notifies Product Office (Clinical Medical Officer, Clinical Review Branch Chief, and/or Clinical Division Director) of new safety issues

4. Medical Officer(s) (MO)

- a. Screens incoming FAERS reports and conduct analyses of aggregated FAERS data for possible new safety information
- b. Looks for features that suggest an association between the product and the adverse event(s) and assesses those associations
- c. Identifies possible safety issues that require further investigation
- d. Discusses possible safety issues with Team Leader and the Branch Chief
- e. Presents proposed internet postings of potential signals of serious risk to SWG for concurrence

5. DPV Pharmacovigilance Staff - Reviews and discusses any relevant preliminary findings and reaches consensus on whether the information represents a safety issue

6. DPV RPM

- a. Routes the draft posting to CDER for preliminary review to ensure consistency with CDER postings and format
- b. Routes the final posting of potential signal of serious risk to OCOD/EDB
- c. Routes the final, cleared posting of potential signals of a serious risk to CDER for Internet posting
- d. Notifies the relevant Product Office when applicants can be notified of the upcoming posting and route the final posting to the Product Office.

VII. Procedures

A. Monitoring FAERS

1. Screen FAERS for assigned products to identify new safety information that may represent a possible safety issue associated with use of a product. **[DPV MO]**

- a. Screening of incoming FAERS reports includes only reports where the product is named as a suspect product.
2. Generate internal surveillance reports, specific to a product or product-class, to identify possible safety issues that may emerge from a pattern of similar adverse events across multiple FAERS reports over the past 12 months and other time intervals. **[DPV MO]**
 - a. Internal surveillance reports are generated quarterly or annually, depending on the product.
 - b. Each report displays counts of adverse events, among all reports and among serious reports, over the review period, as well as counts during a relevant preceding comparator period, with the product of interest as a suspect product. For comparison, the report displays the most common AE terms reported over the past five years. The report also includes a disproportionality analysis using data mining to identify AE terms reported to FAERS with unusual frequency for the product of interest versus all other products. A review of medical literature related to safety of the product and published during the period of interest is also included.

B. Identification of Possible Safety Issues

1. Identify as a possible safety issue any AE or group of AEs that, in the judgment of the reviewing Medical Officer, require(s) further investigation with respect to the safety of the product. **[DPV MO]**
 - a. Safety issues can include AEs possibly attributable to the product or to its manner or circumstances of use.
 - b. Features of a case or group of cases that suggest an association between the product and the adverse event, such as:
 - i. Occurrence of the adverse event in the expected time
 - ii. Absence of symptoms related to the event prior to exposure
 - iii. Evidence of positive dechallenge or positive rechallenge
 - iv. Consistency of the event with the established pharmacological/toxicological effects of the product
 - v. Consistency of the event with the known effects of other products in the class
 - vi. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

- c.** Case review should also assess the severity of the case and the quality of the report.
- d.** To assess if AEs are safety issues, Medical Officers can:
 - i.** Review available medical literature
 - ii.** Contact reporters for follow-up information
 - iii.** Contact the product applicant for additional information as needed
 - iv.** Consult the relevant Product Office as needed
 - v.** Conduct disproportionality analysis
 - vi.** Assemble and review preliminary case series.
- e.** Safety issues warranting further investigation can include but are not limited to:
 - i.** New unlabeled adverse events, especially if serious
 - ii.** An apparent increase in the frequency, severity or specificity of a labeled event
 - iii.** Occurrence of serious events thought to be extremely rare in the general population
 - iv.** New product-product, product-device, product-food, or product-dietary supplement interactions
 - v.** Identification of a previously unrecognized at-risk population (e.g., populations with specific ancestral or other genetic predispositions or co-morbidities)
 - vi.** Confusion about a product's name, labeling, packaging, or use
 - vii.** Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment)
- f.** Possible safety issues can be further evaluated by assembling a case series of adverse event reports for the same product(s) involving the same issue to identify unexpected patterns of events associated with a product.
 - Case series examination includes clinical and demographic characteristics, exposure duration, time to onset, dose, route, lot, co-morbid conditions, and/or concomitant medications.

2. Discuss possible safety issues with the Team Leader or Branch Chief. **[DPV MO]**
3. Discuss any relevant preliminary findings and reach consensus on whether the information represents a safety issue during weekly Branch Meetings. **[Pharmacovigilance staff]**
4. Provide concurrence that the information represents a safety issue. Notify the DPV RPM and the relevant product office (Clinical Medical Officer, Clinical Review Branch Chief, and/or Clinical Division Director) of new safety issues. Note: Not all safety issues meet the criteria for Internet posting. **[Branch Chief]**

C. Assessment and Management of Potential Signals of Serious Risks

1. Assess safety issues at Safety Assessment Meetings (SAMs). **[DPV Division Director, Branch Chief, Medical Officer, Product Office Clinical Medical Officer, Clinical Review Branch Chief, and/or Clinical Division Director and/or other designated personnel]**
2. Provide concurrence for notifying sponsors of newly identified serious safety signals if: **[DPV Division Director and Product Office Director or designee]**
 - a. The issue warrants further evaluation as described in Section VII B.3. or will require potential regulatory actions (e.g., labeling changes, dear healthcare provider notifications, or issuing of an FDA public communication), and
 - b. The issue represents new information that FDA has become aware of since the product was approved, since a Risk Evaluation and Mitigation Strategy (REMS) was required, or since the last assessment of an approved REMs [as defined in FDAAA Title IX, Section 501(b) (3)] was completed, and
 - c. The issue involves serious adverse events, as defined in 21 CFR.600.80, or could be expected to result in such events.
3. Contact the product sponsor and notify them of the newly identified serious safety signal. **[Product Office RPM]**
4. Provide concurrence for posting on the Internet as a potential signal of a serious risk if the issue meets inclusion and exclusion criteria for Internet posting (see Section VII C.5-6). **[OBPV and Product Office Director or Designee(s), DPV Division Director]**
5. Include safety issue in the quarterly posting where:

the issue was already considered by this source to be a safety signal prior to FDA becoming aware of the issue.

- Example: WHO issues a publication describing a new issue of statin products and suicide. This signal had not previously been identified by FDA as a potential signal.
- d. Other sources of safety issue identification that were clearly other than FAERS (and FAERS data did not heavily contribute).
7. Draft Internet posting in accordance with agreed upon format specified in *CDER MAPP 6700.9: FDA Posting of Potential Signals of Serious Risks Identified by the Adverse Event Reporting System*, and notify the relevant Product Office Division Director, and the Product Office clinical branch chief of anticipated Internet postings. Route to OBPV Director and DPV RPM **[Branch Chief and DPV MO]**
 8. Concur with recommended Internet postings. **[OBPV Office Director]**
 9. Route the draft posting to CDER for preliminary review to ensure consistency with CDER postings and format. **[DPV RPM]**
 10. Review Internet posting for compliance with FDAAA **[CBER SWG]**
 - Note: CBER's SWG will determine whether a draft posting warrants review by the Center Director.
 11. Concur with recommendation for posting or make appropriate revisions; return to DPV RPM. **[CBER SWG]**
 12. Route the posting to OCOD/EDB for disclosure review after receiving concurrence from SWG. **[DPV RPM]**
 13. Conduct disclosure review and notify the DPV RPM of the outcome of the review. **[OCOD/EDB]**
 14. Route cleared posting to CDER for Internet posting. **[DPV RPM]**
 15. Route the final posting to the relevant Product Office RPM and notify the Product Office Clinical Branch Chief and RPM that product applicants can be notified of the upcoming posting. **[DPV RPM]**
 16. Contact the product applicant and notify them of the upcoming posting no later than 72 hours prior to publishing the posting on FDA's website. **[Product Office RPM]**

VIII. Appendix

N/A

IX. References

A. References below can be found on the Internet:

1. [Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System \(FAERS\)](#)
2. [CDER Manual of Policies and Procedures \(MAPP\) 6700.9: FDA Posting of Potential Signals of Serious Risks Identified by the Adverse Event Reporting System](#)
3. [FDA Safety Notifications](#)

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Monser	N/A	February 27, 2022	3	Technical update due to 2022 CBER reorganization
Zinderman	Christopher Joneckis, PhD	September 17, 2019	2	Updated to current procedures and to include PDUFA VI requirements
OBE/SWG	Robert A. Yetter, PhD	Oct 18, 2011	1	First version