POLICY AND PROCEDURES

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

FDA Posting of New Safety Information or Potential Signals of Serious Risks Identified in the FDA Adverse Event Reporting System

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PURPOSE

This MAPP describes how Center for Drug Evaluation and Research (CDER) staff develop, review, post, and update quarterly reports of new safety information or potential signals of serious risks of human prescription drug and biological products[1] and human nonprescription drugs[2] identified through the surveillance and evaluation of postmarketing data in the FDA Adverse Event Reporting System (FAERS).[3]

[1] For the purposes of this MAPP, references to *drugs*, and *drug and biological products* include drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262).

[2] For the purposes of this MAPP, the term *nonprescription drugs* describes nonprescription drug products approved under section 505 of the FD&C Act and nonprescription drug products without an approved application under section 505 of the FD&C Act that are governed by section 505G of the FD&C Act (21 U.S.C. 355h) (referred to as *OTC monograph drugs*).

[3] This system was formerly the Adverse Event Reporting System (AERS) and was renamed FDA Adverse Event Reporting System on September 10, 2012.

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). 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."

In 2016, section 3075 of the 21st Century Cures Act amended section 505(k)(5) of the FD&C Act to strike "bi-weekly screening" as required by FDAAA, and inserted "screenings"; it also added the requirement that FDA make 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 CDER and the Center for Biologics Evaluation and Research (CBER) regularly conduct routine safety surveillance to identify new safety information or a potential signal of a serious risk.[4] When a new safety signal for a marketed drug regulated by CDER is identified[5] (from various sources, such as the FAERS database, literature, or regulatory submissions), CDER staff create a newly identified safety signal (NISS) record in CDER's Lifecycle Signal Tracker (LiST) to facilitate timely evaluation, and management of the new safety signal.[6,7]

[4] 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.
[5] CDER's criteria for a NISS are that the information represents: (1) a serious adverse event, medication error, or an adverse event that suggests therapeutic inequivalence or product quality issue, and the information indicates a likely safety signal that warrants further investigation into whether there is a causal association or a new aspect of a known association; or (2) a product quality issue that could negatively affect public health or the benefit-risk profile of a product, and cannot be resolved through existing routine processes (e.g., drug recalls, adverse inspection findings). See MAPP 4121.3 Collaborative Identification, Evaluation and Resolution of a Newly Identified Safety Signal (NISS).
[6] See MAPP 4121.3 Collaborative Identification, Evaluation and Resolution of a Newly Identified Safety Signal (NISS), which describes the policies and procedures for CDER staff for tracking and the pre-evaluation, evaluation, and action phases of a newly identified safety signal (available at https://www.fda.gov/media/137475/download).
[7] CBER has separate but similar processes for tracking, evaluating, and managing new safety information or a potential signal of a serious risk for marketed drugs regulated by CBER. For more information refer to CBER's Standard Operating Procedures and Policies 8420: FDAAA Section 921: Posting of Potential Signals of Serious Risk.

When a NISS advances from the pre-evaluation phase to the evaluation phase, CDER notifies the application holder(s) and/or drug manufacturer(s) of drugs included in the NISS evaluation that a NISS was opened and has been determined to warrant an evaluation.[8] If the determination to evaluate the NISS is based wholly or in part on FAERS data and meets the criteria for inclusion in the quarterly report (i.e., new safety information or a potential signal of a serious risk), CDER will also provide a notification not less than 72 hours before the quarterly report is publicly posted.[9]

Typically, the appearance of a drug on a quarterly report represents the sharing of information with the public while FDA is evaluating the NISS. The appearance in a quarterly report does not mean that FDA concluded that the drug is associated with the serious risk or that FDA identified a causal relationship between the drug and the serious risk. As a result, FDA may not yet be able to determine or communicate what type of regulatory action, if any, to include on the quarterly report.

POLICY

1. The quarterly report will include new safety information or potential signals of serious risks associated with the use of drugs.[10] If new safety information or a potential signal of a serious risk is also associated with a pending compliance or enforcement action, CDER may delay the inclusion in the quarterly report until after the action is taken.

2. CDER will identify new safety information or potential signals of serious risks for inclusion on the quarterly report using NISS in LiST as the CDER data source. CBER staff will identify new safety information or potential signals of serious risks for CBER-regulated products for the quarterly report in accordance with CBER Standard Operating Procedures and Policies 8420.[11]

3. CDER will include a NISS in a quarterly report posted on the FDA website when: (a) FAERS was selected as a signal source during the pre-evaluation phase in LiST, which means that the NISS is based wholly or in part on FAERS data; (b)

[8] If the notification or the timing of the notification might affect an inspection, voluntary product recall, or other potential compliance or enforcement actions (e.g., warning letter, seizure), CDER may delay issuing the notification. See MAPP 4121.3 Collaborative Identification, Evaluation and Resolution of a Newly Identified Safety Signal (NISS) for more information.
[9] As specified in the Prescription Drug User Fee Amendments VI, applicants of generic drugs are excluded from receiving this notification.
[10] New safety information or potential signals of serious risks associated with drugs marketed without an approved application including products authorized under an emergency use authorization or compounded products will generally be communicated by the FDA outside of a quarterly report (e.g., Consumer Updates), as appropriate.
[11] See footnote 7.

the NISS has advanced to the evaluation phase;[12] and the NISS represents new safety information or a potential signal of a serious risk.

4. CDER will notify each application holder[13] of an approved new drug application (NDA) or biologics license application (BLA) that has a drug included on the quarterly report not less than 72 hours (i.e., 3 business days) before the quarterly report is publicly posted unless the notification or the timing of the notification might affect a pending compliance or enforcement action.[14]

5. The quarterly report will post on the FDA website approximately 90 days following the last day of a quarterly report period.

6. When there is non-alignment that cannot be resolved through existing forums for management review during the review of the LiST report and developing the quarterly report, CDER staff should adhere to the policies and procedures outlined in MAPP 4151.8 *Equal Voice: Collaboration and Regulatory and Policy Decision-Making in CDER.*

RESPONSIBILITIES

- **921 Posting Team Project Lead[15]**

    - Coordinates the quarterly report posting process within CDER and CBER.
    - Obtains a report from LiST at the beginning of each quarter and distributes the report to the CDER Office Liaisons.[16]
    - Contacts CBER each quarter to determine if any potential signals involving CBER regulated products should be included in the quarterly report.
    - Reviews and consolidates information received from the CDER Office Liaisons and facilitates discussions to resolve issues, as needed.
    - Develops the draft quarterly report from the LiST report and distributes the draft quarterly report to the CDER Office Liaisons.

[12] A NISS will not advance to the evaluation phase if preliminary information suggests that further evaluation is not warranted (e.g., labeling sufficiently describes adverse event, no action indicated, and/or does not meet the NISS criteria) or there is insufficient information (may warrant further evaluation in the future).

[13] For a NISS that represents a product quality issue associated with an adverse event that meets the 921-posting criteria, the office of the signatory authority in LiST should send the 921-posting notification.

[14] See footnote 8.

[15] A designated staff member from the Regulatory Affairs Staff in the Office of Surveillance and Epidemiology.

[16] CDER Office Liaisons are a designated point of contact in each of the following CDER sub-offices/offices: Office of Pharmacovigilance and Epidemiology (OPE) and Office of Medication Error Prevention and Risk Management (OMEPRM) in the Office of Surveillance and Epidemiology (OSE); Safety Programs and Regulatory Review staff in the Office of New Drugs (OND); Office of Generic Drugs (OGD); Office of Pharmaceutical Quality (OPQ); and Office of Compliance (OC) that communicates with the 921 Posting Team Project Lead.

- Obtains CDER office clearance and disclosure review of the quarterly report and updated quarterly reports prior to web posting.
- Provides the final cleared quarterly report or updated quarterly report to the CDER OCOMM Web Team for web posting.
- Notifies CDER and CBER of the publication of the quarterly report to the FDA website every quarter.
- Verifies all "Notification of Section 921 Posting" **(hereafter referred to as 921-posting notifications)** correspondence has been sent by CDER and CBER.
- Determines the posting date is not less than 72 hours after all 921-posting notifications are issued.
- Initiates the process to update and archive quarterly reports that were previously posted on the FDA website.
- Ensures that the appropriate staff in the Office of the Commissioner[17] are notified if any information in the quarterly report may be of interest to the media.
- Archives all records created in the appropriate electronic record keeping system.[18]

- **921 Posting Team[19]**

  - Reviews the LiST report for every NISS where their respective office/division is part of the NISS team to determine the NISS that should be included in the quarterly report.
  - Reviews and edits the posting language on the draft quarterly report for every NISS that their respective office/division is part of the NISS team.
  - Provides additional information on the background and status of the NISS when questions arise regarding the decision to include in the quarterly report.
  - Reviews and edits language for updates to previously posted quarterly reports.

[17] This notification should include FDA's Office of External Affairs and other staff in the Office of the Commissioner, as applicable.
[18] For more information on managing and retaining records, see MAPP 7600.11, *CDER Electronic Record Keeping Systems* (available at https://www.fda.gov/media/89742/download).
[19] Members include review staff in OSE and OND. May also include review staff in OGD, OPQ, and/or OC. Members of the 921 Posting Team are also members of the NISS team for the NISS that is reviewed to determine if the NISS meets criteria for inclusion in the quarterly report.

- In addition to the responsibilities described above, if the CDER office is listed as the signatory authority for a NISS in LiST, designated staff from the 921 Posting Team:[20]

    - Verifies that the NISS notification to the application holder was issued in the NISS process.[21]
    - Drafts and sends a 921-posting notification to application holder(s) of affected applications that are included in the quarterly report.
    - Ensures 921-posting notifications are archived in the appropriate electronic record keeping system.

- **CDER Office Liaison(s)[22]**

    - Communicates with the 921 Posting Team Project Lead **(hereafter referred to as the Project Lead)** throughout the entire quarterly report posting process.
    - Communicates with the 921 Posting Team and coordinates all LiST report quarterly report comments and quarterly report updates within their respective offices/divisions.
    - Obtains clearance within their office based on their office's internal clearance procedures.
    - Notifies the Project Lead if any information in the quarterly report may be of interest to the media.
    - Notifies and provides instructions to appropriate staff to issue 921-posting notifications.

- **OSE Regulatory Affairs Staff**

    - Serves as the Project Lead.
    - Drafts responses to general inquiries regarding quarterly reports from requestors outside CDER[23] and works with CDER staff as needed to respond to an inquiry.

[20] The designated staff for OND are the Safety Staff (e.g., Deputy Director for Safety/Associate Director for Safety, Safety Regulatory Project Manager).
[21] The Prescription Drug User Fee Act VI specifies that communication of postmarketing safety signals by the FDA to an applicant include consistent and timely notifications. A NISS notification is communicated to the applicant when a serious safety signal involving a product is identified. A 921-posting notification is communicated not less than 72 hours before the public posting of the quarterly report.
[22] See footnote 16.
[23] Inquiries from application holders regarding quarterly reports are typically sent directly to OND and the clinical review division responsible for the CDER-regulated product is responsible for responding to the application holder.

- **OSE Director (or Designee)[24]**

    - Serves as the CDER final clearing official for new quarterly reports and updated quarterly reports, unless the OSE Director determines additional clearance is needed by the Office of Regulatory Policy (ORP).

- **CDER Division of Information Disclosure Policy (DIDP)**
    - Reviews information in quarterly reports and confirms compliance with requirements for public disclosure.[25]

- **CDER Office of Regulatory Policy (ORP)**

    - Provides CDER-level final clearance, as determined by the OSE Director.
    - Determines if a quarterly report should be cleared by the CDER Center Director.

- **CDER Center Director (or Designee)[26]**

    - Provides CDER level final clearance, as determined by ORP.

- **CBER Office of Biostatistics and Pharmacovigilance (OBPV)**

    - Provides new safety information and information on potential signals of serious risk for CBER products for inclusion in the quarterly report, to the Project Lead.
    - Provides updates to new safety information or potential signals of serious risks for CBER products that were previously posted, to the Project Lead.
    - Ensures that 921-posting notifications are sent to application holders of CBER-regulated products.
    - Ensures that new safety information or potential signals of serious risks involving CBER-regulated products that are included in the quarterly report have CBER Center-level concurrence.
    - Obtains CBER disclosure clearance for posting quarterly reports with CBER-regulated products.
    - Notifies the Project Lead if any new safety information or potential signals of serious risk for CBER products appearing in the quarterly report may be of interest to the media.

- **CDER Strategic Initiatives - International Staff - Office of the Center Director**

[24] The OSE Director may designate an individual to serve as the OSE clearing official on their behalf.
[25] The Division of Information Disclosure Policy is responsible for determining the disclosure of information in the updated quarterly report.
[26] The CDER Center Director may designate an individual to provide CDER clearance on their behalf.

- Notifies FDA international partners including but not limited to the European Medicines Agency (EMA), Health Canada, Pharmaceuticals and Medical Devices Agency (PMDA)/Ministry of Health, Labor, and Welfare (MHLW), and Medicines and Healthcare products Regulatory Agency (MHRA) of the upcoming posting of the quarterly report.

- **CDER Office of Communications (OCOMM) Web Team**

  - Publishes the quarterly report on the FDA website as directed by the Project Lead.
  - Updates prior quarterly reports on the FDA website as directed by the Project Lead.
  - Archives prior quarterly reports on the FDA website as directed by the Project Lead.

PROCEDURES

I. Initial Posting

The following procedures describe the process for developing and posting a new quarterly report.

1. Generate the LiST Report of NISS

1.1. During the first week following the close of the reporting interval,[27] the Project Lead:

a. Obtains a report from LiST of the NISS that advanced from the pre-evaluation phase to the evaluation phase during the specified reporting interval.
b. Contacts the designated point of contact in CBER's OBPV, requesting the new safety information or potential signals of serious risks for CBER-regulated products identified during the specified reporting interval.

[27] See Attachment 1 for the schedule for obtaining the data used to create the quarterly report and when each quarterly report is posted to the FDA website.

2. Review of the LiST Report

2.1. The Project Lead reviews the LiST report and follows up with the appropriate information technology staff if there are any discrepancies with the report.

2.2. The Project Lead sends the LiST report to the CDER Office Liaisons in OSE[28] **(hereafter referred to as the OSE Liaisons)**.

2.3. The OSE Liaisons send the LiST report to the OSE members of the 921 Posting Team to review and determine which NISS should be included in the quarterly report[29] (refer to policy statement #3 above).

2.4. The Project Lead reviews and reconciles all comments received. If issues arise, the Project Lead may schedule a meeting with the relevant OSE Liaisons and OSE members of the 921 Posting Team to resolve them, as needed.

2.5. Following the review by OSE members of the 921 Posting Team, the Project Lead sends the LiST report to the other CDER Office Liaisons.[30]

2.6. The CDER Office Liaisons send the LiST report to the appropriate 921 Posting Team members in their respective offices/divisions to review and concur with OSE or provide additional feedback on which NISS should or should not be included in the quarterly report[31] (refer to policy statement #3 above).

2.7. The Project Lead reviews the information received from the CDER Office Liaisons. The Project Lead facilitates discussion with the CDER Office Liaisons to resolve any issues, as needed.

2.8. If needed, the Project Lead may schedule a meeting to resolve outstanding issues. Each applicable CDER Office Liaison and applicable members of the 921

[28] The CDER Office Liaisons in OSE are designated staff from the Office of Pharmacovigilance and Epidemiology and the Office of Medication Error Prevention and Risk Management. The OSE Liaisons receive the LiST report and draft quarterly report for OSE review and have a separate review period prior to the other CDER offices.

[29] A NISS is included in a quarterly report when (a) FAERS was selected as a signal source during the pre-evaluation phase in LiST which means that the NISS is based wholly or in part on FAERS data; and (b) when the NISS advances to the evaluation phase in LiST and the NISS represents new safety information or a potential signal of a serious risk. If a NISS is associated with a pending compliance or enforcement action, CDER may delay the inclusion of the NISS until after the compliance or enforcement action is taken.

[30] The LiST report is provided to the CDER Office Liaisons for review based on the CDER office that is designated as the signatory authority in LiST for each NISS included in the report, following completion of the OSE review.

[31] See footnote 29.

Posting Team discuss each outstanding issue and make a final decision regarding which NISS should be included in the quarterly report.

3. Draft, Distribute, and Review the Quarterly Report

3.1. The Project Lead drafts the quarterly report using feedback provided by the 921 Posting Team on the LiST report and information provided by CBER OBPV to create a three-column table. See Attachment 2: Quarterly Report Template.

The following are considerations when drafting the quarterly report:

Column 1 Header: Drug Name(s)and/or Drug Class

The drug name(s) should appear on the quarterly report as follows:

- For prescription or nonprescription drugs with an approved:
  - NDA or ANDA that has a proprietary name,[32] state the proprietary name followed by nonproprietary name[33] in parentheses (e.g., DRUG-X (drugozide) tablets) as it appears on the approved drug labeling.
  - BLA that has a proprietary name, state the proprietary name followed by the nonproprietary name[34] in parentheses, followed by the dosage form (e.g., DRUG-X (drugimab-jnzt) injection, as it appears on the approved drug labeling.
- For NDAs and ANDAs that do not have a proprietary name, state the nonproprietary name (e.g., drugozide tablets) as it appears on the approved drug labeling.
- For BLAs that do not have a proprietary name, state the nonproprietary name followed by the dosage form (e.g., drugimab-jnzt injection) as it appears on the approved drug labeling.
- For nonprescription drugs approved without an approved application (OTC monograph drugs), state the nonproprietary name (e.g., drugozide oral solution) as it appears on their drug labeling. Include the proprietary name if the drug has a proprietary name.
- For a drug class, if there are:
  - 15 or fewer drugs in the drug class (e.g., glucagon-like peptide 1 (GLP-1) receptor agonists), list the drug class and the proprietary name (if any) followed by the nonproprietary name of each individual drug in the drug class.

[32] The proprietary name of a drug is its brand name (sometimes referred to as the drug's *trade name*).
[33] The nonproprietary name means a name unprotected by trademark rights that is in the public domain. The nonproprietary name for NDAs and ANDAs includes the dosage form and may include the route of administration.
[34] For more information about biological product nonproprietary names, see the guidance for industry *Nonproprietary Naming of Biological Products* (January 2017), available at https://www.fda.gov/media/93218/download. Also see the draft guidance for industry *Nonproprietary Naming of Biological Products: Update* (March 2019), available at https://www.fda.gov/media/121316/download.

- more than 15 drugs in the drug class (e.g., non-steroidal anti-inflammatory drugs (NSAIDs)), only list the drug class. The names of each individual drug in the drug class do not need to be listed.

Column 2 Header: New Safety Information or Potential Signal of a Serious Risk

The new safety information or potential signal of a serious risk should be described in no more than a few words that are easily understood by health care professionals. Preferably, the new safety information or potential signal of a serious risk should use the Medical Dictionary for Regulatory Activities (MedDRA) terminology[35] that is stated in LiST for each NISS. However, it is acceptable for the description to vary from the MedDRA terminology used in LiST if it accurately describes the adverse event or medication error (e.g., use "radiation recall phenomenon" instead of the Preferred Term *Recall phenomenon*). If the NISS applies to a specific population, identify the population (e.g., hypoglycemia in pediatric patients).

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

The *as of* date refers to the date that additional information was updated to describe the actions FDA took after the evaluation of the NISS was completed or action taken by the applicant. Please refer to Attachment 2 for examples of statements that should be included in this column. Other considerations include:

- Use FDA information sources and website links where possible. It is acceptable to provide information from non-FDA sources (e.g., Dear Health Care Provider letters) if FDA otherwise routinely refers to that source or site, or if FDA is working on the issue with a non-FDA organization.

- Use references to medical journal articles if the article addresses the NISS and the author is either from FDA or is the applicant or drug manufacturer.

3.2. After drafting the quarterly report, the Project Lead sends the report to the OSE Liaisons for subsequent review by OSE members of the 921 Posting Team.

3.3. The OSE Liaisons work with OSE members of the 921 Posting Team to review and provide comments to the draft quarterly report and return the draft report to the Project Lead.

3.3. The Project Lead reviews and reconciles all edits and comments received from the OSE Liaisons. If issues arise, the Project Lead may schedule a meeting with the relevant OSE Liaisons and OSE members of the 921 Posting Team to resolve them, as needed.

[35] When there is a difference in spelling between British English and American English, the quarterly report should defer to the American English spelling of the MedDRA term.

3.4. Following the review by OSE members of the 921 Posting Team, the Project Lead sends the draft quarterly report to the other CDER Office Liaisons.[36]

3.5. The CDER Office Liaisons work with the appropriate 921 Posting Team members in their respective offices/divisions to review and provide comments on the draft quarterly report and return the draft report to the Project Lead.[37]

3.6. The Project Lead reviews and reconciles all edits and comments received from the CDER Office Liaisons. If issues arise, the Project Lead may schedule a meeting with each applicable CDER Office Liaison and applicable members of the 921 Posting Team to resolve them, as needed.

4. Clearance and Disclosure Review of the Quarterly Report

4.1. If the quarterly report includes a CBER regulated product, the Project Lead verifies with CBER OBPV that CBER clearance is completed and the new safety information or potential signals of serious risk does not contain information that may be of interest to the media.

4.2. The Project Lead routes the draft quarterly report for CDER clearance. CDER clearance begins by requesting clearance through the CDER Office Liaisons, as appropriate[38] followed by OSE. Each CDER office should also notify the Project Lead if the new safety information or potential signals of serious risk in the quarterly report may be of interest to the media.

4.3. The OSE Director provides final CDER clearance unless the OSE Director determines additional clearance is needed by ORP.[39]

4.4. Following the clearance of the quarterly report by the 921 Posting Team, the Project Lead provides DIDP with the cleared quarterly report to conduct a disclosure review.

4.5. The Project Lead reconciles all DIDP comments.

[36] The draft quarterly report should by reviewed by each CDER office that is designated as the signatory authority in LiST for each NISS included in the draft quarterly report following completion of the OSE review.
[37] The review of the draft quarterly report by the 921 Posting Team includes confirming the inclusion of all applicable drugs and associated application numbers for each NISS.
[38] The draft quarterly report should be cleared by each CDER office that is designated as the signatory authority in LiST for each NISS included in the draft quarterly report.
[39] ORP may provide final clearance if the OSE Director determines that it is necessary. The CDER Center Director may provide final clearance if ORP determines that it is necessary.

5. Communicate the Quarterly Report to FDA Interested Parties

5.1. The Project Lead informs the CDER Office Liaisons, CDER Strategic Initiatives – International Staff and CBER OBPV of an approximate date for when the quarterly report will be publicly available. The CDER Strategic Initiatives – International Staff notifies FDA international partners[40] of the upcoming quarterly report. The Project Lead notifies the Office of the Commissioner, as needed.[41]

5.2. The Project Lead alerts the CDER Liaisons that the quarterly report is cleared and to alert the appropriate staff to initiate and confirm the 921-posting notification to the application holder(s) of each application associated with the NISS, informing them that the NISS will appear on the FDA website[42] (see Step 7: Notification to Application Holders of the Web Posting).

6. Preparation of the Quarterly Report for Web Posting

6.1. The Project Lead forwards the cleared quarterly report to the CDER OCOMM Web Team for placement on a draft webpage.

6.2. The Project Lead reviews the content on the draft webpage and provides any corrections to the CDER OCOMM Web Team prior to the live posting.

7. Notification to Application Holders of the Web Posting[43]

7.1. The CDER Office Liaisons notify the appropriate staff in their respective offices/divisions to:

- Send a 921-posting notification to each application holder of an NDA or BLA informing them that the NISS involving their drug will appear on the quarterly report. The 921-posting notification will occur not less than 72 hours (i.e., 3 business days) before the quarterly report is posted on the FDA website.

- Archive the 921-posting notification in the appropriate CDER electronic record keeping system. The Project Lead will receive an automatic notification from the CDER electronic record keeping system when the communication is archived.

[40] This notification includes but is not limited to the following: European Medicines Agency (EMA), Health Canada, Pharmaceuticals and Medical Devices Agency (PMDA)/Ministry of Health, Labor, and Welfare (MHLW), and Medicines and Healthcare products Regulatory Agency (MHRA).
[41] See footnote 17.
[42] For NISS involving OTC monograph drugs, the Consumer Healthcare Products Association is notified by the office of the signatory authority in LiST that the NISS will appear on the FDA website.
[43] For a NISS that represents a product quality issue associated with an adverse event that meets the 921-posting criteria, the office of the signatory authority in LiST should send the 921-posting notification.

7.2. The Project Lead verifies that all 921-posting notifications were sent to the affected application holders and determines the actual posting date.

8. Post on FDA Web Site

8.1. The Project Lead notifies the CDER OCOMM Web Team of the date the quarterly report can be publicly posted. The posting date will occur not less than 72 hours (i.e., 3 business days) after the last 921-posting notification was sent.

9. Archive the Quarterly Report

9.1. The Project Lead archives all documents created during the quarterly report posting process in the appropriate electronic record keeping system.

II. Updating a Quarterly Report

The following procedures describe the process for updating a quarterly report after an initial quarterly report is published on the FDA website.

1. Generate the Draft of Quarterly Report Updates

1.1. The Project Lead reviews previous quarterly reports semi-annually to identify any NISS that were closed in LiST and that need to communicate the initial FDA action.[44] After identifying each closed NISS, the Project Lead drafts language that describes the regulatory action[45] as documented in LiST and updates the additional information column. Once a NISS is updated to include an initial action, no further updates are made to a quarterly report for that respective NISS.

2. Review the Draft of Quarterly Report Updates

2.1. The Project Lead provides a draft of the quarterly report updates to the CDER Office Liaisons[46] (and CBER, if applicable) for subsequent review by members of the 921 Posting Team in their respective offices/divisions. The CDER Office Liaisons (and CBER, if applicable) provides edits and comments

[44] An update to a quarterly report may include an FDA Drug Safety Communication that describes a potential new safety issue. However, if the Drug Safety Communication does not also describe a regulatory or compliance action taken by FDA, the Drug Safety Communication is not considered an initial action for the purposes of this MAPP.

[45] For actions involving withdrawal of approval of the marketing application or revocation of the biologics license (or if additional information is not available for the drug due to voluntary withdrawal or voluntary revocation after the initial posting), the Project Lead should consult with the Office of Regulatory Policy and the Division of Information Disclosure Policy for appropriate text.

[46] The updates should be reviewed by each CDER office that is designated as the signatory authority in LiST for each NISS being updated in the quarterly report.

to the Project Lead.

- The review of the draft quarterly report updates by the 921 Posting Team should also include confirming the accuracy of each drug listed for the NISS on the report and adding any drug that was added to the NISS record in LiST after the initial quarterly report was published. If a drug is added to the updated quarterly report, the appropriate CDER Office Liaison is responsible for ensuring the application holder(s) are notified that their drug will appear on the quarterly report.

2.2. The Project Lead reviews and reconciles all edits received from the CDER Office Liaisons (and CBER, if applicable). If issues arise, the Project Lead may schedule a meeting to resolve them, as needed.

2.3. The Project Lead provides a draft of the quarterly updates report to the OSE Liaisons[47] for subsequent review by OSE members of the 921 Posting Team. The OSE Liaisons provide edits and comments to the Project Lead.

2.4. The Project Lead reviews and reconciles all edits and comments provided by OSE. If issues arise, the Project Lead may schedule a meeting with each applicable CDER Office Liaison and applicable members of the 921 Posting Team to resolve them, as needed.

3. Clearance and Disclosure Review of the Quarterly Report Updates

3.1. The Project Lead requests clearance through the CDER Office Liaisons[48] and CBER, if applicable, followed by OSE clearance after all edits and comments are resolved.

3.2. The OSE Director provides final CDER clearance.[49]

3.3. Following the clearance of the quarterly report updates by the 921 Posting Team, the Project Lead provides DIDP with the cleared quarterly report updates to conduct a disclosure review of the updated information.

3.4. The Project Lead reconciles all DIDP edits and comments prior to the web posting.

[47] OSE Liaisons receive updates to the quarterly reports for OSE to review and have a separate review period that occurs after the CDER Office Liaisons have provided edits and comments from their respective offices to the Project Lead.
[48] Updates should be cleared by each CDER office that is designated as the signatory authority in LiST for each NISS updated in the quarterly report.
[49] ORP may provide final clearance for updates to quarterly reports if the OSE Director determines that it is necessary. The CDER Center Director may provide final clearance for updates to quarterly reports if ORP determines that it is necessary.

4. Preparation of the Quarterly Report Updates for Web Posting

4.1. The Project Lead forwards the cleared quarterly report updates to the CDER OCOMM Web Team to update the quarterly reports on the FDA website.

4.2. The Project Lead reviews the content on the draft webpage and provides any corrections to the CDER OCOMM Web Team prior to the live posting.

5. Archive the Web Posting and Records

5.1. The Project Lead informs the CDER OCOMM Web Team if any previous quarterly reports can be archived from the FDA website.[50]

5.2. The Project Lead archives all documents created during the process of updating the quarterly reports in the appropriate electronic record keeping system.

REFERENCES

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

CBER SOPP 8420 FDAAA Section 921: Posting of Potential Signals of Serious Risk, effective February 27, 2022
https://www.fda.gov/media/82363/download

Food and Drug Administration Amendments Act of 2007
https://www.congress.gov/bill/110th-congress/house-bill/3580

MAPP 4121.3 Collaborative Identification, Evaluation and Resolution of a Newly Identified Safety Signal (NISS)
https://www.fda.gov/media/137475/download

PDUFA VI Commitment Letter
https://www.fda.gov/media/99140/download

New Safety Information or Potential Signals of Serious Risks Identified from the FDA Adverse Event Reporting System (FAERS)
https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system#QuarterlyReports

[50] A quarterly report is archived on the FDA website after each NISS in the report is updated with an initial action.

DEFINITIONS

FDA Adverse Event Reporting System (FAERS): A database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drugs.

Initial action: For the purposes of this MAPP, it is the first FDA action related to the posted NISS and it includes any regulatory action FDA may take after the evaluation of the NISS is completed or an action taken by the applicant. An initial action can include, but is not limited to the following:

- Any modifications to the drug labeling, including revisions to the carton labeling or container label.
- Development or modification of a Risk Evaluation and Mitigation Strategy (REMS).
- Market suspension, voluntary recall, or market withdrawal.
- An FDA decision to not take a regulatory action because the drug is not associated with the risk or there is insufficient evidence to determine that the drug is associated with the risk.

Once a NISS is updated to include an initial action, no further updates are made to a quarterly report for that respective NISS.

LiST report: A report generated every quarter of newly identified safety signals (NISS) from the Lifecycle Signal Tracker (LiST) that is reviewed by the 921 Posting Team to determine which newly identified safety signals will be included in the quarterly report as new safety information or potential signals of serious risks.

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 by the Secretary 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.

Quarterly report: As required by FDAAA, refers to the list of new safety information or potential signals of serious risks identified by CDER and CBER staff from the FAERS database and is posted to the FDA website every quarter.

Serious adverse drug experience: As defined in section 505-1(b)(4) of the FD&C Act, a serious adverse drug experience is an adverse drug experience that: (A) results in (i) death; (ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug

experience that might have cause death had it occurred in a more severe form); (iii) inpatient hospitalization or prolongation of existing hospitalization; (iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or (v), or a congenital anomaly or birth defect; or (B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described in this definition.

Signal of a serious risk: As defined in section 505-1(b)(6) of the FD&C Act, a signal of serious risk is information related to a serious adverse drug experience associated with use of a drug and derived from: (A) a clinical trial; (B) adverse event reports; (C) a postapproval study, including a study under section 505(o)(3) of the FD&C Act; (D) peer-reviewed biomedical literature; (E) data derived from the postmarket risk identification and analysis system under section 505(k)(3) of the FD&C Act; or (F) other scientific data deemed appropriate by the Secretary.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
3/29/2011	Initial	N/A
9/19/2019	Rev. 1	Updated to include 21st Century Cures and PDUFA VI of notification not less than 72 hours prior to posting.
12/31/2025	Rev. 2	Updated to include new policy statements and a new Responsibilities section; clarified the process in the Procedures section to align with the NISS process; and added process maps.

ATTACHMENT 1: QUARTERLY REPORT SCHEDULE

The following table describes the schedule for obtaining the data used to create the quarterly report and when each quarterly report posts to the FDA website.

	Quarter in Which a NISS Moved into the Evaluation Phase and May Be Eligible for Inclusion in a Quarterly Report	**Generate the LiST Report**	**Web Posting Date**
Quarter 1	January 1 – March 31	First week in April	Approximately June 30
Quarter 2	April 1 – June 30	First week in July	Approximately September 30
Quarter 3	July 1 – September 30	First week in October	Approximately December 31
Quarter 4	October 1 – December 31	First week in January	Approximately March 31

ATTACHMENT 2: QUARTERLY REPORT TEMPLATE

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

January – March 20YY

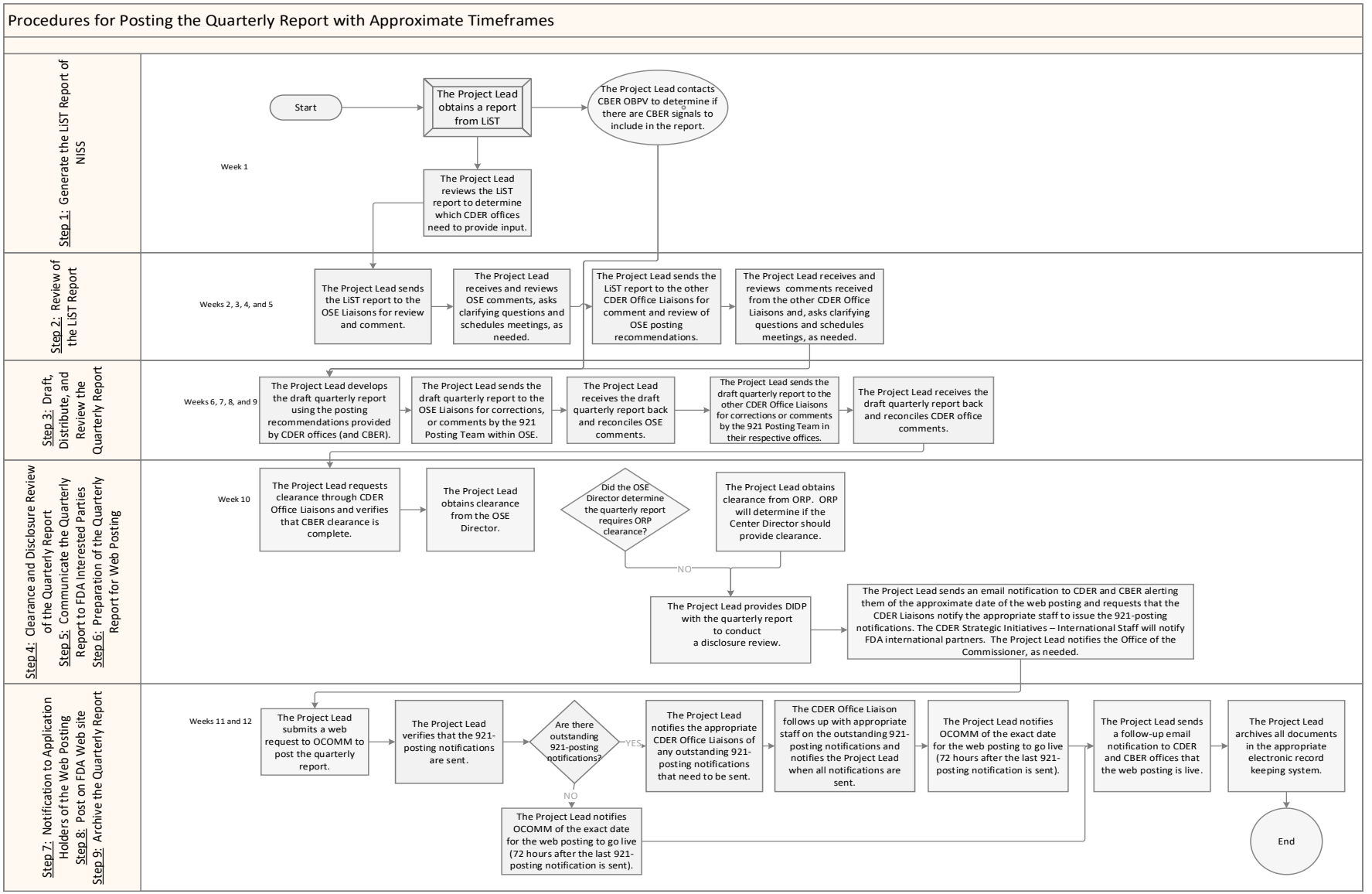
The drug(s) included in any of the new safety information or potential signals of serious risks listed below may also include generic drug product(s) and biosimilar or interchangeable biosimilar biological product(s), as appropriate.

Drug Name(s) and/or Drug Class	New Safety Information or Potential Signal of a Serious Risk	Additional Information (as of Month Day, 20YY)
Refer to page 10 of this MAPP for considerations when stating the drug name or drug class.	State the appropriate MedDRA term that describes the event or provide a description of the event (e.g., drug labeling confusion contributing to medication error).	This section should describe the initial action taken by FDA and any public FDA communications, or an action taken by the applicant. Examples include but are not limited to the following: 1. FDA is evaluating the need for regulatory action. 2. FDA determined that no action was necessary at the time based on available information. 3. FDA has determined that the last approved labeling *[insert drug product name]* is adequately labeled for *[insert risk described in column 2]*, and that no further regulatory action was necessary at the time. 4. The *[insert the name of the section]* section of the labeling was updated in Month 20YY to include information about *[insert description of what was updated]*. 5. The container label(s) and carton labeling for *[insert drug product name]* were revised in Month 20YY to differentiate the drug from *[insert drug product name]*. 6. The container label, carton labeling, and

		Prescribing Information were revised in Month 20YY to mitigate the potential for medication errors. 7. An FDA Drug Safety Communication was issued on Month Day, 20YY. 8. FDA approved a Medication Guide in Month 20YY. 9. FDA approved a Risk Evaluation and Mitigation Strategy (REMS) in Month 20YY. 10. Voluntary recall. Note: For actions involving withdrawal of approval of the marketing application or revocation of the biologics license (or if additional information is not available for the drug due to voluntary withdrawal or voluntary revocation after the initial posting), consult with CDER's Office of Regulatory Policy for appropriate text.*

* This category applies: (1) on or after the effective date of FDA's withdrawal of approval of an NDA or ANDA for a drug product published in the Federal Register; or (2) on or after the effective date of FDA's revocation of the license, as described in FDA's "Purple Book: Database of Licensed Biological Products" or the *Federal Register*. This category does not apply to products that have been discontinued from marketing, provided that approval of the NDA or ANDA has not been withdrawn or the biologics license has not been revoked. However, if FDA has published a notice of intent to withdraw approval of the NDA or ANDA or revoke the biologics license, consult with CDER's Office of Regulatory Policy and the Division of Information Disclosure Policy.

ATTACHMENT 3: QUARTERLY REPORT POSTING PROCESS



ATTACHMENT 4: QUARTERLY REPORT UPDATES PROCESS