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

Version #1

Effective Date: November 1, 2011

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 Adverse Event Reporting System (AERS) in response to the Food and Drug Administration Amendments Act of 2007 (FDAAA), Title IX, Section 921.

II. Scope

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

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) directs FDA to conduct bi-weekly screening of the Adverse Event Reporting System [AERS] database 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. Adverse Event Reporting System (AERS) – AERS is a computerized information database designed to support the FDA's postmarketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS 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 therapeutic biologic products regulated by the FDA.

V. Policy

A. Medical Officers (MOs) in the Office of Biostatistics and Epidemiology (OBE)/Division of Epidemiology (DE) regularly examine the AERS database as part of routine safety monitoring. Staff reviews all serious and direct AERS reports as they are received for possible safety issues. Direct reports include adverse event (AE) reports submitted by consumers, healthcare providers, or others to FDA, as opposed to reports that come from product manufacturers. DE MOs also review Periodic Adverse Event Reports (PAERs), Periodic Safety Update Reports (PSURs), and postmarketing study data to identify possible safety issues.

- CBER uses AERS 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 AERS data, OBE/DE and the applicable Product Office will discuss the issue at the DE Safety Assessment Meeting. Safety issues that are determined by the DE Division Director to meet the criteria for potential signals of a serious risk (see section VII.C.8-10) are posted on the Internet. FDA will post potential signals of a serious risk in the required 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.

C. Potential signals of serious risks are normally based upon groups of AERS reports, although a single AERS report could lead to further evaluation of a potential safety issue.

D. New potential signals of a serious risk will be posted on the AERS 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 AERS 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 AERS 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. Criteria to be used to determine an initial FDA action are: any 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 criteria, 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 FDAAA Safety Working Group (SWG)

1. Reviews Internet posting for compliance with FDAAA

2. Determines whether a draft posting warrants review by the Center Director

C. Office of Communication, Outreach, and Development (OCOD)/Electronic Disclosure Team (EDT)

Provides web/disclosure clearance of draft potential signals

D. Product Office

Office of Blood Research and Review [OBRR],

Office of Cellular, Tissues and Gene Therapies [OCTGT], or

Office of Vaccines Research and Review [OVRR]

1. **Clinical Medical Officer, Clinical Review Branch Chief, and/or Clinical Division Director, or other designated personnel**

    a. Participates in preliminary assessment of safety issues at Division of Epidemiology Safety Assessment Meetings

    b. Participates in discussion of potential signals at Safety Working Group meetings

2. **Regulatory Project Manager (RPM)**

    Notifies the product sponsor of the upcoming posting

E. Office of Biostatistics and Epidemiology (OBE)

1. **Office Director**

    Provides concurrence on recommendations for Internet posting

2. **Division of Epidemiology (DE) Director**

    Provides concurrence on recommendations for Internet posting

3. **Branch Chief**

    a. Assigns each DE Medical Officer a portfolio of products for AERS 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)**

    a. Reviews AERS daily reports for possible new safety information

    b. Generates internal surveillance reports to identify possible safety issues

    c. Looks for features that suggest an association between the product and the adverse event(s) and assesses those associations

    d. Identifies possible safety issues that require further investigation

    e. Discusses possible safety issues with Team Leader and the Branch Chief

5. **DE Pharmacovigilance Staff**

Reviews and discusses any relevant preliminary findings and reaches consensus on whether the information represents a safety issue

6. DE RPMs

a. Routes the draft posting to the CDER 921 project manager for preliminary review to ensure consistency with CDER postings and format

b. Routes the final posting to CBER's Office of Communication, Outreach and Development (OCOD) Electronic Disclosure Team (EDT)

c. Routes cleared potential signals of a serious risk to the CDER 921 project manager for Internet posting

d. Notifies the relevant Product Office when sponsors can be notified of the upcoming posting and route the final posting to the Product Office.

VII. Procedures

A. Monitoring AERS

1. Review each serious and direct AERS report for his/her assigned products within one business day of receipt at OBE to identify new safety information that may represent a possible safety issue associated with use of a product. **[DE MO]**

a. This daily review includes only reports where the product is named as a primary suspect product.

b. A primary suspect product is the first product listed by reporters as a suspect product (i.e., the first product listed on a Medwatch form in Box C1. "Suspect Products"). Secondary suspect products are all other products listed as suspect products.

2. Generate internal surveillance reports to identify possible safety issues that may emerge from a pattern of similar adverse events occurring in multiple reports over the past 12 months and other time intervals. **[DE MOs]**

a. Internal surveillance reports are generated by the Medical Officer quarterly, semi-annually, or annually, depending on the product.

b. Each report displays the most common AE terms in serious reports with the product of interest as a primary or secondary suspect product. For comparison, the report displays the most common AE terms reported over the past three years. The report also includes a disproportionality analysis using data mining to identify AE terms reported with unusual frequency for the product of interest versus all other products.

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. **[DE MOs]**

    a. Safety issues can include AEs possibly attributable to the product or to its manner or circumstances of use.

    b. Safety issues could be 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. Consult the relevant Product Office as needed

        iv. Conduct disproportionality analysis

        v. 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. Potential safety signals can be further evaluated by assembling a case series 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. **[DE 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 DE-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 DE Safety Assessment Meetings (SAMs). **[DE Division Director, Branch Chief, Product Office Clinical Medical Officer, Clinical Review Branch Chief, and/or Clinical Division Director)]**

2. Provide concurrence for posting on the Internet as potential signals of a serious risk if: **[DE Division Director]**

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 meets inclusion and exclusion criteria for Internet posting (see Section VII C.9-10).

3. Include safety issue in the quarterly posting where:

a. The safety issue was clearly identified as a potential signal due to one or more reports in AERS. These issues can stem from any number of activities relating to the use of AERS data, such as the daily review of AERS reports, a review of summaries in the Periodic reports, generation of safety signals using data mining, and/or safety reviews for Therapeutic Biologics (such as new product safety reviews and required pediatric safety reviews).

i. Example 1: A Medical Officer has been monitoring case reports of seizures with product X and notifies the Branch Chief of a safety issue.

ii. Example 2: Stevens Johnson syndrome and hemolytic anemia are identified (based on AERS data) during an 18-month post-approval safety review.

b. The safety issue was initiated by a sponsor who submitted a labeling supplement requesting additions or changes to the safety sections of labeling to address the safety issue. However, FDA had requested the sponsor submission and AERS data had identified or contributed to the issue.

c. The original source was one or more case reports or safety findings from a non-AERS source. However, AERS data heavily contributed to the issue becoming a safety issue.

i. 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.

ii. Example 2: A manufacturer reports possible bacterial contamination of a product; AERS contains numerous reports of patient infection with the contaminating organism.

4. Exclude safety issues from the quarterly posting where:

a. The safety issue was initiated by the Sponsor who submitted a labeling supplement requesting additions or changes (addressing the safety issue) to the safety sections of labeling. This issue was not identified by AERS prior to the Sponsor's submission.

b. The safety issue originated from findings from a clinical trial, epidemiologic study, registry, literature, or any other source (and AERS data did not heavily contribute).

c. The safety issue originated from a foreign regulatory agency, World Health Organization (WHO) or other major/international health organization, and the issue was already considered by this source to be a safety signal prior to FDA becoming aware of the issue.

- Example: WHO Signal publication is released which addresses the 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 AERS (and AERS data did not heavily contribute).

5. 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, the clinical branch chief and the cognizant safety team of anticipated Internet postings. Route to OBE Director and DE RPM **[Branch Chief and DE MOs]**

6. Concur with recommended Internet postings. **[OBE Office Director]**

7. Route the draft posting to the CDER 921 project manager for preliminary review to ensure consistency with CDER postings and format. **[DE RPM]**

8. Review Internet posting for compliance with FDAAA **[CBER Safety Working Group]**.

- CBER's Safety Working Group (SWG) co-chairs will determine whether a draft posting warrants review by the Center Director.

9. Concur with recommendation for posting or make appropriate revisions; return to DE RPM. **[SWG or CBER Center Director]**

10. Route the posting to OCOD/EDT for disclosure review after receiving concurrence from SWG or the CBER Center Director. **[DE-RPM]**

11. Conduct disclosure review and notify the DE RPM of the outcome of the review. **[OCOD/EDT]**

12. Route cleared posting to the CDER 921 Team Project Manager for Internet posting. **[DE-RPM]**

13. Route the final posting to the relevant Product Office RPM and notify the Product Office Clinical Branch Chief and RPM that product sponsors can be notified of the upcoming posting. **[DE-RPM]**

14. Contact the product sponsor and notify them of the upcoming posting. **[Product Office RPM]**

II. Appendix

N/A

III. References

Web links to the references below can be found in the list following the History Section

1. Potential Signals of Serious Risks/New Safety Information Identified from the Adverse Event Reporting System (AERS) website: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm

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 http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm

3. FDA Safety Notifications http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/default.htm

IV. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
OBE/SWG	Robert A. Yetter, PhD	Oct 18, 2011	1	First version