Sentinel Initiative

Final Assessment Report

September 2017

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Section 1 – Executive Summary

Executive Summary

In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA), which mandated the creation of a post-market safety surveillance system for drugs, including biologics. To meet that requirement, the FDA established the Sentinel Initiative to develop and launch the Mini-Sentinel pilot program in 2009, which eventually expanded into the full-scale Sentinel System (Sentinel) in February 2016. The commitment letter attached to the Prescription Drug User Fee Act (PDUFA) V included specific commitments related to the Sentinel.[1] In satisfaction of one of those commitments, the FDA completed an interim assessment in 2015, which highlighted both strengths and weaknesses of the pilot program and identified recommendations to further the maturity of Sentinel. PDUFA V also required a final assessment be completed in 2017. Both the interim assessment and this final assessment are specifically focused on the mandate articulated in FDA's PDUFA V commitment letter, specifically: "[to] evaluate the strengths, limitations and the appropriate use of Sentinel for informing regulatory actions (e.g., labeling changes, [postmarketing reports] (PMRs), and [postmarketing commitments] (PMCs)) to manage safety issues."

The Sentinel system complements the FDA's existing monitoring capabilities, such as MedWatch, by providing administrative and claims data that can be queried to monitor the use of FDA-regulated medical products and potential outcomes of treatment. The Sentinel System allows the FDA to proactively assess the safety of products and, as a result, it is better able to understand their risks. Currently, the Sentinel System has information on over 223 million members combined from 17 different data partnerships. The data are derived from national health insurers and managed care organizations. Sentinel contains information about diagnoses, procedures, and drugs dispensed in these health care systems.

To date, the FDA has broadly succeeded in achieving what was outlined in the PDUFA V commitment letters. Specifically, Sentinel has been widely accepted within the FDA as a useful regulatory decision-making tool for safety issues; awareness of its capabilities among FDA staff has materially increased; it has been incorporated into the regulatory process; and its outputs have been instrumental in deciding a number of critical public health and safety questions. Its data infrastructure and associated suite of tools and methods are increasingly robust, and the question now is no longer if Sentinel will be used in regulatory decision-making, but rather how best to cost-effectively scale and embed it even further. These accomplishments are the result of many factors – prominent among them is the sustained commitment of FDA – both in terms of consistent time and effort invested by staff, and in material funding.

[1] https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf Section XI (pages 25-27).

What follows in this report are the summary findings from a comprehensive final assessment of Sentinel designed to assess the maturity of Sentinel and how it affects regulatory decision-making on safety issues. The report includes four main chapters: (1) an overview of methodology; (2) a summary of Sentinel progress to date; (3) an assessment of Sentinel maturity against the previously-defined Sentinel Maturity Model; and (4) an overview of some priorities for FDA to consider for Sentinel moving forward.

Final Assessment Methodology

There are important methodological considerations associated with the final assessment, many of which are detailed in Section 2, but the summary is:

- The assessment relied on more than 50 interviews with staff from the FDA (including Agency leadership, medical officers, epidemiologists and others with relevant exposure to Sentinel), from the Sentinel Operations Center (SOC), and from data partners. It was also informed by an internal FDA survey and a review of other secondary literature related to Sentinel and other safety surveillance approaches (detailed below).

- Consistent with the interim assessment in 2015, the "Sentinel Maturity Model" (SMM) provides a framework for evaluating the success of Sentinel and identifying specific criteria for individual SMM elements. The six elements captured in the SMM include: (1) strategy and value, (2) analytical tools and technology, (3) methods, (4) talent and organization, (5) governance, and (6) process. The assessment offers both a "score" for each element of the SMM (evaluated FDA-wide, and for the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) individually) that is informed by the sources of input outlined above and a broader set of themes relevant to each SMM element describing in detail more nuanced aspects of the assessment.

Sentinel Initiative – progress to date

Since 2015, there has been notable progress toward implementing a fully mature Sentinel system and embedding Sentinel in the Agency's regulatory decision-making process. Specific findings include:

- Successful transition from Mini-Sentinel pilot to full-scale Sentinel, including finalizing an organizational realignment, enhancing tools for rapid queries, and implementing other operational enablers

- Onboarding of new data partners contributing information on more than 223 million members and incorporating a broad range of data types

- Strengthened integration of Sentinel into the regulatory decision-making process, including use of rapid query tools and expanded protocol-based assessments in CBER, and Active post-market Risk Identification and Analysis system (ARIA) sufficiency determination in CDER

- Material expansion in Sentinel tools, methods, and capabilities to assess safety issues

- Formal implementation and adoption of FDA-wide, and Center-specific, governance

The scope of this progress is evident in a number of important public health findings and regulatory actions – many of which are made available to the public, and a selection of which are profiled below in Section 3.4.

Assessment of maturity based on the Sentinel Maturity Model (SMM)

Reflecting on the previously-established maturity model used to inform the interim assessment, there is also evidence of considerable progress across all elements of the SMM within the FDA, CBER, and CDER. Significant progress has been made in the elements "analytical tools and technology," "talent and organization," and "process," while more modest progress has been made in the elements, "strategy and value," "methods," and "governance." Key findings related to this progress include:

- Significant increases in overall awareness and utilization of Sentinel by FDA staff, and belief that Sentinel is a broadly useful and valuable tool for regulatory decision-making
- Major improvements in the breadth and depth of Sentinel's tools, technologies, and methods, with a drive toward greater modularity and efficiency
- Changes within FDA to address Sentinel's talent and governance challenges, which have improved internal transparency and communication, and elevated awareness and working familiarity with Sentinel among a broad range of FDA staff
- Material progress in both CBER and CDER to formally embed Sentinel into regulatory decision-making, including progress toward formally documenting use in day-to-day operations

An overall summary of the report's findings against the Sentinel Maturity Model is included in the table below, followed by an overview of steps to take toward further maturing Sentinel and embedding it in regulatory processes.

Exhibit 1-1: Summary of SMM scores

SMM criteria[2]	Final assessment maturity score[1] FDA[3]	CBER	CDER
Strategy and value	**3** (*+1*)	**3** (*n/a*)	**3** (*n/a*)
Analytical tools and technology	**3** (*+2*)	**3** (*n/a*)	**3** (*n/a*)
Methods	**3** (*+1*)	**3** (*n/a*)	**3** (*n/a*)
Talent and organization	**2** (*n/a*)	**3** (*+1*)	**3** (*+2*)
Governance	**2** (*n/a*)	**3** (0)	**3** (*+1*)
Process	**2** (*n/a*)	**3** (*+1*)	**3** (*+2*)

1 Sentinel maturity assessed on a 4 point scale, with a score of 4/4 representing full maturity to support use of Sentinel in regulatory decision making safety assessments
2 SMM criteria and scoring methodology described in Section 2
3 FDA score represents the overall Sentinel maturity at the Agency-wide level for all Sentinel stakeholders, and is not a simple composite of the CBER and CDER scores

(*x*) change from interim assessment (09/2015)

A dedicated and consistent effort to further embed Sentinel in regulatory processes moving forward

Based on the opportunities identified in the final assessment, there are a set of additional steps FDA might take – working in cooperation with SOC, data partners and others when appropriate, to further enhance Sentinel's maturity, including:

- Articulating a long-term strategy for full maturity of Sentinel (inclusive of broad goals and an operational roadmap to reach them) and clearly prioritizing a set of policies and programs consistent with that strategy
- Further investing in systematic approaches to assessing data infrastructure and methods gaps, assessing high-feasibility/high-impact areas for improvement, and leveraging governance to prioritize future investments against highest value areas
- Analyzing both staffing and governance needs and instituting appropriate reforms to ensure more effective day-to-day operational oversight
- Supplement the existing portfolio of metrics that FDA uses to conduct more routine performance management of Sentinel, with a targeted addition of measures that articulate the public health impact and value of Sentinel use

Though not the explicit mandate of the final assessment, it nonetheless concludes with a view toward the future and outlines a core set of long-term strategic questions for Sentinel leaders to address. Issues of Sentinel's scalability and sustainability (especially related to reducing assessment cost) are critical as leaders consider both strategic direction and operational considerations. Going forward, leaders will face a series of key decisions about how, when, and why Sentinel is used in order to maximize impact on public health and patient safety.

Section 2 – Assessment Methodology

This assessment uses multiple sources of input – both qualitative and quantitative – to inform the evaluation of Sentinel maturity. Quantitative data came from both internal surveys and Sentinel operational metrics while qualitative insights were gleaned from interviews, working sessions, and other external sources (e.g., publications) – all gathered in the first quarter of 2017. Those sources of input formed a composite evaluation, articulated as a single rating against the core dimensions of the pre-existing Sentinel Maturity Model, developed for the Interim Assessment published in 2015. Where an assessment is made about the degree of progress made along a certain dimension, the report seeks to be as explicit as possible in identifying the source of the determination and the approach taken, but the synthetic nature of the approach inherently involves some degree of subjective determination. The ratings that are provided in this assessment reflect a holistic assessment of Sentinel's current level of maturity. While the assessment provides a holistic view, it places relatively greater emphasis on progress made since the interim assessment to inform this report's conclusions. The ratings that are provided in this assessment reflect Sentinel's overall current maturity. 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.

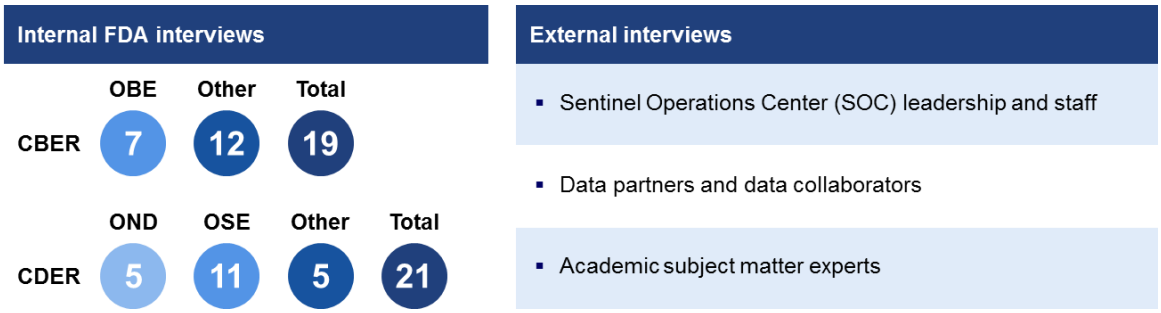
2.1 Assessment sources of input

The report specifically considered the following sources of input in generating the assessment:

- Interviews with current FDA employees at CBER and CDER, as well as other leaders across the FDA who have either overseen or interacted directly with Sentinel (for details see Exhibit 2-1)
- Interviews with leaders and staff at the Sentinel Operations Center (SOC) at Harvard Pilgrim Healthcare Institute, and a selection of affiliated data partners
- Presentations and associated documents from public literature referencing use of Sentinel, including materials from the annual Sentinel initiative public workshops
- A survey provided to a broad subset of FDA staff to assess how Sentinel is perceived and used today across different operational Divisions and regulatory review teams (*for survey details, see Appendix*)
- Existing secondary source literature, including published reports and academic literature, across several categories, including:
  - The 2015 Sentinel interim assessment
  - Reports evaluating Sentinel from independent government entities, including the Government Accountability Office (GAO) and the Congressional Research Service (CRS)

- Internal documents provided by the FDA concerning the operational effectiveness of Sentinel and oversight of Sentinel at multiple levels of management and leadership
- Interviews with other external experts, including those with industry and academic backgrounds

Exhibit 2-1: Interviews conducted for Sentinel Final Assessment



2.2 Approach to applying the Sentinel Maturity Model (SMM)

The 2015 interim assessment established the Sentinel Maturity Model (SMM), which served as the basic framework for evaluating progress of the Sentinel Initiative. The SMM considers six principal components in order to assess program maturity (see further definition in Exhibit 2-2):

- Strategy and value
- Analytical tools and technology
- Methods
- Talent and organization
- Governance
- Process

The final assessment relied on the same framework for evaluating Sentinel maturity, with particular attention paid to developments between 2015 and 2017, though the score presented in the report itself represents an absolute assessment of current maturity.

Exhibit 2-2: Description of Sentinel Maturity Model (SMM) elements

SMM element	Description
Strategy and value	Clear and aligned articulation of settings where Sentinel use creates value – supported by FDA staff and senior leaders – and an accompanying long-term plan that outlines continuous improvement opportunities and broader strategic priorities
Analytical tools and technology	The core technology and platforms scale to integrate larger and richer datasets and more robust analyses
Methods	Standardized methods are used to simplify execution and improve efficiency and effectiveness and increase the number of methods available that answer key public health questions
Talent and organization	Internal and external Sentinel resources match demand and that the resources are optimally configured
Governance	Transparency and oversight around prioritization and other decision making
Process	Operationalization and integration with core workflows and processes and support regulatory decision making fully

This assessment evaluated each of the six SMM components on a 0-4 scale, with 0 being assessed as "low/no maturity" and 4 serving as "full maturity." Each assessed element of the SMM includes sub-criteria outlined below, which are evaluated to inform the overall maturity rating (for details on the scoring rubric, see Appendix table A-1). It deserves mention that the SMM serves as a generalized framework for describing maturity of Sentinel – the path the FDA or individual Centers follow to reach maturity will naturally vary based on program priorities, regulatory considerations, and the nature of the products regulated in each area. The assessment attempts to identify those differences where appropriate, while using the SMM as a consistent reference point for progress toward maturity.

Strategy and value

- Degree of alignment on long-term strategy
- Level of promotion of Sentinel use by FDA leaders
- Percent of potential users that are actively using Sentinel
- Level of confidence in results/usefulness of Sentinel by FDA staff

Analytical tools and technology

- Timeliness and relevance of analytical capabilities and data sources
- Breadth of data infrastructure and capability toolkit
- Presence of management tools that improve Sentinel operations

Methods

- Degree to which methods of analysis are standardized and routine
- Degree to which methods are being improved and refined over time
- Degree to which new methods are created to address emergent questions

Talent and organization

- Strength of training program and frequency of trainings on updated capabilities
- Level of resource ability among FDA staff and collaborating partners
- Degree of organizational preparedness to sustain future growth

Governance

- Strength of FDA oversight systems that set and coordinate strategic direction
- Degree of embedded accountability processes to manage day-to-day operations
- Existence of safeguards to protect patient data privacy

Process

- Level of efficiency of processes, from question submission to results interpretation
- Degree of integration of Sentinel into pre- and post-market regulatory workflows
- Degree to which feedback from metrics is incorporated into system improvements

Understanding that progress may vary between Offices within the FDA, three scores were provided for each component of the SMM: one for the FDA as a whole, recognizing that the SMM speaks to programmatic features of Sentinel, and one each for CBER and CDER, in recognition of the variation in how each Center currently engages with Sentinel.

2.3 Approach to scoring SMM elements

In the Sentinel interim assessment, scores of maturity for the SMM elements of strategy and value, analytical tools and technology, and methods were generated only at the FDA-wide level, while those elements for talent and organization, governance, and process, were provided only for CBER and CDER, with no FDA-wide scores given. In the final assessment, scores are provided for all three organizations (FDA, CBER, and CDER) across all six elements of the Sentinel Maturity Model. Where previous scores exist, they have been included to show where and how much progress has been made. FDA-wide scores include elements of the program shared across all FDA Sentinel stakeholders, and are not simple composites of Center-level assessments. These Agency-wide scores represent progress made toward maturity across the entire dimension as an integrated capability.

Scoring of the SMM elements consists of a combination of inputs (outlined in section 2.1). A number of these inputs inherently relied on perceptions – either gathered through live interviews or survey responses. Perception data carries inherent limitations, as they are reliant on the quality of the tools employed and the potential selection biases associated with colleague experience and exposure to Sentinel. An additional limitation is that a

detailed review of the underlying data architecture and technical aspects of the Sentinel infrastructure was not a primary focus, but instead a more holistic assessment of the broader supporting ecosystem was the intent of this assessment.

The recent change in scoring is driven primarily by the scale of Sentinel as it progressed from Mini-Sentinel to full-scale Sentinel. As Sentinel began, it made more sense to evaluate even the first three elements of the SMM by the individual Centers as well, as variation emerged between them with regard to Sentinel's value proposition, the tools being utilized, and the process of methods development. Conversely, as Sentinel grew, the FDA also began to take on a larger role in coordinating talent, structuring governance, and instituting systematic processes, warranting an FDA-wide score for the last three elements of the SMM. Though this expansion of the scoring process does not permit a relative evaluation over time across all components of the matrix, the data points are nonetheless instructive in assessing Sentinel's absolute level of maturity within the FDA, CBER, and CDER.

Section 3 – Sentinel Initiative Progress to Date

3.1 Update on Sentinel background

For detailed background and a review of the history of the Sentinel Initiative (including legislative history, original Program objectives and goals, Mini-Sentinel pilot program structure, initiative design choices and milestones), please refer to the Sentinel Program Interim Assessment Fiscal Year (FY)15.[2]

This final assessment seeks to provide an update on relevant progress since the time of the interim assessment and specifically is in response to the PDUFA V commitment.[3]

Exhibit 3-1: Update on PDUFA Sentinel initiative milestones met

	PDUFA V commitment:	Date achieved
1	*"FDA will hold or support public meetings engaging stakeholders to discuss current and emerging Sentinel projects and facilitate stakeholder feedback and input regarding Sentinel projects that would be appropriate to meet the goals stated above.*	March 2008 – 2010
2	*Informed by the feedback and input received through the public meeting, in FY 2013 through FY 2017, FDA will fund 4-6 activities, which will include multiple product or class-specific studies or methodology development. These activities will be specifically designed to further evaluate safety signals that, in previous cases, have served as the basis for regulatory action(s) or designed more broadly to help determine the utility and validity of the Sentinel System to evaluate other types of signals in population-based databases. The following are examples of potential activities:* *a) Expanding the active surveillance mechanisms begun for the H1N1 pandemic to substitute for the information gathered in large ad hoc, manufacturer-conducted studies* *b) Evaluating risk for class-wide adverse events (e.g., cardiovascular events, suicidality)*	July 2010 – December 2011
3	*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.*	September 2015
4	*By the end of FY 2017, FDA will conduct (or fund by contract) an 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.*	(month) 2017

In 2017, proposed commitments to be included in PDUFA VI were negotiated[4], and this included an expanded set of commitments related to scaling up and expanding the role of Sentinel over the period spanning 2018-2022, and integrating the system even further into FDA pharmacovigilance activities. These proposed commitments are as follows:

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2 https://www.sentinelinitiative.org/communications/publications/sentinel-program-interim-assessment-fy-15

3 https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf Section XI (pages 25-27).

4 https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf Section K "enhancement and modernization of the FDA drug safety system" (pages 34-36).

FDA will use user fee funds to conduct a series of activities to systematically implement and integrate Sentinel in FDA pharmacovigilance practices. These activities will involve augmenting the quality and quantity of data available through the Sentinel System, improving methods for determining when and how that data is utilized, and comprehensive training of review staff on the use of Sentinel.

a. *FDA will work toward expanding the Sentinel System's sources of data and enhancing the system's core capabilities.*

b. *FDA will enhance its communication with sponsors and the public regarding general methodologies for Sentinel queries, including what the Agency has learned regarding the most appropriate ways to query and use Sentinel data. This can be done through enhancement of existing mechanisms and/or greater frequency of such mechanisms.*

c. *FDA will evaluate additional ways to facilitate public and sponsor access to Sentinel's distributed data network to conduct safety surveillance.*

d. *By the end of FY 2019, FDA will hold or support a public meeting engaging stakeholders to discuss current and emerging Sentinel projects and seek stakeholder feedback and input regarding gaps in the current system to facilitate the further development of Sentinel and its system of Active Risk Identification and Analysis (ARIA).*

e. *By the end of FY 2020, FDA will establish policies and procedures ([Manual of Policies and Procedures] (MAPPs) and [Standard Operating Procedures and Policies] (SOPPs)) to facilitate informing sponsors about the planned use of Sentinel to evaluate a safety signal involving their respective products. These MAPPs and SOPPs will address what types of evaluations and what information about the evaluations will be shared with sponsors, and the timing of such communications.*

f. *By the end of FY 2020, FDA will facilitate integration of Sentinel into the human drug review program in a systematic, efficient, and consistent way through staff development and by updating existing SOPPs and MAPPs, as needed.*

g. *By the end of FY 2020, FDA will develop a comprehensive training program for review staff (e.g., epidemiologists, statisticians, medical officers, clinical analysts, project managers, and other review team members) to ensure that staff have a working knowledge of Sentinel, can identify when Sentinel can inform important regulatory questions, and are able to consistently participate in use of Sentinel to evaluate safety issues.*

h. *By the end of FY 2022, FDA will analyze and report on the impact of the Sentinel expansion and integration on FDA's use of Sentinel for regulatory purposes (e.g., in the contexts of labeling changes, PMRs, or PMCs).*

3.2 Summary of progress since interim assessment

FDA has taken a significant series of strides to mature Sentinel since the time of the interim assessment. While the progress comes across a number of dimensions, this report focuses on five broad themes that encompass major aspects that deserve highlighting. The major themes include:

- Successful transition from Mini-Sentinel pilot to the fully developed Sentinel System, including finalizing an organizational realignment, enhancing tools for rapid queries, and implementing other operational enablers
- Onboarding of new data partners possessing information on more than 223 million total members and incorporating a broad range of data types
- Strengthened integration of Sentinel into the regulatory decision-making process, including use of rapid query tools and expanded protocol-based assessment use in CBER and Active post-market Risk Identification and Analysis system (ARIA) sufficiency determination in CDER
- Material expansion in Sentinel tools, methods, and capabilities to assess potential safety issues
- Formal implementation and adoption of FDA-wide, and Center-specific, governance

The following section provides further detail relevant to each of the foregoing themes.

3.3 Detail on Progress since the interim assessment

Successful transition from Mini-Sentinel pilot to full-scale Sentinel, including finalizing an organizational realignment, enhancing tools for rapid queries, and implementing other operational enablers

The Mini-Sentinel pilot transitioned to a full-scale production system in February 2016. This achievement was the culmination of a number of activities including a formal transfer of overall Agency-wide Sentinel program oversight and associated staff from the Office of Medical Policy (OMP) to the Regulatory Science Staff (RSS) within the Office of Surveillance and Epidemiology (OSE) in CDER. The transition also established new dedicated roles for program management and oversight, and formal reporting structures in CBER and CDER. Within CBER, a Center-level Sentinel core team, recently augmented with new staff, reports directly to the Office of Biostatistics and Epidemiology (OBE) Office Director. In CDER, a Center-level Sentinel core team has a formal organizational "home" in the OSE/RSS, overseen by the OSE Director and Deputy Director. These reporting structures have ensured direct managerial support and visibility for the program, increasing its profile among other leaders within the Centers and the Agency.

Furthermore, transition from Mini-Sentinel to full-scale Sentinel was accompanied by the formalization of a number of established epidemiologic methods into stable tools for rapid queries. There is an important distinction to be made, specifically, these rapid queries were

designed *only* to speed analytic programming and computation time; efforts related to deliberation on study design and specifications of the analyses were intentionally not foreshortened to ensure the scientific soundness of the analyses. Moreover, no short cuts were made to the general epidemiologic paradigm that begins with feasibility analyses and proceeds to inferential analyses, ensuring that FDA decision making relies on the highest quality evidence. Thus, the procedural arc that a single safety issue follows typically draws upon the full complement of available tools, beginning with a summary table and/or descriptive analyses, and ending with one or more inferential analyses or a protocol-based assessment. These specific capabilities are discussed further below in the assessment section of the report.

While an in-depth operational review is not the focus of this report, operational metrics used by the FDA to manage Sentinel– specifically query fulfillment time – indicate a continuing trend toward faster completion and enhanced tool productivity. A couple of examples illustrate the impact, specifically for Level 1, L1 queries, average time between query submission by the FDA and the return of data to the FDA declined over the last year from an average of 99 days (between March 2016 – August 2016) to an average of 44 days (between September 2016 and March 2017). In the same time period, SOC and the FDA have worked together to reduce the time between the SOC finalizing query specifications and returning the data to the FDA – average time between specification finalization and return of data declined from 52 days to 38 days in the same time window referenced above.

Finally, there are a number of other operational enhancements that FDA has implemented to support Sentinel operations. Specifically, FDA has articulated end-to-end processes stemming from safety issue identification to public posting and sponsor notification. There are now numerous standardized templates in place facilitating structured communication between the FDA and SOC, in addition to laying out a scientific framework for classifying signals and deciding on the use of Sentinel. The FDA has also invested in regular (e.g., quarterly) in-person meetings with SOC to plan studies, routine trainings on new tools and data sources, and ideation sessions to frame strategic priorities for the future. And all of this comes against a backdrop of increasing scale of operations year-on-year.

Onboarding of new data partners providing information on more than 223 million members and incorporating a broad range of data types

Sentinel has been successful in establishing and maintaining an extensive and robust network of data partners and data infrastructure to support analyses. The breadth of the data accessible via Sentinel is impressive – at present, Sentinel covers 43 million individuals acquiring data, 223 million unique member IDs, 425 million person-years of observation time, 5.9 billion drug dispensings, and 7.2 billion unique encounters. In terms of person years of observation time, this represents a growth of approximately 20% over the last two years. At present, integration of the Hospital Corporation of America (HCA) in the Sentinel distributed database is underway, as is an effort to bring data from the Centers for Medicare and Medicaid Services (CMS) into Sentinel. Taken together, these new data sources are important because they allow for expanded access to inpatient electronic health records (for chart review) in the case of HCA and further enable analysis of specific populations (e.g., the elderly in the case of CMS).

Strengthened integration of Sentinel into the regulatory decision-making process, including Active post-market Risk Identification and Analysis system (ARIA) sufficiency determination in CDER and regular protocol-based assessment and rapid query tool use in CBER

ARIA has been defined as the core CDER safety use case, and has been meaningfully embedded in regulatory decision-making processes. ARIA represents a subset of Sentinel's full capabilities, leveraging the common data model as well as pre-defined, parameterized, and re-usable modular program analytic tools to produce rapid query-based assessments. ARIA analyses include three "levels," consisting of: (i) descriptive analyses with unadjusted rates (Level 1, L1 query); (ii) adjusted analyses with sophisticated confounding control (Level 2, L2 query); and (iii) sequential adjusted analyses with sophisticated confounding control (Level 3, L3 query). Incorporation of ARIA sufficiency assessments into formal documentation accompanying workflows is progressing well, with early drafts of SOPPs, MAPPs and updates to the CDER 21st Century Desk Reference Guide in development. ARIA has become a core part of CDER regulatory decision-making as evidenced by a noteworthy volume of safety issues subjected to sufficiency assessments, numerous insufficiency memos, Safety Assessment Meetings (SAMs) and other analyses that have either replaced or complemented PMR studies.

In CBER, utilization of ARIA sufficiency is less relevant due to the nature of the product set CBER regulates (e.g., blood and blood components and vaccines) and what is present in available data. Specifically, for preventative vaccines, the fact that products are often administered to healthy individuals, including children, means that any potential rare serious or unexpected adverse outcome identified in Sentinel needs verification through medical chart review. For blood-derived products, the product brand name is usually not present in claims data, so medical chart review is often necessary to ascertain product name and validate adverse outcomes. Given this, CBER routinely leverages ARIA tools for initial analyses but often relies on other Sentinel product-specific programs (e.g., PRISM and BloodSCAN) to frame protocol-based assessments to answer their regulatory questions. CBER's approach to integration reflects their regulated product landscape and, like CDER, associated documentation to support the process of using Sentinel routinely is underway.

Additionally, across both Centers, well-defined mechanisms and approaches for surfacing potential Sentinel questions have been established, and users have clear points of contact within the respective Sentinel teams in each Center. Management routinely confirms that Sentinel is an important regulatory tool when addressing both internal and external stakeholders, and regulatory decision makers are encouraged to utilize Sentinel whenever possible within the Agency. It is important to note that the totality of effort put against integrating Sentinel into regulatory workflows has had a considerable impact – the number of users, the degree of familiarity with Sentinel, and the absolute volume of use in both Centers has increased significantly since the time of the interim assessment.

Material expansion in Sentinel tools, methods, and capabilities to assess potential safety issues

Over the last two years, Sentinel has evolved a series of new tools and capabilities that enable it to answer a set of more nuanced and complicated public health and drug safety questions. As previously described, substantial progress has been made on improving the efficiency of existing tools, FDA has also made progress introducing new tools and strengthening capabilities. While there are numerous examples of growth in Sentinel capabilities, three specifically deserve mention: (1) introduction of the self-controlled risk interval design as an approach to control for time-invariant confounders in the data; (2) development of sequential analysis with propensity score matching, allowing for more rapid signal identification compared to existing statistical approaches; and (3) introduction of TreeScan, which is a tool that can conduct surveillance for thousands of different disease outcomes simultaneously, enabling FDA to scan more broadly for adverse health outcomes of interest that otherwise might go undetected. This pilot program, once scaled, will push Sentinel further into the realm of active safety surveillance by enabling signal identification, as opposed to refinement alone and resolution alone.

In addition, CBER has established Post-Licensure Rapid Immunization Safety Monitoring (PRISM) for the assessment of vaccine safety. Leveraging Sentinel's data infrastructure, PRISM avoids data overlap with the Vaccine Safety Datalink data sources. PRISM has also shown promising potential to become a viable data source to provide subsequent confirmation of randomized control trial (RCT) data to assess vaccine effectiveness. Potential future applications for this PRISM include: (1) evaluating vaccines approved through accelerated or "animal rule" approval processes that only require effectiveness evidence through the demonstration of an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit; (2) evaluating vaccine effectiveness in specific populations (RCT data may not have sufficient data on small subsets such as gender or age group); (3) evaluating effectiveness to prevent rare conditions or more specific endpoints (hospitalization or severe disease); (4) evaluating vaccines when a RCT is not ethical and/or feasible (e.g., Ebola); and (5) supplementing or confirming what has already been learned in RCT. Taken together, these new tools and capabilities introduced over the last several years represent material growth in Sentinel's active safety surveillance capabilities.

Formal implementation and adoption of FDA-wide, and Center-specific, governance

Since the completion of the interim assessment, significant progress has been made across FDA to both establish and implement a set of robust governance mechanisms – both at the FDA-wide level and within CBER and CDER. Specifically, at the FDA-wide level, a governance model with three main levels has been created and implemented in mid-2016 (illustrated further in Exhibit 3-2):

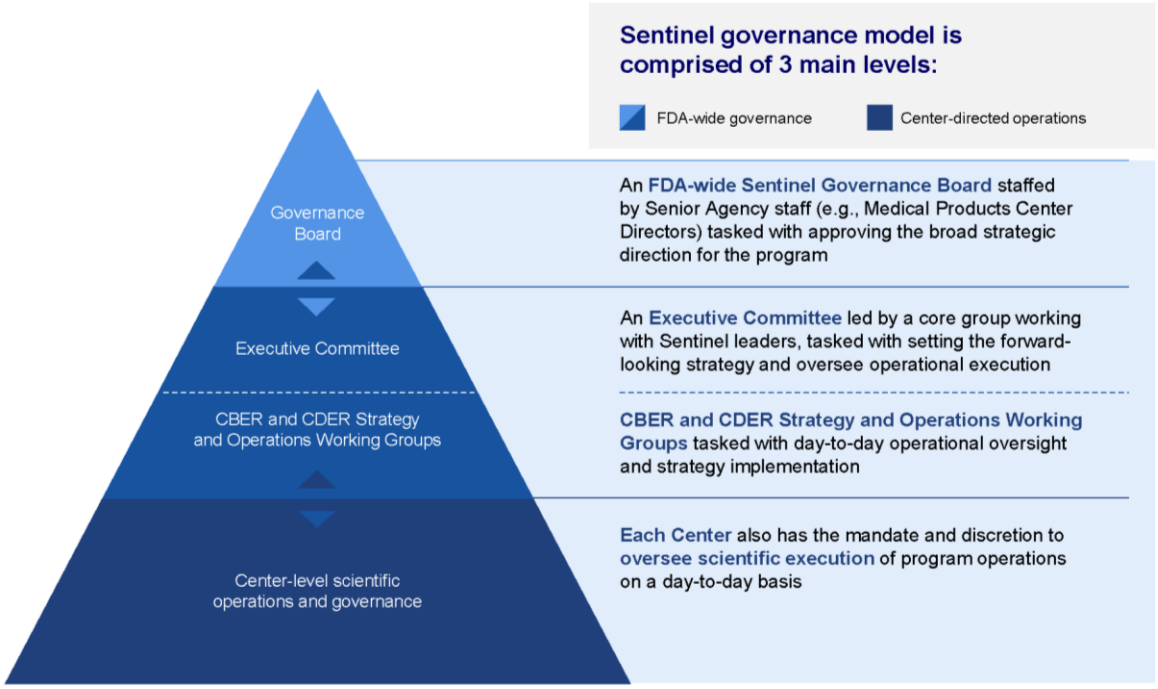
- A Sentinel Governance Board – the senior-most body comprised of medical products Center Directors and a representative from the Office of the Commissioner tasked with setting long-term strategic direction for Sentinel

- A Sentinel Executive Committee – the main executive body comprised of representatives from each of the medical product Centers (CBER, CDER, and CDRH) and chaired by the Sentinel Executive Sponsor – focused on defining strategy for Sentinel, overseeing program performance, and elevating issues to the Governance Board as needed
- CBER and CDER Strategy & Operations Working Groups – consisting of Center representatives with a responsibility for managing day-to-day operations of Sentinel (including all administrative aspects) and surfacing strategic questions and challenges that require debate and resolution at the Executive Committee or Governance Board

The implementation of this governance model has improved operational transparency through the creation of an Agency-wide venue for discussion of Sentinel strategy and operations. To support effective operational oversight, FDA has worked with SOC to develop a portfolio of reports that support routine review and evaluation by the Executive Committee.

In addition to FDA-wide governance, CBER and CDER have both taken strides forward to strengthen intra-Center governance for Sentinel. Each Center has a governance body established and, while mandates and degree of implementation vary across the two, they are generally focused on establishing clearly defined decision-making processes and protocols for surfacing, prioritizing, executing, and overseeing Sentinel projects. They also often serve as the single point of contact for expertise and input as projects unfold, or as a conduit to the SOC when required.

Exhibit 3-2: Schematic of FDA-wide sentinel governance



A number of recommendations were made in the interim assessment and these were aligned to the Sentinel Maturity Model (SMM). The aim of these recommendations was to provide a starting point that would enable Sentinel to expand and transition into a fully operational program from the initial pilot phase (refer to **Appendix Exhibit A-4** for details). Overall, significant progress has been made against each of those recommendations, as evidenced by increased utilization of Sentinel by FDA scientists and decision makers, and by the marked increase in the type and complexity of questions that Sentinel is able to address. A more detailed evaluation of Sentinel – including discrete references to recommendations made in the interim assessment – are contained in Section 4.0 of this report, along with options to consider for further enhancement.

The breadth of this progress is further reflected in the wide range of use cases answering critical – and heretofore unanswerable without considerable time and investment – public health questions. Those use cases are increasingly showcased in public fora, including the annual public meeting of Sentinel where FDA continues to play a central role. A small sample of interesting use cases showcasing Sentinel development and maturity follow in the next section.

3.4 Recent examples of Sentinel in action

Sentinel has made tremendous progress both in terms of methodological evolution, as well as the breadth of questions answered. A number of examples of Sentinel in action were presented at the 2017 Sentinel Initiative Public Workshop, hosted by Duke-Margolis Center for Health Policy (Duke-Margolis).[5] Across the assessment, a number of Sentinel use cases are highlighted to illustrate both the expansion of Sentinel capabilities to support regulatory decision-making and to showcase the public health impact of recent lines of inquiry pursued in Sentinel. In many cases, the core findings of the analysis did not result in direct regulatory action (defined as a communication, label change, or request for PMR/PMC), but instead provided important reassurance to patients and providers by answering a pressing – but heretofore unanswered – public health question. Furthermore, the data produced by Sentinel does play a pivotal role supporting analyses related to safety-related labeling changes, although there is no formal mechanism to track this specific application of the system.

Incidence of cardiomyopathy and heart failure following initiation of medications for attention deficit hyperactivity disorder[6]

Context: Stimulant abuse is associated with cardiomyopathy, but cardiomyopathy rates with stimulants for attention deficit hyperactivity disorder (ADHD) are poorly characterized.

Objective: To assess the incidence of cardiomyopathy and heart failure among ADHD medication users of varying age and duration of usage.

[5] https://healthpolicy.duke.edu/events/ninth-annual-sentinel-initiative-public-workshop

[6] https://www.sentinelinitiative.org/drugs/assessments/adhd-medications-and-heart-failure

Approach: Using the Sentinel distributed database, onset of cardiomyopathy or heart failure among initiators of selected ADHD medications (amphetamine products including lisdexamfetamine, methylphenidate, and atomoxetine) were assessed, both in terms of duration of use and age group (<22, 22-44, 45-64, and 65+ years). A modified Level-1 (L1) descriptive analysis was carried out with data covering ~16 years from 15 Sentinel data partners, and data from approximately two million patients.

Findings: The eldest group (aged 65 and older) were characterized by higher incidence rates of heart failure than younger age groups (>950 cases per 10,000 person years) for days 0-90 of medication use. Among <22 and 22-44 year old patients, rates of cardiomyopathy and heart failure were <50 per 10,000 person years, without clear trends by duration of use.

Implications: In younger patients, the rate of cardiomyopathy and heart failure did not increase over 3 years of ADHD medication use. In older age groups, lower heart failure rates later in treatment could reflect depletion of susceptibles, if patients at risk of developing heart failure with ADHD medication do so early. Labels for all three medication types caution against use in patients with cardiovascular disease.

Prospective Surveillance of Acute Myocardial Infarction (AMI) Events in New Users of Saxagliptin[7]

Context: Saxagliptin, an oral antihyperglycemic agent approved with a PMR for cardiovascular (CV) outcomes trial, was chosen to be the first new molecular entity (NME) to be prospectively monitored in the Mini-Sentinel pilot. Mini-Sentinel results would complement the CV outcomes trial results, and prospective surveillance would help identify safety issues more quickly than conventional observational studies.

Objective: To obtain Sentinel interim safety data on saxagliptin in parallel to clinical trials.

Approach: Protocol-based prospective sequential analysis using new user cohort design was leveraged in order to assess four head-to-head comparisons (sitagliptin, pioglitazone, second-generation sulfonylureas, and long-acting insulin products).

Findings: No evidence was found to suggest a higher risk of acute myocardial infarction (AMI) in saxagliptin users compared to users of comparison drugs.

Implications: The surveillance activity demonstrates Sentinel's ability to provide reassurance data across a panel of marketed products with comparable hazard ratios for AMI versus the PMR clinical trial data. Limitations related to the observational nature of the work were noted, however, positively, the results included gathering nearly 10 times as many saxagliptin user data points, and with head-to-head comparisons to other drugs, rather than controlling versus placebo alone. Additionally, Sentinel results were available before the publication of the randomized control trial results. This prospective surveillance Mini-Sentinel pilot could serve as a model for future prospective surveillance studies at CDER.

[7] https://www.sentinelinitiative.org/communications/publications/risk-hospitalized-heart-failure-among-new-users-saxagliptin-sitagliptin

Risk of seizures associated with ranolazine[8]

Context: Ranolazine is an oral drug prescribed for angina, with possible pharmacological activity related to its effects in the cardiac, central and peripheral nervous systems. Safety signals associated with increased seizures associated with ranolazine were first identified during pre-clinical trials, and language regarding the risk was included in its labeling at its approval. The results of a routine pharmacovigilance surveillance study resulted in the safety labeling change. Continued pharmacovigilance surveillance and case reports of seizures prompted signal assessment.

Objective: To investigate whether ranolazine use is associated with an increased risk of seizures.

Approach: A self-controlled comparator was chosen because ranolazine is often prescribed to patients for whom beta blockers, calcium channel blockers, and nitrates are not effective or tolerated. Due to the nature of this design choice, an L2 Sentinel modular program was utilized. Therefore, comparing ranolazine users to other drug users would not have been appropriate, therefore, a self-controlled risk interval (SCRI) design was employed which compared exposed patients across two different time periods.

Findings: Seizure rate within 10 days (risk interval) of ranolazine initiation is rare and not higher than in days 11-30 (non-risk interval). Older patients, users with prior exposure to anti-epileptic drug (AEDs), and those with renal impairment had somewhat higher seizure rates.

Implications: Seizure signals were originally identified in FDA's Adverse Events Reporting system (FAERS) data, but Sentinel allowed for refinement of the signal, quantification of the variable risk among different subsets of ranolazine users and identification of populations requiring further evaluation (AED users, renal impairment patients, and older patients). This is an example of leveraging the modular query functionality of Sentinel in a capacity that begins to approximate the approach followed during more resource and time-intensive protocol based assessments.

Benefit-risk assessment of nuclei acid test against transfusion transmission of Zika virus[9]

Context: As of early 2017, local transmission of Zika had been confirmed in nearly 60 countries and territories, with over 35,000 laboratory confirmed cases in Puerto Rico alone. Zika infection is associated with a risk of microcephaly during pregnancy, and there is a risk of transfusion transmission through blood. Blood collection in Puerto Rico was temporarily suspended during the peak of the Zika virus outbreak. At this time, FDA assessed whether a nucleic acid test (NAT) of blood for Zika virus (under an Investigational

[8] https://healthpolicy.duke.edu/sites/default/files/atoms/files/slides_2_2_17_sentinel_web.pdf

[9] https://healthpolicy.duke.edu/sites/default/files/atoms/files/slides_2_2_17_sentinel_web.pdf

New Drug application (IND)) could be an appropriate risk management measure. Blood collection resumed with NAT testing on April 3, 2016.

Objective: To determine the baseline risk of transfusion transmitted Zika virus for pregnant women in Puerto Rico and the risk reduction associated to NAT for Zika virus in this population.

Approach: SOC and FDA prioritized this data request as a rapid query, which was completed with a turnaround of approximately five days. This was made possible by the extraordinary efforts of the Sentinel data partners involved. The Sentinel query provided a critical input – unavailable from any other source – for the risk-benefit assessment model: transfused units for pregnant women in U.S. (not Puerto Rico-specific). The output of this model was a predictive cumulative risk summary table based on over 33,000 total reported clinical cases from April 3, 2016 to November 17, 2016.

Findings: The model's output included baseline risk and risk reduction. It showed that NAT for Zika virus reduced risk of transfusion transmission of Zika virus for pregnant women by ~86%, or 0.7 total cases of Zika with blood testing versus 5.4 total cases without blood testing for the period examined.

Implications: In this example, Sentinel data demonstrated the value of real-world use of observational data for regulatory decision making, especially under time-constrained conditions, where no other comparable data sources existed. Potential future applications of the CBER blood transfusion transmission benefit-risk assessment model include: (i) further consideration of donor policies intended to prevent transfusion transmitted human immunodeficiency virus (HIV); and (ii) monitoring safety of vaccines administered in pregnancy.

Section 4 – Assessment of Maturity According to the Sentinel Maturity Model (SMM)

4.1 Overview

Overall, there has been consistent and substantial progress across all six elements of the Sentinel Maturity Model (SMM) since the interim assessment. As the prior section illustrates, Sentinel continues to evolve a robust set of analytical capabilities, while benefiting from strengthened governance, broader awareness within FDA and important operational enhancements that support day-to-day activity. Particularly notable progress has been made in the SMM elements of analytical tools and technologies and methods, reflecting a dedicated commitment by FDA and SOC leadership to build capabilities and approaches that will facilitate a more scalable system and enhance safety surveillance capabilities. Data from an internal FDA survey further supports the overarching conclusion that Sentinel is increasingly maturing and that there has been substantial progress across all six elements.

Nonetheless, this assessment concludes that while Sentinel is clearly mature enough to inform a range of regulatory decisions, it is not yet "fully mature" on any particular dimension of the Sentinel Maturity Model. That conclusion is not unexpected for a program of the scale and ambition of Sentinel. Rather, it reflects the need to continuously improve a vital safety surveillance capability and continue making targeted enhancements to capture Sentinel's full value.

What follows is a detailed assessment of the Sentinel across all six dimensions of the maturity model. Each sub-section contains: (1) an outline of the criteria used to assess maturity; (2) the assessed score (including the summary rationale supporting the score); and (3) an overview of the core themes related to that element that emanated from the assessment. Where appropriate and possible, specific reference has been made to scores from the interim assessment, though direct comparison is not always relevant or possible.

4.2 Strategy and Value

4.2.1 Criteria for element assessment

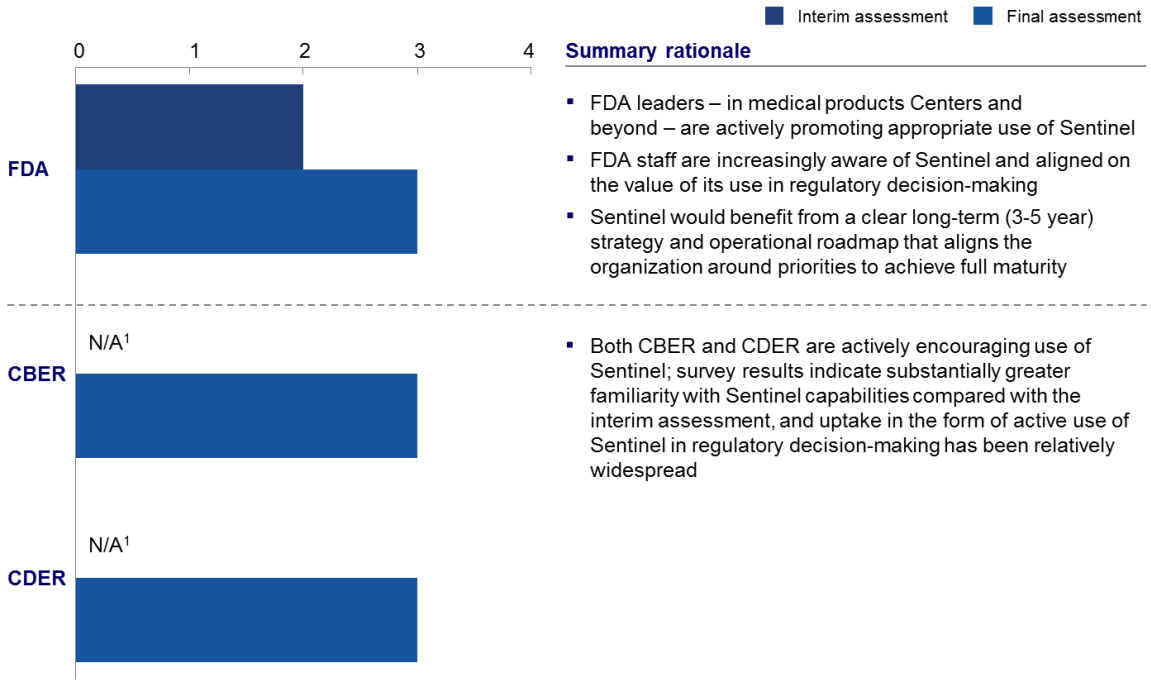
The criteria used to assess the maturity for this element include:

- Annual and long-term (e.g., 3-5 year) strategy is clearly articulated and broadly understood within FDA and by core Sentinel partners.
- Sentinel executive leadership is aligned on the portfolio of priorities to deliver the strategy.
- Leaders regularly engage with and highlight Sentinel capabilities and results to promote the use of Sentinel in safety reviews.

- All or most relevant FDA staff agree that they understand Sentinel capabilities and when to draw on them in the course of regulatory work.
- All or most end-users agree that Sentinel outputs are useful and valid and understand the ways to interpret them.

4.2.2 Assessment according to the maturity model

Exhibit 4-1: Strategy and value score and justification



1 Element was not scored individually for CBER or CDER in the interim assessment

4.2.3 Key themes related to strategy and value

FDA leaders have taken an active role in promoting Sentinel use

At the highest levels of governance (specifically FDA's Sentinel Governance Board), FDA leadership has established a short-term vision for where to take Sentinel, focusing on increasing uptake within the Agency, disseminating priority-use cases, embedding Sentinel into pre-market safety reviews, and exploring avenues for cutting costs and growing scale. The Sentinel core team in CBER regularly shares findings of Sentinel-driven assessments in the context of their Research Impact Series, Office Directors meeting and engagement activities with products Offices. Within CDER, significant efforts have been made to create opportunities for staff to gain exposure to Sentinel use cases and embed Sentinel into a number of Office-level safety and review meetings. Sentinel executive sponsors and program staff continue to organize an Annual Sentinel Public Workshop in conjunction with the Duke-Robert J. Margolis Center for Health Policy. This workshop is the annual event at which Sentinel achievements are presented and discussed, and broad priorities are

communicated both to FDA employees and externally to the health care and scientific communities. Finally, the formal inclusion of Sentinel-related goals in the proposed PDUFA VI commitments further underscores FDA leadership's commitment to Sentinel.

FDA staff are increasingly aligned on the value of using Sentinel in day-to-day work

In a 2015 internal FDA survey, just 36% of respondents self-identified as "current" users, while in 2017, that proportion rose to 65%. The respondents also reported being much more familiar with Sentinel's tools and capabilities than in 2015, with the proportion of respondents who considered themselves "very familiar" with Sentinel increasing from 37% to 77% for "current users" and from 12% to 57% for "potential users."

Furthermore, while there remains an underlying reluctance on the value of observational data in lieu of randomized control trials in both CBER and CDER, the survey also revealed that resistance to the use of observational data in regulatory decision-making had diminished over time. A hesitancy to fully utilize observation data may inhibit the acceptance and use of Sentinel across a broader set of potential users. Fewer than 25% of survey respondents indicated that the challenges of observational data posed a barrier to utilizing Sentinel. Interviews with a wide range of Agency stakeholders – including epidemiology and product Office leadership – further point to broad support of Sentinel's utility as part of the broader set of tools to interrogate potential safety concerns.

The prioritization of innovative use cases has helped to define Sentinel capabilities

An innovative set of use cases has been prioritized in CBER that focus on the most pressing product area issues related to vaccines (PRISM, TreeScan) and blood products (BloodSCAN). Within CDER, Active Risk Identification and Analysis (ARIA) has been defined as the core CDER safety use case, and has become embedded into regulatory decision-making in OSE, with significant uptake in OND. Articulation of the overall Sentinel program objectives has been further defined, as well as the differences between developmental and established capabilities.

There remains a need for a defined long-term strategy and operational roadmap that ensures program sustainability

A number of Sentinel leaders in different settings have articulated a set of forward-looking priorities for Sentinel. These priorities were showcased at both the Annual Sentinel Initiative Public Workshop in February 2017, and through proposed commitments made in the PDUFA VI goals letter.[10] While these sets of priorities are important guideposts for the future, there are nonetheless aspects of the strategy that are missing. Examples of what the Sentinel strategy should aim to address include: (i) defining in actionable terms the specific steps required to ensure delivery of the PDUFA VI commitments, and the relative priority among these should funding become constrained; (ii) although it is beyond the remit of this report, there is a set of non-safety related aspects of Sentinel capability for

[10] https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf Section K, "Enhancement and modernization of the FDA drug safety system" (pages 34-36).

which FDA should develop a clear perspective. These aspects will also have implications for the long-term sustainability of the program. A non-exhaustive list of these might include: alternative use cases for Sentinel (e.g., efficacy); connection to other evidence generation platforms (e.g., the National Evaluation System for health Technology (NEST)); and breadth of access for industry, academic and other stakeholders for Sentinel capabilities and infrastructure.

In addition, Sentinel continues to face an imperative to balance the dual priorities of entering "production mode" and focusing on operational efficiency while also continuing to act as a research and innovation center. Though many interviewees at both the FDA and the SOC agreed that the twin aims were not mutually exclusive, they nonetheless explained that FDA leadership needs to be more explicit about how its organizational and operational decisions will affect both objectives – and then translate those decisions into a clear set of strategic priorities for Sentinel moving forward.

4.3 Analytical tools and technology

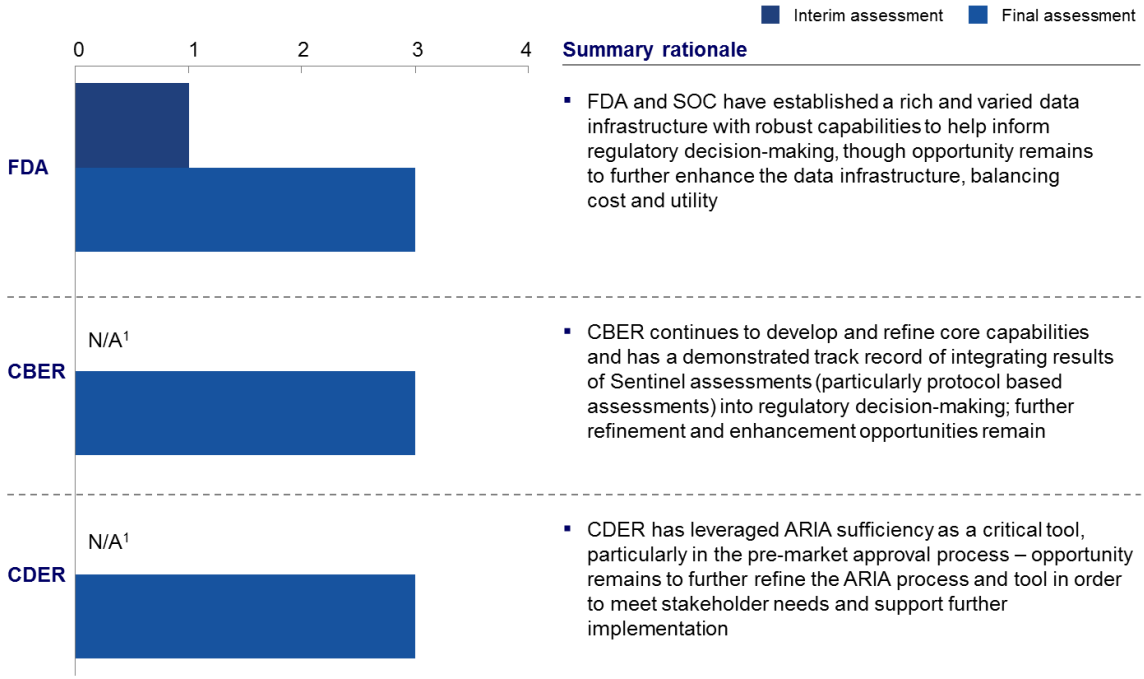
4.3.1 Criteria for fully mature element

The criteria used to assess the maturity for this element include:

- All or most Sentinel outputs are provided to regulatory decision-makers (e.g., review teams) in a timely fashion.
- Data returned from Sentinel queries is factored into pre- and post-market regulatory decisions by review teams.
- Sentinel captures a robust data set capable of answering critical regulatory questions.
- FDA maintains a list of the most effective and relevant data partners and data sources.
- Sentinel is continuously expanding the suite of analytical tools available.
- Sentinel partners are capable of routine reporting around Sentinel activities and providing key performance measures to FDA.

4.3.2 Assessment according to the maturity model

Exhibit 4-2: Analytical tools and technology score and justification



1 Element was not scored individually for CBER or CDER in the interim assessment

4.3.3 Key themes

The Sentinel data infrastructure is extensive and growing in sophistication, incorporating a rich mix of claims data from data partners

The Sentinel data infrastructure has grown in size and now incorporates claims data from most major private payers in the United States. In total, Sentinel has exceeded the earliest expectations around the size of the common data model, and now includes 223 million unique IDs and 7.2 billion encounters. In addition, the ongoing incorporation of data from Hospital Corporation of America (HCA) as well as Medicare represents a significant step forward as Sentinel seeks to further incorporate inpatient electronic health record information (for chart review) in the case of HCA and further enable analysis of specific populations (e.g., the elderly in the case of CMS) into the data set. Expansion of data infrastructure to include a broad set of electronic health records alone is not sufficient, however, as these need to connect to claims data to achieve greater utility. Thus, operationalization of clinical data represents an opportunity to further build out a rich Sentinel data infrastructure, and permit increasingly more robust analyses in the future.

However, the data infrastructure still has opportunities to improve

Despite advancements in data partnerships, there are still limitations with Sentinel data – some of which are more addressable than others in a resource-constrained environment. Sentinel is based on claims data, which is inherently limited in that it only captures

reimbursed health care encounters, procedures, and medications. Thus, Sentinel cannot observe visits to free health care clinics, drug samples given in physician's offices, use of low-cost generic mediations that does not incur an insurance co-payment, or over-the-counter medications. Additionally, many FDA staff explain that data refresh rates take an extended period of time (e.g., quarterly) limiting the utility of the data in contexts where more frequent sequential analysis might be helpful. In other cases, the challenge is more related to sample size and pace of data accrual limiting statistical analysis. In some senses, these challenges are "structural" in nature and not addressable by FDA alone, given the highly fragmented nature of how health care data is captured in the U.S. health care system, but they nonetheless deserve mention. Finally, in many therapeutic areas, Sentinel data (like observational claims data more broadly) suffers from a constrained list of validated health outcomes, limiting the number of medical conditions where Sentinel can be useful.

There are other data infrastructure opportunities that were not deeply explored, but merit further examination as a long-term strategy for the program is further defined (e.g., developing enhanced data manipulation and automated processing capabilities using machine learning and natural language processing for medical chart review). FDA is working with data partners and SOC to expand the number of validated health outcomes utilizing Sentinel data, but there is a persistent question of value for investment that FDA must balance.

Finally, there are discrete opportunities to further enhance Sentinel data in targeted – and potentially cost-effective – ways. A few examples include forming linkages between Sentinel data and existing patient registries, completing the integration of CMS and HCA data (which requires linkage to claims data for maximum utility), and integration of ICD-10 coding for health outcomes of interest. Having said all that precedes, it is noteworthy that 75% of CBER respondents and 71% of CDER respondents noted that the limited scope of questions Sentinel can answer inhibits wider use of the system within FDA. This was the single biggest perceived barrier to broader adoption and is in many ways among the most vexing to cost-effectively address.

CBER leverages a range of tools to inform regulatory decision-making, and the ongoing development of purpose-built tools for CBER-regulated products is significant

Within CBER, Sentinel has often been used in a tailored fashion to answer specific safety-related questions that arise in the course of both pre- and post-market safety reviews. The focus of the Center's Sentinel utilization has consisted primarily of protocol-based assessments, and the majority of resources dedicated to Sentinel to date have focused on development of new tools and capabilities optimally suited for the unique characteristics of products that are regulated by CBER (e.g., BloodSCAN for blood products, PRISM for vaccines). In this regard, the predominant mode for Sentinel maturity differs from CDER, as an ARIA-like rapid query approach is often unsuitable given the limitations of claims data (e.g., lack of specific blood product identifier data). The PRISM system, utilized for vaccine safety, is a more established tool, and this is driven by greater availability of relevant product and outcomes data within Sentinel. CBER continues to invest time and resources in the development of a number of new promising tools, and these will no doubt

lead to enhanced public health impact as additional data gaps (e.g., integration of electronic health records) are addressed and the tools continue to mature.

Sentinel data is being incorporated consistently into CDER regulatory decisions, but there is further opportunity to fully implement

Within CDER, progress has been made to incorporate ARIA into the formal process of pre-market safety review, with members of OSE consistently incorporating consideration of ARIA sufficiency in pre-market safety reviews. The process of formally incorporating ARIA into this process will be completed following the approval of a new MAPP, and incorporation in the 21st Century Desk Reference Guide.

The foregoing text describes a consistent process and framework for evaluating Sentinel's utility in evaluating safety signals via ARIA tools. Importantly, ARIA is only relevant in those cases when a separate post-marketing requirement (PMR) is under consideration, but even so, implementation and adoption of the defined process is still underway and somewhat short of what is considered full maturity. Implementation progress is impeded by a variety of challenges explored throughout this assessment, but the broader point is that the process of implementation will take time and will require refinement to ensure it adequately addresses stakeholder needs across the relevant Offices and Divisions using Sentinel for safety surveillance.

Opportunity to further enhance routine reporting around Sentinel activities and providing key performance measures to FDA

One area of potential opportunity lies in the establishment of a robust operational management infrastructure at the SOC. The SOC has made strides in developing an internally-focused workflow tracking tool, with plans to release access to Sentinel users. This would provide some additional transparency for work that is in queue, or in process, as well as serving as a repository for data elements, documentation and reports linked to submitted projects. However, providing full transparency and oversight of more complex projects (e.g., protocol-based assessments and infrastructure projects) may be more challenging to achieve in the near term without revisiting the way project milestones are defined, and the ways in which contracts for these additional projects are structured.

Capacity devoted to new infrastructure and tools development is constrained

At present, there is finite capacity at SOC to devote toward the development of new infrastructure and tools. Current contract terms with SOC stipulate a total of six "slots" – four are assigned to infrastructure development projects (e.g., adding data elements to HCA inpatient data to improve utility, developing rapid surveillance for influenza vaccines), and two are reserved for major tool enhancements (e.g., standardizing propensity score matching output to increase tool efficiency). It should be noted that other more minor tool enhancements are continuously introduced, but this is not considered part of the core capacity dedicated to the major types of aforementioned projects. Overall, the capacity constraint is a challenge for FDA and Sentinel more broadly as many of these projects can have unclear or extended durations, while the list of potential enhancements grows. More resources (at FDA or SOC) would help, however, they would not solve the problem on

their own, as data partners also have finite capacity to support these large scale projects and there is the persistent challenge of effectively maintaining a production system while simultaneously introducing enhancements.

4.4 Methods

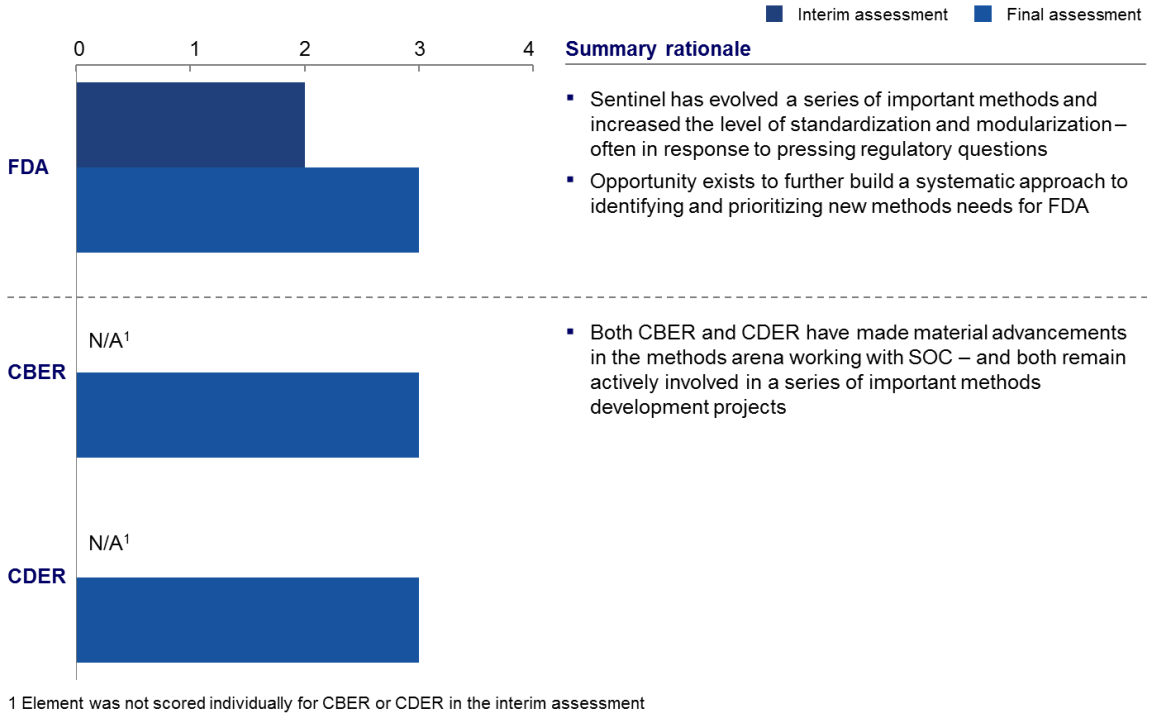
4.4.1 Criteria for element assessment

The criteria used to assess the maturity for this element include:

- Methods of analysis for normal questions/queries are standardized and the methods are well understood by end-users (e.g., FDA epidemiologists and medical reviewers).
- Established methods are refined and improved on a regular basis as evidenced by the introduction of new tools based on methodological innovations.
- New methods that assist FDA staff are developed regularly in response to specific capability needs that will address emerging public health questions and/or new sources of data.
- FDA, SOC, and data partner staff and faculty enjoy a high degree of scientific collaboration in developing new methods.

4.4.2 Assessment according to the maturity model

Exhibit 4-3: Methods score and justification



1 Element was not scored individually for CBER or CDER in the interim assessment

4.4.3 Key themes

Sentinel has effectively transitioned to more standardized and modular approaches while also introducing a substantial set of new and sophisticated methods to answer a broader set of public health questions

Robust methods have been indispensable in light of the limitations associated with observational data. Historically, the challenge has been to take methods that work well in a single database setting and adapt them to the distributed research network setting that defines Sentinel. In recent years, the FDA and its partners have made significant strides in building more standardized and reproducible methods (packaged in what are called "modular programs") that address challenges inherent in the data and work well in the distributed network environment. At the same time, a large number of new methods have been introduced. Newer methods development has enhanced the utility of Sentinel analysis results well beyond the original applications. For example, comparative L2 queries leverage adjusted relative rates or hazard ratios comparing outcomes among two cohorts. Sequential adjusted analyses with sophisticated confounding control are also being tested and refined. These methods will eventually be added to the armamentarium of modular programs available. In 2016 alone, there were more than eight major methods development projects underway. Highlights include disease risk score exploratory methods, optimal propensity score matching strategies for subgroup analyses, evaluating performance of analytic modules using simulation, and quantitative bias analysis. The overall activity level is noteworthy, though the aforementioned challenge of capacity for the system to integrate new methods at a rapid pace persists.

Opportunity exists to further build a culture of continuous evolution for Sentinel methods by systematically identifying and prioritizing new methods needs

Not surprisingly, much of the new methods development for Sentinel has been done in response to pressing public health needs for which Sentinel might plausibly be applied. That process, coupled with some strategic attempts to prioritize core methods that might address the bulk of safety question that arose, produced an important armamentarium of methods and analytical approaches that now form the basis for today's Sentinel studies. That said, there is nonetheless an opportunity to further establish and systematize the approach FDA takes to identifying and prioritizing new methods that will enable FDA to keep pace with advances in the science of fields they regulate. Embracing this opportunity would result in building the culture of continuous evolution deliberately – and engineering a process that proactively evaluates the landscape of needs and defines methods priorities (ideally agreed through the existing formal governance bodies). This is happening to some extent today; one example of this more proactive posture is embodied in the "Big Sim" project (evaluating performance of analytic modules using simulation). Insights generated from this project will then allow for broader prioritization of future methods development, and will serve as a valuable input into the strategic planning process to direct future investment and project prioritization. Another more proactive approach to methods development is captured in the "ARIA plus" concept wherein routine additions to the base

ARIA tools are tracked, and those that are most frequently used are eventually moved into production for more routine use.

The remaining opportunity revolves around conducting the process of new methods identification and prioritization more systematically and leveraging governance to get the right degree of input and buy-in. CDER has established a "sufficiency working group" comprised of FDA and SOC staff; they are tasked with structured analysis of patterns in ARIA insufficiency memos to isolate solutions that cost-effectively reduce ARIA insufficiency. CBER is also undertaking a systematic series of efforts to deliver its development priorities, in some cases focused on enhancements to existing Sentinel infrastructure, and in others, through non-Sentinel based projects to expand the armamentarium of surveillance-based tools available at their disposal.

4.5 Talent and organization

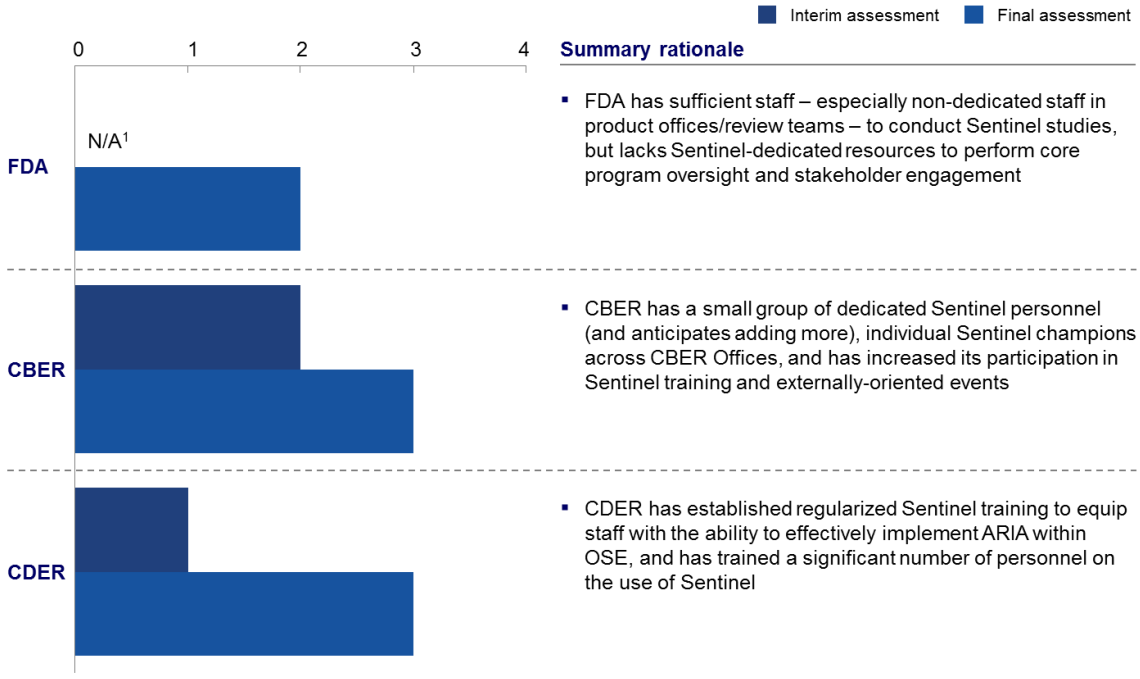
4.5.1 Criteria for element assessment

The criteria used to assess the maturity for this element include:

- Training on fundamental and evolving Sentinel capabilities is regularly provided to FDA staff and attended by a significant percentage of relevant staff.
- The FDA and SOC have sufficient dedicated and non-dedicated resources to respond to all or most of the demand for Sentinel services.
- Sentinel operations are prepared to scale to meet all or most of projected demand growth in the near future.

4.5.2 Assessment according to the maturity model

Exhibit 4-4: Talent and organization score and justification



1 Element was not scored individually for FDA during the interim assessment

4.5.3 Key themes

Staffing levels to support Sentinel at FDA are adequate to support baseline operations, but needs exist for Sentinel-dedicated resources to further enhance program oversight and expansion

[As of the date of this report] or [Currently], there are a modest number of dedicated staff in the core Sentinel teams in both CBER and CDER, tasked with properly administering the core functions of the Sentinel program (e.g., assisting teams with query requests, facilitating collaboration with the SOC). CBER and CDER have independently defined a vision for their future organizational models, consisting of core Sentinel teams linked to a broader set of non-dedicated resources embedded in OBE in CBER and OSE in CDER. The capacity associated with "non-dedicated" staff (e.g., review team epidemiologists and medical officers) is particularly important because it uses embedded capacity within the broader FDA organization that is familiar with Sentinel and able to help define and conduct Sentinel analyses (often with assistance from CBER and CDER core teams). However, it is worth noting that the overall dedicated Sentinel headcount in CDER has actually decreased since the completion of the interim assessment. Following transfer of overall program ownership from OMP during the Mini-Sentinel pilot, OSE did not receive additional full-time equivalent (FTE) resources. Colleague capacity in OSE was primarily accomplished through the greater emphasis on shifting day-to-day Sentinel work to CDER end users (i.e., "non-dedicated" staff), and repurposing of existing RSS colleagues.

In the period following the interim assessment, Sentinel-dedicated staff in CBER assumed a greater project support function, which at times limited their ability to focus on broader management and oversight responsibilities for the program. The effect at times caused strain on CBER's dedicated Sentinel resources, but has been partially offset by the recent addition of new integral CBER Sentinel core team staff. In terms of "non-dedicated" staff, there is an opportunity to expand this resource in the future by increasing the frequency of training and making deliberate decisions around workload that enable non-dedicated staff to manage additional projects like Sentinel. CBER has made further requests to add dedicated personnel to support the program going forward in anticipation of growth in utilization and capacity required to deliver on Center-level priorities.

In addition, though, there are currently a small number of formally-dedicated, FDA-wide Sentinel staff (all currently housed in OSE). The breadth of the Sentinel program has restricted routine fulfillment of program oversight activity – in particular operational oversight (i.e., capacity management) and reliable forecasting of demand. Constrained resourcing has also frustrated attempts to define a longer-term strategy for Sentinel. In short, the breadth of activity associated with managing and overseeing a large-scale production program like Sentinel is considerable, and making targeted accommodations in staffing to ensure adequate resourcing to support strategy and operations oversight across FDA will be an important enabler for Sentinel as it grows.

Training has become a core part of increasing Sentinel uptake across the FDA

A number of formal and informal training initiatives were launched across the FDA to help increase exposure of review and epidemiology staff to core Sentinel use cases and capabilities. These events included the Annual Public Workshop hosted by Duke-Margolis, regular internal training sessions led by the SOC, a PRISM public workshop hosted by CBER (Dec 2016, focused on vaccine applications), and routine monthly safety assessments/informal trainings (attended by Sentinel project team members and Core staff across the Centers).

In general, training has been effective, though there is a consistent desire for more training given the frequent evolution of Sentinel capabilities. Less than 30% of survey respondents in both CBER and CDER cited "insufficient training" as a barrier to greater Sentinel usage, though significant percentages (70%+) noted that training focused on particular topics (e.g., knowing when Sentinel can inform a regulatory question, translating a scientific question into a Sentinel query) would be helpful going forward.

FDA staff remain concerned about organizational support levels affecting the FDA's ability to manage Sentinel as demand grows

Despite progress in both overall staffing support and levels of training, FDA staff are concerned about accessing sufficient technical support – especially within the FDA, though staff turnover at SOC was occasionally cited as a challenge as well. These concerns relate both to maintaining current operational levels and a potential future where Sentinel demand grows. Both SOC and FDA staff noted that the greatest limitation to scaling Sentinel beyond current capacity is in securing funding for additional staffing and identifying

qualified and capable staff to fulfill relatively specialized roles that are central to supporting Sentinel moving forward.

4.6 Governance

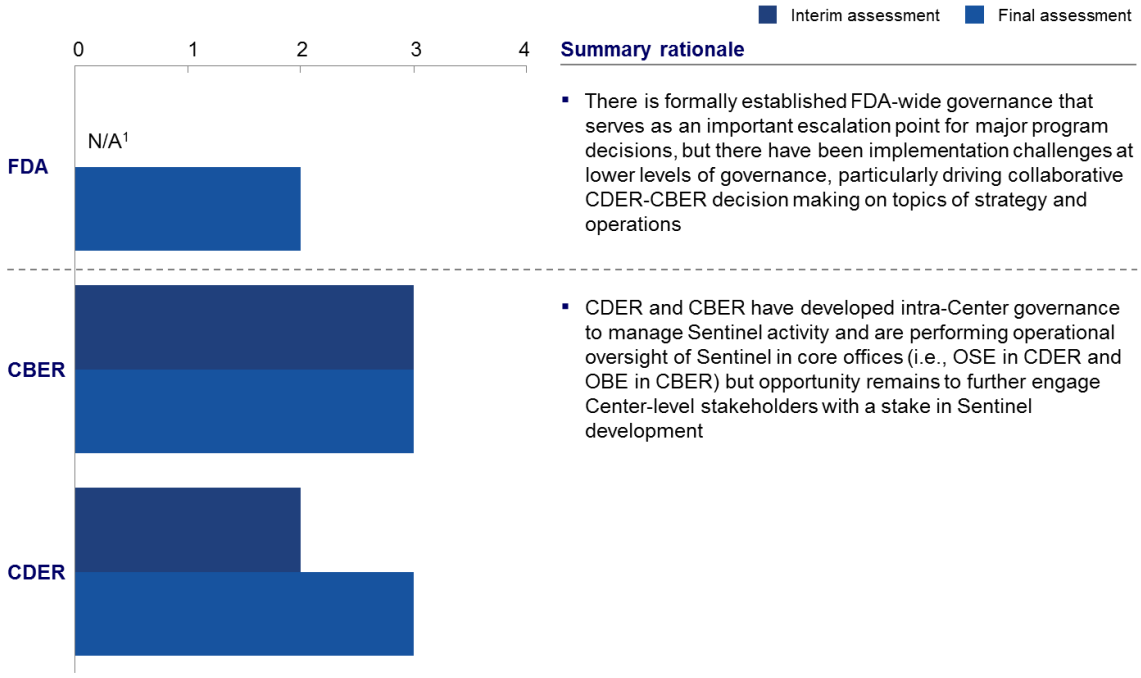
4.6.1 Criteria for element assessment

The criteria used to assess the maturity for this element include:

- Strong governance infrastructure characterized by defined roles and responsibilities and decision-making authority, routinely overseeing program direction and strategy
- Routine pattern of rigorous operational oversight that leverages a wide variety of data-driven support from across the Sentinel network
- Privacy mechanisms between the coordinating center and data partners are firmly established and followed

4.6.2 Assessment according to the maturity model

Exhibit 4-5: Governance score and justification



1 Element was not scored individually for FDA during the interim assessment

4.6.3 Key themes

The FDA-wide governance model is formally established, and is well positioned to achieve even greater impact

Following the completion of the interim assessment, the FDA implemented an agency-wide governance model intended to increase operational transparency and create a space for resolving both operational and strategic issues. This resulted in the creation of the Sentinel Executive Committee and a Sentinel Governance Board (both comprised of members from all medical product Centers and the Office of Commissioner) that have the mandate to provide these core governance functions (*detailed in Section 3 of the report*).

Though the establishment of these formal governance venues represents a positive step for the FDA, from an operational perspective, there are opportunities to get greater value from these structures. First, the Sentinel Executive Committee is the body tasked with articulating strategic priorities and plans for Sentinel (with ultimate approval and endorsement from the Governance Board). While the proposed PDUFA VI commitments represent a high-level set of strategic priorities for Sentinel looking ahead, the body has the formal mandate to articulate the long-term strategy in some tactical and operational detail, yet attempts to start that work have not succeeded to date. Second, there are significant differences in management philosophies among representatives on the FDA-wide bodies in terms of managing data partners and the SOC. For instance, some members view SOC strictly as "vendors to be managed" while others approach them as thought partners in the journey to build Sentinel. While differences in outlook are not in themselves problematic, when they stand in the way of routine communication and collaboration to jointly manage the program – as they occasionally do today – they merit further investigation and challenge from senior leadership.

Finally, given that the Sentinel Executive Committee and Governance Board are meant oversee Sentinel operations, it is critical that they have appropriate input to make effective operational decisions. At present, the bodies have ad-hoc (though increasingly routine) access to certain operational metrics (e.g., current utilization), but would benefit from a broader set of measures of operational success, including measures of value (e.g., how useful were Sentinel outputs in making regulatory decisions) and broader public health impact.

Within both CBER and CDER, there have been well-functioning systems of decision-making with clearly delineated roles and responsibilities

Governance within both CBER and CDER has been quite effective overall, with clear articulation of roles and responsibilities and procedures established within each Center. Sentinel team leads in both Centers have established clear lines of communication internally, and outlined processes for convening meetings, providing clear mechanisms for inquiring about potential projects and managing individual project teams. In addition, both Offices have worked to establish a regular meeting cadence with their constituent users, within their respective immediate Offices, and across CBER's medical products Offices, and CDER's Office of New Drugs where additional Sentinel queries may be initially

surfaced. Within both Centers, Sentinel users are able to clearly identify members of the core teams, and feel empowered to approach these team members directly with questions.

Privacy protections instituted between the coordinating center and data partners have been followed consistently

Sentinel has also taken several steps to both ensure maximum privacy protections for patient data and reduce the amount of patient-level data required to conduct analysis. At its core, Sentinel's approach to data privacy is facilitated through its distributed data model. When a package is created for a query, it is sent through a distributed data query tool (PopMedNet) that leverages a Federal Information Security Management Act (FISMA)-compliant portal in which the software and environment are audited annually. Data partners keep data and execute code locally, returning only minimum necessary information to the SOC.

In addition, as Sentinel has increased the sophistication of its queries that rely on propensity score matching (e.g., L2, and L3), a need for de-identified patient-level data (as opposed to aggregate summary data) has emerged. In order to reduce the amount of patient-level data that is required, Sentinel researchers can do propensity score-matched analysis with only aggregate data, reflecting organizational commitment to limit the use of patient-level data as much as possible.

4.7 Process

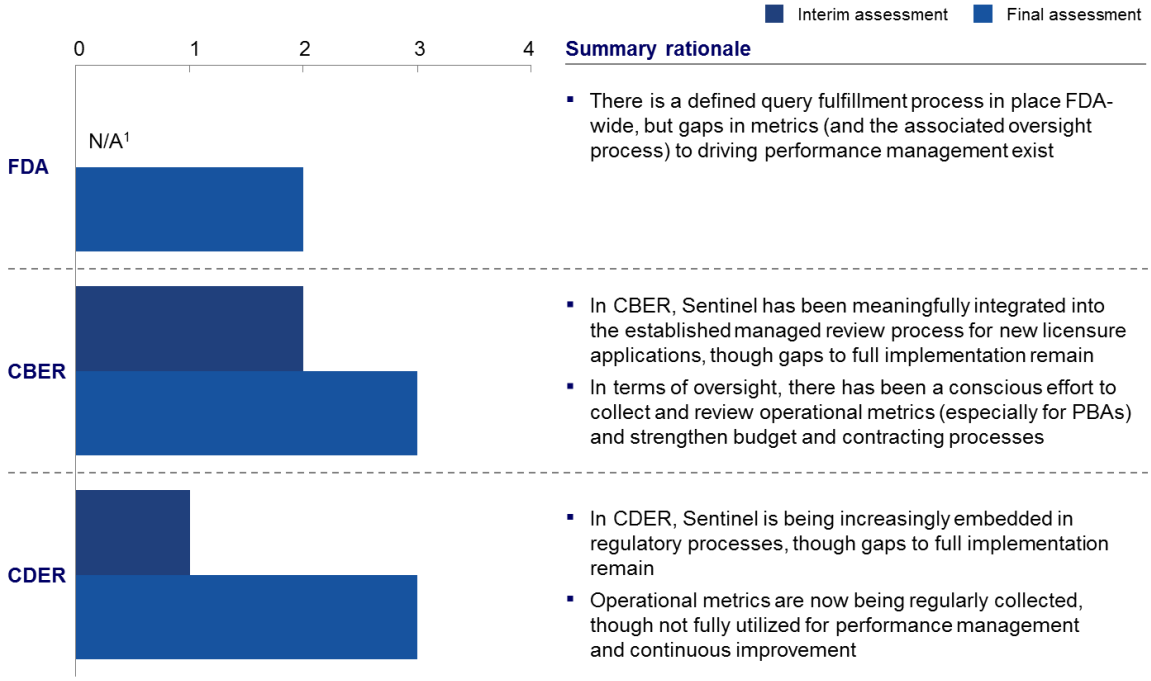
4.7.1 Criteria for element assessment

The criteria used to assess the maturity for this element include:

- Clear processes defined and formalized at FDA around question submission and communication with SOC
- Efficient SOC operation with on-time delivery of all or most requests
- Existence of formalized SOPPs, MAPPs, and reference guides that explicitly integrate consideration of Sentinel into core operations
- Broad-based adherence to the formally documented processes integrating Sentinel into pre- and post-market safety review
- Consistent and frequent utilization of operational metrics to make improvements and revisions to Sentinel operations across Sentinel

4.7.2 Assessment according to the maturity model

Exhibit 4-6: Process score and justification



1 Element was not scored individually for FDA during the interim assessment

4.7.3 Key themes

Both CBER and CDER have made progress with Sentinel process integration, though broader implementation is still possible

In CBER, Sentinel has been used with variability when safety issues arise due to the unique characteristics associated with the medical products being regulated, data availability, and appropriate tools capable of assessing these products. The structure of the OBE ensures that the Sentinel core team has a direct line of communication with the Office Director and Division Directors, and these leaders are fully engaged in safety issues that arise in relation to the Center's portfolio of products. Specifically, CBER's managed review process requires at least one OBE Division of Epidemiology Staff member be a formal member of the license application review team, and Sentinel Core Team members are included in review team discussions concerning any possible application of Sentinel to address a safety question. CBER has completed a draft SOPP describing the engagement of OBE staff and CBER Sentinel staff in the review process as well as an SOPP for the developing and submitting a query, in addition to a standard query form. As processes mature, additional SOPPs will be generated.

In CDER, the process of incorporating Sentinel formally into the pre-market safety review process has been largely successful through the use of ARIA sufficiency analysis. CDER has developed ARIA sufficiency criteria (i.e., can ARIA analysis obviate the need for a PMR or PMC) and standard operating procedures have been drafted for integrating ARIA

into the OSE review processes (e.g., post-market review manual of policies and procedures). Eventually, CDER plans to integrate Sentinel into the next version of the 21st Century Reference Guide, which is likely to be finalized following PDUFA VI authorization. As previously mentioned, however, CDER is still undergoing a broader change management process that involves further refining the ARIA process to support continued implementation across the Center.

There is a well-defined set of documentation describing and supporting Sentinel operations in both CBER and CDER

In both CBER and CDER, there are standardized approaches for submitting a query for a particular question. In both Centers, review teams work with the Sentinel core team to develop a concept brief that is submitted and ultimately reviewed by staff at SOC. These memos allow for determination of whether an analysis will be feasible, as well as potential timelines associated with the request. This only begins the process of study design, in which CBER and CDER review colleagues' work, either directly or in concert with their respective Sentinel Core Team representatives, to specify the parameters of study design. This helps to ensure that, in using Sentinel, colleagues are working from the best available data and utilizing the most appropriate analytical approach.

In CBER, process maps have been defined for Sentinel project surfacing, feasibility assessments, prioritization, execution, and overall project management. Embedding these processes in day-to-day workflows continues to make progress, however, this is done through informal mechanisms given the smaller user base and team structure for the Center. These processes serve as a template for the Sentinel core team and continue to be discussed with active Sentinel users within OBE. In addition, CBER has made tremendous progress in streamlining and optimizing its budgeting and contracting processes, resulting in a marked improvement in the financial management and transparency of spend for CBER Sentinel projects.

In CDER, as previously described in Section 3.3, much of the formal enabling documentation (e.g., MAPPs updates to the 21st Century Desk Reference Guide) is in draft form pending finalization in CDER, thus, finalization of this formal documentation is currently lagging the extent of process embedding in CDER today.

Across both Centers, numerous "best practices" have been recognized by core teams that have proven to enhance the perceived efficiency of individual working groups. For example, Sentinel project team meeting performance (between FDA staff and SOC) is improved when participation includes both the FDA and SOC project leads, subject matter experts (including relevant statisticians, epidemiologists and regulatory policy experts), Sentinel data partners and data experts. The utilization of pre-meetings has also proven an effective way to enhance active participation, and work toward the objective of empowering working groups to take greater accountability in decision making. Finally, issue identification, clarification, and resolution is enhanced by ongoing direct scientific communication between FDA and SOC project leads. Thus, both formal and informal mechanisms of transparency and communication are critical enablers to supporting efficient Sentinel operations.

Standard data describing operational performance is in the early stages of implementation, with further potential for performance management

To date, there are a limited number of operational metrics being collected and reviewed at the FDA and SOC. Metrics like total volume, average query fulfillment time, duration of time at key milestones of query processing, and relevance of query results to regulatory decisions are available within the system – and are increasingly available through dashboard-style outputs. An online query portal is also in the process of development that will improve the capture of the regulatory impact of ARIA analyses, safety issues that were deemed insufficient, and the developmental projects that were launched to improve ARIA sufficiency. Currently, there is still some ongoing discussion regarding how certain metrics should be calculated and reported, but the general direction is toward a more reliable set of operational metrics that are routinely available to FDA decision-makers. Given these outputs are still in their infancy, they are only beginning to affect day-to-day operational decisions and informing opportunities to improve the system. For example, a broader set of operational performance indicators (e.g., fully loaded cost-per-query and detailed project status tracking to defined milestones). In some instances, FDA Sentinel leaders have noted that the simple act of actively tracking and following trends in performance has resulted in greater timeliness and an improved understanding of how things are operating at SOC and data partners.

It is worth noting that CBER has recently invested in deepening oversight of their project portfolio by establishing performance metrics starting in 2016 and has taken steps to strengthen contract management (this is particularly important given CBER projects tend to cut across years and contract vehicles). CBER Sentinel users report that timeliness of projects has improved since the introduction of their monitoring approach and procedures – and broadly they report a greater degree of understanding of project status and resource deployment at SOC. At the same time, SOC colleagues also express a reciprocal desire for greater transparency and context around CBER-initiated projects in order to ensure they can collaborate most effectively to shape appropriate study designs and ensure timely project completion.

As discussed in a prior section, it is a challenge to measure the operational "success" or "value" of Sentinel as it continues to scale over time.

There is early evidence that the process for prioritizing queries based on public health impact is working well

At present, Sentinel users across FDA submit queries to Sentinel core teams at both CBER and CDER before requests are sent into the query for execution with SOC. A significant question at the time of the interim assessment revolved around how FDA would effectively triage and prioritize across requests emanating from CBER and CDER – some of which could be said to "compete" for limited query capacity. While capacity in some domains (e.g., infrastructure projects, protocol-based assessments) remains constrained, the process for redirecting capacity in a moment of urgency appears to work well. A salient recent

example used Sentinel to gather data inputs for a risk assessment of blood transfusion-transmitted Zika virus in Puerto Rico during an epidemic. As that urgent issue arose from within CBER, Sentinel teams across both Centers worked to pause a number of active CDER analyses to create capacity for the urgent query from CBER. The analysis was completed in roughly five days and provided CBER with much-needed insight to inform the response. Additionally, a high-priority query was initiated in mid-2017 under a similar timeframe to answer a question seeking to explore how frequently clinicians prescribe opioids concomitantly with select other medications. Building on this success and ensuring procedures to make prompt operational adjustments work well will be essential as Sentinel demand continues to rise.

Section 5 – Priorities Moving Forward for Sentinel

Building on the Sentinel interim assessment, this report concludes with a set of proposed steps for the FDA to consider in order to help Sentinel reach full maturity. This list is not meant to be comprehensive, but rather identifies a meaningful set of recommendations aligned to the six elements of the Sentinel Maturity Model, with the specific intent of helping Sentinel achieve the intent of the FDAAA mandate – namely to fully integrate Sentinel into regulatory decision-making for safety.

Strategy and value

Proposed steps to consider:

- *Clearly articulate a long-term strategy for Sentinel, building from the PDUFA VI commitments but including an operational roadmap and plan to deliver, in order to align stakeholders on the overall vision for Sentinel, the associated strategic priorities and the actions needed to achieve the vision*
- *Continue to expand the number of internal and external venues in which Sentinel-related insights and the results of key studies are shared and discussed (e.g., parallel demonstrations of ARIA in the postmarketing context when a formal PMR is pursued)*

Numerous interviews highlighted the fact that the FDA has not established a detailed 3- to 5-year vision for how to leverage Sentinel's capabilities and how to sustainably expand Sentinel operations. Articulation of a clear strategy – inclusive of both specific goals and the tactical plan to reach those goals – would help facilitate a series of important conversations at lower levels of the FDA around how to proceed with key operational decisions.

Many interviewees from within the FDA also noted that they found the Sentinel-related insights and use cases extremely powerful when presented in public or open forums (e.g., the annual public meeting, CBER Research Series) and expressed a desire to gain exposure to them on a more frequent basis. While there are a number of opportunities to access relevant information, continuing to present the real public health impact of Sentinel studies (within FDA and in public fora) would be a worthwhile step to consider. In particular, demonstrations on the effectiveness of the appropriate use of observational studies may enable even broader acceptance and use of Sentinel. For example, in post-market requirements involving randomized trials in CDER, parallel demonstrations in ARIA may help to further demonstrate Sentinel's value.

Analytical tools and technology

Proposed steps to consider:

- *Develop a specific list of existing data limitations or gaps, proactively prioritize them by level of importance (and cost/ feasibility to address), and develop an approach to address them*

- *Task external contract partner(s) to develop and formalize a suite of standard tools to address the specific requirements of CBER-regulated products*

Though the development of tools and capabilities since the interim assessment has been notable, challenges around the data infrastructure remain – and is the most frequently cited barrier to further use. Specific suggestions for improving this element include increasing the overall volume and utilization of electronic health record data, including appropriate data linkages to claims data, and increasing data refresh rates from Sentinel partners (e.g., to enable monitoring of new vaccine effectiveness during pandemics, monitor the safety and uptake of new medical products on the timescale of weeks rather than months). It is clear that there is confusion between what FDA end-users expect in terms of data infrastructure characteristics and what SOC and data partner staff believe is feasible or cost-effective to address. In addition, the tools needed to address CBER regulatory needs have yet to achieve sufficient scale and sophistication. Investments to enhance and broaden the suite of tools available to CBER is therefore critical and worth pursuing. In summary, the FDA should undertake a collaborative process that identifies the key data gaps and limitations and establishes a prioritized list to address based on both impact of addressing the gap and feasibility.

Methods

Proposed steps to consider:

- *Invest in implementing a systematic approach to identifying and prioritizing new methods needs, leveraging governance to get the right degree of input and buy-in.*

While progress on new methods development has been noteworthy, the foregoing assessment suggests an opportunity to further establish and systematize the approach the FDA takes to isolating and prioritizing new methods that will enable it to keep pace with advances in the science of fields they regulate. This will require building the culture of continuous evolution and establishing a systematic way of actively evaluating the landscape of needs to define new methods priorities. This would ideally be facilitated through existing governance bodies, further providing a platform for communication of new methods as they are developed, and offering the most logical venue to manage scarce methods development capacity at SOC. If there are approaches that would accelerate methods development (e.g., by working with external contracted partners to develop methods), those should be evaluated as well.

Talent and organization

Proposed steps to consider*:*

- *Conduct an analysis to ensure adequate staffing levels for providing operational oversight and hire additional – especially Sentinel-dedicated – staff as required.*

- *Create more systematized Sentinel training curriculum, with more regular trainings, with SOC providing regular updates to current users.*

As demand for Sentinel capabilities grows, there will be a need to provide both additional end-user support within the FDA and more robust oversight of Sentinel operations to ensure maximum efficiency. To that end, the FDA should conduct an internal analysis of the staffing needed to support these oversight functions and then develop a plan for adding those resources (ideally Sentinel-dedicated), provided sufficient funds are made available or could be reallocated. There has been admirable progress in both CBER and CDER in terms of building "non-dedicated staff" capability of working with Sentinel, but there is still a gap – and a need to invest resources in operational program oversight as Sentinel activity levels rise.

In addition, a formal Sentinel training curriculum should be introduced to onboard the next set of users. Feedback from trainings to date has been overwhelmingly positive, and there is a clear desire for greater learning opportunities. To date, the rate limiting factor has been the capacity of the core team (given the aforementioned resource constraints) to facilitate these events. In order to increase awareness and broaden the base of users, a core training curriculum should be developed, supplemented by routine "refreshers" addressing new tools and capabilities to keep end-users up to date on Sentinel capabilities.

Governance

Proposed steps to consider:

- *Conduct routine review of a range of operational metrics in Agency-wide governance committees and, on a regular basis, leverage these metrics jointly across Centers to inform operational decisions (e.g., capacity management) and improvement priorities.*
- *Ensure that there are separate individuals serving as FDA Sentinel lead, CDER Sentinel lead, and CBER Sentinel lead in order to ensure equitable representation of organizational interests and impartial implementation of an FDA-wide strategy.*
- *Continue to foster closer scientific collaboration with SOC researchers and relevant data partners (specifics below).*

Formal structures of FDA-wide governance were established in 2016 and the governance committees have been successful in increasing the transparency around Sentinel management. However, they have been less successful in providing detailed operational oversight or developing a coordinated view on strategic and operational improvement priorities for Sentinel. Formal processes to address these gaps have been developed, but increased focus is needed in implementation, with a particular focus on addressing communication and coordination breakdowns between CBER and CDER.

Given somewhat divergent needs and interests of end users working with Sentinel, FDA should modify governance representation in a way that ensures internal stakeholders are equitably represented in Agency-wide discussions and in communications with external stakeholders (e.g., SOC). In today's context, this recommendation implies that separate individuals should serve in the positions of FDA Sentinel lead, CBER Sentinel lead, and CDER Sentinel lead such that both CBER and CDER interests are represented equitably in agency-wide deliberations and decisions.

Finally, as Sentinel manages the continuing shift toward "production mode," there is a risk that the bonds of scientific collaboration between FDA staff and collaborators at SOC and data partners may weaken. In order to maximize the quality of Sentinel input and output, the FDA should pay particularly close attention to cultivating and maintaining collaborative relationships. Existing best practices to consider building on as appropriate include: (i) ensuring that major projects include core representation from four stakeholder groups (data partners, SOC, and colleagues representing CBER and CDER), with these colleagues involved throughout the planning process to the extent permissible; (ii) implementing structured approaches to ensure on-time and on-budget project completion (iii) providing all stakeholders an opportunity to comment and give feedback to ensure broad alignment on project goals and objectives; (iv) maintaining operational transparency and clear communication mechanisms to keep stakeholders informed of progress; (v) continuing the ongoing pattern of routine in-person brainstorming sessions to generate fresh ideas and foster active scientific exchange; and (vi) providing feedback (where applicable) on how Sentinel queries were influential in helping the FDA make a regulatory decision.

Process

Proposed steps to consider:

- *Define the standard set of operational metrics (e.g., capacity, performance, timeliness, budget) and a selection of impact/value metrics, ensure their regular collection and integrate them into routine performance management discussions at the Sentinel Executive Committee.*

As Sentinel operations expand, aligning on and continuously measuring a standard set of operational metrics – coupled with a focused set of metrics related to program impact and value – will be critical to ensure proper operational oversight and to address operational issues that arise over time, as suggested in the governance-related recommendations.

Section 6 – Conclusion

Since the interim assessment, the FDA has made considerable progress. Specifically, the FDA, in concert with SOC and partners, have increased internal awareness of Sentinel capability, developed complex analytical tools and methods, invested in a refined supporting organization for Sentinel management (including establishment of agency- wide governance structures), and taken meaningful steps toward embedding Sentinel in regulatory decision-making processes. This progress is further substantiated by the meaningful growth in Sentinel use by FDA stakeholders. By any objective metric, the FDA has fulfilled its core obligations under PDUFA V and met the expectations outlined in FDAAA. More importantly, the FDA has created a robust base upon which to grow Sentinel operations into the future. Interviews and survey data suggest that there is enthusiasm around Sentinel within the FDA and that there is strong momentum toward incorporating Sentinel more fully into regulatory review processes. As Sentinel evolves, its capabilities and demand for its services grow within the FDA, though, there are a number of specific actions to take toward full maturity.

In many cases, the remaining challenges involve issues of execution and implementation (e.g., further formalization of embedding Sentinel in regulatory decision-making, leveraging governance institutions to provide operational oversight, providing more regular training). In other instances, concrete discussions about vision and direction will be needed (e.g., creating a long-term strategy, adjusting the staffing model to meet new demands). The proposed next steps provided in this report are all focused on practical actions the FDA can take to move Sentinel toward full maturity.

Beyond the immediate priority of actions to reach full maturity, there are a series of broader strategic questions related to the long-term sustainability of Sentinel and how to maximize the value of this remarkable asset that will become increasingly important. While not the focus of this assessment, they are nonetheless important to highlight – and are likely best addressed in the context of a broader strategic planning process, as recommended in prior sections of this report. Specifically, core pressing sustainability questions relate to Sentinel's long-term funding model, relationships with data partners, and the talent succession planning internally and at the SOC. From a value maximization perspective, leadership will have to grapple with how Sentinel is used more broadly within the federal government and potentially by other end users. In this context, scale of Sentinel production may become a limiting factor, and special consideration would be required to preserve FDA-dedicated operational capacity. Thus, an examination of the current operating model, which includes both management of routine Sentinel queries, complex epidemiological studies, and new capability development, could be conducted including exploration of alternative models (e.g., operation of multiple specialized coordinating centers or contracting with a subset of data network partners). FDA will need to strike the right balance of Sentinel utilization for core safety use cases while beginning to explore its utility for efficacy-related studies, including prospective randomized clinical trials. Sentinel also has a clear opportunity to integrate into emerging networks of resources within the broader learning health care ecosystem (e.g., the National Patient-Centered Clinical Research Network – PCORnet) for the purpose of generating clinical insights and evidence.

Though long-term sustainability is not the focus of this report, it remains a critically important topic for Sentinel leadership to address in order to secure Sentinel's future. Sentinel's capabilities and data infrastructure present a number of long-term strategic options going forward, and FDA leadership will need to rigorously evaluate the most cost-effective paths to take in order to maximize Sentinel's impact on FDA efficiency, patient safety, and public health. For the purposes of the present assessment however, the FDA should be commended for making considerable progress maturing the Sentinel platform and integrating its use in routine safety-related regulatory decision-making.

Appendix

Exhibit A-1: Evaluation rubric, Sentinel Maturity Model

Strategy and value

Low / no maturity (0)	Medium maturity (2)	Full maturity (4)
▪ No annual or long-term strategy defined and confusion within FDA on short, medium and long term goals ▪ No/poorly defined portfolio of priorities and leadership not well aligned ▪ Leaders never or very rarely engage on Sentinel and do not regularly encourage teams to use Sentinel in safety reviews ▪ Very few FDA staff understand Sentinel capabilities and when to use them during the course of regulatory work ▪ Very few end-users see Sentinel as useful and most lack the ability to interpret results and apply them to day-to-day work	▪ Annual and long-term goals may be loosely defined or are well-defined but not well communicated to other stakeholders ▪ Sentinel executive leadership is aligned on some, but not all priorities ▪ Leaders promote Sentinel capabilities and results, but engagement is inconsistent across teams and/or processes ▪ Some FDA staff agree that they understand Sentinel's capabilities, but many remain unaware of when or how to use Sentinel ▪ Some parts of FDA agree that Sentinel outputs are useful, but significant internal stakeholders remain unconvinced	▪ Annual and long-term (e.g., 3-5 year) strategy is clearly articulated and broadly understood within FDA and core Sentinel partners ▪ Sentinel executive leadership is aligned on the portfolio of priorities to deliver the strategy ▪ Leaders regularly engage with and highlight Sentinel capabilities and results with teams to promote the use of Sentinel in safety reviews ▪ All or most relevant FDA staff agree that they understand Sentinel capabilities and when to draw on them in the course of regulatory work ▪ All or most end-users agree that Sentinel outputs are useful and valid and understand the ways to interpret them

Analytical tools and technology

Low / no maturity (0)	Medium maturity (2)	Full maturity (4)
▪ No or few Sentinel outputs are provided to decision-makers or they are provided in an untimely fashion on a regular basis ▪ Data returned from Sentinel queries is rarely or never factored into pre- and post-market regulatory decisions by review teams ▪ Sentinel captures few/no data fields that assist in answering key regulatory questions ▪ FDA has no or only a very partial list of the most effective data partners and sources ▪ Sentinel is stagnant and does not regularly expand the suite of analytical tools available ▪ Sentinel partners do not possess key capabilities to provide routine reporting around Sentinel activities to FDA	▪ Some Sentinel outputs are provided in a timely fashion, but gaps remain to ensure a smoother process ▪ Data from Sentinel queries is sometimes factored into pre- and post-market regulatory decisions, but inclusion is inconsistent ▪ Sentinel data assists in answering some regulatory questions, but major gaps remain ▪ FDA's list of effective data partners and data sources is missing critically important pieces ▪ Sentinel is expanding available analytical tools, but pace of growth is slow ▪ Sentinel partners capture some key performance measures, but are missing key measures important to FDA	▪ All or most Sentinel outputs are provided to regulatory decision-makers (e.g., review teams) in a timely fashion ▪ Data returned from Sentinel queries is factored into pre- and post-market regulatory decisions by review teams ▪ Sentinel captures a robust data set capable of answering critical regulatory questions ▪ FDA maintains a list of the most effective and relevant data partners and data sources ▪ Sentinel is continuously expanding the suite of analytical tools available ▪ Sentinel partners are capable of routine reporting around Sentinel activities and providing key performance measures to FDA

Exhibit A-1 (continued): Evaluation rubric, Sentinel Maturity Model

Methods		
Low / no maturity (0) ▪ Basic functionality for each type of Sentinel query is not well defined, not codified formally, and cannot easily be reproduced by SOC/data partners ▪ Established methods are rarely or never refined and/or improvements are made but never or rarely communicated in updates to Sentinel users ▪ New methods to assist FDA staff in response to specific capability needs are rarely or never developed	**Medium maturity (2)** ▪ Basic functionality for each Sentinel query is established, but are only informal in nature and/or not easily reproducible ▪ Some established methods are refined regularly, but improvements and/or communication of updates to Sentinel users are inconsistent ▪ Net methods to assist FDA staff are sometimes developed, but pace of development is too slow and/or process of soliciting/obtaining input is inefficient	**Full maturity (4)** ▪ There is a well-defined suite of basic functionality for each type of Sentinel query that is formally codified and broadly reproducible ▪ Established methods are refined and improved on a regular basis as evidenced by improved functionality and communication of updates to Sentinel users ▪ New methods that assist FDA staff are developed regularly in response to specific capability needs that will address emerging public health questions
Talent and organization		
Low / no maturity (0) ▪ Training on fundamental and evolving Sentinel capabilities is never or rarely provided to FDA staff or attended by a small percentage of relevant staff ▪ FDA and SOC have very limited or no dedicated and non-dedicated resources to respond to the demand for Sentinel services ▪ Sentinel operations are highly unprepared to scale to meet projected demand growth in the near future	**Medium maturity (2)** ▪ Training on Sentinel capabilities is provided to FDA staff, but attendance is limited and/or training on new Sentinel capabilities is not adequately provided ▪ FDA and SOC have resources to respond to much of the current demand, but are currently stretched thin ▪ Sentinel operations can scale in a limited fashion, but may not be able to respond adequately	**Full maturity (4)** ▪ Training on fundamental and evolving Sentinel capabilities is regularly provided to FDA staff and attended by a significant percentage of relevant staff ▪ FDA and SOC have sufficient dedicated and non-dedicated resources to respond to all or most of the demand for Sentinel services ▪ Sentinel operations are prepared to scale to meet all or most of projected demand growth in the near future

Exhibit A-1 (continued): Evaluation rubric, Sentinel Maturity Model

Governance

Low / no maturity (0)

- There is no governance infrastructure, or it is weak with ill-defined roles and responsibilities and haphazard oversight of program direction and strategy
- Operational oversight is non-existent or very infrequent
- Privacy mechanisms between the coordinating center and data partners are non-existent or serious breaches of protocol or very common

Medium maturity (2)

- Governance infrastructure is established but lines of accountability are unclear/weak and/or oversight is conducted infrequently
- Operational oversight exists but is inconsistent and/or leverages a small number of data sources from within the Sentinel network
- Privacy mechanisms between the coordinating center and data partners are established, but are not codified formally and/or followed inconsistently

Full maturity (4)

- Strong governance infrastructure characterized by defined roles and responsibilities and decision-making authority, routinely overseeing program direction and strategy
- Routine pattern of rigorous operational oversight that leverages a wide variety of data-driven support from across the Sentinel network
- Privacy mechanisms between the coordinating center and data partners are firmly established and followed

Process

Low / no maturity (0)

- Processes around query submission and communication with SOC are informal, poorly defined, and ad-hoc
- SOC operates inefficiently with few or no requests delivered on-time
- There are not formalized SOPPs, MAPPs, or reference guides, and consideration of Sentinel in core operations is informal
- Few FDA personnel adhere to documented processes integrating Sentinel into pre- and post-market safety review
- Operational metrics are rarely or never utilized in making improvements and revisions to Sentinel operations

Medium maturity (2)

- Many processes around query submission and communication with SOC are formalized, but some remain undocumented or are simply not established
- SOC operates efficiently on many requests, but some are still late
- Some processes are formalized, but formalization is inconsistent across FDA safety review teams
- Many teams adhere to formally integrated Sentinel processes in safety reviews, but overall adherence remains inconsistent
- Operational metrics are analyzed at Sentinel partners, but are only sometimes leveraged to make improvements and revisions

Full maturity (4)

- Clear processes defined and formalized at FDA around question submission and communication with SOC
- SOC operates efficiently with on-time delivery of all or most requests
- Existence of formalized SOPPs, MAPPs, and reference guides that explicitly integrate consideration of Sentinel into core operations
- Broad-based adherence to the formally documented processes integrating Sentinel into pre- and post-market safety review
- Operational metrics are consistently and frequently utilized to make improvements and revisions to Sentinel operations across the Sentinel system

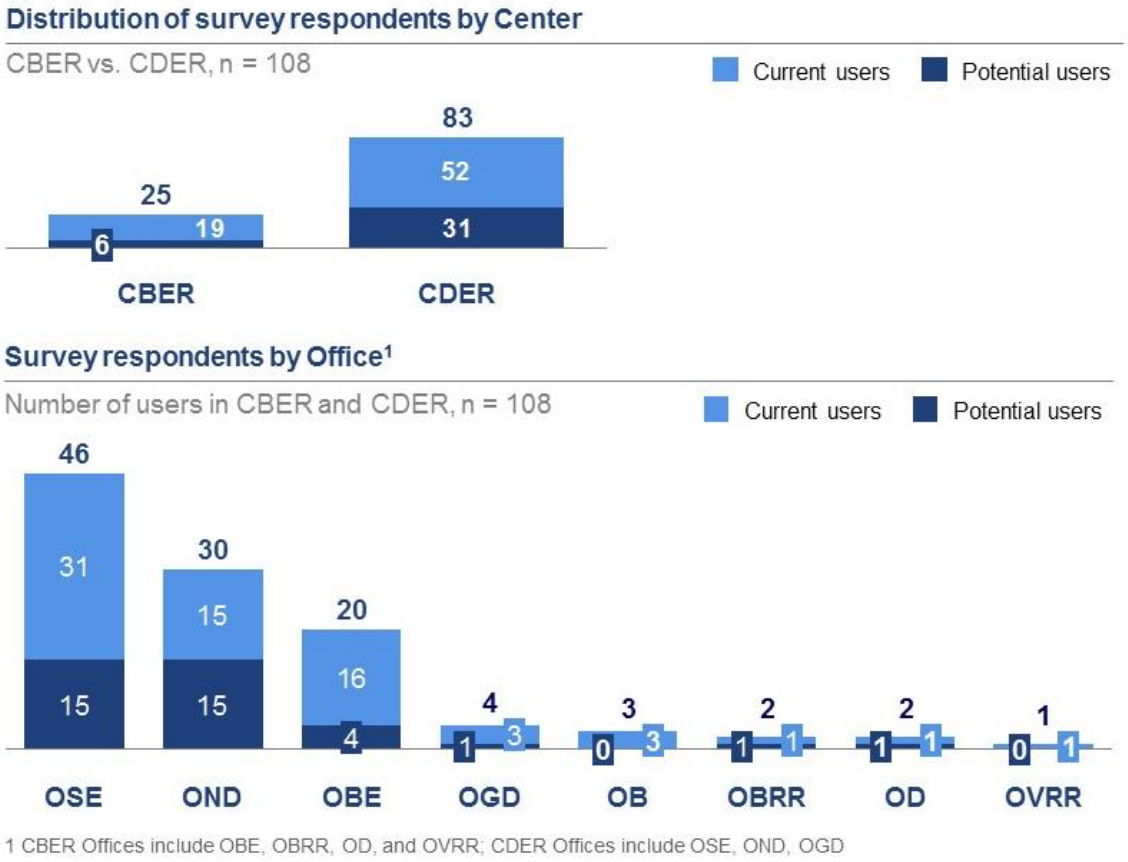
Information on FDA survey

As part of the assessment, a survey was provided to a broader set of FDA employees in both CBER and CDER who were thought to be current or potential users of Sentinel in order to better understand user perceptions of the system (for breakdown of respondents, see **Exhibit A-2**). A total of 263 individuals were identified based on their role at the FDA and invited to take part in the survey (56 from CBER and 207 from CDER) and 108 individuals ultimately completed the survey, yielding a 41% response rate (see **Exhibit A-3**). Initially, respondents were asked to answer a series of identifying questions indicating their role at the FDA and corresponding Office, though assurance was provided that all feedback was anonymous and would not be given in any identifying manner to respondents' managers or superiors.

Respondents were then asked to answer a series of questions concerning their awareness around: (a) overall impact of Sentinel on the FDA and broader public health; (b) recent Sentinel accomplishments; (c) overall exposure to Sentinel and data use practices; (d) recommendations for improving functionality and utilization; and (e) overall awareness of Sentinel capabilities and functionality.

Respondents were also asked to indicate their overall level of familiarity with Sentinel. Those who indicated they understood "a great deal" or "a fair amount" about the types of questions Sentinel is designed to answer were directed to answer a final series of questions. In total, 76 of the 108 respondents (70%) proceeded to this final set of questions, including 56 of the respondents from CDER (67%) and 20 of the respondents from CBER (83%) (**Exhibit A-3**). The final set of questions asked those respondents identified as knowledgeable about: (a) purpose of Sentinel usage and frequency of usage; (b) quality and usefulness of Sentinel results; (c) strength of supporting infrastructure and embedded processes; (d) overall importance of Sentinel to the strategy of respondents' Office; and (d) challenges and opportunities around the talent and organization needed to facilitate Sentinel uptake and growth.

Exhibit A-2: Survey respondents by Center and Office



1 CBER Offices include OBE, OBRR, OD, and OVRR; CDER Offices include OSE, OND, OGD

Exhibit A-3: Flowchart of survey respondents and response rates

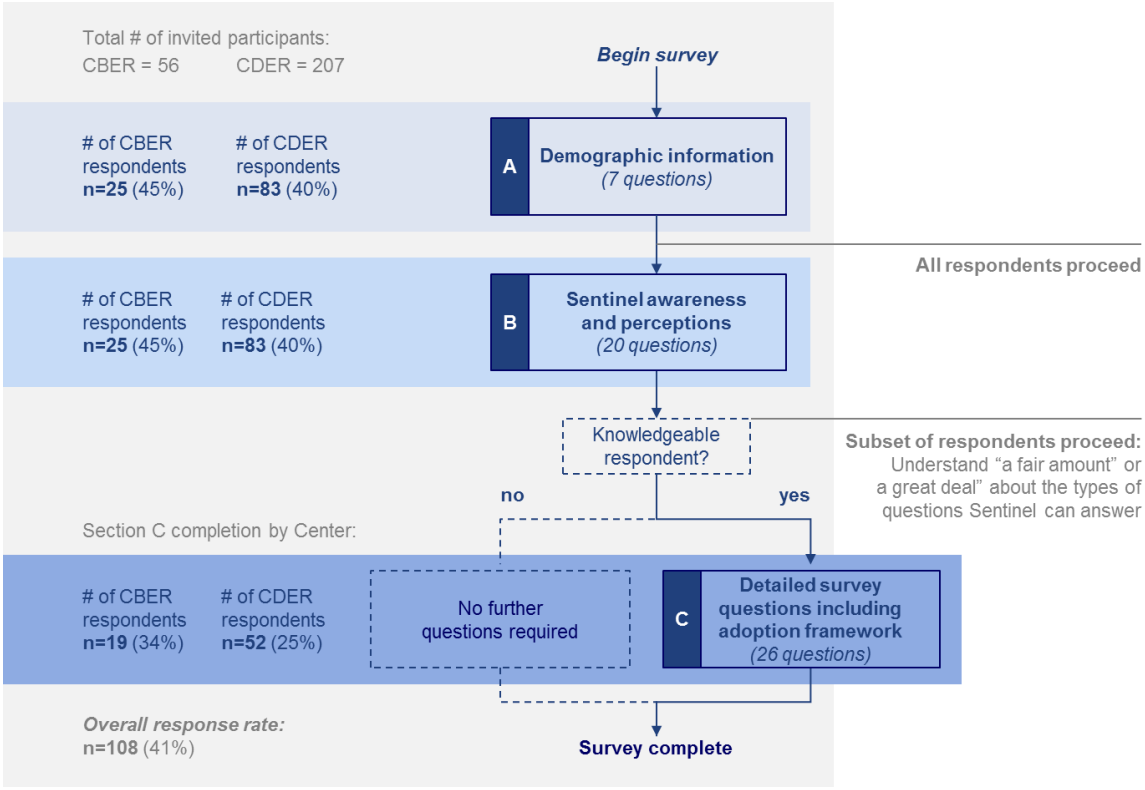


Exhibit A-4: List of recommendations from Sentinel interim assessment[11]

SMM element	Aspiration and goals identified during interim assessment
Strategy and value	▪ Ensure that a broad set of FDA scientists are aware of the Sentinel System's capability and are committed to regular use ▪ Prioritize use-cases in which the Sentinel System can add the most value for regulatory decision making
Analytical 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)

[11] Table adapted from the Sentinel interim assessment (2015): https://www.sentinelinitiative.org/communications/publications/sentinel-program-interim-assessment-fy-15