POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

Notifying Applicants of Sentinel Analyses and Results

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PURPOSE

This MAPP describes the policies and procedures for notifying an applicant or a holder of a new drug application or a biologics license application about certain types of safety studies conducted in the Sentinel System. The active risk identification and analysis (ARIA) system is the part of the Sentinel System that may be used to evaluate potential serious risks in drug products when FDA has determined that this system under section 505(k)(3) of the Federal Food Drug and Cosmetic Act (FD&C Act) is sufficient to analyze the potential serious risk. This MAPP describes the content, method, and timing of applicant notifications related to the use of ARIA. This MAPP includes policies and procedures for notifying applicants when an analysis is conducted in Sentinel ARIA and the results of that analysis. Applicant notification is not expected for postmarket studies consisting of descriptive ARIA analyses conducted as part of FDA's routine pharmacovigilance and such studies are not addressed in this MAPP.

BACKGROUND

Section 905 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) mandated the creation of an active post-market risk identification and analysis system also referred to as the new pharmacovigilance system.[1,2] In May 2008, FDA announced the launch of the Sentinel Initiative, a public health program designed to build and implement a national electronic system for monitoring the performance of FDA-approved medical products that led to the creation of the Sentinel System.[3] FDA established the Sentinel System (Sentinel), a comprehensive active

[1] Section 505(k)(3) of the FD&C Act
[2] See Sentinel Website for additional information: https://www.sentinelinitiative.org/background
[3] The Sentinel Initiative. https://www.fda.gov/media/79652/download

surveillance system, to complement FDA's existing postmarket capabilities and to monitor the safety of approved drugs[4] using large sets of electronic health care data.

Within Sentinel, the ARIA system comprises predefined, parameterizable, reusable routine analysis tools combined with the electronic data in the Sentinel Common Data Model.[5,6] FDA considers the Sentinel's ARIA system to be the active postmarket risk identification and analysis system for the purposes of section 505(k)(3) of the FD&C Act. In February 2016, FDA integrated the fully operational Sentinel System into its program for human drug review and determined that Sentinel's ARIA system would meet the mandate described in Section 905 of FDAAA.

Sentinel's ARIA system has several major roles:

- To investigate potential risks associated with the post-approval use of a drug that were identified during the review of a drug application (original or efficacy supplement) or when FDA becomes aware of new safety information.[7,8,9]
- To monitor medical product safety following product approval, including signal identification, refinement, and evaluation.
- To improve FDA's understanding of how medical products are used after product approval, through the use of real-world data.

The Sentinel System uses a distributed database design, where data partners harmonize their data using a common data model but retain physical and operational control of their own data. To run an analysis, a coordinating center develops executable code and distributes it to all participating data holders who run the analysis on their own systems and return the results to the coordinating center to aggregate. Thus, whenever an analysis is executed in the Sentinel's ARIA System, an *analytic package* is created and sent to all data holders who are contributing data to a given analysis. This analytic package is an electronic folder containing all analytic code and study parameters necessary to complete an analysis. When made publicly available, the analytic package allows other investigators to replicate the analysis in other systems that have data formatted in the Sentinel Common Data Model. Thus, the analytic package plays a critical role in

[4] For the purposes of this MAPP, all references to "drugs" refers to FDA-approved human drugs, including both brand and generic drugs as well as biological products.
[5] Information about the ARIA analytic tools is available on the FDA's Sentinel web page at https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria
[6] The Sentinel Common Data Model is the standardized data structure employed by all Sentinel data partners. Information about the Common Data Model is available at https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model
[7] FDA Guidance for Industry: *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*
[8] Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(o)(3)) authorizes FDA to require certain postmarketing studies and clinical trials for prescription drugs approved under section 505(c) of the FD&C Act and biological products approved under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262).
[9] Before requiring a postmarketing study, FDA must find that adverse event reporting under section 505(k)(1) of the FD&C Act and the active postmarket risk identification and analysis system under section 505(k)(3) of the FD&C Act will not be sufficient to meet the study purpose to assess a known serious risk related to the use of the drug; to assess signals of a serious risk related to the use of the drug; or to identify an unexpected serious risk when available data indicate the potential for a serious risk.

communicating the details of each Sentinel analysis with drug applicants and ensuring transparency with all stakeholders.[10]

The core scientific capabilities of Sentinel's ARIA system are continually improving and are expected to grow over time; ARIA currently affords three different types of analyses:

- Level 1 analyses are descriptive analyses conducted to characterize drug use in populations (e.g., among children or pregnant women), patterns of drug use (e.g., duration of use, concomitant use with other drugs, or by indication), or to calculate rates of health conditions of interest.
- Level 2 analyses are inferential analyses conducted to identify cohorts of interest and perform complex adjustment for confounding; they typically generate effect estimates and confidence intervals.
- Level 3 analyses are inferential analyses conducted to identify cohorts of interest and perform complex adjustment for confounding repeatedly as part of prospective sequential analysis. A Level 3 analysis is a prospective Level 2 analysis that performs repeated analyses as data are accumulated over time.

POLICY

1. The Office of New Drugs (OND) will notify the applicant of a drug application (original or efficacy supplement) when OND and the Office of Surveillance and Epidemiology (OSE) intend to initiate a study and have determined that Sentinel ARIA is sufficient to assess a potential serious risk under section 505(o) of FD&C Act.
    a. Notification is made in the approval letter.
    b. Notification is also made during the Late Cycle meeting.

2. OSE will notify the applicant when the study parameters are finalized and before posting.
    a. Notification is made by email and the analytic package or study protocol (for protocol-based assessments) is posted to the Sentinel Initiative website.
    b. The notification and website link are provided at least 2 business days prior to posting.

3. OSE intends to notify the applicant when OSE first releases Sentinel ARIA study results (e.g., at a scientific conference or on the Sentinel Initiative website):[11]

[10] Protocol-based assessments that use either full custom programming or data outside of the Sentinel Common Data Model are not considered part of ARIA. However, because they are inferential analyses, OSE intends to follow the same principles and processes described in this MAPP for applicant notification. Additionally, when full programming is used, FDA plans to post the study protocol as opposed to an analytical package, which is posted for ARIA Sentinel analyses.

[11] The study results will contain the key study parameters and all Sentinel results that were discussed, presented, or incorporated into FDA's regulatory decision-making process. OSE intends that the published study results will comprehensively identify the information considered during any decision-making process associated with the study results, except for information excluded as confidential commercial information.

a. Notification is made at least 2 business days prior to the first public release of study results, unless the release is part of an FDA Advisory Committee package or in a peer-reviewed publication. When an Advisory Committee meeting is scheduled, the study results generally will be in the Advisory Committee background package that applicants receive 30 days prior to the meeting.

b. OND intends to send the study results to applicants when the study results inform a regulatory action, such as a safety-related labeling change. For example, if FDA is requiring a safety labeling change, then the Agency will provide the supporting Sentinel data to the applicant as part of its justification for taking the regulatory action.

4. When FDA deems that urgent communication about the safety of an FDA-approved product is necessary, notification to the applicant prior to the release of Sentinel ARIA results may not be possible. In these situations, which may involve adverse events that are emergent threats to public health that require immediate action to mitigate or prevent harm, timeliness and transparency to the public are paramount.[12,13]

5. Drug applicants of medical products serving as comparators in a Sentinel ARIA Assessment will not be notified unless the comparator medical product is also under evaluation.

6. Notification letters include both the drug name (or drug class) and the health outcome(s) of interest being studied.

The following charts summarize whether and when an applicant is notified of an ARIA Sentinel analysis. Whether an applicant is notified depends on the type of analysis requested by FDA. Table 1 summarizes this information.

Table 1: ARIA Analyses and Applicant Notification

Type of analysis	Postmarket studies FDA has determined the ARIA system is sufficient for the purposes of section 505(o)(3)(B)	Postmarket studies conducted as part of FDA's routine pharmacovigilance
Descriptive ARIA analyses (Level 1)	This MAPP describes the applicant notification processes	No applicant notification
Inferential ARIA analyses (Level 2 and Level 3)	This MAPP describes the applicant notification processes	This MAPP describes the applicant notification processes

[12] See FDA Guidance Drug Safety Information – FDA's Communication to the Public (March 2007); FDA's Draft Guidance Drug Safety Information – FDA's Communication to the Public (March 2012, revision 1).

[13] FDA may choose to release study results in a variety of ways including posting Sentinel ARIA results on the Sentinel Initiative website, presenting results at Advisory Committee meetings or scientific conference, or through a Drug Safety Communication.

When and how an applicant is notified depends on the stage of the study and when the results from the study are first made public. Table 2 provides some examples.

Table 2: Examples of the Applicant Notification Process

Example 1: Potential Serious Risk Identified During Review of a Drug Application (Original or Supplement)

Stages	Applicant Notification (Yes/No)
Actions during the approval process	
1. FDA decides to initiate a study	Yes, in the approval letter (and during Late Cycle Meeting, if applicable)
Actions after FDA approval	
2. FDA finalizes study design and parameters	Yes, via email and posting of ARIA analytic package (or study protocol) on the Sentinel Initiative website
3. FDA presents results at a scientific conference	Yes, via email because this is the first public release of results
4. FDA publishes results in a scientific journal	No, because applicant notification is not planned if the first public release of study results is through a scientific publication
5. FDA posts results report on Sentinel website	No, because we anticipate results would have been released previously as described in steps 3 and 4. However, applicant can be notified if steps 3 or 4 have not occurred

Example 2: Potential Serious Risk Identified in the Postmarket Phase

Stages	Applicant Notification (Yes/No)
1. FDA decides to initiate a study	No, because applicant will be notified under the NISS procedures[14]
2. FDA finalizes study design and parameters	Yes, via email and posting of ARIA analytic package (or study protocol) on the Sentinel Initiative website
3. FDA presents results at an Advisory Committee Meeting	No, because applicant will have been notified in the briefing package
4. FDA presents results at a scientific conference	No, because results have been released previously during an Advisory Committee meeting
5. FDA publishes results in a scientific journal	No, because applicant notification is not planned if the first public release of study results is through a scientific publication

[14] For Newly Identified Safety Signals (NISS), applicant notification generally occurs no later than 1 month from the time the NISS evaluation phase begins, as described in MAPP 4121.3 "Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)." The notification serves to inform the applicant of the NISS but is not intended to communicate information about the studies used to evaluate the NISS, including any use of ARIA.

6. FDA posts results report on Sentinel website	No, because we anticipate that results would have been released previously as described in steps 3, 4, and 5. However, applicant can be notified if steps 3, 4, or 5 have not occurred

RESPONSIBILITIES

In the Pre-approval Phase, During Review of an Application (Original or Efficacy Supplement):

OSE is responsible for:

- Uploading into CDER's electronic archival system the completed review memo that describes FDA's ARIA sufficiency determination for all potential serious risks that require further study identified during the review of an application.
    - The OSE Division of Epidemiology (DEPI) reviewer will use the criteria for Sentinel ARIA sufficiency determinations described in the guidance for industry entitled Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.
- Coordinating with OND on the ARIA sufficiency determination to inform the postmarket requirement/postmarket commitment (PMR/PMC) development template, the Late Cycle Meeting, and the approval letter.
- Reviewing the draft approval letter for content related to the studies to be conducted in Sentinel ARIA or studies to be conducted as a PMR in which Sentinel ARIA was deemed not sufficient.

OND is responsible for:

- Using the Sentinel ARIA sufficiency determination to inform the PMR/PMC development template when OSE has determined that Sentinel ARIA is not sufficient to address the potential serious risk.
- Using the Sentinel ARIA sufficiency determination to inform the Late Cycle Meeting and/or Approval Letter, as appropriate.

In the Post-approval Phase, During or After the Conduct of the Sentinel ARIA Study:

OSE is responsible for:

- Setting a target date for the applicant notification that is at least 2 business days prior to posting a Sentinel analytic package (or study protocol) and prior to releasing study results.
- Drafting the applicant notification letter, which will describe the product under evaluation, the health outcome of interest, source of the safety concern, and the online location of the analytical package. Coordinate clearance of the notification letter to the applicant with the relevant review division.

- Signing and sending the applicant notification letter.
- Posting the analytic package, as appropriate.
- Releasing study results.

OND is responsible for:

- Sending study results to applicants to facilitate regulatory action, as appropriate.

PROCEDURES

1. Communications to the Applicant During Review of New Drug Applications/Biologic License Applications or Efficacy Supplements

- OSE DEPI reviewer will copy the OND clinical reviewer when the Sentinel ARIA sufficiency memo is uploaded into CDER's electronic archival system and notify the OND clinical reviewer that the sufficiency determination(s) can be used to inform the PMR/PMC development template.
- OND Regulatory Project Manager (RPM) will use the Sentinel ARIA Sufficiency Determination to inform the draft approval letter.
- OSE DEPI reviewer will coordinate with the OND clinical reviewer, OND Deputy Director for Safety (DDS), OND Associate Director for Safety (ADS), and OND RPM to communicate the Sentinel ARIA sufficiency determination to the applicant at the Late Cycle Meeting. If the sufficiency determination is made after the Late Cycle Meeting, the sufficiency determination will be communicated to the applicant in the approval letter.
- OND RPM will send the OSE DEPI reviewer the draft approval letter containing template language that communicates the Agency's intent to assess a serious risk in Sentinel ARIA.
- OSE DEPI reviewer will review, revise as appropriate, and concur with the Sentinel ARIA template language included in the product approval letter.

2. Communications to the Applicant Occurring After Approval

A. Notification Before Posting the Analytic Package or Study Protocol

After the Sentinel ARIA study parameters have been finalized, and all data partners have successfully executed the analysis program without error, OSE will post the analytic package containing all study parameters and analytic programming code on the Sentinel Initiative website. For protocol-based assessments, OSE will post the study protocol on the Sentinel Initiative's website.

- OSE Sentinel Team Program Manager will coordinate setting:
  - a target posting date for the analytic package or study protocol
  - a date to notify applicants at least 2 business days before the posting date
- OSE Sentinel Team Program Manager will draft the notification letter(s) using the available CDER template.

- OSE Sentinel Team Program Manager will coordinate clearance of the notification letter to the applicant. OND review division DDS, ADS, Safety Regulatory Project Manager (SRPM), OSE DEPI reviewer and OSE DEPI team leader will review, revise as appropriate, and concur with the content of the applicant notification letter.
- OSE Sentinel Team Program Manager will sign the letter, enter the applicant notification letter into CDER's electronic archiving system (e.g., DARRTS) and email the automatically generated electronically signed letter to the applicant. The email will be sent to the applicant on the same day that the letter is signed.
- OSE Sentinel Team Program Manager will coordinate the posting of the analytic package on the Sentinel Initiative website.

B. Notification Before Initial Public Release of the Results of a Sentinel ARIA Inferential Study or Level 1 Analyses Deemed Sufficient Under Section 505(o)(3).

OSE Sentinel Team Program Manager will notify relevant applicants at least 2 business days before the first public release of the results of a Sentinel ARIA inferential study (i.e., level 2 or level 3 analysis) or Level 1 Analyses Deemed Sufficient Under Section 505(o)(3) on the Sentinel Initiative website.

Note: Applicant notification is not planned if the first public release of study results is through a scientific publication or the study results are part of an Advisory Committee briefing document.

- OSE Sentinel Team Program Manager will determine whether the criteria for notification to the applicant are met:
    - Confirm that this is the first public release of the results of a Sentinel ARIA analysis.
    - Confirm that the method of public release is not through a publication or an Advisory Committee briefing document. Examples of public release of information for which FDA intends to provide applicant notification include presentations at scientific conferences or posting results on the Sentinel Initiative website that can often occur prior to official publication.
- If the notification criteria are met, the OSE Sentinel Team Program Manager will draft the notification letter(s) using the available CDER template.
- OSE Sentinel Team Program Manager will coordinate clearance of the notification letter to the applicant. OND review division DDS, SRPM, OSE DEPI reviewer and OSE DEPI team leader will review, revise as appropriate, and concur with the content of the applicant notification letter.
- OSE Sentinel Team Program Manager will sign the letter, enter the applicant notification letter into CDER's electronic archiving system (e.g., DAARTS) and email the automatically generated electronically signed letter to the applicant. The sign off date should correspond with the date that the email was sent to the applicant.

When FDA deems that urgent communication about the safety of an FDA approved product is necessary, notification to the applicant prior to the release of Sentinel ARIA analytical results may not be possible. CDER may choose to release study results of any Sentinel analysis without

early applicant notification. In this scenario, the notification letter will be sent by the OSE Sentinel Team Program Manager after the study results are publicly released.

REFERENCES

1. Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, October 2019. https://www.fda.gov/media/131980/download
2. Detailed information about the ARIA system is available at the Sentinel System website: https://www.sentinelinitiative.org/
3. https://www.fda.gov/media/99140/download (FDA PDUFA VI)
4. Section 505(k)(3) of the FD&C Act.

DEFINITIONS

New safety information with respect to a drug, means information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by FDA about—

(A) a serious risk or unexpected serious risk associated with use of the drug that FDA has become aware of (that may be based on a new analysis of existing information) 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

(B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

EFFECTIVE DATE

This MAPP is effective upon date of publication.