POLICY AND PROCEDURES

OFFICE OF THE CENTER DIRECTOR

Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)

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PURPOSE

Consistent with FDA's mission to promote and protect public health, the Center for Drug Evaluation and Research (CDER, the Center) monitors the benefit–risk profile of drugs over their lifecycle and takes regulatory or compliance action when necessary to ensure their continued benefit–risk balance. This manual of policies and procedures (MAPP) describes the policies and procedures in CDER for collaborative identification, evaluation, and resolution of a *newly identified safety signal* (NISS) associated with marketed drugs.[1]

[1] *Marketed drugs* refers to approved drug products, including those that are licensed as biological products (biologics), marketed yet unapproved drug products, products marketed under monograph regulations, compounded products, and medical gases.

Multiple offices in CDER, including the Office of Compliance (OC), Office of Generic Drugs (OGD), Office of New Drugs (OND), Office of Pharmaceutical Quality (OPQ), Office of Surveillance and Epidemiology (OSE), and Office of Translational Sciences (OTS) have roles in identifying, evaluating, and resolving a NISS, depending on the office's role in CDER and the staff's expertise. This MAPP describes at a high level how and when communication flows from one office or discipline to another. More detailed information can be found in office-specific procedures. This MAPP also describes how CDER's Incident Management Plan[2]—the process for managing incidents during an existing or potential emergency—converges with the process described in this MAPP.

CDER's Drug Risk Management Board (DRMB) will conduct periodic reviews of the policies and procedures described in this MAPP to ensure that CDER is following the MAPP in a consistent fashion.

POLICY

CDER will:

1. Include each NISS in CDER's central database[3] to facilitate timely evaluation and management. A safety signal that is not a NISS (i.e., does not meet the NISS criteria on pages 4-5) is followed through office-specific policies and procedures, but need not be centrally documented.

2. Encourage CDER staff to open a NISS in any organizational unit that has been identified through product safety surveillance, review work conducted as part of various scientific and regulatory responsibilities, and/or awareness through data sources (see Attachment 1 table 1).

3. Ensure consistency with established pharmacovigilance drug review practices and principles from FDA's Best Practices in Drug and Biological Product Postmarket Safety Surveillance (Best Practices) document[4] throughout the NISS process.

4. Allow an individual CDER staff member, during the pre-evaluation phase, to determine whether a NISS requires an evaluation or not. However, a team of

[2] CDER Incident Management Plan, for internal FDA use only, available at http://inside.fda.gov:9003/downloads/cder/counter-terrorismandemergencycoordinationstaff/ucm288900.pdf.

[3] A *central database* refers to Appian, which will archive materials into CDER's system of record.

[4] U.S. Food and Drug Administration. Draft Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff, available at https://www.fda.gov/media/130216/download.

representatives from the relevant scientific and regulatory disciplines[5] is always required, during the evaluation phase, to determine whether a NISS is classified as an *important potential risk* or a *potential risk*.

5. Form a team to evaluate a NISS. Each NISS team will include a *Signal Identifier*, a *Safety Lead*, a *Signatory Authority* (in some cases, the same CDER staff member can serve in all three roles), and a *Project Manager*. A *Safety Lead* must add a *Team Member* to the evaluation if requested and if the discipline is not already included in the evaluation.

6. Complete an evaluation within 6 months for a NISS categorized as an *important potential risk* and within 12 months for a NISS categorized as a *potential risk*.

7. Be transparent to industry and the public about CDER's postmarket safety work. (See page 9 for more details about notifying application holder(s) or drug manufacturer(s)).

8. Escalate an *emergency NISS* to CDER leadership to inform next steps and evaluation timeline for the NISS. An emergency NISS is one that has resulted in fatalities, has the potential to affect a large number of patients, and if it is promptly acted upon, lives could be saved or the chances for other severe harms reduced.

9. Seek alignment on NISS-related decisions and recommendations. When there are differing professional opinions among team members, efforts will be made to resolve disagreements through discussion at existing forums for management review (e.g., DRMB, Medical Policy and Program Review Committee (MPPRC), or CDER Council for Pharmaceutical Quality (CPQ)).

10. Consider the NISS team's recommendations incorporating philosophy and practices of Equal Voice. The *Signatory Authority* is responsible for all NISS-related decisions after considering the NISS team's recommendations. When there is non-alignment that cannot be resolved through existing forums for management review, the policies and procedures outlined in the following MAPPs should be followed.

    - 4151.8 *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decision*
    - 4151.1 Rev 1 *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*
    - 4151.2 Rev 1 *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director*

[5] The team generally includes CDER staff members who are cross-office or cross-discipline.

PROCEDURES

The evaluation and management of a *newly identified safety signal* (NISS) occurs in three phases:

1. Pre-evaluation phase
2. Evaluation phase
3. Action phase

(See Attachment 2 for a flowchart of the procedures.)

The pre-evaluation and evaluation phases of a NISS can be iterative and involve consideration of several factors, many at multiple time points throughout the process and in different ways using principles from the Best Practices document. Management review of these phases is conducted on a periodic basis (see page 13).

1. PRE-EVALUATION PHASE

The pre-evaluation phase begins with identifying a NISS and ends with triaging a NISS. The pre-evaluation can be completed by an individual CDER staff member, but often involves staff from other offices, as appropriate, to answer the following questions:

- Is this a NISS?
- Does this NISS warrant or not warrant further evaluation?

a. Identifying a NISS

Using medical and scientific judgment and procedures consistent with established pharmacovigilance practices[6] for identifying safety signals or established review practices for identifying quality signals,[7] CDER staff apply the general criteria to determine if data from a signal source is a NISS, using the Best Practices document as needed.

i. CDER's criteria for a NISS

The information represents:

[6] FDA guidance for industry, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, available at: https://www.fda.gov/media/71546/download.

[7] Data from a quality signal source (See Attachment 1 table 1).

- a serious adverse event[8]; medication error[9]; 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-

- 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).

ii. The CDER staff member who identifies the NISS, or the member's supervisor (e.g., Team Leader or Branch Chief), becomes the *Signal Identifier*.

iii. The *Signal Identifier*, or by request and as appropriate per office procedures the project management staff, searches the central database to determine if the safety signal is already in the central database:

- If there is not a NISS, create a NISS. **(Move to triage the NISS.)**
- If there is a closed NISS, re-open the NISS. **(Move to triage the NISS.)**
- If there is an open NISS, notify the *Signal Identifier* or *Safety Lead* of the open NISS. The *Signal Identifier* or *Safety Lead* of the open NISS incorporates the new data from the source. (Join the pre-evaluation or evaluation phase, as appropriate. Do NOT open a NISS and move to the evaluation phase independently of the existing NISS team.)

💻 For step-by-step directions to document, see the user guide.

b. Triaging a NISS

[8] A *serious adverse event* (a term used interchangeably with a *serious drug experience*) is defined as any adverse event (AE) that involves patient outcomes of death, life-threatening AEs, inpatient or prolonged hospitalization, persistent or significant disability/incapacity, congenital abnormality, or other serious important medical events. Or when, based upon appropriate medical judgment, the AE may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the listed outcomes (21 CFR 314.80).

[9] *Medication error* means any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of a health care professional, patient, or consumer. The medication error may or may not result in an adverse event.

i. During the pre-evaluation phase, the *Signal Identifier*, in collaboration with representatives from other offices, as appropriate, uses principles in the Best Practices document to determine whether or not, based on currently available information, the NISS warrants an evaluation.

- To help differentiate activities that may be completed during the pre-evaluation and evaluation phases. (See Attachment 1 table 2 reproduced below.)

Attachment 1 Table 2: Examples of activities that may be completed during the pre-evaluation and evaluation phases.

Pre-evaluation activities	Evaluation activities
These are preliminary activities that can help decide whether the NISS warrants further evaluation or not.	These are activities that can be completed when a NISS *warrants* further evaluation.
• Collect crude counts of FAERS[10] reports • Collect crude estimates of drug use • Complete an initial literature search to find reports or potential frequency of occurrence of an adverse event • Complete a search of similar applications to determine if the quality issue has been addressed in previous applications • Send an information request to a sponsor • Initial assessment of postmarket quality defect for potential scope, frequency of reporting, and trends • Review existing site inspection report(s)	• Request an ARIA[11]analysis • Complete a full FAERS review • Complete a substantial literature review • Request a new site inspection • Request new product testing • Review clinical trial data

ii. *Signal Identifier* should consider possible pending actions that may involve the drug or drug class (e.g., pending labeling supplement, new original ANDA approvals, or compliance actions) and contact other offices as appropriate.

iii. *Signal Identifier*, in collaboration with representatives from other offices, as appropriate, decides that the NISS warrants an evaluation. **(Move to the evaluation phase.)**

-OR-

Signal Identifier, in collaboration with representatives from other offices, as appropriate, decides that the NISS ***does not*** warrant an evaluation and closes the NISS in the central database by:

[10] FDA Adverse Event Reporting System

[11] Active Risk Identification and Analysis

- Determining whether:

    1. Preliminary information suggests further evaluation is not warranted (e.g., labeling sufficiently describes adverse event, no action indicated, and/or does not meet the NISS criteria.)
    -OR-
    2. There is insufficient information (may warrant further evaluation in the future).

    -AND-

- Summarizing in 2 to 3 sentences the reason for closing with an option to upload a work-product (i.e., memo or email). (Classified as an *indeterminate safety signal*.)

- For an *indeterminate safety signal* where preliminary information suggests further evaluation is not warranted, **exit the process and follow routine pharmacovigilance or surveillance procedures**.

- For an *indeterminate safety signal* when there is insufficient data, decide whether it should be actively monitored.

    - If actively monitored, specify the CDER staff member responsible and estimated timeframe in which additional data are anticipated to become available. (At a pre-specified interval of time, assess new data to determine if *indeterminate safety signal* should be re-evaluated. If active monitoring is no longer necessary, exit process and follow routine pharmacovigilance or surveillance procedures.)

    - If not actively monitored, **exit process and follow routine pharmacovigilance or surveillance procedures**.

⌛ Triaging should generally be completed within 45 days after a NISS is identified.

💻 For step-by-step directions to document, see the user guide.

2. EVALUATION PHASE

The phase begins when the *Safety Lead* is identified (i.e., a CDER staff member), who facilitates the evaluation of the NISS and makes a recommendation to the *Signatory Authority*. The phase ends when the *Signatory Authority* of the NISS makes a final decision. A NISS evaluation must be completed by a NISS team that

includes representatives of the scientific and regulatory disciplines using principles in the Best Practices document. The NISS team answers the following questions:

- Is the NISS an *identified risk, indeterminate risk,* or *refuted risk*?
- Should there be a regulatory or compliance action(s)?
- Should there be communication(s) to the public (e.g., Drug Safety Communication or Drug alert/statement)?

a. Planning the evaluation

i. *Signal Identifier* contacts the designee from the office with *Signatory Authority* (see Attachment 1, table 3) and jointly determines who will be the *Safety Lead* (see Attachment 1, table 4).

- In some cases, the same CDER staff member may serve in these three roles: *Signal Identifier*, *Safety Lead*, and *Signatory Authority*.

ii. *Safety Lead* identifies the team members necessary for evaluating the NISS.

- The NISS team must include the *Signal Identifier*, the *Safety Lead*, the *Signatory Authority* (the same staff member may serve in these three roles), and the *Project Manager*.
- The *Project Manager* generally comes from the same office as the *Safety Lead*.
- The NISS team should include other CDER staff members representing the scientific and regulatory disciplines relevant to the evaluation of the NISS. An OSE staff member must be included in the NISS team if FAERS reports or epidemiology studies are reviewed (see Attachment 1, table 5).

iii. *Safety Lead*, with input from the NISS team, as appropriate, plans for the evaluation by considering the following factors:

- Preliminary classification of the NISS. A NISS can be initially classified in three ways: as a *potential risk*, an *important potential risk*, or an *emergency*. If the currently available information suggests that a *potential risk* has or could have a negative impact on public health or has a negative impact on the benefit–risk profile of a drug, the risk will be considered an *important potential risk*. The preliminary classification can be changed

later if, for example, the NISS team receives new information to warrant a reclassification. (See Attachment 3 for classifying a NISS as an *important potential risk*.)

- The evaluation timelines. Timelines for an evaluation should be as follows: 12 months for a *potential risk*, 6 months for an *important potential risk*, and timeframe as determined by CDER leadership for an *emergency*.
- The data to be reviewed and additional data needed.
- Preliminary re-assessment of the benefit–risk profile based on data from the signal source.
- Possible regulatory or compliance action(s).
- Potential early communication (e.g., Drug Safety Communication or Drug alert/statement) to the public about the *important potential risk* or *potential risk*.
- Timing of follow-up communications to the NISS team. Regular meetings to discuss an ongoing evaluation may be helpful in complex situations and can be held on an ad hoc basis.

iv. *Safety Lead* or *Project Manager* assigns work to the team members, including goal dates for completion of the final review.

⌛ Planning the evaluation should generally be completed no later than 1 month following identification of the *Safety Lead*.

💻 For step-by-step directions to document, see the user guide.

b. Notifying an application holder(s) or drug manufacturer(s)

- *Project Manager* of the NISS evaluation asks the project manager(s) from the CDER office with Signatory Authority to notify application holder(s) and/or drug manufacturer(s) of drug products included in the NISS evaluation including unapproved drug products, if appropriate, that the NISS was opened and warrants evaluation. (See Attachment 1, table 6.)[12]

[12] 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), the *Safety Lead* will decide to issue the notification or delay the timing of the notification.

⏳ Notifications should generally be completed not later than 1 month from when the *Safety Lead* is identified.

c. During the evaluation

i. *Safety Lead* should consider the following factors:

- Additional questions raised by relevant subject matter experts and data needed (e.g., information requests to an application holder or drug manufacturer).
- Other information that becomes available and requires additional scientific or regulatory input (the *Safety Lead* can add CDER staff members to the NISS team).
- Potential need for additional public communication or external stakeholder input.
- Preliminary or recent regulatory or compliance action(s) that may mitigate the apparent risk.
- Potential barriers to completion of comprehensive reviews within timeframes.

ii. *Safety Lead*, considering the NISS team's input, may reclassify the *potential risk* to an *important potential risk* if the information (i.e., after completing a review) suggests that a *potential risk* has, or could have, a negative impact on public health or has a negative impact on the benefit–risk profile of a drug (see Attachment 2).

iii. *Signatory Authority* confirms, if necessary, that an activity meets a threshold for extending the timeframes to make a final decision, up to 6 months, including waiting for:

- A pending response to an information request from the application holder or manufacturer.
- Pending input from a special government employee (SGE), advisory committee meeting, CDER advisory meeting (e.g., CDER regulatory briefing, regulatory briefing, REMS Oversight Committee meeting), or Drug Safety Board meeting.
- Pending input from inspection or testing.

d. Making a recommendation

i. *Safety Lead* considers the NISS team's input and seeks alignment to make a final recommendation to the *Signatory Authority* about classification of the evaluated safety signal as an *identified risk, indeterminate risk* or *refuted risk* and potential regulatory or compliance action(s) to address an *identified risk* or *indeterminate risk.*

- The recommendation should be finalized leaving sufficient time for the *Signatory Authority* to make a decision within 6 months for an *important potential risk* and 12 months for a *potential risk* from the decision that a NISS warrants further evaluation.

ii. *Safety Lead* ensures that the discussion and decisions for the comprehensive review will be made in accordance with CDER's policy on Equal Voice. If there are disagreements among the team members, the *Safety Lead* will seek to resolve the differing professional opinions through discussion at existing forums for management review (e.g., DRMB, MPPRC, or CDER CPQ).

e. Making a final decision

i. *Signatory Authority* makes a decision, including:

- Classification of the NISS as an *identified risk, indeterminate risk*, or *refuted risk.*
- Regulatory or compliance action(s) or no regulatory or compliance action(s).
- Communication(s) or no communication(s) to the public.

ii. *Signatory Authority* ensures that the discussion and decisions for the comprehensive review are made in accordance with CDER's policy on Equal Voice. If there are disagreements among the team members, seeks to resolve the differing professional opinions through discussion at existing forums for management review (e.g., DRMB, MPPRC, or CDER CPQ).

iii. *Safety Lead* ensures that the team member's analyses, results, conclusions, and recommendations are documented in their final review and that the review is archived in the central database.

iv. *Safety Lead* completes an integrated review memorandum that summarizes the NISS team's recommendations in the central database, unless a review already sufficiently summarizes the NISS team's

recommendations.

v. *Signatory Authority*, or designee, documents the classification decision and actions (i.e., regulatory or compliance action(s) and communication(s) to public) in the central database.

- If planned actions, **move to the action phase.**
- If no planned actions and classified as an *identified risk* or *indeterminate risk*, decide whether risk should be actively monitored.
- If actively monitored, specify the CDER staff member responsible and estimated timeframe in which additional data are anticipated to become available. (At a pre-specified interval of time, assess new data to determine if risk should be re-evaluated. If active monitoring determined to be no longer necessary, exit process and follow routine pharmacovigilance or surveillance procedures.)
- If not actively monitored, exit process and follow routine pharmacovigilance or surveillance procedures.
- If no planned actions and classified as a *refuted risk*, exit process and follow routine pharmacovigilance or surveillance procedures.

⌛ Evaluation should be completed within 6 months for an *important potential risk* and 12 months for a *potential risk*.

💻 For step-by-step directions to document, see the user guide.

For a NISS managed under the Center's Incident Management Plan (IMP)

1. When the Center Director, or their designee, deactivates (i.e., ends) an Incident Task Force, a member of the Counter-Terrorism and Emergency Coordination Staff (CTECS) will identify the office with Signatory Authority responsible for implementing the remaining regulatory and compliance action(s).
2. The *Signatory Authority* (identified above), or their designee, documents the key situation report(s) (i.e., summary documents created during CDER's incident response) in the central database.
   - If there is an open NISS, document. **(Move to the action phase.)**
   - If there is not a NISS, create a NISS and document. **(Move to the action phase.)**
   - If there is a closed NISS, re-open a NISS, and document. **(Move to the action phase.)**

3. ACTION PHASE

a. *Signatory Authority*, or their designee, coordinates the implementation of the action(s) (e.g., regulatory action, compliance action, and/or communications to the public) of multiple offices, as applicable.

b. When the action(s) are complete, the *Project Manager* documents the outcome(s) in the central database and completes a closure memo to close the NISS.

- If an *identified risk* or *indeterminate risk,* document decision whether risk should be actively monitored.
- If actively monitored, specify the CDER staff member responsible and estimated timeframe in which additional data are anticipated to become available. (At a pre-specified interval of time, assess new data to determine if risk should be re-evaluated. If active monitoring determined to be no longer necessary, exit process and follow routine pharmacovigilance or surveillance procedures.)
- If not actively monitored, exit process and follow routine pharmacovigilance or surveillance procedures.
- If a *refuted risk*, exit process and follow routine pharmacovigilance or surveillance procedures.

💻 For step-by-step directions to document, see the user guide.

4. MANAGEMENT REVIEW

As directed by CDER's Drug Risk Management Board, the super-Office Director or designee from each office will:

- Implement standard operating procedures or targeted training to make sure the Office adheres to the policies and procedures described in this MAPP.
- Identify any policy and procedure improvements and/or general training needs.

DEFINITIONS

This MAPP includes certain pharmacovigilance terms used by the International

Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has aligned other terminology with that used in established guidance documents on good pharmacovigilance practices. The MAPP also introduces definitions for the following new terms: *indeterminate safety signal*, *indeterminate risk*, and *refuted risk*.

Compliance Action: Compliance actions can include warning letters, untitled letters, injunctions, seizures, recalls, regulatory meetings, and other actions to obtain corrective actions by the firm to address violative drugs. (See definition for *Regulatory action*.)

Emergency (as defined for this MAPP)**:** A NISS, *potential risk*, or *important potential risk* that has resulted in fatalities, has the potential to affect a large number of patients, and if it is promptly acted upon, lives could be saved or the chances for other severe harms reduced.

Identified risk: An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples of identified risks include:

- An adverse reaction that is adequately demonstrated in non-clinical studies and confirmed by clinical data.
- An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance) or a parameter of interest suggests a causal relationship
- An adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.[13]

Important potential risk (as defined for this MAPP): A *potential risk* that has or could have a negative impact on public health or has a negative impact on the benefit–risk profile of the product. What constitutes an *important potential risk* will depend on several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. An *important potential risk* is considered an *emergency* if it has resulted in fatalities, has the potential to affect a large number of patients, and if it

[13] ICH guideline E2C (R2) *Periodic benefit-risk evaluation report* (PBRER) Step 5, available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/12/WC500136402.pdf.

is promptly acted upon, lives could be saved or the chances for other severe harms reduced. (See Attachment 3.)[14]

Indeterminate risk (as defined for this MAPP): An untoward occurrence for which, following a comprehensive assessment, the findings are inconclusive with regard to the association with the medicinal product of interest.[15]

Indeterminate safety signal (as defined for this MAPP): A safety signal for which current available information is insufficient to support a causal association between a drug and/or an adverse event and does not, based on the current available information, warrant further evaluation.[16]

Newly identified safety signal (NISS) (as defined for this MAPP): A new safety signal prompting further evaluations and/or actions.[17] (For operational purposes, safety signals include medication errors and product quality issues that may lead to clinical adverse events. The NISS criteria are applied to safety signals to identify NISS for central tracking at CDER.)

Potential risk: An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest, but where this association has not been confirmed.

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[14] This definition is modified from the ICH E2C(R2) guideline definition, which provides a combined definition for *important potential risk* and *important identified risk*, as follows: "An identified risk or potential risk that could impact on the risk-benefit profile of the product or have implications for public health. CDER believes it is important to distinguish between potential risks and identified risks because the potential risks pertain to safety signals for which a causal association between the drug and the adverse event has not yet been determined; whereas the identified risks pertain to safety signals for which a causal association has been established."

[15] CDER refers to *indeterminate risks* because in some instances, due to uncertainties about or inconsistences in the data available about a safety signal, it is not possible to ascertain whether there is adequate evidence of an association between a drug and an adverse event.

[16] The ICH E2C(R2) guideline describes *indeterminate signals* as "false signals based on medical judgment and a scientific evaluation of the currently available information." An *indeterminate safety signal* is distinct from a *closed signal*, which ICH defines as "signals detected during the PBRER reporting period, for which an evaluation was completed during the reporting interval."

Because ICH distinguishes between *signals* and *risks* and to explain how CDER selects among certain signals to identify those that require further evaluation, CDER has established *indeterminate safety signals* as those signals indeterminate based on preliminary assessment of currently available information.

[17] This definition is modified from the ICH guideline E2C(R2) definition, which describes a *newly identified signal* as: "A signal first identified during the [PBRER] reporting interval, prompting further actions or evaluation. This term could also apply to a previously closed signal for which new information becomes available in the reporting interval prompting further action or evaluation. Because this MAPP is focused on drug safety signals and is not limited to signals identified during a fixed reporting interval, the modified definition reflects the safety focus.

Examples of *potential risks* include:

- Nonclinical safety concerns that have not been observed or resolved in clinical studies.
- An adverse event(s) observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), or the parameter of interest, raises a suspicion of, but is not large enough to suggest, a causal relationship.
- An event that is known to be associated with other products of the same class or that could be expected to occur based on the properties of the medicinal product.[18]

Project Manager: Staff member who works with the *Safety Lead* to manage the operational activities associated with a NISS evaluation (which may be different from the project manager(s) who notifies the application holder(s) or manufacturer(s) and coordinates actions (e.g., regulatory, compliance and communications to the public) during the evaluation and action phases).

Refuted risk (as defined for this MAPP): A *potential risk* or *important potential risk* for which, following comprehensive assessment of relevant and available information, there is adequate evidence that an association with the medicinal product of interest is unlikely.[19]

Regulatory action: Regulatory actions can include requesting or requiring sponsors to make a safety labeling change; make a REMS or REMS modification; initiate study(ies) or trial(s) to further evaluate drug safety; and/or remove the product or indication from the market. (See definition for *Compliance action*.)

Safety Lead: Staff member who facilitates the evaluation of a NISS and makes a final recommendation to the *Signatory Authority.*

Safety Signal (as defined for this MAPP)**:** Information from one or more sources that suggests a new potential causal association, or a new aspect of a known association, between an intervention[20] and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify further action to verify.[21]

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[18] CDER maintained the ICH E2C(R2) definition of *potential risk*. For the purposes of this MAPP *risk* is used to refer to a known or potential adverse effect of the drug (adverse event).

[19] The ICH E2C(R2) guideline describes *closed signals*. Although not described specifically, the ICH E2C(R2) guideline contemplates situations in which, following an evaluation of a safety signal, it may be concluded that there is not an association between a drug and an adverse event. In those cases, CDER will refer to the signal as a *refuted risk.*

[20] A marketed drug (refer to footnote 1).

[21] The definition of *safety signal* that is provided in this MAPP is modified from that in FDA's 2005 Good Pharmacovigilance Practices guidance. FDA previously referred to a *drug safety signal* as "a concern about

Signal: Information that arises from one or multiple sources (including observations and experiments) that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event, or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify.[22]

Signal Identifier: Staff member (or the member's supervisor (e.g., Team Leader or Branch Chief)) who identifies and triages a NISS.

Signatory Authority: Staff member who makes the final decision of the NISS (which may be different from the *Signatory Authority*(ies) responsible for completing the actions (e.g., regulatory, compliance, and communication to the public) during the action phase).

Signal source: Source of information that the staff routinely use in any CDER organizational unit to identify signals.

EFFECTIVE DATE

This MAPP is effective on April 30, 2020.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
4/30/2020	N/A	Initial

an excess of adverse events compared to what would be expected to be associated with a product's use." The revised definition no longer limits safety signals to those that occur at a higher frequency than expected, thereby allowing for different aspects about an adverse event observed with a drug.

An *adverse event* can be any unfavorable or unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An *adverse event* can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

[22] The definitions of a (safety) *signal* are varied and evolving. Sources of definitions of a signal include the World Health Organization**,** FDA's Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Guidance, the Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII, the European Medicines Agency, and ICH guideline E2C (R2) Periodic benefit-risk evaluation report (PBRER) Step 5. The CDER definition provided in this MAPP combines important aspects of a signal, including that a signal can be adverse or beneficial.

ATTACHMENT 1 – Cited Tables

Table 1 - Examples of data sources that could be used to identify a NISS

Type	Data Source
Clinical data (including pharmacovigilance and pharmacoepidemiologic data)	• New or supplemental marketing applications (NDA/BLA) • Completed IND clinical trials • Postmarket (Phase 4) clinical trials • Case reports (including those submitted to FAERS) • Case series • Postmarket (phase 4) observational studies • Sentinel (ARIA) queries • 15-day reports • Periodic safety reports (PBRER, PSUR, PADER, PAER) • Published medical literature
Quality data	• Drug Quality Reporting System (DQRS) reports • Field Alert Reports (FARs) • Biologic Product Deviation Reports (BPDRs) • Inspection reports • FDA (or other) field intelligence • FDA 3911 • FD&C Act §704(a)(4)) • Recalls/seizures (21 CFR 7.41) • Consumer complaints • Submissions to the various incidents groups mailboxes throughout CDER (e.g., OPQ Office of Surveillance, CDER OC Incidents, Compounding Incidents) • Published medical literature
Other	• Citizen petitions • Congressional inquiries • Professional society scientific presentations • Institute for Safe Medication Practices (ISMP) reports • Patient/consumer website/blog • Media reports • Public inquiries submitted to Division of Drug Information • Drug Safety Oversight Board inquiries. • Foreign regulatory agencies (e.g., European Medicines Agency (EMA)) and organizations (e.g., Uppsala Monitoring Centre (UMC)) • Industry

Table 2 - Examples of activities that may be completed during the pre-evaluation and evaluation phases.

Pre-evaluation activities	Evaluation activities
These are preliminary activities that can help decide whether the NISS warrants further evaluation or not.	These are activities that can be completed when a NISS *warrants* further evaluation.
• Collect crude counts of FAERS reports • Collect crude estimates of drug use • Complete an initial literature search to find reports or potential frequency of occurrence of an adverse event • Complete a search of similar applications to determine if the quality issue has been addressed in previous applications • Send an information request to a sponsor • Initial assessment of postmarket quality defect for potential scope, frequency of reporting, and trends • Review existing site inspection report(s)	• Request an ARIA analysis • Complete a full FAERS review • Complete a substantial literature review • Request a new site inspection • Request new product testing • Review clinical trial data

Table 3 - Identifying the Appropriate Signatory Authority of the NISS (Determination based on the actions that could result from a comprehensive review.)

Is the important potential risk or potential risk related to a(n)	Designee from the office with Signatory Authority
NDA, BLA, or nonprescription monograph	OND Division Director or Deputy, including the Deputy Director for Safety (DDS) from the relevant division – or – OND Office Director or Deputy
ANDA	OGD Director of Clinical Safety and Surveillance Staff (CSSS)
Drug quality issue for application products (*with* an adverse event)	OMQ Office Director or Deputy – or – OC Deputy Director
Drug quality issue for application products (*without* an adverse event)	Chair of the CDER Council for Pharmaceutical Quality
Compounded drugs	Associate Director for Compounding – or – OC Office Director or Deputy
Marketed unapproved new drugs	OUDLC Director or Deputy – or – OC Office Director or Deputy
Proprietary names	OSE Division of Medication Error Prevention and Analysis Director

Table 4 - Considerations for determining the Safety Lead

1. Product considerations	
	Safety Lead
Active moiety of an NDA, BLA, ANDA, or nonprescription monograph product	OND Deputy Director for Safety (DDS) or Clinical Team Leader
Marketed unapproved new drugs	OUDLC Director or Deputy or designee
Compounding issue	Associate Director for Compounding – or – Division Director or designee
2. Signal source or type of safety issue considerations	
Medication error -or – Data based largely on observational pharmacoepidemiologic studies or analyses of spontaneous postmarket adverse event reports	OSE Deputy Division Director or designated Team Leader
Clinical trial data	OND DDS or Clinical Team Leader
Nonclinical (animal) data	OND or OGD Pharmacology/Toxicology staff
Clinical pharmacology or pharmacogenomic data	Office of Clinical Pharmacology Director or Clinical Pharmacology Division Director or Clinical Pharmacology Team Leader
3. Product quality/manufacturing considerations	
Bioequivalence of an ANDA product	OGD Director of CSSS
Product quality issues, including current good manufacturing practice (CGMP) issues (with an adverse event)	OMQ Deputy Director or Policy Staff Director
Product quality issues, including current good manufacturing practice (CGMP) issues (without an adverse event)	Chair of the Postmarket Quality Committee
Drug-device combination product, including those for an issue related to the device portion	OND DDS or Clinical Team Leader, OGD Director of CSSS (for ANDAs)

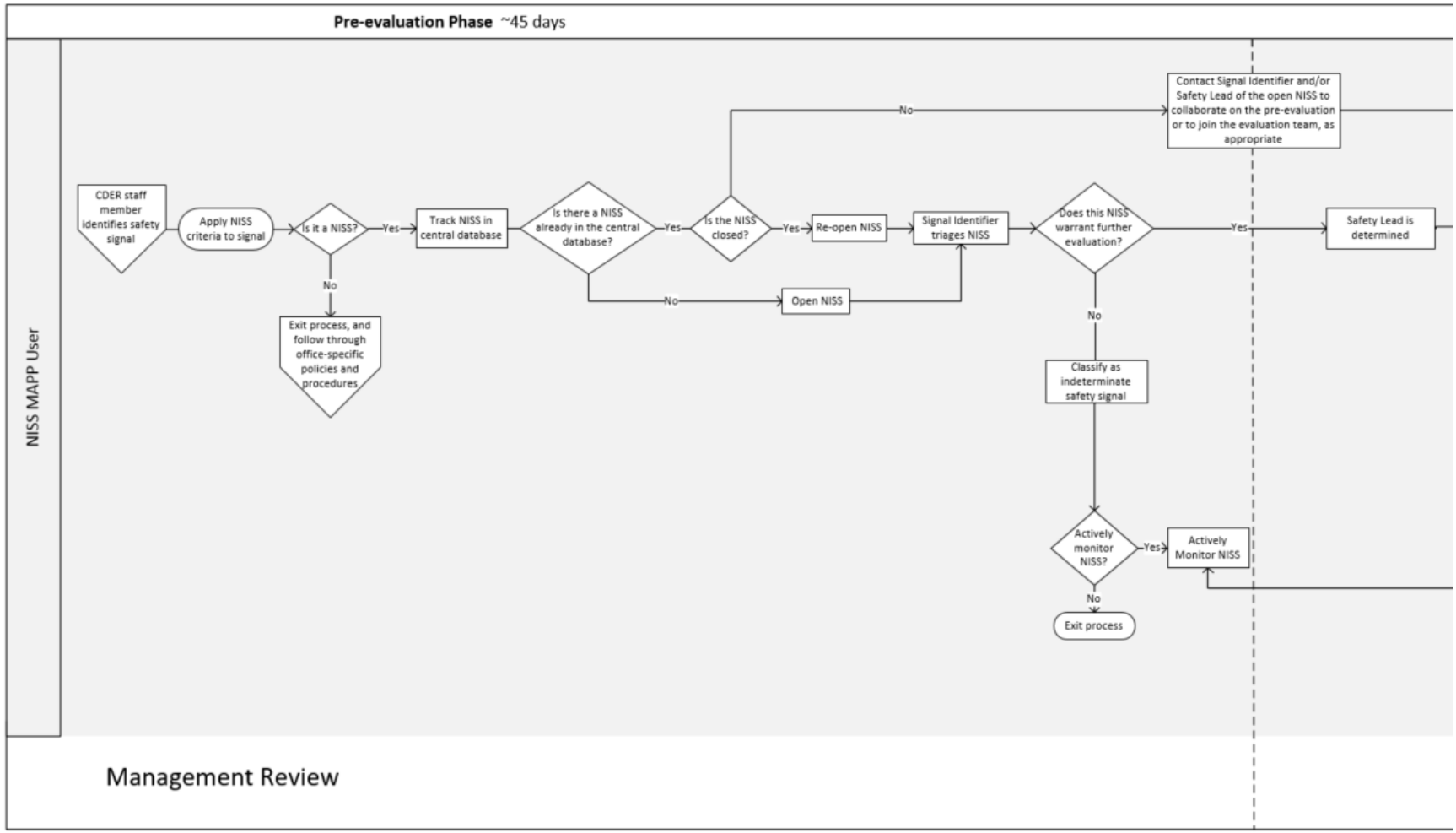
Table 5 - Guidelines for identifying appropriate staff (*Team members* should come from Offices within CDER that have the scientific and regulatory disciplines needed for evaluating a NISS.)

Signal source, additional data needed, or product consideration	Office with scientific and regulatory disciplines
Spontaneous reports/case report/ case series	OND, OSE/DPV
Clinical trials	OND, OTS/OB; OSE
Medication errors	OND, OSE/DMEPA, OPQ
Drug utilization	OND, OSE/DEPI-DU
Observational study data	OND, OSE/DEPI; OTS/OB
A product with a REMS	OND, OSE/DRISK, OSE/PM, OGD
A product with ANDAs	OGD, OND, OSE, OPQ, OC (OMQ)
Nonclinical (animal) data	OND
Clinical pharmacology, drug interaction/pharmacogenomic data	OCP, OND, OGD
Unapproved product, compounded drug	OC, OSE, OND, OPQ, OC (Incident Coordination Group (ICG), OUDLC, OMQ)
Product quality	OPQ, OC (OMQ), OSE, OND, OGD
Drug-device combination product	CDER Product jurisdiction officers (to identify staff from other centers or Office of Combination Products that should be notified)

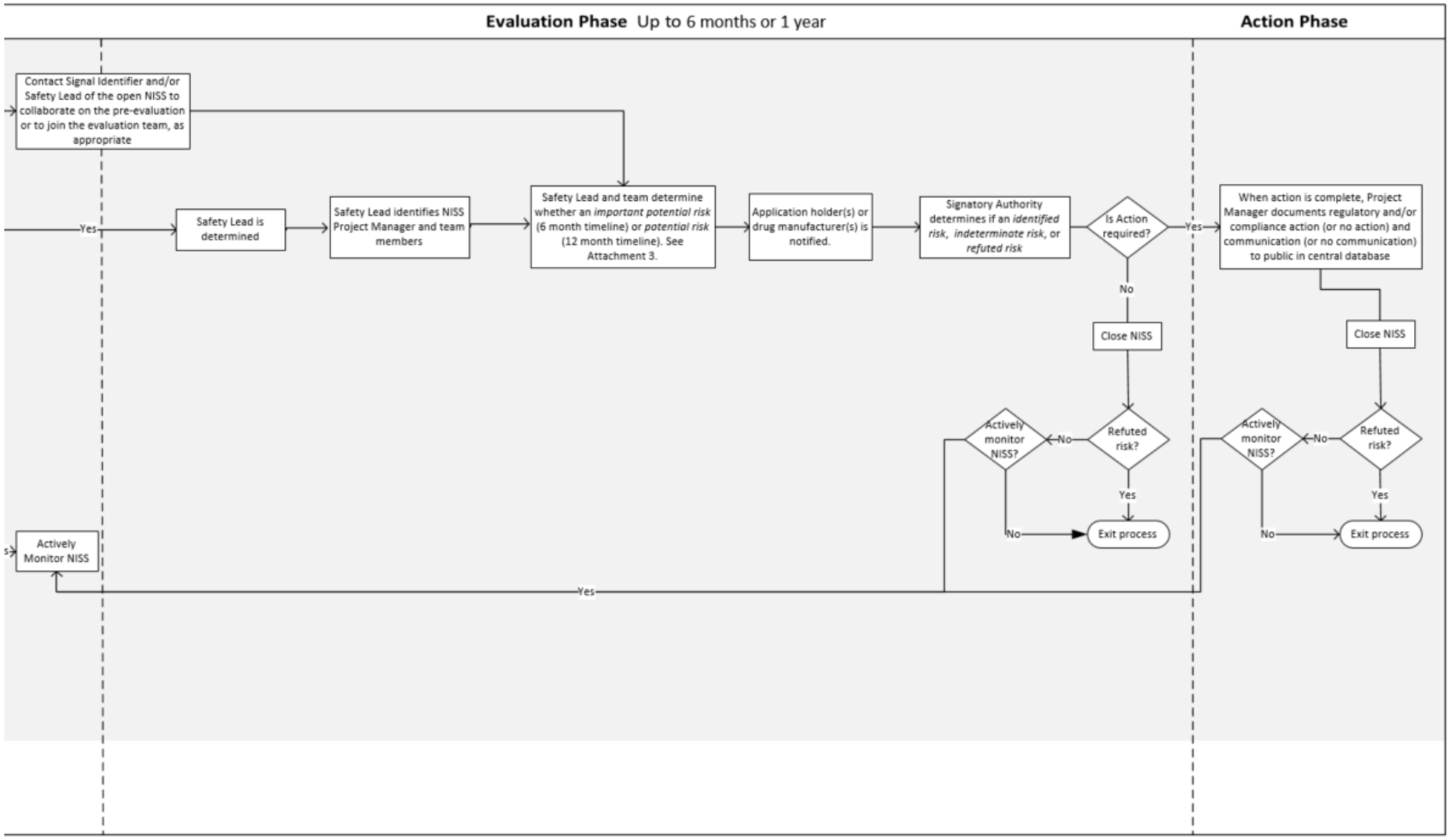
Table 6 - Staff for notifying the application holder(s) or manufacturer(s) during the evaluation

Is the *important potential risk* or *potential risk* related to a(n)	Job title, from the relevant division, for which the appropriate staff member comes
NDA, BLA, or nonprescription monograph	OND Regulatory Project Manager or Safety Regulatory Project Manager (SRPM)
ANDA	OGD Regulatory Project Manager or CSSS Project Manager
Marketed unapproved drug products, compounded drug products	OC Project Manager
Drug quality issue for application products (*with* an adverse event)	OC Project Manager
Drug quality issue for application products (*without* an adverse event)	OPQ Regulatory Business Process Manager (RBPM)

ATTACHMENT 2 – Pre-eval Flowchart



ATTACHMENT 2 (cont.) – (Eval/ Action Phases)



ATTACHMENT 3 – Identifying Important Potential Risks

Identifying important potential risks will help prioritize and establish timelines for the evaluation phase. CDER distinguishes between *potential risks* and *important potential risks* so that the Center can direct resources more effectively toward those medical products that pose the greatest potential risk to patients. This prioritization also is intended to ensure that staff who are working in different offices across CDER have a common understanding of the relative urgency of *potential risks* and direct attention to those that need to be addressed more expeditiously (i.e., *important potential risk*s).

To determine whether a *potential risk* is an *important potential risk*, requiring more immediate action, the NISS team uses principles from the Best Practices document to consider the following factors, which will provide an initial understanding of the impact of a *potential risk* on public health.

- Seriousness of the potential risk[23]
- Estimated size of the population exposed to the drug
- Suspected probability of harm to patients (or persons) exposed to the drug.

The assessment may involve some additional gathering of data beyond that considered in the preliminary signal evaluation. Additionally, the NISS team may consider other factors that include, but are not necessarily limited to, the following:

- Seriousness of the adverse event relative to the seriousness of the disease or condition being treated[24]
- Risk posed to vulnerable populations[25]
- Clinical setting in which the drug is used
- Potential to mitigate risk in the populations that could be affected
- Availability and risk profile of therapeutic alternatives.

An *important potential risk* is considered an *emergency* if it has resulted in fatalities, has the potential to affect a large number of patients, and if it is promptly acted upon, lives could be saved or chances of other severe harms reduced.

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[23] World Health Organization. *The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products*, available at http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf.

[24] FDA's regulations at 21 CFR 312.300(b)(1) define *serious disease or condition* as a "disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."

[25] Under 21 CFR 56.107(a), vulnerable populations include children, prisoners, pregnant women, or handicapped or mentally disabled persons.