Assessment of Systems and Processes to Support Evaluation of Postmarket Safety Signals

Public Summary

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Executive Summary

The Food and Drug Administration (FDA) protects public health in part by ensuring the safety and efficacy of drugs and biologics. The Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) serve to fulfill this mission by monitoring benefit-risk profiles of drugs and biologics over their respective lifecycles. FDA may take regulatory or compliance action, if necessary, to ensure that a favorable benefit-risk profile is maintained in the postmarket setting. CDER and CBER have defined policies and procedures for managing postmarket safety signals, which include identifying safety signals and bringing together relevant expertise to prioritize, evaluate, make timely decisions, and act to address identified concerns. It is in the best interest of all stakeholders – applicants, FDA, patients, and the American public – for FDA to efficiently and effectively review, communicate on, and provide oversight of postmarket safety signals.

Under the Prescription Drug User Fee Act (PDUFA), FDA committed to the "timely and effective evaluation and communication of postmarketing safety findings related to human drugs" in the PDUFA VI commitment letter (*"PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022"*).[1] The commitment letter describes an FDA effort to improve postmarket drug safety by developing or refining processes for managing the review, oversight, and communication of postmarket drug safety issues for drugs and biologics in both CDER and CBER. CDER developed and implemented a process to identify, manage, and resolve a newly identified safety signal (NISS), which involved creating a workflow management tool (see Manual of Policies and Procedures [MAPP] 4121.3[2] and Lifecycle Signal Tracker [LiST][3]). CBER follows the processes for identifying and managing postmarket safety issues outlined in Standard Operating Procedures and Policies (SOPP) 8420: Food and Drug Administration Amendments Act (FDAAA) Section 921: Posting of Potential Signals of Serious Risk.[4] CBER most recently updated SOPP 8420 in 2019, which was then followed by the launch of the Division of Epidemiology (DE) Reviewer Guide. The goal of the DE Reviewer Guide is to align CBER with CDER's NISS process. To support continued process improvement and better understand how the processes and tools are working, FDA contracted Eastern Research Group, Inc. (ERG) to conduct the assessment and produce an internal report. Although PDUFA VI does not require a public summary, FDA is making this Executive Summary publicly available.

The purpose of the ERG assessment was to characterize how FDA's data systems and processes support the management of postmarket drug safety issues and identify what good practices and opportunities for improvement exist to best meet the needs of FDA staff and external stakeholders. FDA identified five key assessment objectives, which were translated into a set of assessment questions. To perform the assessment, ERG established a set of measurable evaluation metrics that are directly related to FDA's key assessment objectives and questions. These metrics established a structure for the data that needed to be collected to generate results. ERG collected descriptive information on CDER and CBER safety

[1] See *https://www.fda.gov/media/99140/download*
[2] MAPP 4121.3 outlines the policy and procedures for the collaborative identification, evaluation, and resolution of a new identify safety signal. Available at *https://www.fda.gov/media/137475/download*.
[3] LiST serves as the workflow management application for procedures outlined in MAPP 4121.3
[4] See *https://www.fda.gov/media/82363/download*

issues, examined CDER and CBER policies related to postmarket safety management, surveyed users of CDER's postmarket safety issue workflow management system, and gathered CDER and CBER staff feedback on postmarket safety processes through interviews.

Timing of the Assessment

While the assessment included evaluation of safety issue processes in both CDER and CBER, it is important to note the timing of the assessment relative to recent and ongoing implementation of new processes in CDER. Over the past five years, CDER has worked to develop and implement the NISS process and LiST workflow management tool. CDER staff began tracking NISS using the LiST tool on April 30, 2020. ERG's assessment involved collecting data within the first year of the launch of CDER's new workflow management tool. The interviews and survey were conducted about one and a half years after the launch of the new and refined processes. This was a time when staff were becoming familiar with the new procedures and systems. As a result, some of the challenges identified during this early stage of the assessment have been addressed as the staff have gained familiarity with the new procedures over the two years since they were introduced. In the sections below, ERG notes where CDER continues to address a particular assessment finding.

Answers to Assessment Questions

The assessment findings are organized by assessment question. ERG synthesized answers to the assessment questions using the collected data. Key objectives 1 and 2 address findings related to the CDER process. Key objective 3 addresses findings related to the CBER process. Key objectives 4 and 5 relate to both CDER and CBER.

Key Objective 1: Assess CDER's safety-related review process and safety signal landscape

How were decision criteria outlined in MAPP 4121.3 applied during each phase of the NISS process?

MAPP 4121.3 provides guidance for the evaluation and management of NISS through three phases (pre-evaluation, evaluation, action). In the first two phases, staff work to answer key questions[5] highlighted in MAPP 4121.3, and then act as needed in the final phase. Each of these questions are associated with a set of criteria and/or steps. Staff applied decision criteria for each key question as outlined in MAPP 4121.3. As a whole, CDER staff expressed that the decision criteria and steps outlined in MAPP 4121.3 are clear and that their activities are aligned with these criteria and steps.

To what extent were the process steps and timelines outlined for each phase in MAPP 4121.3 and related SOPs and job aids adhered to?

During interviews, ERG walked through each phase of MAPP 4121.3 with CDER staff. As a whole, staff activities aligned with criteria and steps outlined in MAPP 4121.3 in all phases. Most NISS in the CDER NISS cohort[6] met the 45-day pre-evaluation timeline. Some CDER staff voiced challenges with meeting

[5] The key questions for the pre-evaluation phase are: Is this a NISS? Does this NISS warrant further evaluation? The key questions for the evaluation phase are: 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)?

[6] The CDER NISS cohort includes all NISS opened from May 1, 2020, through April 30, 2021.

this timeline for some of the NISS they worked on (e.g., waiting for application holder responses to information requests and accumulating other data can take more than 45 days). For the evaluation phase, the majority of NISS met the specified 6- or 12-month timeline, with CDER staff in agreement that the evaluation phase timelines are appropriate.

Other job aids, like MAPP 5232.3[7] and the Office of Surveillance and Epidemiology (OSE) Standard Operating Procedure (SOP), were found to align with MAPP 4121.3 wherever procedures and timelines overlapped.

What are staff perspectives on the utility of the MAPP 4121.3 and associated materials (e.g., SOPs, job aids, and FAQs)?

CDER staff consider MAPP 4121.3 to be an effective resource. They believe MAPP 4121.3 is broad enough to allow for wider applicability to different CDER offices/divisions and flexible enough for staff to use their knowledge and expertise to make subjective determinations. The office- and division-level supplemental aids help address any ambiguity that exists in MAPP 4121.3. These supplemental aids (e.g., OSE SOP, MAPP 5232.3) are seen as effective and important resources within their respective offices. FDA is currently developing additional supplemental job aids (e.g., development of an Office of New Drugs [OND] aid is ongoing).

To what extent do safety signals conforming to the NISS definition have a NISS opened?

Drug Safety Operations (DSO)[8] staff and ERG gathered safety signals from internal CDER sources. These safety signals were collected during the first year of the launch of MAPP 4121.3 and LiST, when staff were becoming familiar with the new procedures and systems. In a few cases, NISS were not opened even though they met the NISS criteria. The vast majority of the safety signals either met the NISS criteria and were opened as a NISS or did not meet the NISS criteria and were not opened as a NISS. OSE, OND, and Office of Compliance (OC) performed at a similar level in regard to opening NISS in accordance with the criteria. Following the conclusion of ERG's data collection efforts, CDER staff have become more familiar with the procedures and have improved their understanding of the NISS criteria in MAPP 4121.3. Staff were also provided additional targeted guidance related to opening NISS.

What was the landscape of the CDER NISS cohort?

Of the NISS in the CDER cohort, OSE and OND opened the vast majority of NISS. The FDA Adverse Event Reporting System (FAERS) was the most common signal source for the NISS cohort, followed by published literature and drug safety surveillance summaries. When a signal type was selected by a LiST user, medication errors were the most common signal type[9]; however, by design the signal type is only selected when the adverse event is not caused by the active ingredient. The majority of NISS opened in the CDER NISS cohort were closed during the pre-evaluation phase.

[7] MAPP 5232.3 is an internal OC and OPQ policy document detailing policy and procedures for opening and resolving product quality NISS.
[8] DSO is within CDER's Office of the Center Director. The DSO staff provides policy analysis, program management and implementation, and project leadership for cross-office and Center-level drug safety issues and initiatives.
[9] The options for signal types, if selected, are compounded drug, drug interaction, medication error, quality issues and unapproved product. If a signal type not selected, then default is that the adverse event was caused by the active ingredient(s).

What is working well and what is not working well throughout the process?

With the launch of MAPP 4121.3 and LiST, CDER has implemented an effective safety-related process for reviewing safety signals that is viewed positively by the majority of staff working with it. MAPP 4121.3, along with other key resources, have turned what is a complex operation into a well-structured and efficient process. Although CDER's safety-related review process is widely viewed positively, challenges remain. For example, as already noted, CDER staff sometimes find it challenging to meet the 45-day pre-evaluation phase timeline because of delays related to receiving additional data. Ensuring that fully developed supplemental job aids are available to all super offices and groups has also been a challenge. CDER has implemented a continuous improvement process that is addressing these challenges and those identified by this assessment.

Key Objective 2: Assess CDER's LiST data system

How useful and effective is the LiST database in support of the NISS process?

Based on LiST user survey responses, the NISS process is generally well supported by the LiST database in the areas of NISS pre-evaluation, evaluation, and action. For the active monitoring[10] and management review[11] features, a subset of respondents considered the LiST database to be supportive overall, but a greater proportion of respondents answered, "do not know" or "not applicable." Compared to the pre-evaluation, evaluation, and action phases, the LiST database is considered less useful with regard to the active monitoring and management review features.

How comprehensive is the LiST database?

Similarly, survey respondents considered the LiST database to be more comprehensive with respect to documentation of the pre-evaluation, evaluation, and action phases than the active monitoring and management review phases of the NISS process. Some survey respondents would find value in more information that is not currently required to be captured by the LiST database (e.g. details about intermediate process steps).

What is the level of completeness, timeliness, and accuracy of LiST data?

The largest proportion of respondents to the LiST user survey expressed confidence in the accuracy and completeness of the LiST data, while, as noted above, a few were not confident in the accuracy or completeness of the data. Some survey respondents identified issues with incomplete data due to underutilization of LiST by some staff and inaccurate lengths of time in pre-evaluation or evaluation phases. One scenario mentioned is where the user does not open a NISS until a review is ready to be archived, so the actual time in pre-evaluation is not accurately reflected in the system. Notably, in a

[10] Active monitoring is an option available in LiST when closing a signal at the end of each phase of the NISS process. Anything beyond routine pharmacovigilance, such as when a reviewer has setup some additional activity (e.g., reoccurring FAERS/literature queries, plans to screen data for a signal that has accumulated since the last review at a prespecified time point), is considered active monitoring.

[11] Management review activities include implementing standard operating procedures or targeted training to make sure the Office adheres to the policies and procedures described in this MAPP and identifying any policy and procedure improvements and/or general training needs.

separate analysis of data in NISS-related documents and data in LiST, ERG found that the data matched in almost all cases; all mismatches were the result of errors in the source documents.

Timeliness of data reflects how accurately the data represent the current status of a NISS. ERG identified a single issue with the timeliness of LiST data: Some staff delay opening a NISS to allow for more time to conduct pre-evaluation activities, meaning at any given time, CDER staff could be working on safety signals that fit the NISS criteria, but have yet to be opened in LiST.

How easy and efficient is the LiST system data entry?

Most respondents to the LiST user survey reported that LiST is "reliable," "quick to navigate," and "intuitive."

What is working well and what is not working well with the LiST system?

Most users who shared their opinions on the LiST system said that LiST is generally working well in all aspects discussed above. Within these areas, some LiST users identified minor challenges with the LiST system and speculated how these issues might be addressed. LiST users recognized that experience and familiarity with the LiST system contributed greatly to their sense of the user friendliness of LiST and that infrequent users of LiST will likely encounter challenges. CDER releases periodic enhancements to LiST intended to address identified challenges. CDER has addressed many of the challenges identified by the ERG assessment using these periodic enhancements and by providing CDER staff with the ability to easily request enhancements through a transparent process.

Key Objective 3: Assess CBER's postmarket safety-related review process and landscape for PDUFA products

To what extent were the evaluation criteria and process steps outlined in SOPP 8420: FDAAA Section 921: Posting of Potential Signals of Serious Risk adhered to?

SOPP 8420 describes the policy and procedures for CBER staff in developing and publicly posting quarterly lists of potential signals of serious risks identified in FAERS. SOPP 8420 provides step-by-step guidance for monitoring FAERS, identifying possible safety issues, and assessing and managing potential signals of serious risks, in addition to specific criteria for which safety issues should be included in quarterly postings. CBER staff described their activities as well aligned with the procedures outlined in SOPP 8420. Staff believe the criteria for identifying potential signals of serious risks for public postings are easy to follow. Most CBER staff have limited experience working with SOPP 8420, as quarterly postings of potential signals of serious risk for CBER products is not a common occurrence. Many of these staff have much more experience using the DE Reviewer Guide, discussed below, which is well aligned with SOPP 8420.

CBER leadership has an in-depth understanding of SOPP 8420 and is heavily involved in all steps of the safety issue process, so they are able to ensure adherence by the medical reviewers at every step of the process.

What are staff perspectives on the utility of the SOPP 8420 and the DE Reviewer Guide for reviewing safety issues?

CBER staff consider both SOPP 8420 and the DE Reviewer Guide to be effective resources. SOPP 8420 and the DE Reviewer Guide help ensure a consistent process for safety issue review and management while serving as an especially great resource for new employees or employees with limited experience. CBER staff suggested that it would be beneficial to expand SOPP 8420 to be inclusive of vaccine products so that there is a central document for all products managed by CBER. Alternatively, a separate center-level SOPP should be developed, similar to CDER's MAPP 4121.3.

What is the landscape of CBER reviewed postmarket safety issues?

Nearly half of the safety signals in the CBER cohort[12] reached phase 3[13] of CBER's postmarket safety signal process. The majority of safety signals in the CBER cohort were for therapeutic products and FAERS was the most common signal source.

What is working well and what is not working well throughout the process?

CBER has developed and effectively implemented thorough procedures for identifying, evaluating, and resolving postmarket safety issues. These procedures are effectively outlined in SOPP 8420 and the DE Reviewer Guide. Due to CBER's relatively small size compared to CDER, whenever a postmarket safety issue is emerging, there is a culture of consensus building as the issue moves through the review process. This means that staff members and leadership in each relevant CBER Office are generally involved in or at least aware of each phase of the postmarket safety issue process, as the teams maintain frequent contact with one another. This open communication ensures that the entire team is up to date and aware of all activities related to any safety issue. Although CBER's postmarket safety-related review process is widely viewed positively, CBER staff face some challenges within the process. CBER staff have dealt with drastically increased report volume since the start of the COVID-19 pandemic. In addition, staff turnover results in loss of product knowledge that is challenging to immediately fill. As described above, expanding SOPP 8420 or developing a separate center-level SOPP, similar to CDER's MAPP 4121.3, would provide a central resource document covering most of CBER's products.

Key Objective 4: Assess Center-level and Office-level management oversight

In CDER, how is the management review section of MAPP 4121.3 being operationalized at the office level?

Super-offices in CDER (e.g., OSE and OND) have some level of involvement in management review of the NISS process through the Drug Safety Team (DST)[14], the NISS Implementation Team,[15] Safety

[12] The CBER safety issue cohort included CBER postmarket safety issues identified from May 1, 2019 through April 30, 2021.
[13] Phase 3 in CBER's postmarket safety review process is similar to the action phase in CDER's NISS process.
[14] DSTs are advisory bodies for strategic coordination, collaboration, and discussion of important and urgent postmarket safety issues, including but not limited to NISS. There are currently nine DSTs, each of which is responsible for a specific therapeutic area.
[15] The NISS implementation team was responsible for supporting the implementation of MAPP 4121.3. In addition to other implementation activities, they were responsible for identifying process improvements based on user feedback and developing process governance and management. The NISS implementation team no longer meets.

Requirements Team (SRT),[16] and the Change Request Committee (CRC)[17] for LiST. These groups, in addition to others, helped ensure CDER-wide adherence to MAPP 4121.3 while also supplying super office directors a platform for discussing policy and procedure improvements or general training needs. In addition to being involved in these initiatives, super-offices have their own unique structure and activities related to management and oversight of NISS.

In CBER, how is the office/division-level oversight and concurrence being operationalized?

CBER communicates on safety issues through multiple, periodic cross-office meetings. CBER staff find that these meetings are effective forms of communication. Leadership from DE and product offices are in attendance at these meetings and are heavily involved in all steps of the safety issue process. As a result of leadership involvement and their in-depth understanding of SOPP 8420 and the DE Reviewer Guide, leadership are able to ensure adherence to procedures at every step of the process.

What is the current role and activity of Center-level management for postmarket safety?

CDER

Senior CDER Leadership serve as members in the Drug Risk Management Board (DRMB) and Medical Policy and Program Review Council (MPPRC) and provide Center-level guidance for challenging safety issues on what action should be taken and how to communicate to the public. In addition to this, Senior CDER leadership are involved with Center postmarket safety initiatives (e.g., through the DRMB or as an Executive Sponsor).

CBER

CBER management staff participate in Safety Working Group (SWG) meetings, enabling them to provide guidance on challenging and severe safety issues that have been escalated for management staff input. CBER management encourages the culture of collaboration prevalent throughout the center. The center director also assists in the determination of whether a 921 posting is required for a safety issue.

How do analytics tools (e.g., reports and dashboards) inform actions of CDER management and staff?

Both LiST and periodic safety-related meetings are key resources for management to keep informed about NISS. Prior to the development of NISS-related dashboards, CDER staff relied solely on LiST query features to obtain data of interest. CDER management staff are interested in having easy access to key metrics of the NISS within their portfolio, including how many NISS are currently open, what phase they are in, and how long have they been in that phase. These data can assist with day-to-day tracking of NISS and higher-level resource management research. CDER is expanding the set of tools available to enhance management oversight of the safety-related review processes. The DST dashboard is viewed as an effective tool for staying informed on a portfolio of NISS. The Pharmacovigilance Strategies (PVS) and NISS dashboards have already launched, and with the DRMB dashboard soon to launch, the tools for efficient management and research of NISS in CDER are expanding.

[16] SRT serves as a resource to CDER staff engaged in review of postmarketing safety issues, providing direct guidance on interpretation and implementation of the FDAAA authorities. SRT assists in developing safety-related internal policies and guidelines, as well as review of FDA communications regarding FDAAA authorities and requirements.
[17] The LiST CRC was established to discuss future enhancements to LiST. The LiST CRC no longer meets.

What is working well and what is not working well throughout the process of management oversight of safety-related review processes in both CDER and CBER?

CDER

CDER has an effective structure in place for management oversight of the safety-related review process both at the center and super office levels. Safety-related meetings throughout CDER (e.g. DST meetings) serve to keep leadership informed of, and involved in, NISS-related decisions, in addition to ensuring that staff are adhering to the steps outlined in MAPP 4121.3. CDER is adding to its portfolio of tools for the efficient management and research of NISS.

CBER

CBER's postmarket safety issue operations enable leadership in CBER offices and divisions to be more involved throughout the postmarket safety issue process. This increased involvement helps ensure staff adhere to the process steps in SOPP 8420 and the DE Reviewer Guide and assists with the identification of process improvements or general training needs.

Key Objective 5: Assess communication to industry

To what degree were application holders notified when serious safety signals were identified? Were application holders notified within 72 hours of posting potential signals of serious risk (921 postings) in accordance with MAPP 6700.9 (CDER) and SOPP 8420 (CBER) timelines?

FDA generally met their requirements for sending out application holder notifications as detailed in CDER's MAPP 4121.3 and 6700.9 and CBER's SOPP 8420. However, some instances were identified where a sponsor notification (i.e., when a NISS moved to the evaluation phase) was either not sent or was not sufficiently documented. FDA is implementing improvements to the process for sending and documenting application holder notifications.

To what degree does the MAPP 6700.9 (CDER) align with FDA's statutory requirement to post signals of serious risk identified in FAERS?

MAPP 6700.9 was developed in response to the addition of subsection (k)(5) to USC 355, which required quarterly postings of potential signals of serious risks identified through FAERS. Section 3075 of the 21st Century Cures Act (Cures Act) amended section 505(k)(5) to include subsection (k)(5)(C), which required FDA to make publicly available the criteria for the public posting of adverse event signals and the guidelines for best practices for the surveillance of the adverse event surveillance system. MAPP 6700.9 aligns with USC 355 Subsection (k)(5)(A) and subsection(k)(5)(C)(ii).The MAPP is fulfilling its intended purpose by focusing on criteria described in (k)(5)(A) and (k)(5)(C)(ii). The guidelines that detail best practices described by (k)(5)(C)(i) are contained in the draft document Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff.[18]

[18] See *https://www.fda.gov/media/130216/download*

To what degree are FDA staff adhering to posting criteria in MAPP 6700.9?

CDER staff reported that their activities generally aligned with MAPP 6700.9. Some staff believe the inclusion and exclusion criteria are described well and easy to follow, while others find the criteria to be confusing, stating that better descriptions and examples could increase clarity. While FDA staff are adhering to the criteria for posting as outlined in MAPP 6700.9, FDA has not recently updated past postings on a quarterly basis[19] as detailed in MAPP 6700.9.

To what degree was FAERS used to identify the signals on the 921 website? To what degree did FAERS contribute to those signals (CDER)?

FAERS was identified as a signal source in LiST for over half of the safety signals included in a 921 quarterly report. The remaining signals did not have FAERS as a signal source in LiST, but FDA staff determined that FAERS *contributed* to those signals separate from the sources captured in LiST.

What are the time and resource commitments in CDER to determining whether or not a signal is a potential signal of serious risk that should be included in the quarterly report on the 921 website?

CDER staff involved throughout the 921 process reported that there is a resource burden associated with determining whether or not FAERS contributed to a safety signal. The size of the burden depends on the number and complexity of the signals. Frequent interactions are needed among super-offices, including between OSE and OND. CDER is addressing the challenges related to MAPP 6700.9 and the resource needs identified by this ERG assessment.

What is working well and not working well with FDA's communication to industry and the public?

FDA (CDER and CBER) communicates with industry as outlined in policy documents (i.e., MAPP 6700.9 and SOPP 8420) and adheres to statutory requirements from USC 355 subsection (k)(5) regarding public postings of potential safety signals. Although FDA's communication with industry and the public generally aligns with processes outlined in policy and is viewed positively by FDA staff, challenges remain, including lack of clarity in MAPP 6700.9's inclusion and exclusion criteria[20] and the need for updates to past public postings. FDA is addressing challenges informed by this assessment.

[19] There is no statutory requirement for FDA to make quarterly updates. Updates to the FAERs previously posted signals last occurred on April 16, 2020, prior to the shift in resource priorities due to the COVID 19 pandemic.
[20] It is important to note that the inclusion/exclusion criteria affect the public posting of the signal and not the communication with industry concerning FDA evaluation of a signal.