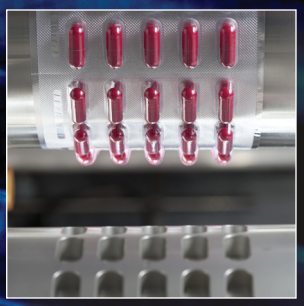

Sentinel Program Interim Assessment (FY 15)

To evaluate the strengths, limitations, and the appropriate use of Sentinel for informing regulatory actions to manage safety issues.

September 24, 2015

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Section 1 | Executive Summary

1.A BACKGROUND

The Food and Drug Administration (FDA) Amendments Act (FDAAA), signed into law in 2007, required FDA to develop a system for postmarket risk identification and analysis of drugs, including biological products such as vaccines. FDA subsequently established the Sentinel Initiative, a multiyear effort to build a comprehensive system to analyze health outcomes across large sets of electronic health data.

In 2009, FDA launched Mini-Sentinel, a pilot program designed to test the feasibility of the core Sentinel precept: to access and analyze healthcare information from a variety of data sources, and to use that data to improve FDA decision making. Since its inception, Mini-Sentinel has achieved several important objectives and has successfully informed FDA decision making during safety reviews of approved drugs and vaccines.

Central to the successful operation of Mini-Sentinel is the Mini-Sentinel Operations Center (MSOC), which serves as an intermediary between FDA and the organizations (e.g., insurers, health maintenance organizations) providing data for the initiative. Since 2009, FDA and its chosen partner, Harvard Pilgrim Health Care Institute, have developed and operated the MSOC, identified and recruited data partners, developed methods to analyze data, and ensured the integrity and quality of patient records.

As of October 2014, Mini-Sentinel had formed partnerships with 19 data partners to provide expertise in addition to data covering 178 million lives—a notable accomplishment considering that many organizations were initially wary of sharing valuable and sensitive data.[1]

In anticipation of a progress assessment for Sentinel, the Prescription Drug User Fee Act (PDUFA) Reauthorization Performance Goals and Procedures FY2013-2017 states:

> By the end of FY 2015, FDA will conduct (or fund by contract) an interim assessment to evaluate the strengths, limitations and the appropriate use of Sentinel for informing regulatory actions (e.g., labeling changes, PMRs, and PMCs) to manage safety issues.

In accordance with the requirements of the PDUFA V letter, this report and the fact-based analysis herein were prepared by an independent, third-party adviser. This report does not analyze nor validate compliance with any applicable federal regulations.

1.B METHODOLOGY

To produce this independent assessment, primary and secondary research was conducted in the first quarter of FY2015. Sources of input for this assessment include the following:

- More than 25 interviews with FDA officials involved with the Sentinel Initiative (on a not-for-attribution basis) between September and October 2014
- Multiple interviews with leaders in the MSOC and external drug safety experts from academia and industry
- Existing literature on Sentinel Initiative progress, including those produced by the Government Accountability Office and the Congressional Research Service, as well as documents produced by FDA and the MSOC on the establishment and functionality of the Sentinel Initiative
- A survey of FDA medical officers and safety reviewers to confirm and/or clarify the insights collected in individual interviews

1.C KEY FINDINGS

FDA, along with its Mini-Sentinel partners, led by Harvard Pilgrim Health Care Institute, has made substantial progress in meeting or exceeding all key progress milestones associated with Sentinel. Through the Mini-Sentinel pilot, FDA has begun building the processes, systems, and internal capabilities required for Sentinel to help FDA address potential safety concerns associated with approved medical products.

Mini-Sentinel experience differs across CBER and CDER

Use of Mini-Sentinel across FDA is not homogenous. The use of Mini-Sentinel by the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) to address safety questions has evolved simultaneously, yet separately.

Such separate development is rational, as the Centers are markedly different. CDER has a much broader mandate, many more employees, and the nature of postmarket drug surveillance differs meaningfully from postmarket surveillance of biologics.

Consequently, each Center has customized the infrastructure, personnel, processes, and procedures that support Mini-Sentinel to reflect the needs of its respective users. The results of these choices have important implications on talent and organization, governance, and process infrastructure.

Current use of Sentinel by FDA

Sentinel complements FDA's existing postmarket surveillance of drugs and vaccines by enabling FDA to refine risk signals identified through other channels.

Both Centers that utilize Sentinel have a core group of early adopters who are sophisticated and frequent users; however, both Centers show limited awareness among the broader population of safety reviewers. FDA has established comprehensive processes and governance mechanisms to manage the input of safety concerns, the specification of queries, and the review of results.

The impact of Sentinel on regulatory decision making

Sentinel can impact FDA regulatory decision making in two key ways:

- **Improved active surveillance.** Whereas FDA's existing surveillance systems continue to alert FDA to potential health safety risks, Sentinel enables FDA to understand better and estimate more accurately the incidence of a given safety risk in a relevant population. In most cases, the combination of Sentinel data and insights from other FDA resources informs regulatory decision making by broadening FDA's active surveillance capability, leading FDA to examine safety questions in ways that would be impossible without Sentinel.

- **FDA agency action.** Even if an FDA action is not taken as a direct result of a Sentinel query, Sentinel data has important implications on how drugs and biologics are used and stimulates a wider set of pharmacoepidemiological evaluation options, which ultimately can help both CBER and CDER make better decisions across its regulatory jurisdiction. In many instances when FDA does not take direct action, Sentinel data confirms that existing labels and communications accurately describe the safety risks.

Notable FDA actions

In a few circumstances, FDA is prompted to take an explicit regulatory action as a direct result of Sentinel data. Such actions include FDA safety communications and FDA label changes. Several of these notable instances were uncovered through FDA stakeholder interviews and primary research, and are detailed in this assessment, including the following:

- **Dabigatran.** FDA ascertained that bleeding rates associated with dabigatran, a new drug, were not significantly higher than bleeding rates associated with warfarin, an older drug, despite the large number of postmarket adverse event reports of serious and fatal bleeding events. FDA's finding led to a safety communication and currently ongoing protocol-based assessment.

- **Rotavirus vaccine.** FDA identified that administration of rotavirus vaccine (Rotateq) led to an increased risk of intussusception (a serious abdominal condition), which was not detected during clinical trials prior to approval. Information led to an FDA label change.

- **Olmesartan.** FDA confirmed results of case studies that demonstrated increased risk of sprue-like enteropathy with long-term olmesartan use, but it did not find class effects. Findings led to FDA safety communication and label change.

- **Influenza vaccine.** FDA found no increase in risk of febrile seizures in children after receiving vaccination with Fluzone. Findings led to FDA safety communication.

CBER and CDER process infrastructure

CBER and CDER have a similar process infrastructure with several meaningful differences:

- The CBER process approach tends to be collaborative, involving both the CBER Sentinel lead and the CBER reviewer who initially identified the safety concern. CBER has created an initial set of processes and procedures to support its use of Mini-Sentinel.

- CDER's process infrastructure is driven by heavy involvement of the Center Sentinel lead. The CDER safety reviewer generally is not involved in the conversion of a safety question into a Mini-Sentinel query or the coordination with the MSOC. CDER also has chosen not to formalize or codify its process infrastructure.

Even though some differences in process and infrastructure are to be expected, both Centers have opportunities for improvement, as noted in the Sentinel Maturity Model.

Opportunities to increase the utilization of Sentinel data to inform regulatory decisions

Sentinel holds the promise of increased utilization by FDA reviewers to inform regulatory decisions regarding approved products. To assess progress toward the goal of broad adoption, it is important to look at Sentinel relative to cross-industry best practices in real-world data and analytics deployments.

1.D SENTINEL MATURITY MODEL (SMM)

A Sentinel Maturity Model (SMM)[2] is used in this Interim Assessment to analyze Sentinel's progress toward full maturity across six key dimensions. The assessments represent where Sentinel is today relative to full maturity in the future. Since the initiative is still transitioning from Mini-Sentinel to the full Sentinel System, it is not expected to be at full maturity at the time of this assessment.

- Assessment of Sentinel platform
  - *Strategy and value.* Medium level of maturity in this category. Leaders actively promote use of Sentinel, and success stories exist, but broad awareness and use of Sentinel capabilities remains low.
  - *Analysis tools and technology.* Low level of maturity. A rich data infrastructure to support growth exists, but more sources of data (e.g., inpatient exposures) and analytical capabilities are needed.
  - *Methods.* Medium level of maturity. A strong set of standardized methods are available for statistical analysis, but methods will need to continue to evolve as more tools and data sources are integrated.

- Assessment of CBER and CDER progress
  - *Talent and organization.* Medium level of maturity for CBER. Low level of maturity for CDER. Both Centers have skilled users, but broader user base has cited need for additional training. CBER has integrated users well throughout its process. CDER has not integrated its users into the query-type selection or specification processes. Both Centers will need some additional flexibility to manage higher demand in the future-state Sentinel System, but CBER's smaller range of products and experience may limit the extent of new resources needed.
  - *Governance.* High level of maturity for CBER. Medium level of maturity for CDER. CBER has strong oversight and transparency, and oversight and support for users has been established, but a portion of users still prefer greater autonomy. CDER users have role clarity but need more process transparency.
  - *Process.* Medium level of maturity for CBER. Low level of maturity for CDER. CBER has established end-to-end process, but many queries are bespoke and effort-intensive. Additionally, both CBER and CDER need to develop metrics to measure performance, user satisfaction, and usage trends.

The SMM assessment indicates that FDA has made progress toward developing a sophisticated analytics system that can increase its active surveillance capability to make regulatory decisions on postmarket drugs and vaccines. However, to meet the growing demand for use in the future, both CBER and CDER will want to consider taking targeted actions to increase the maturity of Sentinel and encourage broader adoption and use.

This assessment highlights key areas for FDA leadership to focus on as Sentinel matures. Several critical steps can be taken to evolve and improve Sentinel's capacity to support FDA regulatory decision making—and improve overall health outcomes.

Section 2 | Assessment Methodology and Report Structure

2.A METHODOLOGY FOR CONDUCTING THIS ASSESSMENT

Background

This Interim Assessment is a requirement of the Prescription Drug User Fee Act (PDUFA), as noted below.

> "By the end of FY 2015, FDA will conduct (or fund by contract) an interim assessment to evaluate the strengths, limitations and the appropriate use of Sentinel for informing regulatory actions (e.g., labeling changes, PMRs and PMCs) to manage safety issues."
>
> – PDUFA Reauthorization Performance Goals and Procedures FY2013-2017

Sources of input

Primary sources of input for this assessment include the following:

- Interviews with FDA employees in the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER). Interviewees included reviewers with direct experience working with Mini-Sentinel data as well as senior leaders in CBER and CDER.

- A brief survey of FDA employees to provide an opportunity for a broader set of employees (beyond those interviewed) to provide input to confirm and/or clarify the insights collected in individual interviews.
- Interviews with leaders in the Mini-Sentinel Operations Center (MSOC) as well as at participating data partner sites.
- Interviews with external drug safety and epidemiology experts from leading academic institutions and with industry experience working for biopharmaceutical companies.
- Interviews with experts on information technology adoption and advanced data analytics.
- Review of published reports and/or scholarly literature on the following topics:
  - Reports on interim progress of the Sentinel Initiative, including those produced by the Government Accountability Office and the Congressional Research Service
  - Internal documents produced by FDA and the Mini-Sentinel Operations Center (MSOC) on the establishment and functionality of the Sentinel Initiative
  - Literature associated with the strengths and limitations of Sentinel data
  - Literature associated with the products for which Sentinel data has informed a regulatory decision by FDA
  - Best practices and barriers to overcome in the establishment of advanced data analytics programs

Conclusions in this Interim Assessment are also informed by interviews with experts in information technology adoption and literature on benchmarks and organizational best practices in the establishment of advanced data analytics programs such as Sentinel. An overview of all interviews conducted can be seen in **Exhibit 1**.

Exhibit 1: Interviews conducted for Sentinel Interim Assessment

		OSE	OGD/ OND	OBE	OVRR/ OBRR	Total completed
Internal FDA interviews	CBER	-	-	6	4	10
	CDER	8	7	-	-	15
	Total internal					25
External interviews	Mini-Sentinel Operations Center (MSOC) leadership					
	Data partners and data collaborators					
	Pharmaceutical industry: Heads of Safety, Chief Medical Officers, and Heads of R&D					
	Academic subject matter experts					

Section 3 | Introduction to the Sentinel Initiative

3.A ESTABLISHING THE SENTINEL INITIATIVE

3.A.1 Legislative history of the Sentinel Initiative

In 2007, the U.S. Congress passed and President George W. Bush signed the Food and Drug Administration Amendments Act (FDAAA). FDAAA required FDA to develop a system capable of postmarket risk identification and analysis to assess the safety of previously approved drugs.[3] FDAAA required that the new system access healthcare data from 25 million individuals by July 2010, increasing to 100 million individuals by July 2012.

In response to the FDAAA mandate, FDA established the Sentinel Initiative and outlined a plan to launch a pilot program known as Mini-Sentinel, which would eventually expand into the full Sentinel System.

3.A.2 Objectives and goals for the Sentinel Initiative

In accordance with the FDAAA mandate, the Sentinel Initiative is designed to serve as a system to analyze and assess safety risks in FDA-approved drugs and medical products using electronic health data. The Sentinel Initiative primarily offers signal refinement and evaluation support for existing signal identification capabilities.

The primary goal of Sentinel is to help FDA scientists better understand, refine, or refute an identified safety signal and determine whether the safety concern merits regulatory action.

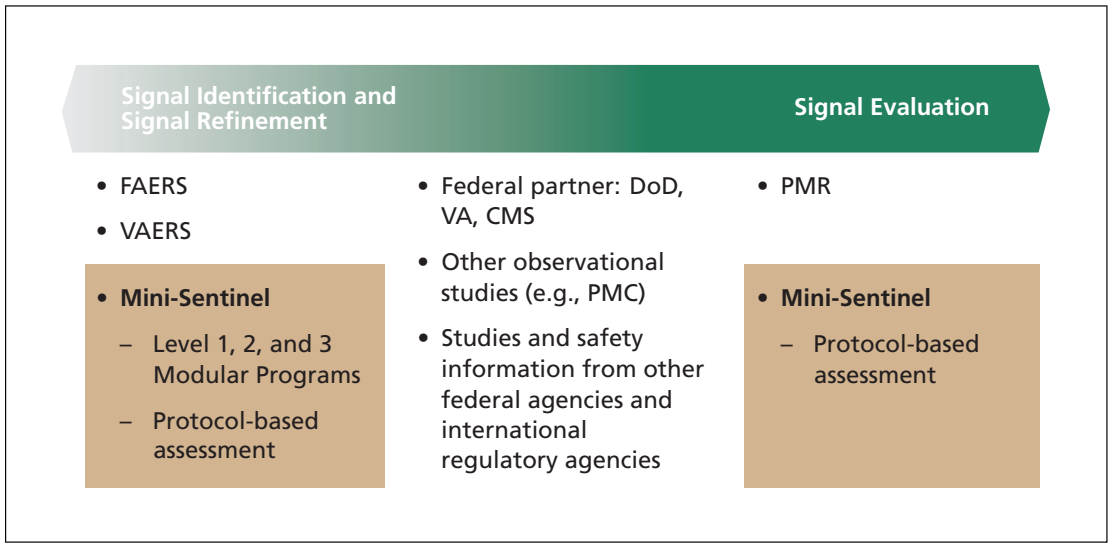
FDA set several internal objectives for the Sentinel Initiative, including the following:

- Identify data partners for Sentinel
- Create the ability to define the set, or cohorts, of individuals exposed to a drug or medical product or with specified health outcome characteristics
- Create an automated, computer-based mechanism that enables FDA scientists to analyze data to better understand a safety concern
- Understand how to use the resulting analysis to inform a regulatory decision
- Develop an approach to integrate certain epidemiological approaches such as adjusting for confounding variables[4]

3.A.3 Existing **postmarket** surveillance resources

Part of FDA's longstanding mission is to monitor the safety risks posed by drugs and medical products approved for marketing and use in the United States. The Sentinel Initiative is designed to complement, not replace, existing postmarketing surveillance resources, which alert FDA scientists to potential health risks, referred to as "safety questions." Sources for the pharmacovigilance information are described in **Exhibit 2**.

Exhibit 2: Mini-Sentinel complements the full suite of FDA postmarket surveillance safety assessment tools



Existing postmarket surveillance resources include the following:

- **Individual adverse event reports.**
- **Mandatory reports of potential safety issues from drug and biologics product manufacturers.** Applicants are required to alert FDA within 15 days of discovering adverse events that are both serious and unexpected in approved medical products.[5]
- **Voluntary reports.** FDA maintains a program called MedWatch that receives voluntary reports of potential safety issues associated with the use of medical products from patients, physicians, hospitals, providers, insurers, and other healthcare workers. Product Centers use the reported data accordingly:
  - The Center for Biologics Evaluation and Research (CBER) Office for Biostatistics and Epidemiology (OBE) compiles incoming reports and uses the Vaccine Adverse Event Reporting System (VAERS) to analyze them. CBER uses FAERS for non-vaccine biologics products.
  - The Center for Drug Evaluation and Research (CDER) Office of Surveillance and Epidemiology (OSE) compiles incoming reports and uses the FDA Adverse Event Reporting System (FAERS) to analyze them.
  - Collectively, FAERS and VAERS are known as the Adverse Event Report System (AERS).
- **Periodic reports.**
  - *Periodic Adverse Drug Experience Report (PADER) or Periodic Adverse Experience Report (PAER).* FDA requires sponsors and manufacturers to submit a PADER or PAER on the reported safety experience of drug or medical products.
  - *Periodic Benefit-Risk Evaluation Report (PBRER), and Periodic Safety Update Report (PSUR)/Development Safety Update Report (DSUR).* In lieu of submitting a PADER or PAER, drug and medical product manufacturers may submit PBRERs and PSURs/DSURs. Developed by the International Conference on Harmonization (ICH),[6] PBRERs and PSURs are used by FDA to evaluate postmarket risk for a single active moiety, or individual medical product. PBRER and PSUR analyses include a review of indications, dose types, dose regimen, and routes of administration. Both reports are produced as medical analyses of drug/product safety and risk, rather than aggregations of data. DSURs, also developed by the ICH, contain clinically significant safety findings from ongoing clinical trials of marketed drugs.

- **Study-based reports.**
  - *Postapproval studies (PAS)*. Drug sponsors or medical product manufacturers may perform a PAS after approval to further assess the safety of a drug or medical product.
  - *Postmarketing commitments (PMC)*. Drug sponsors may voluntarily perform additional clinical trials or studies, though they are not compelled by FDA to do so.
  - *Postmarketing requirements (PMR)*. FDA may mandate, as a condition of approval, a PMR, which compels drug sponsors or product manufacturers to conduct a clinical trial or a post-approval safety study to investigate a safety issue.

- **Other resources.**
  - *Studies and reports from international regulatory agencies.* OBE and OSE maintain contact with international counterparts to share information on safety issues found in similar drugs or medical products. FDA will monitor international clinical trials and safety reports produced by international regulatory bodies.
  - *Medical literature.* FDA scientists routinely review published journal articles and case reports related to drug safety.
  - *Other observational data.* FDA scientists also conduct formal pharmacoepidemiological studies to evaluate safety issues using observational data from public and private data sources, including collaboration with the Department of Defense, the Department of Veterans Affairs, and the Centers for Medicare and Medicaid. FDA also has several external sources for observational data. For instance, CDER often conducts pharmacoepidemiological studies through private research firms.
  - *Premarket information and registries.* FDA continuously reviews information from data it has collected in the premarket evaluation process, and it may also consult drug registries as appropriate.

3.A.4 Limitations of existing voluntary surveillance resources

A significant portion of FDA's postmarket surveillance originates from voluntary reports. As mentioned above, FAERS and VAERS are collectively known as the Adverse Event Report System (AERS), which is subject to structural weaknesses that are outlined below.

Reporting bias. One structural weakness is reporting bias, which includes both under- and overreporting. Underreporting occurs when physicians lack awareness of a possible connection between a health incident and a medical product. Underreporting tends to be especially pronounced if a health incident is associated with a well-established medication or a common medical event.

Overreporting can occur in several ways. For example, media attention related to a specific safety issue might stimulate a sharp increase in reporting. Similarly, a product that is new to the market may also result in overreporting. In general, reporting trends tend to vary over the lifecycle of a product (i.e., reporting becomes less frequent as products mature).

Lack of causal clarity. Another structural weakness is the "lack of causal clarity" in which voluntary adverse event reports may provide insufficient information to make a systematic evaluation on causation. For instance, a reported adverse event may have an unclear connection with a medical product, may be caused by the condition the drug is indicated to treat, or may be due simply to user error.

Lack of information. Finally, voluntary reports typically lack information about the underlying population. Voluntary reports nearly always lack a "denominator," which would describe the actual incidence of health outcomes of interest across an exposed population. Voluntary reports also typically lack the actual rate of drug utilization and information about the underlying population's status quo rate of susceptibility to the health condition in question.

These structural limitations often constrain FDA's ability to make decisions on voluntary reports alone. The Sentinel Initiative was designed to help address these limitations by leveraging new technologies to analyze a much broader set of electronic health data.

3.A.5 How the Sentinel Initiative helps inform regulatory decisions

Sentinel helps inform regulatory decision making in two key ways:

1. **Improved active surveillance.** Sentinel data is an important addition to the tools available to FDA safety reviewers; however, in most cases, Sentinel results are not dispositive. The FDA reviewer must consider the Sentinel results in addition to other available information to strengthen or weaken the connection between a drug or vaccine and a health outcome of interest.

   In many cases, successful use of Sentinel for regulatory decision making is characterized by a combination of Sentinel data with insights from other FDA resources. Sentinel data helps fill the gaps outlined above by enabling FDA to do the following:

   – Study population subgroups and special populations (e.g., females ages 21 to 35) and evaluate such populations over longer periods of time

   – Characterize the size and distribution of epidemiology (e.g., background rates, age, and sex distribution) and health outcomes of interest (e.g., liver failure), and find rare or low-incidence events that are nevertheless statistically significant in large populations

   – Analyze frequently occurring events (e.g., renal toxicity, fractures) that may be associated with a postmarket medical product but may be underreported by healthcare professionals

   – Provide FDA safety reviewers with an approximate "denominator" that better enables reviewers to understand the prevalence of a safety concern ("the numerator") across a relevant population

   With these additional capabilities, Sentinel can improve FDA's capacity for active surveillance. Sentinel data has important implications on how drugs and vaccines are used and stimulates a wider set of pharmacoepidemiological research capabilities by enabling more accurate investigations of safety risks that lead to greater scientific certainty.

   In addition, Sentinel helps with decisions not to act. Such cases are characterized by FDA determining that, despite numerous adverse event reports, existing labeling or safety communications adequately describe risks of a drug, and explicit action is not warranted.[7] Sentinel's ability to provide a "denominator" can be particularly helpful in such instances.

2. **FDA agency action.** In some circumstances, FDA will be prompted to take an FDA regulatory action to address a narrow issue that Sentinel data has surfaced. Such actions include FDA safety communications, FDA label changes, and the affirmative decision to not take action. This report considers three such circumstances, which are defined below:

   – *Recalls and withdrawals.* In rare circumstances, if FDA determines that use of or exposure to the product can cause serious health consequences, FDA may request or require that a company recall or withdraw a drug or medical product from the market in the United States. In such cases, FDA often conducts a benefit-risk analysis, taking into account the seriousness of the medical condition and an acceptable level of safety risk.

   – *Label changes*. FDA considers labels a significant method to help the public and healthcare professionals understand the safety and effectiveness of a drug or biologics product. In the past, if FDA identified a safety concern via AERS or other sources, it could request that drug sponsors make appropriate labeling changes, which typically occurred only after an extended, and open-ended, negotiation. However, upon passage of FDAAA, FDA gained authority to mandate that sponsors change a product's safety label if FDA finds "reasonable evidence" of an "association" with a safety concern.[8] Under FDAAA, FDA may require that a drug sponsor submit proposed label changes (or a rebuttal) for FDA review and approval within a strict timeline.

– *Safety and risk communications.* FDA also issues public communications to help the public and healthcare professionals better understand the risks and benefits of FDA-regulated drugs and biologics products. At times, communications will also be used to alert the public to an emergency, or to reassure the public if safety concerns reported in the media are unfounded or overstated. FDA uses several channels to issue its public communications, including Drug Safety Communications, FDA Drug Safety Podcasts, and its Twitter account @FDA_Drug_Info. It may also submit articles for publication in widely read medical journals.

The public health impact and regulatory impact is summarized in **Exhibit 3**.

Exhibit 3: Public health and regulatory impact of Mini-Sentinel pilot to date

Improved signal refinement

- **Mini-Sentinel has supported affirmative FDA decisions to not take action** if it determines that existing labels and communications adequately describe benefits and safety risks.
- **Mini-Sentinel has supported existing FDA regulatory investigations** by characterizing the distribution (e.g., age and sex) of health outcomes of interest.
- **Mini-Sentinel has supported ongoing drug surveillance,** including identification of drug-use patterns across the United States.

FDA agency action

- 0 **Withdrawals or recalls**
- 2 **Label changes**[1]
- 3 **Safety communications**

1 Includes the olmesartan label change decision, in which Mini-Sentinel data helped support a correlation found in clinical studies and FAERS.

Section 4 | Mini-Sentinel Pilot Program and Progress to Date

4.A EVOLUTION OF THE MINI-SENTINEL PILOT PROGRAM

4.A.1 Mini-Sentinel: Structure and progress

The Mini-Sentinel pilot was designed as a fully operational postmarket surveillance tool that can utilize medical data from a number of sources and assess safety issues in FDA-regulated drugs, medical devices, vaccines, and other biologics.

As previously discussed, the Mini-Sentinel pilot was designed to complement other resources at the disposal of FDA scientists rather than identify and confirm safety risks on its own.

The goals for the Mini-Sentinel pilot included helping FDA better understand the feasibility and challenges of accessing data from disparate sources to inform medical product safety surveillance.

Other initial goals for the Mini-Sentinel pilot were the following[9]:

- Recruiting data partners to supply healthcare data

- Selecting an operating center contract entity to conduct analysis and interact with data partners
- Executing successful queries on the data
- Testing different program designs and structures for the future

As of the time of this assessment, the Mini-Sentinel pilot has formed partnerships with 19 data partners to provide analysis of source data, and it has run hundreds of queries on FDA safety questions. The Mini-Sentinel pilot has met every requirement to date in the FDAAA legislation as well as the Prescription Drug User Fee Act (PDUFA), as shown in **Exhibit 4**.

Exhibit 4: FDAAA/PDUFA Sentinel Initiative milestones required/met

	Requirement	Deadline	Date achieved	Current status
Public meetings on Sentinel design	"FDA will hold or support public meetings engaging stakeholders to ... facilitate stakeholder feedback" on how best to use Sentinel to "evaluate drug safety issues that may require regulatory action"	End of FY 2013	Mar 2008–Jan 2010	FDA held series of stakeholder meetings ('08), formed Federal Partner Working Group ('08), held public workshops facilitated by Brookings ('09-'10)
Number of lives covered	• 25 million lives covered • 100 million lives covered	• July 2010 • July 2012	July 2010–Dec 2011	178 million lives
Number of queries or studies	FDA will fund 4 to 6 activities, including "multiple product or class-specific studies or methodology development" that are designed to (a) evaluate safety signals that support regulatory action, or (b) help determine the utility and validity of the Sentinel System	End of FY 2017	First queries run in 2010	The Mini-Sentinel pilot now runs hundreds of queries per year and demonstrated 4 successful cases of regulatory decisions influenced by Sentinel analysis

4.A.2 Mini-Sentinel: Design choices

FDA has made several important design choices in the development of the Mini-Sentinel pilot since the passage of FDAAA.

To maintain the integrity of the data and protect patient privacy, FDA decided that its scientists and safety reviewers would never directly access Mini-Sentinel pilot data. Instead, Mini-Sentinel uses a "distributed data"[10] approach, such that each participating data partner retains full operational control over its database. The Mini-Sentinel pilot, in accordance with plans for the full Sentinel System, uses an independent operations center to work directly with data partners, receive summary results of analyses, and convey the information to FDA.

The Office for Human Research Protections in the U.S. Department of Health and Human Services determined that the regulations administered by that office (i.e., the Common Rule[11]) do not apply to the activities included in FDA's Sentinel Initiative. Therefore, data partners are not required to obtain Institutional Review Board approval to use patient data as part of Mini-Sentinel.

4.A.3 Mini-Sentinel: Establishing the operations center

In September 2009, after soliciting proposals and conducting an open procurement process, FDA selected Harvard Pilgrim Health Care Institute, to develop and operate the Mini-Sentinel Operations Center

(MSOC), which serves as an intermediary between FDA and the data partners.[12] The MSOC works directly with FDA to develop the specific query tools (e.g., summary table, modular program, protocol-based assessment) used to search the multisource database, and it works directly with data partners to ensure data standardization and data quality for querying.

The MSOC is responsible for managing relationships with participating data partners. The MSOC directly collaborates with data partners to determine the feasibility of certain types of analysis and to maintain, update, and refresh the data as needed. Prior to executing a query, for example, the MSOC conducts a series of verification procedures to identify any errors that might exist in a dataset, and it will work with the data partner if needed to update the data or otherwise resolve the issue.

4.A.4 Mini-Sentinel: Working with data partners

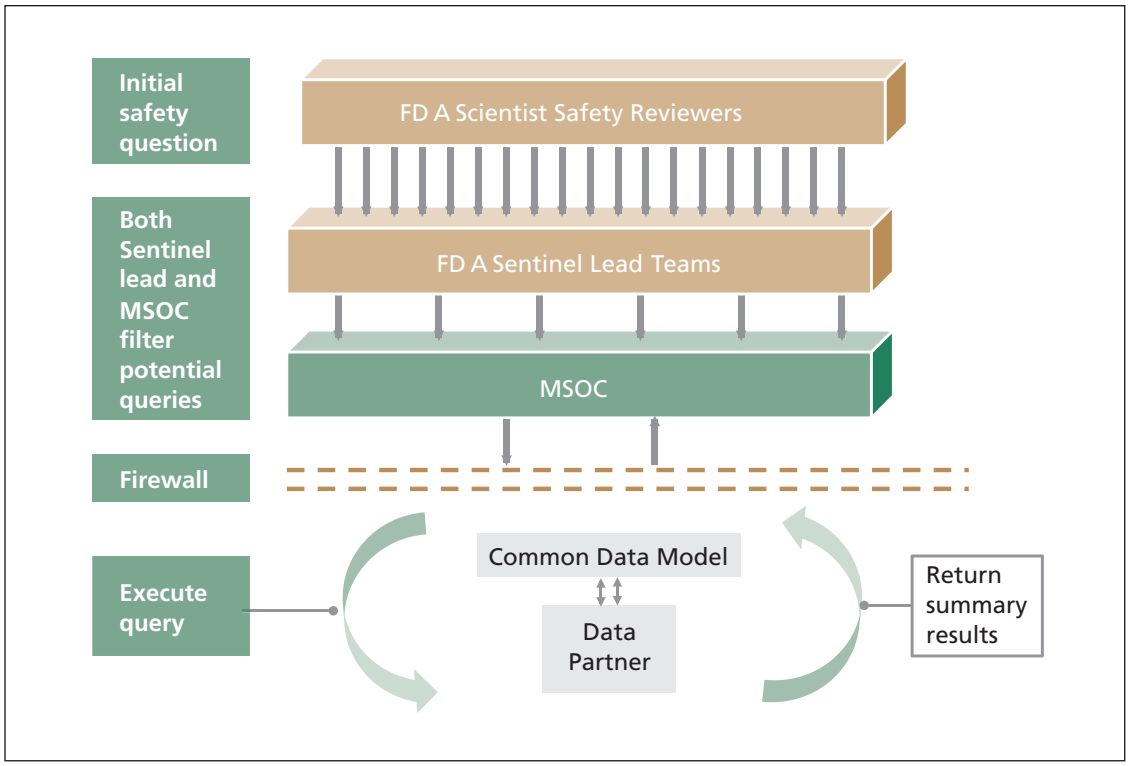
As of October 2014, the MSOC has recruited 19 data partners, listed below. Of the data currently available to the MSOC, 86% is provided by 4 of the 19 current data partners.[13] Additional detail on these data partners is available in **Exhibit 5**.

Exhibit 5: Current Mini-Sentinel data partners

Category	Entity and description
Division of health insurer	**Aetna, Inc. – Aetna Health Informatics** Informatics specialist arm of Aetna, large health insurance payer, with more than 35 million enrollees in the United States.
	HealthCore, Inc. The clinical outcomes research subsidiary of Anthem (formerly WellPoint, Inc.), a large health insurance payer, with more than 68 million enrollees in affiliated health plans.
	Humana Comprehensive Health Insights, Inc. The health economics and outcomes research subsidiary of Humana, Inc., a large health insurance payer with 12 million members in medical benefits plans and approximately 8 million in specialty health plans.
	Kaiser Permanente Center for Effectiveness and Safety Research (Georgia, Mid-Atlantic, Hawaii, Colorado, Northwest, Northern California A research center with more than 400 researchers, clinicians, and analysts in Kaiser Permanente's 8 regional research centers. The center is an arm of Kaiser Permanente, a large integrated managed care consortium of both payers and providers of care with 9.5 million members in the United States.
	Optuminsight, Inc. The software and health information division of Optum, the population health management platform of UnitedHealth Group, a large health care benefits user. Optum serves more than 63 million members.
Health care provider	**The HMO Research Network (Group Health Research Institute; Harvard Pilgrim Health Care Institute; HealthPartners Institute for Education and Research; Henry Ford Health System: Public Health Sciences Department; Marshfield Clinic Research Foundation; and the Meyers Primary Care Institute)** A consortium of health care delivery organizations, including more than 1,400 scientists and research staff with health care and content expertise.
	Lovelace Clinic Foundation A nonprofit health services research organization comprised of physicians, hospitals, health plans, and academic institutions.
Hospital system	**Vanderbilt University Medical Center** A collection of hospitals, clinics, and physician practices and affiliates covering 9 hospital systems and 48 hospital locations in and around Nashville, Tennessee. The Vanderbilt University Medical Center analyzes Tennessee Medicaid patient data for Mini-Sentinel.

As noted above, at no point in the Mini-Sentinel pilot process does the MSOC or FDA physically manage or retain the patient information owned by these data partners. Instead, data partners convert their data into the Mini-Sentinel Common Data Model (MSCDM). The MSOC then provides standard computer program instructions, known as queries, specifically formulated to run on data within the MSCDM. The data partners themselves execute these instructions on the data and return the results to the MSOC. This design choice keeps all identifiable patient information protected behind the respective data partner firewalls. This process is illustrated in **Exhibit 6**. It should be noted that in certain circumstances individual-level data, typically deidentified or a HIPAA limited data set, may be shared by the data partner for a limited number of individuals, to support a protocol-based analysis.

Exhibit 6: Mini-Sentinel interaction with data partners. All data and analysis performed behind a firewall



The MSCDM, which was jointly developed by FDA, the MSOC, and participating Mini-Sentinel data partners, is critical to the success of the entire Mini-Sentinel process. The specialized coding structure of the MSCDM links patient claims data with an anonymized patient identifier.[14] This enables MSOC analysts to create a single set of standardized queries that will work with a wide array of data partners, who retain clinical data in a variety of formats.

On a routine basis, data partners collect the necessary data and convert it into the MSCDM, so that the data is "refreshed" and can be used at any given time. Data partners do not typically collect data for a specific request, with the exception of protocol-based assessments that include chart reviews. At each "refresh," the MSOC's team of quality analysts works directly with the data partners to validate and characterize the data. While data partners typically have rigorous quality control, the MSOC also runs a series of quality checks to ensure that it is appropriate for use in Mini-Sentinel.

Once the data partners run a query, the results are shared with the MSOC. The MSOC postprocessing team then reviews and examines the results and creates a summary report that it shares with FDA.

4.A.5 Mini-Sentinel: Capabilities and limitations in supporting regulatory decision making

The Mini-Sentinel pilot supports three main types of data collection and analysis activities, as illustrated in **Exhibit 7** and described below.

Exhibit 7: Mini-Sentinel analysis types

Analysis type	Description	Approx. time to completion
Data summary tables	• Data compilations of individual age groups, genders, or both, with incident counts of medical outcomes, including diagnoses, medical procedures, and exposure to certain medical products.	~1 week
Modular program queries type 1, 2, and 3	• Standard computer programs that run several searches on a dataset and return a result. • The programs can be customized using various input parameters that define medical product exposures, diagnoses, date ranges, age ranges, and other implementation details.	3 weeks – 6 months
Protocol-based assess-ments	• Long-term studies that enable (a) a more detailed analysis of patients exposed to certain health events, (b) adjustment for confounding factors, and (c) comparison of occurrence and event rates between differing drugs or medical products. Protocol-based assessments typically involve investigators from collaborating institutions with subject-matter expertise as well as MSOC and FDA staff.	1 – 3 years

Increasing complexity: Less complex queries → More complex queries

Choosing among the program types is contingent on the complexity of the problem, the health outcomes of interest, the public health impact, and the level of urgency.

Data summary tables

Data summary tables are compilations of patient data, such as listings of individual age groups or genders with incident counts of certain medical outcomes, including diagnoses, medical procedures, and exposure to certain medical products.

For example, a summary table can provide a breakdown by age group, gender, year, drug coverage status, and medical coverage status for a number of individuals given a certain medical treatment, including administration of a certain generic drug. In addition, summary tables can specify care setting, such as inpatient, outpatient, or emergency.

These standardized tables are developed utilizing a program created by the MSOC and executed against the MSCDM held by each data partner. The resulting data tables remain in each data partner's secure environment for querying. The results are generated through rapid querying and are, by far, the quickest method of analysis available with the Mini-Sentinel pilot database, and can be executed in as little as one to two weeks.

Modular program queries

Modular program query capabilities are divided into three levels to handle increasingly complex safety questions.

- Level 1 queries, also known as Cohort Identification & Descriptive Analysis (CIDA), provide descriptive statistics, unadjusted and adjusted incidence rate ratios (adjusted for data partner, age group, sex, and calendar year), and an analytic dataset for input to Level 2 queries. Level 1 queries can provide information such as the incidence of a health outcome of interest in cases of certain procedures, demographics, and outpatient dispensing claims.
- Level 2 queries are one-time queries that perform more complex analytical adjustment or confounding factors. At this time, Level 2 queries are able to incorporate propensity scores for improved matching of comparison groups.
- Level 3 queries are derived from Mini-Sentinel's Prospective Routine Observational Monitoring Program Tools (PROMPT). These newer queries were developed via collaboration between FDA and the MSOC to perform advanced statistical analysis allowing for sequential monitoring of newly approved products as usage increases among the broader population. Level 3 queries also enable the MSOC and FDA to perform propensity score matching, set risk assessment thresholds, query the database in a continuous manner, and design an assessment plan for sequential assessment.

At the time of publication, Mini-Sentinel had recently revamped its modular program capabilities into the structure described above. Prior to that change, Mini-Sentinel had various modular programs that were capable of performing many of the activities noted in Level 1 or Level 2, but did not allow for streamlined integration into more complex assessments. FDA is working to expand its capabilities by developing Level 2 and Level 3 queries to handle more complicated safety questions as an alternative to a lengthy protocol-based assessment. These advanced queries hold significant potential for helping FDA refine a signal or safety question and decrease response times.

The time-to-completion for modular program queries is typically four to six weeks but can vary based on personnel, current workload, and urgency. Improper identification of the safety question and MSOC backlog can both delay the process. In addition, Level 3 modular programs may take longer than six weeks because the sequential analysis process tends to be more involved.

Protocol-based assessments

Protocol-based assessments are customized studies that enable a more detailed analysis of a potential safety issue. Protocol-based assessments require ad hoc programming to provide data to inform the safety issue of concern, and they are much more resource-intensive. Typically, a working group comprised of subject-matter experts from collaborating institutions as well as MSOC and FDA staff is formed to manage the assessment, and the entire process can take as long as one to three years, depending on the amount of data needed to accrue (i.e., these are often sequential in nature, meaning that analyses may be performed quarterly, or even more frequently, as exposure to a medical product is obtained). Often, protocol-based assessments will contain a review of medical records by data partners to validate findings.

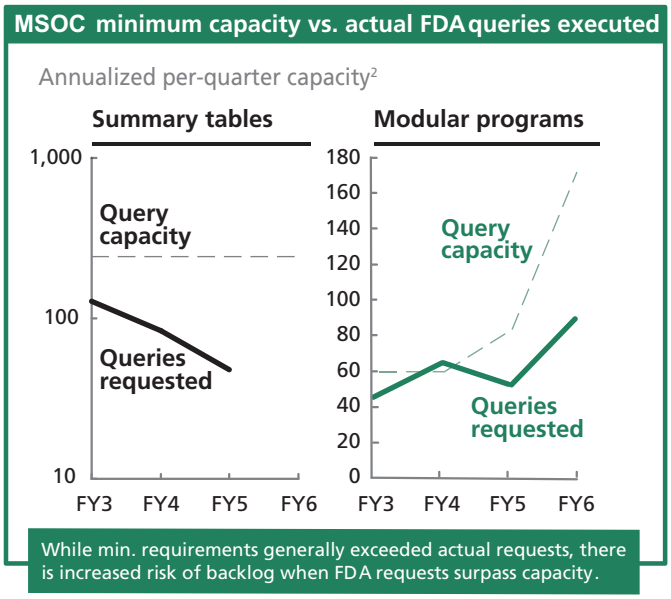
Capacity

While the MSOC helped build the MSCDM and query tools, it also worked to ensure it could actively manage FDA query requests without creating a backlog. From 2011 to 2014, the MSOC and data partners utilized a forecasting mechanism to ensure that the Mini-Sentinel pilot had the capacity to manage a steady increase in FDA demand for simultaneous rapid querying. In general, the required query capacity that MSOC was required to meet exceeded queries requested (**Exhibit 8**). However, it is important to note that in Fiscal Year 4 (September 2012 to September 2013), FDA queries requested for modular programs outstripped query capacity, creating a short-term backlog. While the required limit has since been raised significantly, backlog remains a tangible risk that both CBER and CDER leadership must monitor carefully.

Exhibit 8: Expanding query capacity over time to meet FDA demand

Development

- The MSOC is required to establish a query capacity[1] for both summary tables and modular programs.
- As of Q1 FY 2015, all requirements have been met.
  - MSOC executes 100+ total queries per year.
  - Technical sophistication of MPs has increased substantially over the contract period.



1 At end of each contract year, the MSOC and data partners are required to establish the administrative and technical capability requests up to a minimum amount. Contract also specifies minimum staff resources and types of modular program queries.
2 A single query execution can yield large datasets with 60+ patient exposures, outcomes and cohort definitions; Fiscal Year 3 (FY3) is Sept. 23, 2011 – Sept. 22, 2012; FY4 is Sept. 23, 2012 – Sept. 22, 2013, etc.

Source: FDA, Mini-Sentinel Operations Center

Limitations

While the Mini-Sentinel database is extensive, several structural constraints may inhibit its ability to inform regulatory decision making. These constraints result from limitations on the data available from participating partners rather than FDA's design choices. For example:

- The Centers for Medicare and Medicaid Services are not yet included as a data partner, which markedly limits the number of individuals over age 65 that can be accessed by Mini-Sentinel and, accordingly, the number of regulatory decisions on products primarily used by the elderly.
- The Mini-Sentinel database is primarily composed of insurance claims data, which does not contain the detailed information typically included in a patient's medical history. The database contains only limited inpatient data, mostly related to procedures and diagnoses, but does not include laboratory data or data related to drug intake or drug exposures.

In addition, certain limitations are associated with the use of observational data in general. For example, many FDA scientists consider observational data to have a greater potential for bias from exposure/disease misclassification and residual confounding than controlled, randomized clinical trials. These perceived shortcomings make some FDA safety reviewers reluctant to use any resource that uses observational data, including Mini-Sentinel.

4.B MINI-SENTINEL PILOT KEY MILESTONES

4.B.1 Key accomplishments to date in establishing Mini-Sentinel

The Mini-Sentinel pilot has crossed several milestones in establishing a fully functional system. Accomplishments to date include the following:

- **Creating a functional operating center.** The MSOC is fully operational and has developed tools to access electronic health data, ensure data quality and characterization, and effectively conduct analyses and compile summary results for further FDA analysis.

- **Forming a cooperative agreement with the Brookings Institution.** FDA signed a cooperative agreement with the Brookings Institution in Washington, DC, to collaborate on workshops and working meetings to develop and refine the goals of the Mini-Sentinel program, as well as to define methods to conduct active medical product surveillance.

- **Securing participation of 19 data partners.** Wide participation of data partners is an important accomplishment. Interviews conducted for this assessment reveal that some data partners were originally cautious and reluctant to join the Mini-Sentinel pilot, but the rigorous procedures established by the MSOC and FDA to protect the integrity of patient data helped ensure the current rate of participation.

- **Creating the MSCDM.** Creating a Common Data Model that kept the firewalls of the data partners intact while also being useful to analysis ensured the participation of some of the largest health insurers and providers in the United States.

- **Recruiting a broad group of data collaborators.** In addition to the data partners listed above, the Mini-Sentinel pilot has attained participation from a number of health groups as collaborators. Collaborators provide frequent technical, methodologic, biostatistical, clinical, and organizational expertise to the MSOC and FDA. Since 2009, collaborators have participated in the Mini-Sentinel Planning Board and working groups and specific projects to help develop the MSCDM, the Mini-Sentinel analysis types, and other Mini-Sentinel pilot activities. A list of collaborators as of October 2014 are outlined in **Exhibit 9**.

Exhibit 9: Mini-Sentinel collaborating institutions

Category	Entity and description
Health insurance org	• America's Health Insurance Plans – Clinical Affairs Department
Hospital systems	• The Brigham and Women's Hospital – Division of Pharmacoepidemiology and Pharmacoeconomics and Division of General Medicine • Cincinnati Children's Hospital Medical Center James M. Anderson Center for Health Systems Excellence
Universities and medical schools	• Columbia University – Department of Statistics • Duke University School of Medicine – Clinical Research Institute • Rutgers University – Center for Health Services Research on Pharmacotherapy, Chronic Disease Management and Outcomes at the Institute for Health Care Policy and Aging Research • The University of Alabama at Birmingham – Center for Outcomes and Effectiveness Research and Education • University of Illinois at Chicago Medical Center – Departments of Pharmacy Administration, Pharmacy Practice, General Internal Medicine and Biostatistics • University of Iowa – Department of Epidemiology in the College of Public Health • The University of Pennsylvania School of Medicine – Center for Clinical Epidemiology and Biostatistics and Department of Biostatistics and Epidemiology • The Weill Cornell Medical College in New York – Department of Public Health
Research firms	• The Critical Path Institute • Outcome Sciences, Inc. – a Quintiles company • Risk Sciences International

- **Ensuring privacy of patient data.** Because Mini-Sentinel uses the electronic health data of more than 100 million U.S. private insurance plan participants, it is critical that FDA and the MSOC ensure the privacy of patient data. Given the strict firewalls in place with data partners, FDA scientists are several layers removed from the patient data (with the infrequent exception of chart ranking and adjudication-related activities), making it highly unlikely that individual data would be compromised by Mini-Sentinel pilot activities. To date, no data breaches have been reported; however, it is still essential to remain vigilant and up-to-date in protecting patient privacy.

- **Executing successful queries.** As detailed in later sections of this Interim Assessment, a significant accomplishment of the Mini-Sentinel pilot is establishing a process that translates a safety question into a Mini-Sentinel query and retrieves results that can inform a regulatory decision.

- **Building an effective working relationship with the MSOC.** The Centers that are primary users of the Mini-Sentinel pilot have established strong working relationships with the MSOC. The relevant personnel and FDA have worked effectively with the MSOC to make joint decisions on analysis type and query structure by collaborating in working groups for protocol-based assessments.

4.B.2 Upcoming milestones

As of October 2014, the Hospital Corporation of America (HCA) had agreed to include inpatient data as a part of Sentinel activities. HCA hospitals comprise 5 percent of all hospital patient visits across the United States, which will significantly add to Mini-Sentinel pilot's ability to utilize anonymized inpatient record data. FDA is looking to add additional data partners and other data varieties.

As the Mini-Sentinel pilot evolves, FDA plans to increase the capabilities for queries. FDA also plans to increase its capability and capacity to handle complex statistical problems such as adjusting for confounders, performing sequential analysis, and designing additional studies in a semiautomatic fashion.

4.C CASE STUDIES: MINI SENTINEL IMPACT ON FDA REGULATORY ACTION

4.C.1 Case study: Dabigatran[15]

4.C.1.a Background

Dabigatran etexilate mesylate is a blood-thinning (anticoagulant) medication used to reduce the risk of stroke in patients with nonvalvular atrial fibrillation (AF), the most common type of heart rhythm abnormality. FDA approved dabigatran in October 2010 to reduce risk of strokes in people with AF. **Dabigatran** was marketed as an alternative to warfarin (another frequently prescribed anticoagulant), offering similar results without requiring frequent blood tests.

Soon after dabigatran's approval, FDA received a large number of postmarket adverse-event reports of serious and fatal bleeding events among dabigatran users.

FDA began an investigation into dabigatran's potential association with a greater number of fatal bleeding events than would have been expected, based on observations in the large clinical trial that supported its approval.

Utilizing FDA Adverse Event Reporting System (FAERS), FDA identified a greater number of adverse-event reports of fatal bleeding associated with dabigatran than with warfarin.

FDA sought to determine the cause of the higher number of adverse-event reports: greater awareness and scrutiny over dabigatran because it was new to the market, relative underreporting of warfarin issues, or whether it truly represented a higher risk of fatal bleeding, which differed from those seen in the clinical trial, which was already included in the drug's labeling.

4.C.1.b Role of Mini-Sentinel pilot

FDA used the Mini-Sentinel database to investigate the actual rates of gastrointestinal bleeding and intracranial hemorrhage for new users of dabigatran and compared this to the rate seen in new users of warfarin.

FDA convened a team and developed a modular program query to rapidly assess this potential safety issue. (Mini-Sentinel's modular programs enable estimation of the incidence rates for bleeding diagnoses and drug use within certain populations.)

The Mini-Sentinel database was queried for instances of hemorrhages associated with the new use of dabigatran or warfarin. The results indicated that bleeding rates associated with dabigatran use during the period of interest did not appear to be higher than those associated with warfarin.

There were limitations to the Mini-Sentinel analysis, including a lack of adjustment for confounding variables[16] and a lack of medical review to adjudicate findings. Nevertheless, CDER leadership agreed that the results were sufficient for a safety communication, with a full protocol-based assessment recommended for future investigation.

4.C.1.c Regulatory action taken

FDA released a safety communication on November 2, 2012, which affirmed that bleeding rates associated with dabigatran did not appear to be higher than those for warfarin, which is consistent with the large clinical trial used to approve dabigatran.[17]

4.C.1.d Main conclusion and implications

This case study exemplifies the use of Mini-Sentinel to produce data with sufficient statistical power to affirm that a drug did not pose an undocumented safety risk to the public. FDA took an FDA action – issuance of a safety communication in part to calm public concern.

In looking to apply this case study to other instances, FDA should consider that the comparison drug, warfarin, has been in widespread clinical use for over 60 years, reducing potential uptake issues among the patient population. It may prove difficult to find a comparison drug as widely used in future cases.

4.C.2 Case study: Rotavirus[18]

4.C.2.a Background

RotaTeq and Rotarix are liquid oral vaccines approved, in 2006 and 2008, respectively, for use in infants and children for the prevention of rotavirus gastroenteritis, an infection that causes gastroenteritis (common symptoms of which are vomiting and diarrhea).

In 1999, another rotavirus vaccine, RotaShield, was withdrawn from the market for increased risk of intussusception,[19] leading to concerns about similar effects from RotaTeq and Rotarix. In 2010, the Office of Vaccines Research and Review (OVRR) and the Office of Biostatistics and Epidemiology (OBE) requested a Mini-Sentinel review of the risk of intussusception with rotavirus vaccine administration because international studies showed increased safety risk.

4.C.2.b Role of Mini-Sentinel pilot

FDA conducted a study within Mini-Sentinel's Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program, a component of the Mini-Sentinel pilot focused on vaccine surveillance. The study

demonstrated an increased intussusception risk with RotaTeq, but results were inconclusive for Rotarix because of insufficient patient exposures. The increased risk of a rare event was not discovered during the clinical trials prior to approval; however, it was detected using Mini-Sentinel PRISM as a result of a very large universe of data available for observation (613,000 infant-years observed). The Mini-Sentinel PRISM study—the largest study of intussusception after rotavirus vaccines to date—identified an increased risk of intussusception that translates into one- to one-and-one-half additional cases of intussusception per 100,000 first doses of RotaTeq.[20]

4.C.2.c Regulatory action taken

FDA required a change in the prescribing information in RotaTeq based on the study results, but no change was required for Rotarix because of insufficient exposures.

4.C.2.d Main conclusion and implications

The Rotavirus case demonstrates the power of Sentinel analysis. The ability to assess case status and confirm vaccine exposure in claims containing an intussusception diagnosis is a new capability for FDA. However, it should be noted that the ability to make similar comparisons is rather uncommon and may not be as easily executed for other Mini-Sentinel pilot queries.

4.C.3 Case study: Olmesartan[21]

4.C.3.a Background

Olmesartan is an angiotensin II receptor blocker (ARB) approved for the treatment of hypertension, alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and heart attacks.

In the years following olmesartan's approval on April 25, 2002, several serious cases of sprue-like enteropathy, a serious intestinal problem, were reported via FAERS and indicated a relationship to long-term olmesartan use. In 2012, FDA undertook a comprehensive evaluation of the situation using several resources, including Mini-Sentinel.

Using FAERS, FDA identified 23 serious cases of olmesartan-related severe sprue-like enteropathy. All patients improved clinically after discontinuation of olmesartan, and a positive rechallenge (recurrence of diarrhea after restarting olmesartan) was seen in 10 of the cases.

In addition, two published scientific articles also found a correlation between olmesartan and sprue-like enteropathy, one published in June 2012 by the Mayo Clinic and another published in the American Journal of Gastroenterology in 2013.

4.C.3.b Role of Mini-Sentinel pilot

To assess potential ARB-class effects, FDA queried the Mini-Sentinel pilot database and Centers for Medicare and Medicaid Services (CMS) data for celiac disease (as a marker for enteropathy and other gastrointestinal symptoms) after exposure to ARBs. Mini-Sentinel pilot and CMS Medicare assessments of codes for celiac disease showed that at a two-year minimum exposure, olmesartan users had a higher rate of celiac disease diagnoses than users of other ARBs. Although the power of interpretation is limited by the small number of events observed and uncertainty of celiac disease code validity, these results support the academic and FAERS data, suggesting the lack of a class effect.

4.C.3.c Regulatory action taken

On July 3, 2013, FDA approved label changes to include intestinal problems (sprue-like enteropathy) linked to olmesartan. This FDA regulatory action was based on the constellation of findings from multiple sources, including Mini-Sentinel pilot data.

4.C.3.d Conclusion

This case demonstrates how Sentinel can contribute to and help validate existing FDA resources. After reviewing clinical cases and FAERS findings, FDA scientists remained uncertain of a tangible connection. However, the Mini-Sentinel pilot and CMS clinical data help support that a correlation was restricted to olmesartan and did not extend to the entire class of ARBs, which are a staple of antihypertensive treatment. This case example demonstrates the valuable role of the Mini-Sentinel pilot as an additional resource for safety reviewers, even if its results would not have been dispositive on a standalone basis.

4.C.4 Case study: Influenza vaccine[22]

4.C.4.a Background

FDA and the Centers for Disease Control and Prevention (CDC) routinely monitor the safety of all U.S. vaccines by using several safety surveillance systems, including the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). VAERS collects and analyzes information from reported adverse events (e.g., health problems or possible side effects) that occur after vaccination. During the 2010–2011 influenza season, FDA and CDC detected an increase in the number of reports to VAERS of febrile seizures following vaccination with Fluzone.[23] Fluzone was the only influenza vaccine recommended for use for the 2010–2011 flu season in infants and children 6 to 23 months of age.

4.C.4.b Role of Mini-Sentinel pilot

To further investigate febrile seizures after vaccination with Fluzone as well as other trivalent inactivated influenza vaccines (TIVs), FDA initiated a study using its Mini-Sentinel PRISM program. The study identified 842,325 children between the ages of 6 months and 59 months who met eligibility criteria, ensuring that sufficient prevaccination and follow-up information would be available to investigators. Among those meeting the criteria, 68 confirmed cases of febrile seizures were identified within 20 days after receipt of TIV.

The study showed no statistically significant association between TIVs and increased risk of febrile seizures.

4.C.4.c Regulatory action taken

Based on these findings, FDA did not request changes to the prescribing information for Fluzone or any of the other influenza vaccines, which have been used for decades.

4.C.4.d Conclusion

This case exemplifies instances in which FDA makes a regulatory decision not to act. Similar to the dabigatran case example, the Mini-Sentinel database was able to provide the denominator, and thus more closely approximate the actual incidence of febrile seizures in the study population. Based on this information, FDA was able to reassure the public that the influenza vaccine was safe, which was of significant public health impact. No FDA resource other than Sentinel could have provided this type of data-driven reassurance in such a short time.

Section 5 | Overview of Processes and Procedures

5.A MINI-SENTINEL PILOT QUERY PROCESS FLOW AND PROCEDURES

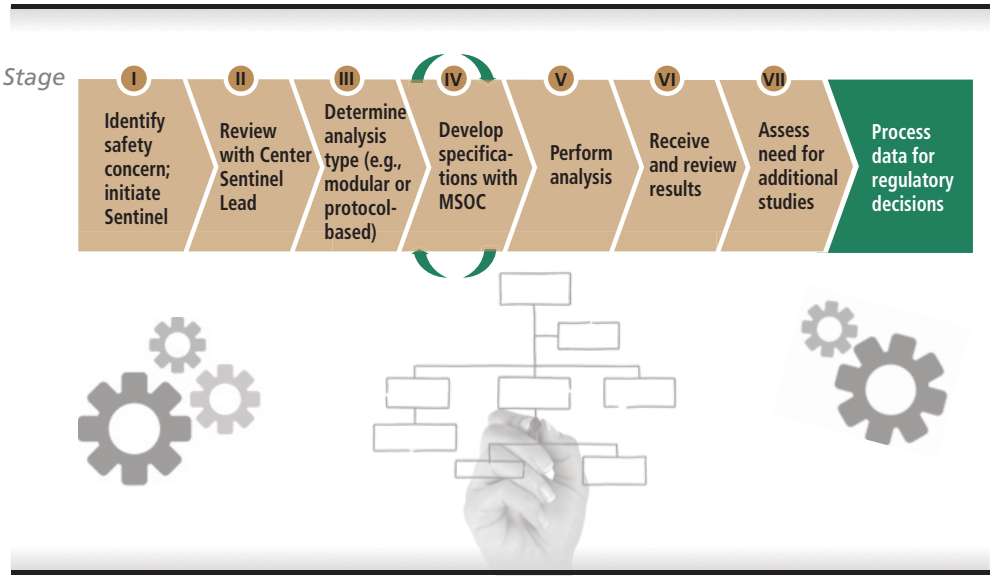
As part of the Mini-Sentinel pilot, FDA employees have begun to develop processes and procedures to generate queries, analyze data, and inform regulatory decisions using Mini-Sentinel pilot data. These processes and procedures allow FDA and the Mini-Sentinel Operations Center (MSOC) to manage and support the use of Mini-Sentinel more effectively and efficiently.

This section provides an overview of the process flows currently in use. At FDA, the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) have evolved separately. Each Center has customized Sentinel processes and procedures to meet the needs of its users. Accordingly, this section describes the process across CBER and CDER separately. This section also highlights opportunities to strengthen processes and procedures further in preparation for an expected increase in utilization of Sentinel in the coming years.

5.A.1 Processes to manage use of Mini-Sentinel data at CBER and CDER

At time of this assessment, CBER has a draft version of standard operating policies and procedures (SOP) for pharmacoepidemiologic studies conducted in FDA's Sentinel System. CDER did not have a formal SOP describing CDER Sentinel processes. Accordingly, the processes explained below were constructed based on numerous interviews with CBER and CDER stakeholders in addition to a consultation of CBER's draft SOP. Exhibit 10 depicts the seven key steps in such a process flow.

Exhibit 10: Mini-Sentinel pilot process flow[1]



1 This process flow was largely reconstructed based on interviews with FDA employees.

The primary difference between CBER and CDER processes is in the nature and extent of interactions between the initial FDA reviewer and the Center Sentinel Lead across the query process.

The approach that CBER takes can be described as a collaborative approach to query generation and initial review, involving both the CBER Sentinel Lead and the CBER reviewer—either from the product office or the Office of Biostatistics and Epidemiology (OBE)—who first raised the safety concern. The Sentinel Center Lead coordinates internal process management for Sentinel queries.

CDER's process is driven by heavy involvement of the CDER Sentinel Lead in triaging query requests and managing the conversion of a safety question into a Sentinel query. Beyond the initial stages, the CDER Sentinel Lead does involve the CDER safety reviewer in the subsequent process steps.

Both Centers also receive support from the Office of Medical Policy (OMP), which can help coordinate with the MSOC. OMP, though situated as part of CDER, has typically supported the prioritization and submission of many Sentinel queries, particularly in time-sensitive situations. While OMP has provided support to several query types, it does not support protocol-based assessments.

5.B CBER

5.B.1 CBER process overview

The CBER process for managing Mini-Sentinel pilot requests is characterized by a standardized approach to process flow, which is codified in a draft SOP. The CBER process also tends to feature significant involvement of the FDA scientists throughout, as shown in **Exhibit 11**. The CBER process has yielded an efficient tool to manage the Mini-Sentinel pilot process, but a few gaps remain on the path to frequent and sustained Sentinel System usage.

Among the strengths of the CBER management of the Mini-Sentinel pilot process is a clear and consistent set of procedures. Most CBER safety users interviewed for this assessment supported the transparency and predictability in the CBER processes. Another strength is a structured, team-oriented process that consistently involves the initial CBER reviewers[24] and is associated with high overall CBER user satisfaction. Further, the CBER process has enabled the cultivation of advanced Sentinel pilot users who have helped initiate development of future capabilities, such as a data-mining tool called TreeScan.

Specifically, the safety reviewers at CBER participate in every stage of the Mini-Sentinel pilot query process except for Stage V, which is performed by the MSOC and the data partners. CBER medical officers and epidemiologists participate in meetings with the MSOC working team to discuss the analysis plan of each query and review the results along with the Sentinel Lead.

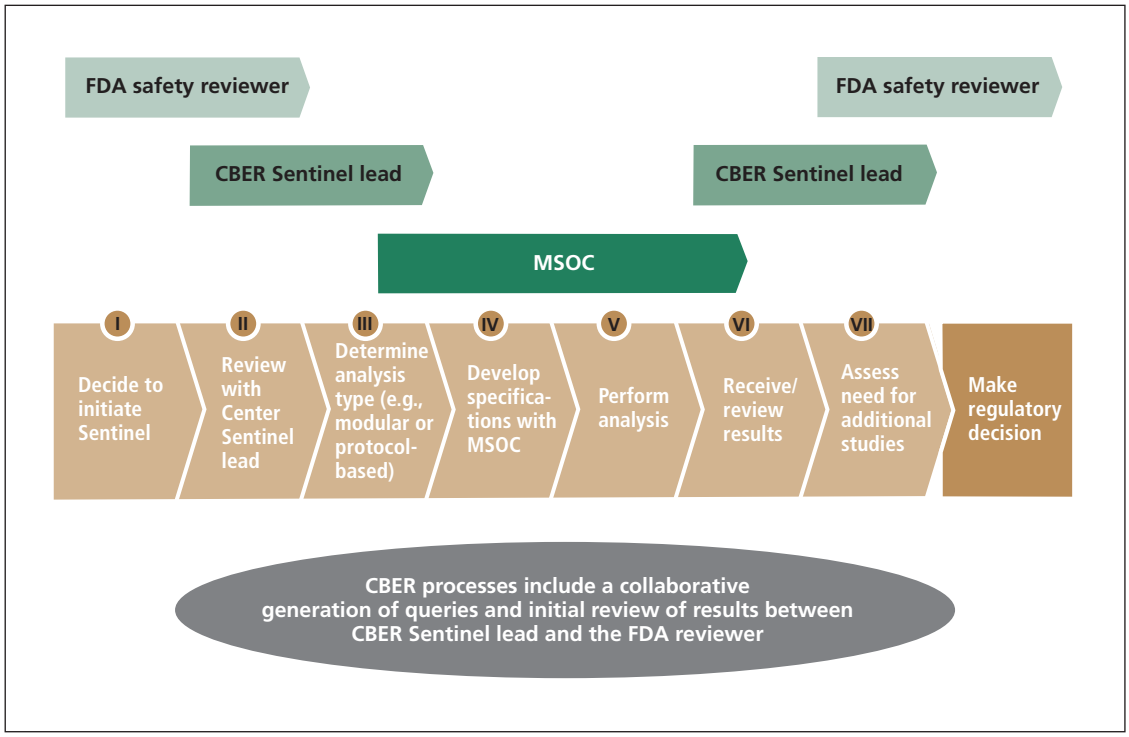
In general, stakeholders in CBER agree that the decision-making process and the criteria for decision making are transparent. However, there is sentiment that the rigidity of the process and the involvement of safety reviewers throughout create significant demands on the reviewers' time.

As CBER finalizes the process that it will use to manage Mini-Sentinel queries in the future, it should consider the advantages and limitations of its current process in order to execute a higher volume of queries efficiently across a broader dataset.

Among areas that may require improvement for CBER are limited training and personnel resources, which have inhibited wider adoption among mainstream users, and CBER communication efforts, which have not fully disseminated knowledge of the Mini-Sentinel pilot's query potential.

By building greater awareness and use of the Mini-Sentinel pilot and providing training to more potential users, CBER can promote broader adoption.

Exhibit 11: Involvement of FDA personnel in the CBER Mini-Sentinel pilot process flow



5.B.2 Detailed description of CBER processes and key implications

Stages I and II: Safety concern identified; review with the Sentinel Lead

CBER's use of the Mini-Sentinel pilot begins when, in the course of the CBER Biologics License Application process or in the course of postmarket surveillance, an FDA product office reviewer or a safety reviewer in the Division of Epidemiology (DE) identifies a safety issue that could benefit from Sentinel data analysis. The DE reviewer then discusses the option with FDA colleagues, including other reviewers, supervisors, and FDA management from both the product office and the OBE. The safety question will then be discussed at the next Safety Assessment Meeting (SAM; held monthly for vaccine products and twice monthly for blood products).

At a SAM, the DE staff works with the relevant product offices to discuss the safety question, review Mini-Sentinel pilot capabilities, identify or clarify the regulatory actions that may be affected, and decide whether a role for Sentinel is appropriate. DE staff and the product office will provide input on the general availability and limitations of the current Mini-Sentinel's population database and the possible findings for a relevant biologics product. A decision to proceed is often made quickly, and the relevant FDA reviewer is then required to write a review memo and a recommendation for action.

The CBER Sentinel Lead is responsible for fielding all potential Mini-Sentinel pilot queries. If FDA officials at the SAM determine that Sentinel should be initiated, the CBER Sentinel Lead typically will organize a Sentinel safety team to manage the process.

Implications of process choices in stages I and II

The CBER SAM consideration process is deliberate and consistent, which leads to high predictability in the time required to process a safety question—a benefit that could increase participation among FDA sci-

entists. The SAM consideration process relies on a standardized and consistent checklist, which gives the safety reviewers a high degree of trust in the equity and transparency of the CBER process. Accordingly, such reviewers may become more comfortable in using the Mini-Sentinel pilot.

In addition, because CBER has developed a consistent method to track instances in which the use of Sentinel is discussed, CBER staff can more easily look for patterns in submission types to learn how to improve the efficiency of the process.

Among the disadvantages of such a deliberate process is that CBER procedures could potentially deter participation from those FDA scientists who may feel constrained by time. The time required of the scientists is contingent on the complexity of the issue and the need for additional data, analysis, or both.

Stages III and IV: Determine analysis type; develop query specifications with MSOC

To determine analysis type, DE staff and the relevant product offices arrive at a general consensus after considering the scientific question being asked, timeline requirements, and available staff resources. Attendees at the SAM will further consider data availability and reliability as well as confounding variables. SAM members may begin their analysis review biased toward the modular program query, but may shift to a protocol-based assessment as circumstances dictate.

While group consensus is always sought, final decisions are made at the OBE level. The initial FDA reviewer is included in this process and can help clarify that the original safety question is being addressed. As with CDER, this stage will also include choosing a combination of National Drug Codes, diagnosis codes, procedure codes, and laboratory result values (or ranges of values).

After deciding which type of analysis to perform, the Sentinel Lead creates a Sentinel study team (SST) to manage the process of refining the analysis and working with the MSOC to select the correct insurance claims codes used for an inquiry. SSTs are typically composed of the initial reviewer, a Division-level representative from the OBE, and a representative from DE. In practice, this team typically consists of both a junior FDA reviewer and a senior manager, which has improved both collaboration and training of CBER reviewers.

As in the case of CDER, the development of query specifications can be highly iterative. The MSOC frequently requests additional information, and specifications may go through several revisions before being finalized. It is also possible that after finalizing a specification, the MSOC may later conclude that a query cannot be faithfully executed, either because of insufficient or inconsistent data or other technical reasons. For full protocol-based assessments and studies, DE assigns an FDA study lead as co-investigator.

Once the draft study protocol has been developed, DE shares it along with a summary overview at the next SAM. Subsequently, the SST will review product office comment and post it on the Internet for a 14-day public comment. The SST will review all comments it receives and make changes as necessary.

Implications of process choices in stages III and IV

FDA reviewers and DE staff must actively participate in the execution of a Mini-Sentinel analysis by being part of an SST. Through the process of query development or formulation and the selection of relevant claims codes, the FDA reviewer can become more familiar with the capabilities and limitations of Sentinel, which can increase the quality and precision of future Sentinel queries.

As SSTs develop a better understanding of the circumstances in which Sentinel use is appropriate, they also can reduce the burden on the Sentinel Lead in developing the query analysis type and specifications. This is essential at CBER, which currently has little full-time support staff beyond the Sentinel Center Lead. The standardized process at CBER also ensures consistent application of review criteria.

A disadvantage of this structure is the added burden of SST meetings on an FDA reviewer's schedule, which can deter active participation in the Sentinel process. As mentioned earlier, the rigorous procedures and requirement of frequent input from a diverse array of sources could also create capacity constraints on limited staff as the number or frequency of queries increases.

5.C CDER

5.C.1 CDER process overview

Since early 2011, when CDER ran the first summary tables and modular program queries, an established process has supported the translation of safety questions into Mini-Sentinel pilot queries.

The most distinct feature of the CDER Mini-Sentinel pilot process is the influence of the Sentinel Center Lead across the process stages. The original FDA safety review team is heavily involved in Stages I, II, VI, and VII, but is less active in Stages III and IV, as shown in Exhibit 12. The CDER Sentinel Lead is the primary decision maker, who provides expert input into the query process and coordinates the process with other FDA stakeholders and the MSOC.

Specifically, the CDER Sentinel Lead is responsible for: (a) initiating Mini-Sentinel, (b) collecting information from the relevant FDA safety teams, (c) determining which analysis type is most appropriate, (d) developing query specifications with the MSOC, and (e) summarizing the results. In addition, the Lead serves as the primary facilitator of communication between FDA scientists and the MSOC.

Given the role of the CDER Sentinel Lead as an intermediary between CDER safety reviewers who initially raised the safety concern and the MSOC, there are typically no direct discussions between the MSOC and the CDER safety reviewers.

Noteworthy features

The CDER process has several noteworthy features. CDER stakeholders consider the working relationship between the CDER Sentinel Lead and the MSOC to be effective. Strong lines of communication have helped ensure that the Mini-Sentinel pilot query specifications are continually refined and improved. In addition, through repeated interactions with the MSOC, the Sentinel Center Lead has steadily improved expertise and knowledge of Sentinel capabilities. The expertise of the Sentinel Lead has helped CDER to develop, prioritize, and submit high-quality queries to the MSOC efficiently and effectively, and it has decreased overall process times.

The CDER process is also characterized by effective cultivation of several "advanced" users, who have been instrumental in key Mini-Sentinel pilot successes (e.g., dabigatran, discussed in Section 4.C.1). Such users run queries frequently and have built extensive experience using the Mini-Sentinel pilot. These users tend to be very familiar with the nuances of the Sentinel query process, and they work in an effective, collaborative manner with the Sentinel Center Lead.

Areas for improvement

This Interim Assessment also found areas for improvement in the CDER process. For instance, CDER stakeholders have expressed a need for greater transparency into the decision-making process and more standardization and consistency in the process. Results from the internal FDA survey were consistent with these findings.

The lack of extensive process documentation increases the risk of inconsistency in the application of Sentinel queries, uncertainty and confusion among the broader set of users on the criteria required for a Sentinel query, and disparity in how queries are executed and how they should be used.

Another area for improvement is the integration of performance metrics that measure the efficiency and effectiveness of the process.

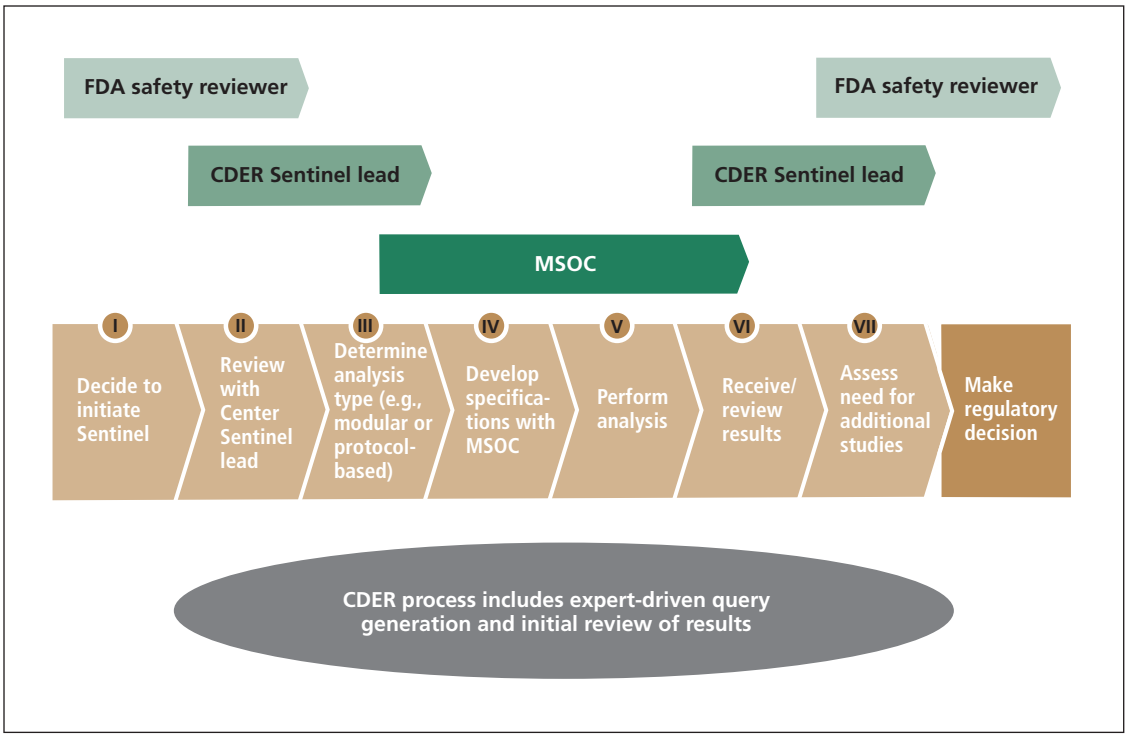
Going forward

As CDER continues to build and manage Sentinel queries in the future, it should carefully consider the advantages and limitations of its current process and the needs of the full Sentinel System.

For instance, broader CDER reviewer input into the query development process would likely increase direct experience with query specification, which could decrease confusion and could ultimately stimulate adoption and use of Sentinel.

In addition, while the CDER Sentinel Lead has a highly effective working relationship with the MSOC and is instrumental in helping CDER safety reviewers make use of query results, it should carefully consider the staff resources needed to continue this level of involvement without creating bottlenecks. If query volume increases sharply, the Sentinel Center Lead will either need to hire staff or enable CDER safety reviewers to work autonomously.

Exhibit 12: Involvement of FDA personnel in the CDER Mini-Sentinel pilot process flow



5.C.2 Detailed description of CDER processes and key implications

Stages I and II: Safety concern identified; review with the Sentinel Lead

Stage I of the Sentinel process flow within CDER commences when a CDER medical officer or safety reviewer, in the course of postmarket surveillance, identifies a safety question that could benefit from Sentinel analysis. After gaining the support of supervisors, the CDER safety reviewer will involve the CDER Sentinel Lead.

During Stage II, the safety reviewer and the CDER Sentinel Lead collaborate to determine whether Sentinel is an appropriate tool to help address the safety question. In most instances, the safety reviewer and relevant team members communicate the safety concern to the CDER Sentinel Lead with a description of the analysis desired from Sentinel. Relying on experience, the CDER Sentinel Lead will review the description and decide whether it warrants a Mini-Sentinel query. Decisions are often made in less than one week, with the CDER Sentinel Lead typically making the decision without requiring consultation with others across FDA.

During these first two stages, the CDER Sentinel Lead typically does not employ formal submission forms, checklists, or standard procedures; much of the dialogue takes place informally, via email or in person.

Implications of process choices in Stages I and II

Eschewing standardized procedures for Stages I and II allows the Sentinel Center Lead to respond quickly to atypical safety questions. Time-to-completion of Stage II is frequently under a week and often less than a day. However, the informal nature of these first two stages increases the risk of ambiguity, allows for potentially inconsistent application of decision-making standards, and can lead to high variability in completion time.

Indeed, CDER stakeholders interviewed for this assessment expressed that the criteria to proceed with a safety question can feel arbitrary and seem to vary across decisions. Other stakeholders cited that the time to receive a decision frequently varies. Stakeholders cited these factors as deterrents to greater Sentinel use.

Limited training and a lack of familiarity with common Sentinel use cases can also inhibit wider adoption among the broader set of CDER users. CDER stakeholder interviews also revealed limited knowledge of Mini-Sentinel query types and occasional misunderstanding of the capabilities and potential uses of query results. One opportunity to improve adoption among more mainstream users may be increased involvement in the decision-making process, which could improve awareness and knowledge of Mini-Sentinel's queries and potential.

Stage III: Determine Mini-Sentinel pilot analysis type

After deciding to use Sentinel, the Sentinel Center Lead convenes an open meeting to collect information on the safety question. This open meeting is attended by the initial CDER safety review team as well as other CDER personnel who can help clarify the safety question or the regulatory issue. In many cases, these CDER personnel have a specific expertise or experience that can help define the safety question, and they have been invited by the initial safety review team. While the open meeting welcomes attendance from any manner of CDER personnel, in practice the attendance can vary as the invitation is done on an ad hoc basis by both the initial safety review team and the Sentinel Lead. Further, at the time of this evaluation, no system is in place to ensure such meetings have a consistent representation from a comprehensive set of CDER divisions.

During the open meeting, the FDA safety team reviews the case for Sentinel use and recommends one of three analysis options: summary table, modular program query, or protocol-based assessment. (The differences among these options are described further in Section 4.A.5.)

Following the open meeting, the Sentinel Lead will typically involve the initial FDA reviewers only as needed, and will largely make its decision on the analysis option without direct consultation with other personnel across CDER.

Implications of process choices in Stage III

The Sentinel Center Lead retains decision-making authority, which reduces potential conflict, and which interviews suggest has helped reduce time-to-completion over time. However, it is important to note that

the fewer opportunities that the broader CDER personnel have to provide input, the lower the likelihood that the Sentinel Center Lead will be able to consider all relevant criteria at hand. The CDER Sentinel Lead must strike a balance between managing an efficient process and soliciting and reviewing all relevant information. Additionally, the risk of relegating decision-making authority to any small team without a published and documented set of decision criteria can increase the potential for unintentional bias.

Stage IV: Develop query specifications with the MSOC

After selecting an analysis type, the Sentinel Lead typically works directly with the MSOC to select the precise claims codes used to create a query. This stage can include choosing a combination of National Drug Codes, diagnosis codes, procedure codes, and laboratory result values (or ranges of values).

As in Stage III, the CDER Sentinel Center Lead has typically conducted its process without heavy involvement of other CDER personnel. The CDER Sentinel Lead typically involves other FDA reviewers on an ad hoc basis. Personnel from the Office of Surveillance and Epidemiology often contribute at this stage, although no formal process requires such input. In complex cases, the Sentinel Lead may contact the initial FDA safety team to confirm that the safety question is being accurately addressed.

Stage IV can be highly iterative, as the MSOC frequently requests additional information from the relevant FDA personnel and the specifications may go through several revisions before being finalized.

At this stage it is also possible that the MSOC and Sentinel Lead will determine that a query cannot be executed. This can occur for a number of reasons, such as the Common Data Model data being less sufficient or less consistent than initially estimated. The Sentinel Lead typically informs the initial safety review team of this decision, but is not required to inform all who were involved in the process.

Implications of process choices in Stage IV

The decision to manage the query specification process largely independently of the initial CDER safety review team necessitates frequent interaction between the CDER Sentinel Lead and the MSOC, which has helped the CDER Sentinel Lead develop a high level of sophistication in query submission and has steadily increased the Center Lead's technical knowledge of Sentinel System capabilities.

However, this design choice also limits CDER safety reviewers' ability to develop their own Sentinel skills, which makes them increasingly reliant on the Sentinel Center Lead to identify when to initiate Mini-Sentinel and how to translate a safety concern into a Sentinel query.

CDER safety reviewers who lack deep understanding of Mini-Sentinel priority-use cases may opt not to use Sentinel in relevant cases due to a lack of knowledge or may not be able to contribute a meaningful perspective. In addition, the lack of involvement itself could dampen enthusiasm, further lessening use.

Another implication of this design choice is the increased influence of the Sentinel Lead, which could potentially lead to bias, unless controlled by a rigorous process or strict oversight, neither of which is currently part of the CDER process.

Stages V, VI, and VII: Perform analysis; review results; assess need for additional studies

Once the analysis specifications are chosen, the MSOC initiates the analysis process with its data partners and aggregates the results. This stage can vary from a quick execution to an additional iterative process, contingent on the complexity of the query and the data partner's flexibility. The MSOC largely conducts Stage V without direct involvement from FDA. The MSOC process is described in detail in Section 4.A.4 above.

Upon completing the analysis, the MSOC distributes the results to the relevant FDA contact, in this instance, the CDER Sentinel lead. The CDER Sentinel Lead then reviews the results and consolidates the most relevant data and graphs into a summary report, typically two to three pages in length. The CDER Sentinel Lead will then meet with the original CDER reviewer and other relevant FDA personnel to discuss the findings. In this meeting, the Sentinel Lead describes the significance (or lack thereof) in the data and, in conjunction with the FDA safety team, determines whether a different query structure (e.g., a different exposure window) could improve the relevancy of the results or if additional Mini-Sentinel pilot queries are needed.

The FDA safety review team considers the Mini-Sentinel pilot results in the context of other data (e.g., FAERS, international studies) and decides how these results affect the safety question and whether regulatory action is needed. The CDER Sentinel Lead is not involved in the regulatory decision. The role of the Sentinel Lead is to assist in interpretation of the data based on an intimate understanding of Mini-Sentinel. The role of regulatory decision-making resides with the FDA safety review divisions.

As noted in Section 3.A.5, in most cases Mini-Sentinel pilot results are not dispositive. The FDA reviewer considers the Mini-Sentinel results in addition to other available information on the safety of the product in question, such as clinical trial data or spontaneous reports. Typically, there also will be extensive discussion of the various data sources among the senior leadership of the CDER office. It is through this discussion that a regulatory decision often emerges.

Implications of process choices in Stages V, VI, and VII

Numerous FDA safety team members interviewed for this assessment stated that the summary report was helpful in quickly understanding Mini-Sentinel analysis. Contingent on staffing levels, this is an important feature to retain as Sentinel matures.

5.D FUTURE STATE CONSIDERATIONS

Going forward, the utilization of Sentinel data by FDA reviewers is likely to increase. In order to prepare for the expected increase in utilization, there are a number of factors to consider today regarding the processes that CBER and CDER use. These considerations include the following:

- Both CBER and CDER could define and collect a set of metrics that measures the performance of the process.
- Both CBER and CDER could begin to estimate future capacity needs and implications on resources.
- Both CBER and CDER could consider the tradeoffs between the two models of reviewer and Sentinel Lead interaction currently in use today.
- CDER could prepare manuals of policies and procedures (MAPPs) that describe the process in detail.
- CDER could enhance the transparency of decision making regarding query selection and prioritization.

Define and collect a set of metrics that measures the performance of the process

Measuring the performance of the process would reveal bottlenecks that can limit the rate of adoption by new users or create churn among current users. There should be a continuous feedback loop to make adjustments to the process as needed. Performance metrics can inform strategic decisions regarding method development and data partner query capacity.

Begin to estimate future capacity needs and implications on resources

The number of Mini-Sentinel pilot queries continues to increase with time. In order to accommodate the expected growth, a need is anticipated for additional resources at FDA, the MSOC, and all data partners. A strategic planning process would help prevent a backlog of queries.

Consider the tradeoffs between the two models of reviewer and Sentinel Lead interaction currently in use today

CBER and CDER have separately developed models of interaction between the Sentinel Lead and the safety reviewer. While inherent differences exist, such as the size of the Centers and the number of products involved, each Center can likely improve by assessing the choices made by the other and incorporating appropriate learnings.

Prepare MAPPs and SOPs that describe the process in detail

CBER will likely want to continue to update its SOP to improve clarity and accuracy and to facilitate user education. CDER could create MAPPs that detail the end-to-end Mini-Sentinel pilot query process. A comprehensive MAPP would enable new and potential users to engage in an efficient manner. The MAPP and SOP could contain the expected duration for each step and for each type of query (e.g., summary table, modular program query, protocol-based assessment).

Enhance the transparency of decision making regarding query selection and prioritization

Decisions regarding the appropriateness of using the Mini-Sentinel pilot to answer a safety query and prioritization of submitted queries should be made in a fair and transparent manner, using criteria that will enable the Sentinel System to have the greatest public health impact. The OMP and the CDER Sentinel Lead could hold frequent public meetings to discuss these issues with CDER colleagues.

Section 6 | Assessment of Progress Toward the Full Sentinel Initiative

6.A OVERVIEW: PROGRESS MADE, BUT SIGNIFICANT WORK REMAINS

The Mini-Sentinel pilot has achieved a number of milestones and has effectively demonstrated the potential of the full Sentinel System. However, significant progress remains before FDA can deploy the full-scale Sentinel System.

This assessment has created a set of assessment criteria—the Sentinel Maturity Model (SMM)[25]—to assess progress to date and identify areas of opportunity. The SMM leverages cross-industry best practices in real-world data and analytics to analyze the progress of the Sentinel Initiative toward full maturity. There are three key dimensions of the Sentinel platform: (1) strategy and value, (2) analytical tools and technology, and (3) methods.

In addition, the SMM assesses the progress of the capabilities of the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) across three dimensions: (1) talent and organization, (2) governance, and (3) process.

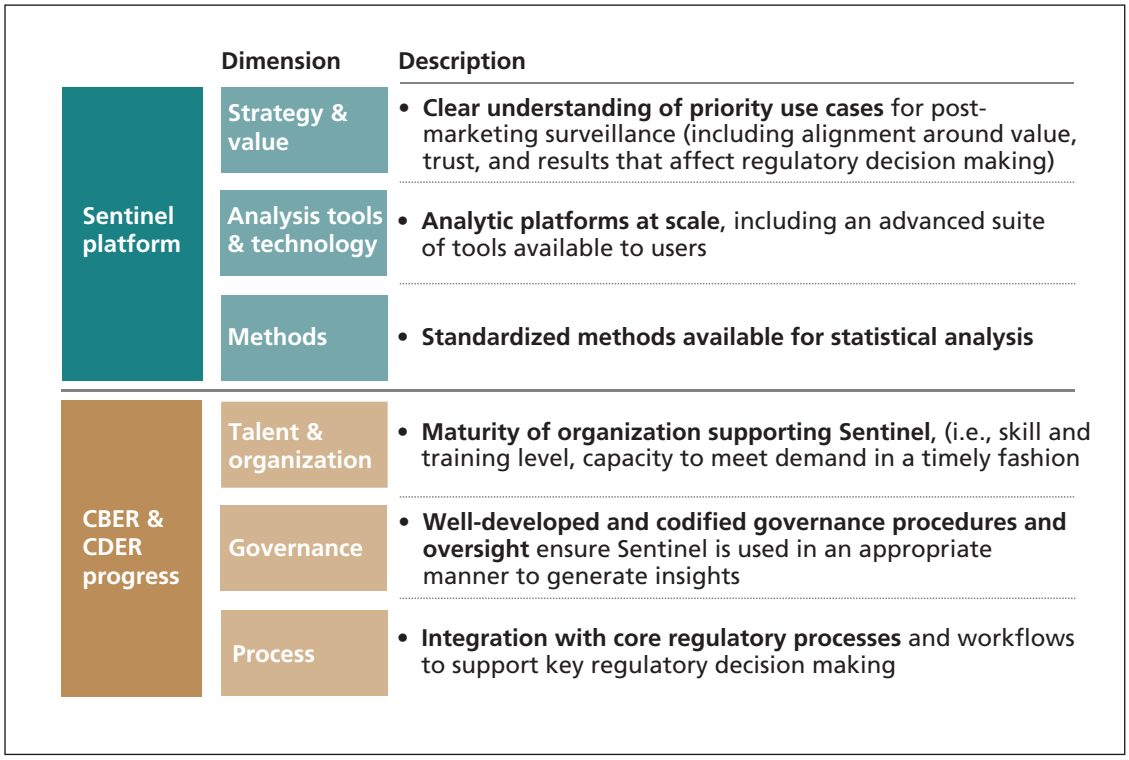
It is important to note that the SMM identifies areas of opportunity as the Mini-Sentinel pilot transitions to a fully mature advanced data analytics system. Mini-Sentinel, which remains in the pilot stage, it is not expected to be at full maturity at the time of this assessment.

This section provides an introduction to the SMM, assesses progress of the Sentinel Initiative and CBER/CDER against each maturity dimension, describes aspirations for a fully mature Sentinel System, and describes emerging priorities going forward.

6.A.1. Introduction to the Sentinel Maturity Model (SMM)

The SMM, as noted above and outlined in **Exhibit 13**, leverages cross-industry best practices in real-world data and analytics and is used in this Interim Assessment to analyze the progress of the Sentinel Initiative toward full maturity.

Exhibit 13: Overview of Sentinel Maturity Model (SMM)



- Maturity of the Sentinel platform
  - *Strategy and value.* Ensures clear articulation of highest priority-use cases to drive strategic alignment across the organization and maximize value from the Sentinel Initiative
  - *Analytical tools and technology.* Ensures the core technology and platforms scale to integrate larger and richer datasets and enable sophisticated tools for accurate analyses
  - Methods. Ensures standardized methods are used to simplify execution and improve efficiency and effectiveness
- Maturity of CBER and CDER
  - *Talent and organization.* Ensures that the supply of internal and external Sentinel resources matches demand and that the resources are optimally configured to attract top talent, build scale, be responsive to customer needs, and capture efficiencies
  - *Governance.* Ensures transparency and oversight around prioritization and other decision making
  - *Process.* Ensures operationalization and integration with core workflows and processes to support regulatory decision making fully

6.B ASSESSMENT OF PROGRESS ACROSS THE SENTINEL MATURITY MODEL (SMM): SENTINEL PLATFORM

The criteria for the three dimensions of the SMM for the Sentinel platform and CBER/CDER progress are detailed in **Exhibit 14** and **Exhibit 15**.

Exhibit 14: Summary of Interim Assessment of Sentinel Initiative: *Sentinel platform*

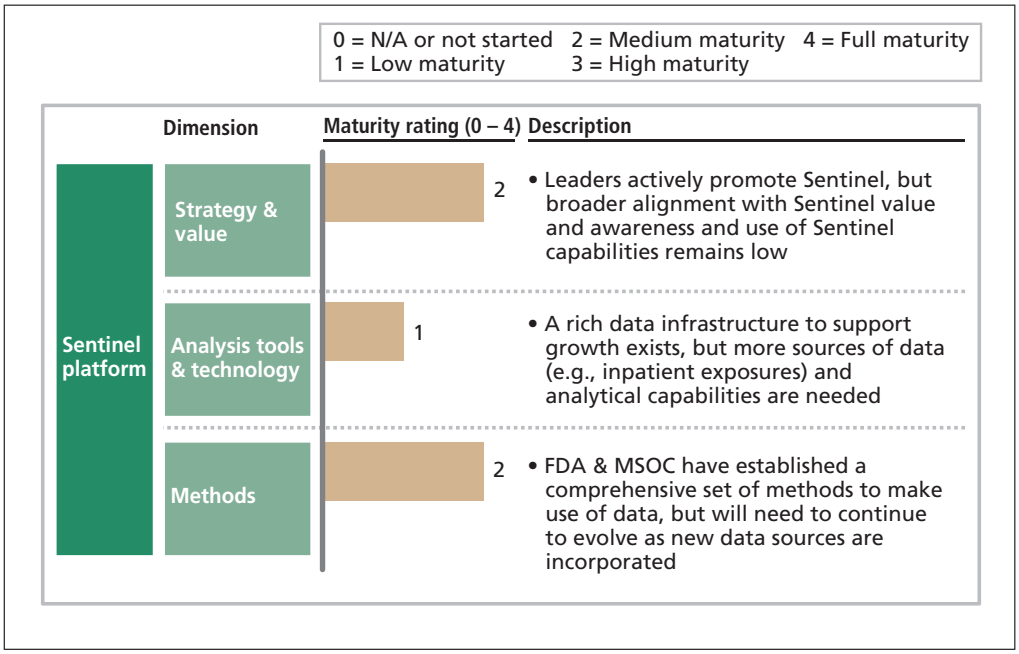
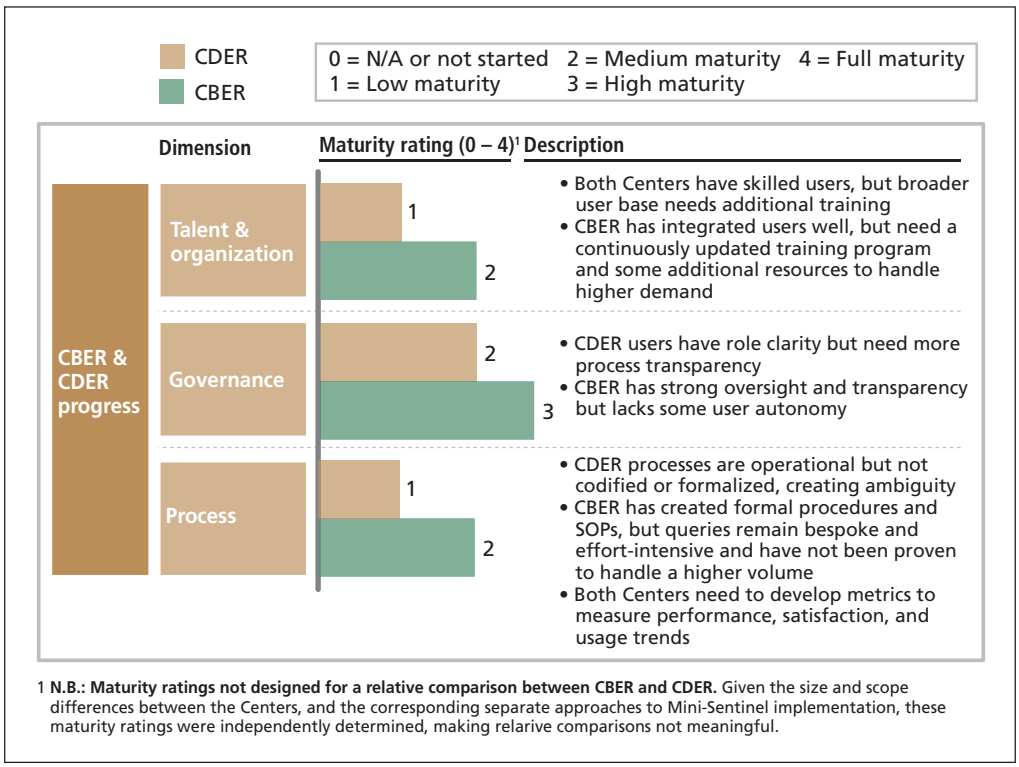


Exhibit 15: Summary of Interim Assessment of Sentinel Initiative: *CBER/CDER maturity*



1 **N.B.: Maturity ratings not designed for a relative comparison between CBER and CDER.** Given the size and scope differences between the Centers, and the corresponding separate approaches to Mini-Sentinel implementation, these maturity ratings were independently determined, making relarive comparisons not meaningful.

6.B.1 Strategy and value

The criteria used to assess the maturity for this dimension include the following[26]:

- FDA leaders endorse and promote appropriate use of Sentinel.
- End-users understand the questions that Sentinel can inform.
- End-users are aligned on the value and use of Sentinel and trust the results.

Overall, the Sentinel platform has achieved a Medium (2/4) rating across the strategy and value criteria. FDA leadership at CBER and CDER has actively promoted the use of Sentinel. Communication has been strong, and all users have been exposed to success stories.

Both Centers have cultivated a core set of advanced users who can quickly recognize priority-use cases, believe the results are of high value, and have actively used those results in their postmarket surveillance process. However, a majority of current users responding to both stakeholder interviews and an internal FDA survey expressed an uncertainty over which questions Sentinel was best suited to answer. In addition, a broad set of potential users continues to question the inherent value of observational data and remains unconvinced about how Sentinel outputs can address aspects of their role. The uncertainty and concerns from the broader set of users, which were identified in interviews, remain significant barriers to greater use.

6.B.2. Analytical tools and technology

The criteria used to assess the maturity for this dimension include the following[27]:

- Development of analytical capabilities and data resources that can produce timely and relevant results to inform regulatory decisions
- Creation of a rich data infrastructure to support growth and next-generation capabilities, including broader data sources and advanced analytics capabilities
- Establishment of a comprehensive platform to document previous query specifications to support future use

Overall, the Sentinel platform has achieved a Low (1/4) rating across the analytical tools and technology criteria.

The Mini-Sentinel pilot program has been very successful at recruiting 19 data partners that have collectively contributed data on more than 178 million patient lives, though the figure may include some double counting. It has executed hundreds of queries, several of which have resulted in public communications about safety issues.

Although insurance claims data has historically comprised the majority of data available from data partners, as of October 2014 Hospital Corporation of America inpatient data will begin to be incorporated into Mini-Sentinel, which will add an important new dimension to the Mini-Sentinel database. The Mini-Sentinel Operations Center (MSOC) continues to enrich its analytical tools and computing resources as a bridge to the full Sentinel System.

This development is particularly significant because a majority of respondents to the FDA internal survey indicated that their use of the Sentinel System would increase if the database included a wider variety of data sources, such as inpatient data, laboratory, or imaging data.

The technology platforms will need to continue to evolve rapidly to meet internal needs and changes in the external marketplace.

6.B.3 Methods

The criteria used to assess the maturity for this dimension include the following[28]:

- Standardized methods in place for analysis of data
- Accurate use of tools and review capabilities to interpret Sentinel data
- Frequent and consistent use of Sentinel data by FDA safety review teams

Overall, the Sentinel platform has achieved a Medium (2/4) rating across methods criteria.

FDA has partnered closely with the MSOC to establish a comprehensive set of standardized and well-developed analysis tools. Each of the Mini-Sentinel pilot analysis types (summary tables, modular program queries, and protocol-based assessments) adapt to differing health outcomes, population types, and statistical complexity. The MSOC also helps to ensure that data-use methods are formal, standardized, and consistent.

Separate from the MSOC involvement, the methods have not yet been established to provide the results of Sentinel data to review teams in a consistent manner. Both CBER and CDER tend to interpret and act on results on an ad hoc basis. CBER and CDER user stakeholders expressed that the Sentinel-driven methods to generate drug safety insights need further integration.

In addition, as Sentinel matures, FDA will need to evolve methods to manage workload as new analysis tools, data partners, and data sources are incorporated.

6.C ASSESSMENT OF PROGRESS ACROSS THE SENTINEL MATURITY MODEL: CBER AND CDER MATURITY

Athough the assessment below gives ratings to both CBER and CDER, it is important to note that these Centers are not directly comparable. CBER focuses on biologics, vaccines, and blood products. CDER is a vastly more complex organization, with a broader scope, a higher volume of products to review, and a larger number of personnel. CDER has a responsibility to review all postmarket drugs, while CBER is focused on a lower volume of biologics. Accordingly, the expectations of maturity at the time of this assessment differ between CBER and CDER.

6.C.1 Talent and organization

The criteria used to assess the maturity for this dimension include the following[29]:

- End-users are proficient in use and have access to a comprehensive, accessible, and continuously updated training program.
- FDA is appropriately resourced, at all levels, to support Sentinel growth.

CBER has scored a Medium (2/4) rating across the talent and organization criteria.

CBER has held a number of user trainings and has made them accessible to all users. In addition, some CBER end-users have helped co-create queries with the MSOC. Nevertheless, opportunity still remains to systematize the user training and enhance end-user capabilities. A majority of the current user respondents in the internal FDA survey at CBER cited a need for additional training to support Mini-Sentinel pilot use.

In addition, CBER has incorporated user skill development into the query execution process by requiring less-experienced Sentinel study team (SST) members to learn from more senior members. While CBER

support is strong and information is available, it currently lacks a comprehensive, accessible, and continuously updated Sentinel training program. In addition, a quantifiable measure of growth of Sentinel proficiency is not in place.

Additionally, both Centers are constrained by the small number of full-time employees who triage and process current Mini-Sentinel pilot queries and are not well positioned to meet growing volume demand. This has already led to occasional backlogs and delays in the review of certain queries. This situation will only worsen as the demand for Sentinel grows; however, it may affect CBER to a lesser extent. CBER's smaller range of products and existing experience with vaccine active surveillance may limit the extent of new resources needed.

CDER has scored a Low (1/4) rating across the talent and organization criteria.

CDER has cultivated a group of advanced users who are highly proficient at navigating the Sentinel system, but the skill and knowledge levels among the broader set of users remains low and has been a limiting factor in the processing of queries. Many CDER stakeholders interviewed for this report cited that an unfamiliarity and confusion over Sentinel capabilities was a factor that limited Sentinel use, and a clear majority of respondents in the internal FDA survey at CDER cited a need for additional training.

While the CDER Sentinel Lead has made training opportunities widely available, respondents said it has not sufficiently incorporated FDA reviewers into the Sentinel process, which can limit skill development. CDER also lacks a comprehensive and continuously updated training program and an ability to measure growth in Sentinel proficiency.

6.C.2 Governance

The criteria used to assess the maturity for this dimension include the following[30]:

- Establishment of a strong oversight infrastructure to ensure the Sentinel System is used in an appropriate manner
- Effective protection of patient data privacy (according to HIPAA, Common Rule)
- Effective functioning of a lead decision maker who can triage and support Sentinel use in a transparent manner

FDA and the MSOC have established a robust distributed-data model with secure firewalls that effectively protect patient data and virtually eliminate privacy concerns from data partners (as discussed in greater detail in Section 4).

Across the organization, FDA, including the Center Sentinel Leads and the Office of Medical Policy (OMP), has made substantial progress in establishing strong oversight and governance mechanisms. Interviews indicate that OMP has been effective in providing both CBER and CDER a balance of support and autonomy. Users across both Centers agree that the Sentinel roles are clear and well established, as is elaborated below.

CBER has scored a High (3/4) rating across the governance criteria.

CBER has established a strong Sentinel Center Lead, who has enlisted the Safety Assessment Meeting (SAM) and SSTs to support the processing of queries. Most CBER stakeholders interviewed agreed that the Sentinel System process accurately captured user intent and that the Sentinel Lead was accessible and responsive. While a majority of CBER respondents to the internal FDA survey regarded their processes as transparent, these CBER users also felt that additional FDA support was needed to increase their usage rate and autonomy.

CDER has scored a Medium (2/4) rating across the governance criteria.

CDER has established a clear and authoritative Sentinel Center Lead who can prioritize queries and manage the submission process. Nearly all CDER users rely on the Sentinel Lead to submit requests and manage prioritization. Few stakeholders interviewed cited confusion around roles and responsibilities. While many advanced users said the Sentinel Center Lead was highly accessible and captured user intent well, some mainstream users cited difficulty in getting information once the Sentinel query process began.

In addition, only a minority of current user respondents to the internal FDA survey felt that CDER's end-to-end processes were transparent. In stakeholder interviews, some CDER reviewers cited a lack of robust explanations for instances of query denial, a lack of transparency in the development of CDER Sentinel query specifications, and a need for improvement in overall clarity of communications.

6.C.3 Process

The criteria used to assess the maturity for this dimension include the following[31]:

- Efficient Sentinel Initiative processes that manage end-to-end use, from query submission to result interpretation
- Effective integration of the Sentinel Initiative into regulatory workflows
- Cultivation of tools to continuously measure relevant metrics, including Sentinel performance, usage trends, and user satisfaction

CBER has scored a Medium (2/4) rating across the process criteria.

CBER has established processes to manage end-to-end use, with formal and standardized working groups, including the SAM and the SST. CBER process formalization has helped sustain a high level of participation and a medium level of satisfaction among CBER safety reviewers. The CBER processes are clearly defined with articulated roles and responsibilities, and they are documented in its draft SOP, which has also helped reduce user uncertainty and increase outcome and temperate consistency.

Despite these positive signs, CBER has opportunities for improvement. CBER's process infrastructure, although well developed, has not developed a mechanism to ensure that use of Sentinel will be considered by safety reviewers in all relevant circumstances, nor has it developed a means to manage the higher volume that will accompany the full Sentinel System. In addition, survey results show that several CBER stakeholders cited that the query process management is an added burden that does not easily integrate with the existing tasks and responsibilities of safety reviewers. Only a minority of respondents agreed that processes were well integrated into regulatory workflow, which will be necessary to handle higher volume. As the Sentinel Initiative matures, both CBER and CDER will need to develop the capability to continuously measure relevant metrics, including Sentinel performance, user satisfaction, and usage trends.

CDER has scored a Low (1/4) rating across the process criteria.

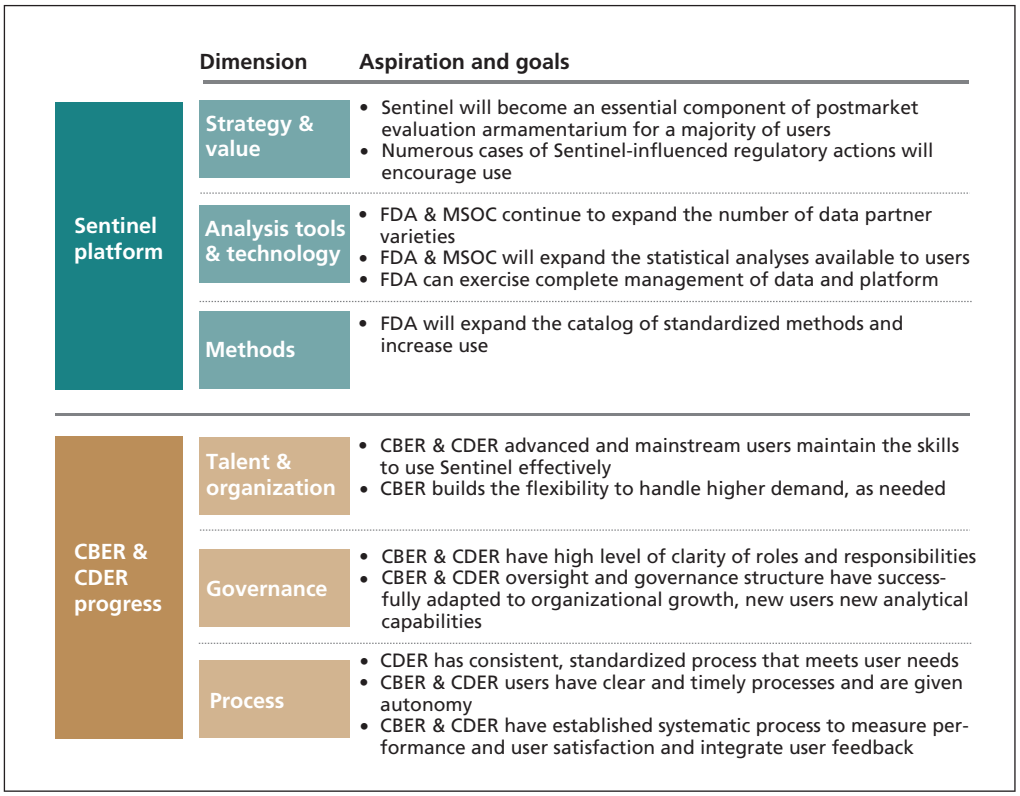
CDER has established processes to manage end-to-end use, from query submission to result interpretation. However, these internal processes tend to be ad hoc and informal. For example, CDER uses no formal query submission forms or standardized review processes and many queries tend to have a bespoke methodology that is customized to current needs. CDER also lacks a mechanism to ensure that use of Sentinel will be considered by safety reviewers in all relevant circumstances.

In addition, the Mini-Sentinel pilot process environment is not fully integrated into the core workflows of CDER. As Sentinel matures, CDER will likely need to develop infrastructure to manage a larger and more rapid throughput of requests that is fully embedded into the core regulatory workflows.

6.D ASPIRATIONS FOR A FULLY MATURE SENTINEL SYSTEM

As the Sentinel Initiative progresses toward full maturity, it will need to sustainably scale up to meet growing demand and unlock new sources of value and further the mission of the Agency. **Exhibit 16** summarizes the potential aspirations for a fully mature Sentinel System.

Exhibit 16: Aspirations and goals as Sentinel continues to mature



6.E EMERGING PRIORITIES GOING FORWARD

FDA has made significant progress across all parts of the SMM and a clear path exists to achieve scale and maturity by 2017. Realizing these aspirations will require action along multiple dimensions:

- Strategy and value
  - Ensure that a broad set of FDA scientists are aware of the Sentinel System's capabilities and are committed to regular use
  - Prioritize use-cases in which the Sentinel System can add the most value for regulatory decision making
- Analysis tools and technology
  - Enhance the Sentinel System's sources of data and its core capabilities to support regulatory decision making
- Methods
  - Expand the catalog of standardized methods and increase use
- Talent and organization
  - Improve the skills and training of key personnel to enable FDA scientists to use the Sentinel System more effectively.
  - Build organizational capacity to support future demand

- Governance
  - Create mechanisms within CBER and CDER that ensure Sentinel is considered in all appropriate instances and Sentinel data is fully utilized, when appropriate
  - Expand CDER governance process from pure submission to co-creating analyses
  - Increase transparency into the decision-making process, particularly in CDER, and expand the user autonomy and involvement across both Centers
- Process
  - Establish a standardized and codified process that integrates the Sentinel Initiative into relevant workflows
  - Establish the capability to measure relevant metrics (e.g., user adoption, usage trends, performance, user satisfaction)

Section 7 | Conclusion

The Sentinel Initiative was designed to run queries to analyze health outcomes across a broad set of electronic health data. To date, the Mini-Sentinel pilot has formed partnerships with 19 data partners, who have provided source data covering 178 million lives.

Although much work remains as Sentinel transitions to the fully mature Sentinel System, FDA's accomplishments to date, including having built a resource to conduct active surveillance and deploying it in a pilot setting, are significant. Interviews and research indicate that it has not been surpassed by another regulatory body in the United States or elsewhere.

In the implementation and execution of Mini-Sentinel, FDA has met or exceeded the requirements of FDAAA and the Prescription Drug User Fee Act (PDUFA), as previously outlined in **Exhibit 4** in Section 4.A.1 of this Interim Assessment and shown again here as **Exhibit 17**.

Exhibit 17: FDAAA/PDUFA: Sentinel Initiative milestones required/met

	Requirement	Deadline	Date achieved	Current status
Public meetings on Sentinel design	"FDA will hold or support public meetings engaging stakeholders to … facilitate stakeholder feedback" on how best to use Sentinel to "evaluate drug safety issues that may require regulatory action"	End of FY 2013	Mar 2008–Jan 2010	FDA held series of stakeholder meetings ('08), formed Federal Partner Working Group ('08), held public workshops facilitated by Brookings ('09-'10)
Number of lives covered	• 25 million lives covered • 100 million lives covered	• July 2010 • July 2012	July 2010–Dec 2011	178 million lives
Number of queries or studies	FDA will fund 4 to 6 activities, including "multiple product or class-specific studies or methodology development" that are designed to (a) evaluate safety signals that support regulatory action, or (b) help determine the utility and validity of the Sentinel System	End of FY 2017	First queries run in 2010	The Mini-Sentinel pilot now runs hundreds of queries per year and demonstrated 4 successful cases of regulatory decisions influenced by Sentinel analysis

The Mini-Sentinel pilot has accomplished several other goals over its first five years:

- **MSOC.** The Mini-Sentinel Operations Center is fully operational and has established itself as an intermediary between FDA and the initiative's growing roster of data partners.

- **Common data model and distributed-data approach.** These significant technical milestones have been created and have helped mitigate the concerns of potential data partners about the security and privacy of patient data. Further, they are data safeguards that have enabled FDA to meet FDAAA requirements to access healthcare data from 25 million individuals by July 2010 and 100 million individuals by July 2012.

  - *Data partners*. As of October 2014, the Mini-Sentinel pilot can access data from 18 healthcare providers and insurers, resulting in patient data from 178 million individuals.

- **Queries.** FDA and MSOC have successfully developed a core set of processes for turning safety concerns into Mini-Sentinel pilot queries.

- **CBER and CDER.** The two primary users of the Mini-Sentinel pilot within FDA – the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research – have evolved the structure further with their own designs, delivering unique benefits.

- **Mature data analytics system**. Good progress has been made toward this goal, which can augment existing postmarketing surveillance programs and aid decision making:

  - Strong governance; clear oversight procedures; an effective hierarchy in place

  - Mission and capabilities clearly articulated by FDA leadership

  - Group of advanced users, highly proficient at navigating the Sentinel System, cultivated by FDA

  - Fully operational process that effectively manages Mini-Sentinel pilot queries, resulting in some early successes in analyzing safety questions

Sentinel can also influence regulatory decision making through either improved active surveillance or through FDA agency action.

Sentinel data enables FDA to improve active surveillance by better understanding and more accurately estimating the incidence of a given safety risk in a relevant population.

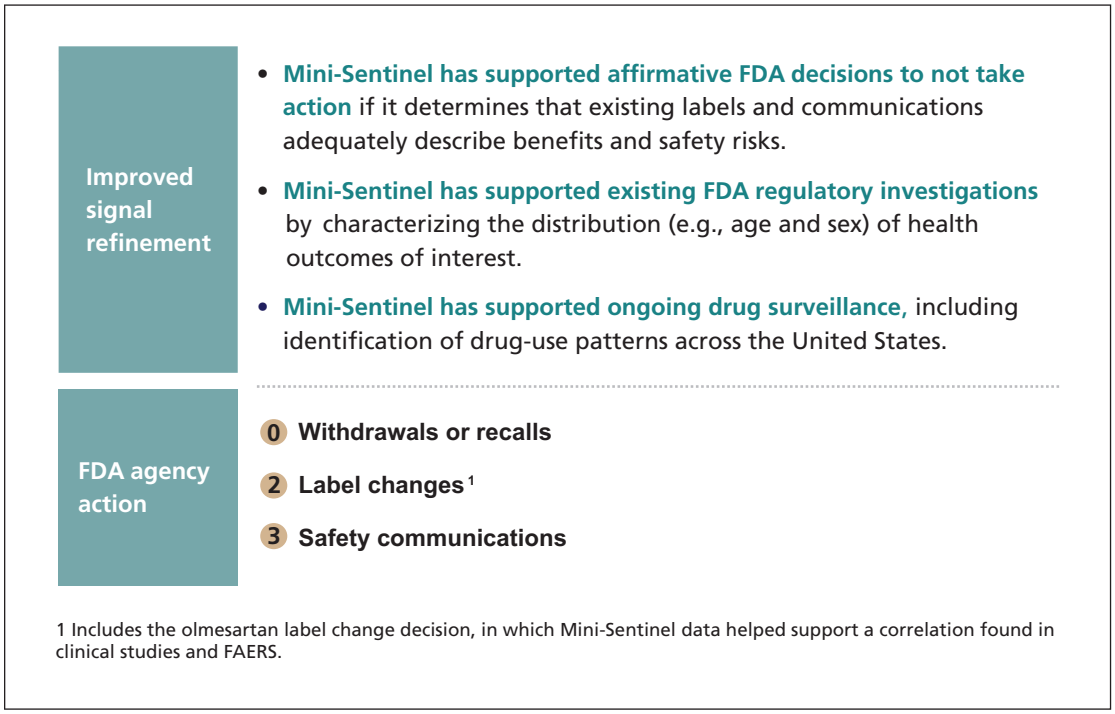
The combination of Sentinel data and insights from other FDA resources can help stimulate a wider set of pharmacoepidemiological research capabilities by enabling more accurate investigations of safety risks that lead to greater scientific certainty. Improved active surveillance helps both CBER and CDER make better decisions across its regulatory jurisdiction.

In many instances when FDA does not take direct action, Sentinel data could provide supporting information that existing FDA labels and communications are accurately describing both risks and benefits of a drug, and additional action is not warranted.

In cases when FDA does take action as a direct result of Sentinel, the data may help confirm or disconfirm the likelihood of a safety risk, in which case FDA may alter a label to incorporate the new risk, or it may communicate to the public that new fears may be overstated.

Exhibit 18 (as shown in **Exhibit 3** in Section 3.A.5 of this Interim Assessment and repeated here) illustrates the public health and regulatory impact that Mini-Sentinel has had to date.

Exhibit 18: Public health and regulatory impact of Mini-Sentinel pilot to date



1 Includes the olmesartan label change decision, in which Mini-Sentinel data helped support a correlation found in clinical studies and FAERS.

Although the MSOC is enriching its analytical tools and computing resources as a bridge to the full Sentinel System, significant gaps remain. As the Sentinel Initiative matures, FDA will need to consider the following:

- Expanding the system's sources of data
- Enhancing the system's core capabilities
- Implementing new processes for performance measurement
- Improving the skills and training of key personnel to enable them to use the Sentinel System more effectively, including an ability to identify use-cases across the broader user base

The lack of performance metrics is characteristic of data analytics programs in an early stage of development. However, as the Sentinel Initiative matures, in order to drive a broad and sustainable adoption of the system, it needs to consider the following:

- Enhancing the ability to gauge user satisfaction via metrics such as adoption rate and churn across both CBER and CDER
- Addressing a number of advanced user capabilities that are currently underdeveloped across both CBER and CDER

By 2017, aspirations for Sentinel System capabilities include the following:

- Increased user participation in Sentinel Initiative workshops and development of Sentinel Initiative methodologies across both CBER and CDER
- Access to a full set of modular programs and tools, particularly for CDER users

- More systematic and consistent processes for triggering the Sentinel System and processing safety questions across both CBER and CDER

- Assurance that CDER users have greater transparency of Sentinel studies under way to increase familiarity and comfort with Sentinel use, in addition to improving user knowledge

By 2020, a fully mature Sentinel System should be accessible to all FDA scientists, who can use it to do the following:

- Take advantage of high-level customization capabilities to identify, refine, and evaluate safety questions with few or no backlogs

- Regularly use the Sentinel System in the course of safety and risk assessment to deliver on FDA's vision for the Sentinel Initiative as a valuable resource to support regulatory decision making

Endnotes

[1] To protect patient privacy, FDA cannot directly access the patient data used in Mini-Sentinel. FDA uses an independent operations center to work directly with data partners, who maintain full control over their data. More detail is available in Section 4.A.2.

[2] Business proprietary material.

[3] Food and Drug Administration Amendments Act (FDAAA) of 2007, §905.

[4] Confounding variables occur when both the independent and dependent variables are correlated with an external variable. For instance, if a certain characteristic (e.g., age) has a direct relationship on both the medical treatment and the likelihood of recovery, reliable conclusions cannot be drawn unless that characteristic is appropriately accounted for in the analysis.

[5] *Code of Federal Regulations*, title 21, "Drugs for Human Use: Postmarketing Reporting of Adverse Drug Experiences," § 314.80 (2014); "Biologics: Postmarketing Reporting of Adverse Experiences," § 600.80 (2014).

[6] A joint effort between the regulatory authorities and pharmaceutical industry of the EU, Japan, and the United States to discuss scientific and technical aspects of drug registration.

[7] Our assessment found that in cases when FDA chooses not to act it continues to closely monitor the issue.

[8] *Code of Federal Regulations*, "Specific Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products Described in 201.56(b)(1)," title 21, § 201.57(c) (2014).

[9] As cited by Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) leadership in internal memoranda.

[10] This distributed data approach ensures that the Mini-Sentinel pilot is compliant with both the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Federal Information Security Management Act of 2002 (FISMA)—two key laws that protect the privacy of patient data in the United States.

[11] *Code of Federal Regulations*, "Protection of Human Subjects," title 45, § 46 (2009).

[12] In October 2014, Harvard Pilgrim competed again and was awarded an additional five-year Sentinel contract.

[13] An agreement to incorporate inpatient data from the Health Corporation of America has been completed and is underway as of October 2014.

[14] The MSCDM contains a standardized coding schema (e.g., ICD-9-CM, HCPCS/CPT, and NDC) that is designed to limit ontologic mapping.

[15] The content of this case study was compiled through FDA stakeholder interviews, interviews with subject-matter experts, a review of FDA public communications, and published academic articles.

[16] Accounting for possible differences in the patient populations for the two drugs that may relate to bleeding outcomes, such as age and the presence of other medical conditions.

[17] "FDA Drug Safety Communication: Update on the Risk for Serious Bleeding Events with the Anticoagulant Pradaxa (Dabigatran)," U.S. Food and Drug Administration, November 2, 2012, http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm.

[18] The content of this case study was compiled through FDA stakeholder interviews, interviews with subject-matter experts, a review of FDA public communications, and published academic articles.

[19] Intussusception is a serious and potentially life-threatening condition that occurs when an intestine becomes blocked or twisted. Patients with intussusception are at risk for an abdominal hole or infection or both.

[20] "FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception," U.S. Food and Drug Administration, June 13, 2013, http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm356758.htm.

[21] The content of this case study was compiled through FDA stakeholder interviews, interviews with subject-matter experts, a review of FDA public communications, and published academic articles.

[22] The content of this case study was compiled through FDA stakeholder interviews, interviews with subject-matter experts, a review of FDA public communications, and published academic articles.

[23] Trivalent inactivated influenza vaccine or TIV.

[24] Includes a product office clinical reviewer and an OBE reviewer.

[25] Business proprietary material.

[26] As shown in Exhibit 13: Overview of Sentinel Maturity Model.

[27] As shown in Exhibit 13: Overview of Sentinel Maturity Model.

[28] As shown in Exhibit 13: Overview of Sentinel Maturity Model.

[29] As shown in Exhibit 13: Overview of Sentinel Maturity Model.

[30] As shown in Exhibit 13: Overview of Sentinel Maturity Model.

[31] As shown in Exhibit 13: Overview of Sentinel Maturity Model.