FDA

Sentinel System

FIVE-YEAR STRATEGY

2019-2023

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Section 1 – Executive summary

FDA is an information-driven agency that requires robust data to make regulatory decisions. The Sentinel Initiative, launched in 2007, grew from a legislative mandate to develop a safety surveillance system using existing data to become one of FDA's premier evidence-generation platforms. Using its multi-site, privacy-preserving, curated data infrastructure and suite of analysis tools, Sentinel now proactively monitors medical product safety, provides a critical engine for methodological innovation, and serves as a platform to advance the science of real-world evidence. Fully implemented in 2016, the Sentinel System is now a core feature of FDA's post-market safety surveillance armamentarium and a vital testbed for advanced technologies and approaches. Recognizing the need to shape the Sentinel System's development for a changing drug development and safety ecosystem, FDA proposes the following five-year strategy and road map.

In the next five years, FDA will focus its investment on innovations emerging from new data science disciplines, such as natural language processing and machine learning, and seek to expand its access to and use of electronic health records (EHRs). FDA will balance this forward-looking strategy by incorporating core gains from the prior decade that witnessed the creation of the largest and most advanced medical product safety surveillance system to date that includes the Sentinel Common Data Model, a quality-checked distributed network, and suite of state-of-the-art analysis tools. The strategy directs Sentinel to reach beyond its current boundaries while preserving capabilities and key accomplishments. By 2023, FDA envisions a more robust Sentinel System: a transformative, multi-purpose national data and scientific resource center for evidence-generation that a wide array of stakeholders use to inform all aspects of healthcare decision-making.

To realize this vision, FDA will pursue five strategic aims. First, enhance and expand the Sentinel System's foundation, including data, infrastructure, operations and technology. Second, augment its safety analysis capabilities using advances in data science and signal detection. Third, use the Sentinel System to accelerate access to and broaden the use of real-world data (RWD) for real-world evidence (RWE). Fourth, broaden the Sentinel System's ecosystem of stakeholders to pursue the vision of a national resource. Finally, disseminate knowledge and advance regulatory science to encourage innovation and meet the Agency's scientific needs.

These strategic aims serve as guiding lights, allowing flexible and adaptive implementation. Acknowledging the rapidly changing healthcare system and ongoing scientific progress, FDA must be able to seize upon new and emerging opportunities. This will allow FDA to remain agile, learn from actions taken, and still be responsive to legislative mandates. Moreover, to stay current on key scientific fronts, several of the strategic aims notably highlight the centrality of continuing to build a Sentinel scientific community where investigators can contribute meaningfully to improve the Sentinel System. FDA has an important leadership role in enabling such a scientific community to develop and thrive.

This document outlines how the Sentinel System and FDA-Catalyst, as part of the broader agency-wide Sentinel Initiative, can continue to grow and achieve this ambitious vision. The cumulative impact of all five aims should be substantial and allow stakeholders to continually discover new approaches and grow the Sentinel System with a vigorous scientific community and a secure future for the next five years and beyond.

Section 2 – FDA's strategy for the Sentinel System

A decade of progress sets the stage for the next five years

In the ten years since its inception, the Sentinel System has developed into a vital safety surveillance tool for FDA. The Sentinel Initiative grew from a legislative mandate under section 905 of the FDA Amendments Act (FDAAA) of 2007, directing FDA to develop methods to obtain access to disparate data sources and establish a post-market risk identification analysis system to link and analyze safety data from multiple sources. The Sentinel Initiative began with the Mini-Sentinel pilot in 2009 – an incubator intended to inform the design of a full-scale Sentinel System. By 2011, Mini-Sentinel reached a milestone when it surpassed 100 million patient lives covered across these data sources. By 2012, Mini-Sentinel had developed reusable programming tools for routine queries, which helped to establish more efficient production-like capacity. Following this progress, FDA launched the full-scale Sentinel System in 2016 as a core resource in the armamentarium of tools for post-market safety surveillance.

To facilitate this system, FDA launched the Sentinel Initiative to develop the Sentinel Common Data Model (SCDM) and a set of customizable tools in a patient privacy preserving "distributed data system," as opposed to a single consolidated database. The system was designed to deliver a near real-time capability to augment, but not replace, FDA's existing post-market safety surveillance activities.

The Sentinel System's evolution includes full implementation of the Active Post-market Risk Identification and Analysis (ARIA) capability, which enables FDA to evaluate post-market safety signals using RWD, with greater speed and efficiency than ever before. FDA's ARIA sufficiency process determines whether the Sentinel System or ARIA data coverage and analyses are sufficient for evaluating a potential safety concern. If ARIA is determined to be insufficient to address the safety concern and achieve the regulatory objective, the Sentinel System's highly standardized suite of modular programs and data in SCDM cannot be used for a safety evaluation. In such instances, potential safety concerns may need to be evaluated through costlier and more time-intensive approaches, including sponsor-led post-market requirement (PMR) studies, protocol-based analyses, including medical record review, or projects developed to address gaps in the Sentinel System's suite of programs.

ARIA modernized safety surveillance by capitalizing on electronic healthcare data and advanced epidemiological methods, and expands FDA's capabilities in the realm of post-market pharmacovigilance for approved medical products. When FDA finds ARIA *sufficient* to evaluate a safety concern, the Sentinel System may obviate the need for post-market safety studies performed by sponsors, such as those in industry. Prior to approval, FDA reviewers determine the likelihood of the Sentinel System's ability to generate high-quality evidence to address an identified safety concern that will require further study after the drug is marketed. When a new safety concern is identified in the post-market setting, ARIA sufficiency determines the feasibility of using the Sentinel System based on real-world utilization of the approved medical product to answer questions related to safety, for example through quantitative analysis or outcome validity determination.

The totality of activities associated with the Sentinel Initiative over its lifespan has surpassed the original FDAAA mandate, as evidenced by the robust integration of the Sentinel System into the Agency's post-market safety work and the development and expansion of the Sentinel Initiative's FDA-Catalyst activities. FDA-Catalyst supplements data from Sentinel Network Data Partners with data from interventions or interactions with members and/or providers. FDA is committed to

continually increasing the scope of safety signals the Sentinel System evaluates by identifying opportunities to improve data, tools and methods. Since the transition to full-scale Sentinel System, FDA has completed a host of projects to develop methods and data linkages, such as the mother-infant linkage that enables studies of the impact of drug exposures during fetal development, and a sophisticated plasmode simulation used to evaluate a wide range of novel approaches to propensity score analyses. In addition, many Sentinel System capability development projects are already underway, such as an evaluation of three signal detection methods (TreeScan, sequence symmetry analysis, and information component temporal pattern discovery), and a project to use machine learning and natural language processing to develop a more efficient algorithm to ascertain anaphylaxis.[1]

In response to the Prescription Drug User Fee Act (PDUFA) V commitments, FDA also conducted a "Final Assessment" to evaluate progress since the transition from mini- to a full-scale Sentinel System. The assessment commended several accomplishments, including the transition to full-scale Sentinel System operations and formally embedding ARIA into the regulatory decision-making process. The assessment report also cited continued opportunities for growth, including the need for a forward-looking Sentinel System strategy to guide FDA investments in support of the Sentinel System. Parts of FDA's five-year strategy address these growth opportunities.

The Sentinel System is a unique and powerful tool with a host of potential applications in the service of public health, but FDA – the primary sponsor of the Sentinel System – has limited resources. It must therefore prioritize investments carefully to maintain the Sentinel System's long-term financial and operational sustainability. This document lays out FDA's vision and strategic objectives for the Sentinel System and describes a five-year road map to achieve them.

FDA's strategic vision for the Sentinel System

FDA's vision for the Sentinel System is to achieve a sustainable national resource to monitor the safety of marketed medical products and expand real-world data (RWD) sources use to evaluate medical product performance. (See **Exhibit 1**).

FDA's strategic plan for the Sentinel System reflects several Agency objectives:

- Accelerate use of the Sentinel System within FDA and scale capabilities to meet needs

- Explore the utility of real-world data as a tool to support drug development and assess medical product performance

- Facilitate response to legislative mandates regarding medical product safety and effectiveness evaluation

- Expand the Sentinel System by facilitating its use by other stakeholders, and foster innovation and development.

FDA's five-year strategy aims to provide a concrete roadmap for the Sentinel System to achieve its vision and objectives. The strategy sets clear aims and defines underlying initiatives to measure progress.

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[1] For a comprehensive list of ongoing and completed projects, please visit
https://www.sentinelinitiative.org/sentinel/methods

VISION

A sustainable national resource to monitor the safety of marketed medical products, and expand real-world data sources used to evaluate medical product performance

STRATEGIC OBJECTIVES

| Accelerate use of the Sentinel System within FDA and scale capabilities to meet needs | Increase the utility of real-world data to support drug development and assess medical product performance | Facilitate response to legislative mandates regarding medical product safety and effectiveness evaluation | Expand Sentinel by facilitating its use by other stakeholders, and foster innovation and development |

STRATEGIC AIMS

| Enhance the foundation of the Sentinel System (data, infrastructure, operations, technology) | Further enhance safety analysis capabilities by leveraging advances in data science and signal detection | Accelerate access to and broader use of real-world data for generation of real-world evidence | Create a national resource and further open the Sentinel System by broadening the Sentinel user base | Disseminate knowledge and advance regulatory science to encourage innovation and meet Agency scientific needs |

**Exhibit 1. Vision, strategic objectives and aims for the Sentinel System**

Scope and approach

The strategy emerged from a comprehensive data-gathering and strategic development process that engaged a broad set of FDA stakeholders and select external experts. Internal engagement included an anonymous survey of Sentinel System users in the Center for Drug Evaluation and Research (CDER) and interviews with Sentinel Initiative leadership and users.

This document presents the strategic roadmap for the next five years of the Sentinel System's development. The strategy focuses on two chief components: the Sentinel System and FDA-Catalyst which used common Sentinel System infrastructure. The Sentinel System involves carrying out observational studies, while FDA-Catalyst studies involve direct interactions or interventions with patients and/or healthcare providers. Both platforms can address questions of safety and effectiveness.

This plan focuses on the Sentinel System and FDA-Catalyst and does not touch upon the Center for Biologics Evaluation and Research (CBER) Biologics Effectiveness and Safety (BEST) Program. Together, these three components form the basis for the overall Sentinel Initiative. (See **Exhibit 2**). Nor does the Sentinel System strategy comment on other FDA-regulated medical product safety programs, such as the Center for Devices and Radiological Health's (CDRH)

National Evaluation System for Health Technology (NEST) system. These Center-specific programs are designed to meet distinct needs not covered by the current Sentinel System. For example, CBER requires near real-time safety and effectiveness surveillance capabilities for vaccine and blood products. New capabilities established through BEST will contribute to the evolution of the Sentinel Initiative, informing best practices for utilization of RWD effectiveness studies, including causal inference methodologies, and the application of innovative technologies. Similarly, CDRH's NEST program aims to bolster the generation of high-quality evidence for medical device evaluation and regulatory decision-making. As these programs mature, there may be additional opportunities for interconnected initiatives in furtherance of Sentinel Initiative objectives.
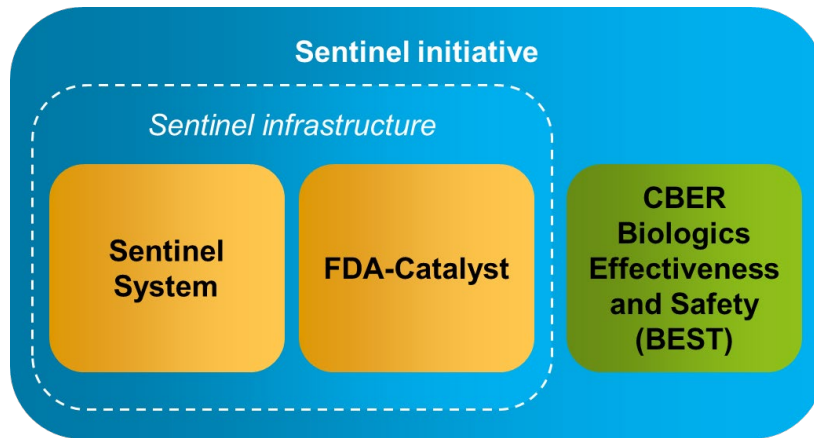
**Exhibit 2. This strategy focuses on the Sentinel System and FDA-Catalyst**

The Sentinel System strategy defines actions that FDA will carry out. It does not specify priorities or initiatives for other ecosystem participants, although the strategy refers to a range of stakeholders, given their relevance to the Sentinel System's long-term maturation.

Five strategic aims will guide FDA's Sentinel System activities (see **Exhibit 3**):

A. Enhance the foundation of the Sentinel System

B. Further enhance safety analysis capabilities

C. Accelerate access to and broader use of real-world data to generate of real-world evidence or evaluate medical product performance

D. Create a national resource by broadening the Sentinel System user base

E. Disseminate knowledge, and advance regulatory science to encourage innovation.

This plan describes the rationale and objectives for each strategic aim and a specific set of initiatives that FDA will pursue to realize these aims. Initiatives are cross-referenced against existing FDA goals in the appendix (**Table 1-3**).
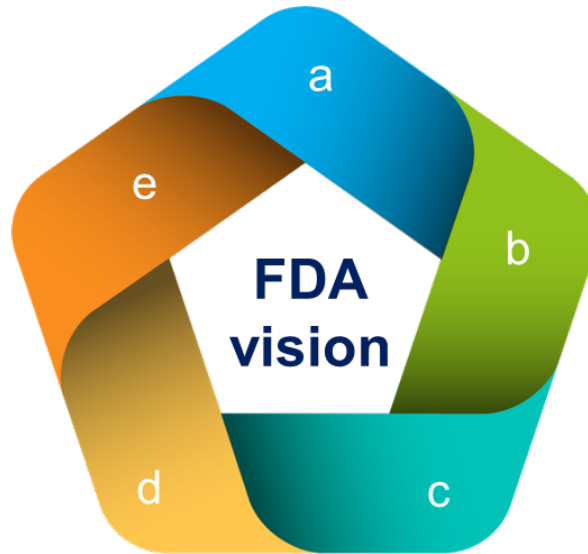
FDA vision

A sustainable national resource to monitor the safety of marketed medical products, and expand real-world data sources used to evaluate medical product performance

a **Enhance the foundation of the Sentinel System**
- Expand data sources and linkages
- Improve data infrastructure and methods development
- Enable more effective use through operational improvements

b **Further enhance safety analysis capabilities**
- Increase ARIA sufficiency
- Leverage advances in data science and signal detection

c **Accelerate access to and broader use of real-world data**
- Enable new avenues for generating real-world evidence by investing in access to and approaches to use of electronic health records
- Conduct specific real-world data-driven demonstration projects to explore the universe of addressable effectiveness questions

d **Create a national resource by broadening the Sentinel user base**
- Improve operations and procedures for accessing tools, methods, and results
- Evolve the Sentinel System operating model
- Engage directly with potential users and develop a Sentinel scientific community

e **Disseminate knowledge, and advance regulatory science**
- External outreach and convening across the learning healthcare ecosystem
- Provide transparency, and encourage innovation and collaboration

Exhibit 3. Five-year strategy for the Sentinel System

Section 3 – Five-year strategic aims

3.1 Strategic Aim A: Enhance the foundation of the Sentinel System

The Sentinel Initiative was established to assess the safety of approved medical products and identify their risks more reliably. From its full deployment in 2016, the Sentinel System has emerged as an important tool to help FDA staff safeguard the public. Since the completion of the Mini-Sentinel pilot phase, FDA staff have used the System to conduct more than 250 safety analyses, and it is now embedded in the regulatory review process through the ARIA process. With the development of FDA-Catalyst, use of the Sentinel System is now expanding beyond safety into efficacy.

The Sentinel System's capabilities, tools, data infrastructure and innovative approaches continue to expand and mature. Sentinel staff continuously refine Sentinel System processes to drive operational efficiency and standardization. In setting priorities, FDA will consider a range of factors, including addressing legislative mandates and PDUFA goals; analysis of ARIA sufficiency; the chance to seize quick wins and "low-hanging fruit"; and the availability of transformative methods or technology.

To continue to grow and mature the Sentinel System's capabilities, FDA will emphasize enhancements to three foundational elements over the next five years: (see **Exhibit 4**)

Foundational elements	Example focus areas

1 Strengthen **Data platform**	• **Expand data breadth**
	   – Add new data types/ partners (e.g., access new patient groups)
	 • **Increase data granularity**
	   – Strengthen targeted linkages and access to EHRs to address the largest gaps in safety (e.g., mother-baby, laboratory results)
	   – Integrate with National Death Index and Surveillance Epidemiology and Ends Results (SEER) to broaden HOIs (e.g., death, cancer)
	 • **Increase data diversity** – (e.g., incorporate patient-reported outcomes)

2 Enhance **Methods**	• **Causal inference methods** • **Data mining capability building** • **Data preparation** and evaluation techniques • Continued utilization of **privacy-preserving methods**
3 Upgrade **Operations**	• **Streamline** processes and workflow • Promote **flexible use** of data sources • Expand **training** and **capability building** opportunities • Reinforce culture of **continuous improvement and innovation**

Exhibit 4. Three foundational elements will augment the Sentinel System

1. **Expanding data sources and linkages so that the Sentinel System can answer a broader range of questions.** Strengthening the Sentinel System's data infrastructure is the most meaningful way to enhance its foundation and broaden the questions it can address. This includes adding data sources, improving existing data sources and expanding the Sentinel Common Data Model. As they consider options for improving data infrastructure, the

Sentinel Initiative leadership team will prioritize activities based on their impact across three dimensions:

- *Coverage (breadth).* The Sentinel System network now includes over 200 million individual member records. While this is a broad data source, gaps remain across populations of interest, including ethnic minorities, rare-disease patients, pregnant women and infants. By adding data sources that include previously underrepresented groups, such as Medicare for people 65 and older, the Sentinel System can now address safety questions in cohorts that were previously unavailable. As the Sentinel System continues to expand in population coverage, FDA will weigh the utility and benefits of additional coverage against applying resources efficiently in other areas.

- *Granularity (depth).* FDA will expand the range of questions the Sentinel System can answer by adding granularity to available data, especially about health outcomes in disease-specific events, for example, functional status and cause of death; patient characteristics obtained from EHRs, such as body mass index (BMI), ejection fraction and symptom reporting; and important exposure variables.

- *Duration (longitudinally).* FDA will increase the longitudinal duration of patient data to enable a new category of analyses in which length of drug exposure is a key variable of interest, such as in long-term drug use for the treatment of chronic diseases or cancer, in evaluating a safety outcome.

FDA will prioritize four types of data improvements in the next five years:

i. **Scale up capabilities related to mother-infant linkage** to evaluate in-utero exposure, medical product usage during pregnancy and post-natal outcomes

ii. **Work to integrate national and state registry linkages** including the National Death Index (NDI), Surveillance Epidemiology and Ends Results (SEER), and other rare-disease registries, to the extent possible as determined by individual registry governance limitations

iii. **Continue to increase the number of validated Health Outcomes of Interest** (HOIs) through record review, drawing from increased availability of EHR linkages

iv. **Expand linkage to EHR data sources from Sentinel System Data Partners** and explore potential expansion to incorporate other data partners, such as the National Patient-Centered Clinical Research Network (PCORnet), and increase the availability of full medical records, including improved access to the Medicare chart review process, prioritizing electronic sources from integrated delivery systems.

2. **Enhance data infrastructure and methods to improve the utility of available data sources:**

i. **Expand the Sentinel Common Data Model** categories, including structured data fields from EHRs and standardized information from novel data sources, to provide greater flexibility for the incorporation of new fields. This approach would continue to evolve the

set of existing SCDM data tables, by continuing to support existing[2] or launching new projects to bolster SCDM data flexibility, such as by incorporating clinical laboratory test results, including vital signs data and BMI

ii. **Determine optimal approaches for incorporating unstructured EHR data into the SCDM** by evaluating other common data models, including the potential for harmonization or interoperability with, or incorporation of, emerging industry data standards

iii. **Develop new data quality assurance standards and process** to enable more flexible and timely quality assurance for new data types, such as unstructured text, and to enable harmonization and modernization of the Sentinel System with alternative common data models (CDMs)

iv. **Develop and refine EHR validation methods** to promote extraction of structured EHR data fields, such as semi-automated reviews of digitized EHRs to enable endpoint, HOI and confounder validation

v. **Continue to develop new statistical methods for estimating causal risk** in the distributed data setting, for example to bolster signal identification in situations where there are numerous confounders

vi. **Explore privacy-preserving distributed methods** to link patient records across datasets, including the evaluation of different linkage approaches such as encrypted patient identifiers and algorithm-matching techniques across deidentified datasets.

3. **Improve operational efficiency to help FDA staff continue to engage more effectively with Sentinel System partners**

When data and customizable tools allow, the Sentinel System enables FDA investigators to perform sophisticated epidemiologic analyses more efficiently, without costly and labor-intensive manual patient medical record reviews. The Sentinel System improves on previous approaches, and its efficiency in safety-related analysis can be improved in several ways:

i. **Streamline the Sentinel System query intake and scoping process** to improve FDA staff productivity. Initiatives include:

(a) *Developing an internal FDA IT interface for managing aspects of the Sentinel System* to provide FDA staff with a centrally managed user portal that can also serve as a Sentinel System knowledge repository. Such a portal could be integrated as a component of an existing CDER workflow tracking or content management system and would help to improve FDA staff productivity despite a growing Sentinel System-related workload in the future.

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[2] Examples of ongoing SCDM projects supporting integration of clinical laboratory test results include diabetes and chronic kidney disease

(b)   ***Establishing an internal FDA investigator-accessible reference case library*** of Sentinel System queries, analyses, standardized methods and approaches, and results interpretation. This resource would complement existing training for FDA staff.

(c)   ***Continuously improving existing on-demand, web-based query tools*** for managing Sentinel System work. Today, the Sentinel System's "Query Portal" enables web-based business workflow and collaboration between FDA and the Operations Center. FDA will continue to improve this tool and may expand it to incorporate new capabilities based on the needs of FDA users or the Sentinel System management team. FDA is also supporting the development of a graphical user interface that allows FDA users to directly specify simple routine queries such as drug utilization. In the future, this platform could be used more broadly and incorporate additional capabilities, including tools to assist during initial query refinement.

ii. **Promote flexible use of data sources, prioritizing content from data partners and** vendors based on specific elements of a safety query. The Sentinel System will take the following steps to move in this direction:

(a)   ***Use an optimal number of Sentinel System data partner network members for queries***, based on the specific population and methodological approach required to address the safety question. This would allow greater flexibility in contracting with Sentinel System data partners, including differential data refresh frequency.

(b)   ***Direct queries to data partners based on their unique strengths*** and encourage data partners to evolve their participation based on unique strengths and local analytic capabilities. The characteristics of datasets available through the Sentinel System Partner network vary widely. Some provide robust linkages between claims and structured EHR data fields, for example, while others have access to robust patient sub-populations, such as those over age 65. Using the special strengths of data partners will help users innovate and help balance cost, efficiency and partner engagement.

(c)   ***Continue to provide safety staff with access to anonymized commercially available data sources,*** including vendors who provide access to "on-demand" data sets, especially for preliminary analyses. These data sources will continue to be used to assess background rates, refine diagnostic and reimbursement algorithms, and iterate and bolster Sentinel System analyses.

iii. **Evolve specialization across production and development within the Sentinel System** to support the dual objectives of promoting standardization in the analytic production system and advancing specialization in the development system. This approach separates "routine" safety queries with minimal programming requirements from more complex analyses that require customized data linkages, novel analytic methods or other evolving capabilities. This approach may provide a range of benefits: capacity preservation; the predictability of cost and time for routine queries; an ability to contract with specific Sentinel System network partners for specialized analyses; and the use of specialized resources for development. Coordinated management of a common infrastructure will be critical for tracking workflow, performance and quality, administrative activities, communicating and security across these systems. This operating vision is predicated on the notion that the Sentinel System is constantly evolving, and that elements of the development system today may be shifted into production once mature.

iv. **Continue to expand training and development opportunities** among FDA staff to support productivity and augment end-user experience. As Sentinel System capabilities evolve, staff will need to keep pace by broadening their analytical and methodological competencies. For example, as new data linkages and HOIs are developed, Sentinel System queries that initially resulted in an ARIA-insufficient determination are increasingly possible. Identifying key training needs, providing greater access to on-demand training resources, and increasing FDA staff exposure will promote their development.

v. **Reinforce a culture of continuous improvement** to boost productivity, process efficiency and optimize cost as the Sentinel System matures, evolves and expands. For example, Manual of Policies and Procedures (MAPPs) can be continuously refined as new capabilities and processes are introduced.

vi. **Selectively incorporate innovative technologies.** The Sentinel System will continue to serve as a "laboratory" for innovative technology experiments in addition to operational initiatives that help it run more efficiently day-to-day. Proof-of-concept projects will help the Sentinel System transform over the long term. FDA will aim to explore five high-potential innovation themes (see **Exhibit 5**):

Natural Language Processing (NLP)	**Establish standards for NLP** to identify complex health outcomes defined by multiple data elements
Advanced analytics	**Support maturation of advanced analytics,** including machine learning to improve evaluations of drug safety and effectiveness
Novel data sources	**Analyze utility of novel data sources** including patient generated data
Data interoperability	**Explore harmonization of the Sentinel common data model** with other established and complementary models to expand the breadth of Sentinel System data
Emerging disruptive technologies	**Explore promising technologies** through rapid prototyping or demonstration projects

Exhibit 5. Select Sentinel System innovation initiatives

(a) **Establish standards for natural language processing (NLP)** of unstructured data, including best practices for regulatory use. This technology can capture valuable clinical and patient information presented as unstructured text in EHRs and enrich structured data, such as for the insurance claims now available for analysis. Incorporation of data derived from NLP will enable the Sentinel System to identify previously undetected complex health outcomes, defined by multiple data elements, and directly enhance its abilities to assess patient safety and efficacy. Applications of NLP should ultimately enhance productivity during data collection and analysis. Staff

using the Sentinel System will need to monitor the performance of NLP algorithms, as small changes in source data may require adjustments to ensure accuracy.

(b) **Establish best practices for using other types of advanced analytics** in post-market safety. Machine learning can advance key elements of safety evaluations, including HOI validation, propensity score matching and patient phenotyping. The technology may also help investigators evaluate or refine new HOIs that traditionally take significant manual effort. To realize this potential, the Sentinel System will provide an optimal learning ground where machine learning technology can be tested and improved, ensuring that it is used in scientific and responsible ways to evaluate drug safety and efficiency. This will require developing dependent technologies and methods.

(c) **Explore the utility of novel primary and secondary data sources**. New clinical data sources are being introduced to the healthcare ecosystem quickly with the diffusion of once costly technologies, such as genome sequencing, and novel collection media such as wearables that capture huge amounts of data outside traditional healthcare settings. These additional sources can help improve all dimensions of data quality, including coverage, granularity and duration. FDA will work to understand their potential application and utility in safety monitoring and RWE generation for effectiveness. For example, incorporating genomics data may provide additional HOIs as endpoints, but using such data would require modifications to the Sentinel System common data model. Additional considerations for new data source integration include validation, security, confidentiality, privacy and legal concerns.

(d) **Enhance interoperability** between the SCDM and other major common data models to selectively supplement data breadth and granularity. The SCDM provides a common structure to enable the analysis of data across a variety of sources. To continue to broaden its scale, FDA might modernize the Sentinel System by harmonizing its SCDM with other established CDMs such as the Observational Medicinal Outcomes Partnership, PCORnet, Informatics for Integrating Biology at the Bedside (i2b2), and/or industry standards such as the American Medical Association's Integrated Health Model Initiative, and link them with the Sentinel System data infrastructure. Exploring opportunities to enhance SCDM interoperability may become a long-term priority as alternative CDMs gain utility and evolve. As a part of exploring innovation in the Sentinel System context, an initial assessment of the broader CDM landscape, such as disease-specific CDMs, will help FDA establish objectives and a timeframe for evolving the SCDM.

i. **Monitor novel technologies and their potential implications for Sentinel System infrastructure and analysis.** The pace of technology innovation requires FDA to continuously monitor promising new technologies for potential applications. Blockchain, for example, is a digital ledger technology that makes records using cryptography. This may allow patients to permit access to their personal health data while maintaining their privacy. Some novel technologies are disruptive and garner intense interest. FDA will carefully assess their potential benefits, including efficiency gains and new capabilities. The Sentinel System can serve as a laboratory for exploring promising technologies. A flexible pool of funds set aside for investment in small-scale experiments will enable an FDA-dedicated Sentinel System Development Center to ideate and quickly prototype promising technologies.

3.2 Strategic Aim B: Further enhance safety analysis capabilities

As described in Strategic Aim A, improving the Sentinel System's foundation will greatly benefit its safety analysis capabilities – the core of the Sentinel System.

Within safety, foundational improvements will help FDA achieve two major goals:

1. **Increase ARIA sufficiency.** FDA's successful investment in expanding the range of questions addressable by the Sentinel System will improve ARIA sufficiency (defined in Section 2). In the two years following the establishment of the ARIA process, about 50% of potential analyses were ARIA-sufficient. ARIA sufficiency determination is driven by the Sentinel System's ability to conduct analysis sufficient to meet the regulatory question based on five dimensions: study population; exposure (drug); HOI; clinically necessary covariates; and the availability of standard tools for conducting analysis without additional customized programming. Data adequacy remains the major obstacle: most analyses that are ARIA-insufficient do not capture the HOI in the target. To date, the largest epidemiologic classifications for insufficiency include study population, exposure and outcome. Although a 100% ARIA sufficiency target is not realistic for a such a highly standardized tool, improvements in data capture will help close the gap.

2. **Enhance active signal detection in the post-market setting.** While the Sentinel System has transformed the way safety signals are assessed in the post-market setting, FDA still relies on non-Sentinel System sources such as company-generated signals, clinical trials, the Adverse Event Reporting System, medical literature and lay media to identify the first potential safety signals. Supplemental signal detection capabilities will enable the Sentinel System to mature as an integrated post-market safety surveillance asset. Current signal detection sources will continue to play an important role in the assessment of medical product safety, but the Sentinel System is uniquely positioned to fill a gap in the systematic analysis of large data sets to yield novel safety signals that may otherwise go undetected.

   One Sentinel System development project in this area, TreeScan, aims to systematically and proactively scan for potential safety issues. TreeScan is designed to "*simultaneously evaluate thousands of potential adverse events or disease outcomes to determine if any occur with higher probability among patients exposed to a specific pharmaceutical drug, device, or vaccine, adjusting for the multiple tests inherent in the many adverse events evaluated.*"[3] By expanding signal detection capabilities across the full breadth of available data sources, the Sentinel System would no longer be limited to testing hypotheses of a specific product against a prespecified single adverse outcome, but would instead test a drug against the full universe of observed adverse outcomes. Fully deployed, an advanced signal detection capability could examine all exposure variables across drugs, devices and vaccines against all potential health outcomes simultaneously, and may ultimately help to transform drug safety surveillance from a reactive to a continuous, real-time process.

   Realizing the potential of active signal detection will require overcoming significant challenges. As a system built on unguided evaluation of big data, active signal detection is exposed to the inherent risks of false positive and false negative findings. In addition to multiple testing, the new capability will also need to account for a variety of confounders across outcomes and for the granularity of available data. To overcome these challenges, the Sentinel System's future active signal detection capability will draw on epidemiologic,

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[3] Description of pharmacovigilance capability of TreeScan: https://www.treescan.org/

statistical and clinical expertise to test and improve its algorithms in an iterative fashion through validation studies.

Active signal detection will benefit from targeted resource allocation in the next five years. In expanding safety surveillance from a strictly reactive process to include proactive processes and move to the next horizon in terms of safety, FDA will need to establish transformative capabilities beyond foundational enhancements. Actions will include:

i.   **Supporting dedicated staff time and knowledge-sharing** among Sentinel System leadership and key Sentinel System experts to support TreeScan development and other signal detection tools

ii. **Convening leaders in active signal detection** from across disciplines to encourage scientific exchange and support TreeScan refinement (see strategic priority D below)

iii. **Promoting analytic innovation** through exploratory and demonstration projects that expand the repertoire of available analytic tools and allow investigators to tailor each tool's capabilities to the specific drug and clinical scenario of concern

iv. **Attracting novel external development** through coordinated activity at a Sentinel System Innovation center responsible for developing new methods, tools and infrastructure. For example, new incentives could attract non-FDA stakeholders to independently develop new approaches to signal detection

v.   **Developing methodologies** to track and measure progress against hypothesis generation, tolerance of background signals and false positives, and speed of analysis.

3.3 Strategic Aim C: Accelerate access to and broader use of real-world data to evaluate effectiveness

The Sentinel System is a powerful tool with a broad range of applications in the service of public health. At its inception, a group of senior Sentinel Initiative stakeholders wrote, "health care data represent a precious resource that must be used to the fullest possible extent to promote the public health, while the rights of patients and consumers are protected. … [T]he Sentinel System can and should become a national resource for evidence development and a cornerstone of a learning health care system."[4] Progress over the last decade toward that objective has been substantial. Beyond the universe of safety-focused applications in the prior strategy, the Sentinel System will enable a wide range of other public health endeavors, including supporting the drug development process, enhancing drug utilization review, measuring the impact of risk management, facilitating public health intervention impact assessments, pandemic surveillance, and a host of other scenarios in which a comprehensive view of the nation's health is required. In short, the Sentinel System has the potential to catalyze meaningful change in the healthcare ecosystem, including the use of real-world data in drug development.

The FDA-Catalyst program uses the Sentinel System's infrastructure to expand FDA's ability to gather information about the performance of regulated medical products following FDA approval.

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[4] "Developing the Sentinel System – A National Resource for Evidence Development." Behrman R.E. Benner J.S., Brown J.S., McClellan M., Woodcock J., and Platt R. New England Journal of Medicine, 2011; 364:498-499

This program relies on the Sentinel System's infrastructure to identify cohorts of interest and conduct analyses. Unlike the Sentinel System, its activities may involve interventions and interactions in addition to the use of routinely collected data.[5] FDA-Catalyst has used the Sentinel System to define and promote the effective use of RWD research approaches, including facilitating infrastructure advances, promoting innovative methods, and piloting novel use cases. In doing so, FDA-Catalyst has advanced the adoption of RWD approaches by the broader drug development ecosystem. Deployed at scale, FDA-Catalyst and the Sentinel System will accelerate this process. Specifically, they offer a credible platform on which FDA, as a science-driven regulatory voice, can define, test and shape regulatory-grade data, methods and analytic standards for the drug development process.

FDA-Catalyst represents a unique mechanism to help FDA explore the universe of questions that can be addressed using RWE, and establish best practices for study design and data quality for effectiveness questions using RWD, as these may differ from those used for safety requirements. By carrying out these activities, FDA-Catalyst will help inform the development and issuance of guidance on the utility of RWE for addressing efficacy questions. This is in support of FDA's broader mandate regarding the evaluation of RWE outlined in the 21st Century Cures Act. (See Appendix **Table 3**).[6]

FDA-Catalyst will continue to serve as a platform to accelerate RWD infrastructure and methods in the drug development ecosystem through demonstration projects. One example of a pathfinding demonstration project is the open source FDA-MyStudies app.[7] Because FDA does not develop drugs and biologics, industry participation will be necessary to build this ecosystem. The following strategic initiatives may therefore be linked to projects falling under the purview of FDA-Catalyst:

1. **Establishing standards for high-quality RWD and evaluating RWE applications.** FDA-Catalyst is a credible platform for demonstration projects to provide insights or learnings that may inform the development of relevant expertise in RWE application. Given its experience, FDA-Catalyst will continue to serve as a development hub for important infrastructure that supports the Sentinel System, but with a focus on interaction or intervention. FDA-Catalyst will help to further develop fundamental RWD capabilities by allocating resources toward four areas related to technology, methods and data infrastructure development:

   i. **Enhance linkages to more granular data sources relevant to effectiveness demonstrations.** To accelerate RWE applications, FDA-Catalyst must continue to incorporate linkages to new relevant data sources including EHRs, including data sources such as medical images, and primary data obtained directly from patients, such as from M-health[8] and wearable devices. Priorities will include preserving patient confidentiality and developing analytic methods that link data held by different organizations.

   ii. **Use new data sources to enhance trials.** The Sentinel System has significant potential for enhancing links across data sources. This has implications for patient engagement,

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[5] "FDA-Catalyst" *Sentinel Initiative.* Website accessed 12-01-2018.

[6] United States. *21st Century Cures Act*. H.R. 34, 114th Cong. (2015-16)

[7] "FDA In Brief: FDA launches new digital tool to help capture real world data from patients to help inform regulatory decision-making" *US Food & Drug Administration News & Events.* Website accessed 12-01-2018.

[8] M-heath or mobile health, including the use of mobile phones and other wireless technologies

including helping patients navigate the clinical trial recruitment process. For example, some disease registries have longitudinal data on select patient populations. By linking disease registries with other primary and secondary RWD sources, the registries may become vehicles for patient engagement, increasing access and potentially accelerating drug development.

iii. **Expanding and validating HOIs relevant for effectiveness.** The Sentinel System can incorporate and validate new HOIs in transparent ways, supporting both safety analysis-related and RWE-driven efficacy use cases. It will need to validate new HOIs as new RWD sources are introduced. Validation in this context will differ from that in the safety analysis-related context, as clinically relevant endpoints will be developed and validated by using RWD sources beyond claims and medical records, such as primary patient and physician-generated data. That said, the individual evidentiary standards for efficacy and safety claims will remain consistent. This expansion of HOIs will rapidly increase potential efficacy and effectiveness endpoints. Continuous engagement with medical reviewers and external stakeholders will help accelerate the adoption of the RWD-sourced HOIs, which can be prioritized based on relevance and feasibility in a transparent manner.

iv. **Reusable infrastructure**. Since FDA has always prioritized transparency, it posts validated Sentinel System methods, tools and data standards on the Sentinel website.[9] This practice will continue as the Sentinel System expands. As infrastructure capabilities advance, they can be made available on other web-based hosting services. This can expand to other Sentinel System assets, including patient interface software or apps. Disseminating this infrastructure will drive the adoption of validated instruments already compliant with FDA data standards and promote their acceptance and enhancement by the broader RWE ecosystem.

v. **Methodologic best practices for causal inference.** Accelerating the use of RWE for regulatory decision-making requires clear methodologic practices and high-quality data. The Sentinel System and FDA-Catalyst can support such efforts as testbeds for comparing the results of observational analyses with those from randomized controlled clinical trials. Establishing concordance rates based on RWE from observational studies using the Sentinel System may yield insights into the degree of concordance (e.g., how might Sentinel System results complement those obtained from a clinical trial?) and the portion of the data with no concordance. Lack of concordance enables FDA and its partners to conduct root-cause analyses that may yield different answers and reveal opportunities for enhancement across both development paradigms. Understanding where and how divergence occurs can help FDA and other stakeholders create methodologic standards for observational research, including the extent to which such data may be used to support causal inferences regarding treatments. Evaluating how causal inferences can be drawn from RWD will be an ongoing process that the Sentinel System can help shape.

As more stakeholders use the Sentinel System to explore the value of RWE for efficacy, some will have successes, such as filling data gaps with patient-generated data, and some will face challenges, such as use cases that cannot be sufficiently addressed using RWD. FDA will navigate these by following its tradition of transparency with the Sentinel System.

Using transparent processes, including data choices, methods and analytic strategies, will ensure the continued credibility of Sentinel System analyses. Other mechanisms, including rigorous

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[9] "Sentinel is a national medical product monitoring system" *Sentinel Initiative.* Website accessed 12-01-2018.

review processes and a commitment to disseminate findings, will also promote confidence in the Sentinel System among internal and external stakeholders and help broaden the Sentinel System's role in drug development.

3.4 Strategic Aim D: Create a national resource by broadening the Sentinel user base

The Sentinel System has significantly matured as a national safety surveillance system by linking a wide range data resources under a shared analytic umbrella. Recognizing the potential of such a system, FDA reaffirmed its commitment to develop the Sentinel System into a national resource in the PDUFA VI goals letter, noting that it will "evaluate additional ways to facilitate public and sponsor access to the Sentinel System's distributed data network to conduct safety surveillance."

FDA envisions the Sentinel System as both the gold standard for safety surveillance and a tool for holistically enhancing the understanding of medical product performance. To achieve this vision, multiple stakeholders need to use the Sentinel System and contribute to the evolution of its capabilities and infrastructure. Although many stakeholders already engage with the Sentinel System, FDA will deepen their involvement by broadening awareness and access, and enable broader utilization of Sentinel System tools, methods and data infrastructure.

Expanding access to and use of the Sentinel System is valuable for several reasons:

- Expanding the breadth and volume of questions asked of the Sentinel System should accelerate its growth and expand its potential scope

- Increasing the number of stakeholder interactions with the platform should help establish it as a robust, open, self-sustaining resource in the drug development ecosystem

- Public health should improve as users translate insights into actions that benefit patients.

The Sentinel System is configured as an open national resource, but it is not widely used beyond FDA. Today, the community of Sentinel System users beyond FDA can interact with the System in three ways:

A. **Use open-access tools, methods and published analyses, outputs and available simulated datasets.** These elements may inform work outside FDA and outside of the Sentinel System data partner network. Users of Sentinel System capabilities include, for example, the National Institutes of Health's Health Care Systems Research Collaboratory Distributed Research Network, the Patient-Centered Outcome Research Institute's PCORnet, the Biologics and Biosimilars Collective Intelligence Consortium, and industry. A synthetic use file known as SynPUF provides access to a simulated dataset that enables the public to create their own analytics packages in a sandbox environment, such as translating the Medicare Claims SynPUF into the SCDM. While a host of stakeholders use Sentinel System capabilities, uptake remains slow. Understanding, using and modifying the modular programs requires a high degree of expertise that is a barrier to usage.

B. **Access Sentinel System capabilities through the Innovation in Medical Evidence and Development Surveillance (IMEDS) program.** This public-private partnership with the Reagan-Udall foundation provides private-sector entities with access to the Sentinel System infrastructure.

C. **Access via the Operations Center.** The Sentinel System Operations Center is permitted to provide non-FDA parties with an alternative mechanism to IMEDS for accessing the Sentinel System.

FDA recognizes that access methods should be simpler and wider if the Sentinel System is to become a sustainable national resource. Expanding usage will mean balancing the benefits users of and partners derive and the costs and capacity implications. FDA will focus on three objectives to reduce barriers and increase Sentinel System utilization by stakeholders throughout the broader learning healthcare ecosystem:

1. **Improving operations and procedures** for accessing tools, methods and results to create a broader ecosystem not reliant on FDA-sponsored Sentinel infrastructure. Tools, methods, and results are available to the public through the Sentinel Initiative website. FDA will streamline user access to help increase utilization of these resources. Opportunities for improvement include:

   i. Developing clearly defined and communicated points of contact for users outside of FDA to enable their exploration of potential uses for their specific needs

   ii. Improving the public-facing interfaces and infrastructure, such as by improving the clarity of links on the Sentinel Initiative website (www.Sentinelinitiative.org) to help external parties gain access

   iii. Continuing to promote the availability of Sentinel System methods, tools, and infrastructure on online developer community websites, such as GitHub.com, including appropriate user guides and support documentation to ease navigation

   iv. Making the existing tools available in a broader range of programming languages

   v. Engaging regularly with non-FDA users to obtain feedback on user experience, including recommendations on operational and process-related improvements

   vi. Routinely publishing information on the use of Sentinel System tools, methods or data infrastructure by a variety of stakeholders to demonstrate the breadth of possible work supported with the national resource.

FDA will also facilitate public understanding of how tools and capabilities can be used, and inform the public about how the Sentinel System is impacting public health. (See Strategic Aim E for a detailed list of activities related to convening, communication and dissemination.)

2. **Evolving the operating model to achieve the vision of creating a national resource.** The Sentinel System provides a unique value proposition not available with other data resources, including:

   - Unmatched scale and patient life years covered; as of mid-2017, resources included 425 million person-years of quality-checked observational data

   - Demographically diverse insured patient populations in a single common data model

   - Access to consolidated and standardized data sets with the volume required to evaluate rare health outcomes, rare diseases, and vulnerable populations, such as pregnant women, the elderly and children

   - Potential for direct collaboration with academicians, epidemiologists and clinicians associated with the Sentinel System data partner network.

Given this unique value proposition, FDA envisions the Sentinel System as a national resource to address a variety of questions for different stakeholders in the learning healthcare ecosystem. For example, sponsors could use the Sentinel System to address safety questions identified during FDA review and replicate analyses using robust RWD. Similarly, researchers may benefit from the scale of the Sentinel System in studying broad public health questions. To achieve this vision, FDA will support three types of activities to broaden access:

i. **Establishing a refined operating model for the Sentinel System.** FDA will use the process associated with re-competition of the Sentinel System operating contract to improve the Sentinel System operating model from 2019 through 2024. (See conceptual **Exhibit 6**.) A lead Operations Center would have diverse responsibilities including managing the data partners network, contracting, workflow tracking, and operational planning, including capacity and prioritization, data request coordination and management of Federal Information Security Management Act-compliant IT systems. FDA will aim to maintain an Innovation Center that works closely with the Operations Center to ensure tight control over the establishment of new Sentinel System capabilities. In this conceptual model, a central Operations Center would be the primary curator of the SCDM and would develop a strategy to prioritize continuous tool and data development and enhancement. The Center would also deliver and expand on user training, help to continue modernizing the SCDM, and direct resources toward evolving new priority capability areas. In the near term, the Operations Center would manage routine Sentinel System queries. Over time, the management of production capacity could be transitioned to additional Analytics Centers. A small number of distinct Analytics Centers could interact directly with stakeholders or "customers" to design, refine and analyze queries, and develop innovative methods to further evolve the Sentinel System. While opening the Sentinel System as a national resource is unlikely to defray the cost of maintenance in the near term, this approach would include four benefits:

(a) Increasing points of engagement with the Sentinel System, as users could interact with multiple Analytics Centers to develop and run queries, with oversight and coordination by an Operations Center

(b) Allowing FDA to support Operations Center management of increased query volume, accelerating growth, improving efficiency and production speed, and developing methods for unexplored queries

(c) Providing an alternative mechanism for broadening capacity and spurring externally driven innovation, enabling growth in the quantity and breadth of questions that can be addressed in the Sentinel System

(d) Attracting new partners and helping to increase the sustainability of the Sentinel System through continued diversification of the Sentinel System Data Partner network.

ii. **Define a fit-for-purpose governance model between FDA and the Operations Center.** As demands on the Sentinel System rise and the operating model of the Sentinel System evolves, FDA may elect to modify its governance model. Given its position as a majority user, intimate knowledge of capabilities and a vested interest in shaping the evolution and direction of the program, FDA will play a strong advisory role, through its contracting vehicles and interactions with key personnel, on a host of operational topics including:

(a) Operational processes, workflow tracking and continuous improvement

(b) Quality assurance

    (c)   Capacity planning and resource allocation

    (d)   Implications of contracting, financial models, and potential reinvestment strategies

    (e)   Capability gaps and opportunities

    (f)   Conflict of interest policies.

    iii. **Partner directly with other federal agencies, such as the Centers for Disease Control and the National Institutes of Health, to conduct demonstration projects that broaden Sentinel System utilization.** FDA regularly convenes stakeholders in the healthcare learning ecosystem across a range of topics. As access to the Sentinel System expands, FDA will support its utilization with other public-sector partners to broaden the user base. A subset of Sentinel System use cases may align across FDA and other federal agencies. When possible, FDA will identify opportunities to partner with those agencies to conduct demonstration projects that highlight the capabilities of the Sentinel System in these new contexts. By doing this, FDA will continue to spur external stakeholder interest, promote the use of the Sentinel System, and simultaneously drive innovation.

The Sentinel System can significantly broaden its value as a national resource over the next five years. As it continues to evolve and mature, its value to FDA and the broader learning healthcare ecosystem will grow. FDA will remain an active participant to help the Sentinel System achieve the vision of becoming the gold standard for safety surveillance and medical product usage, and will do so in an accessible and open manner in partnership with the broader healthcare ecosystem.
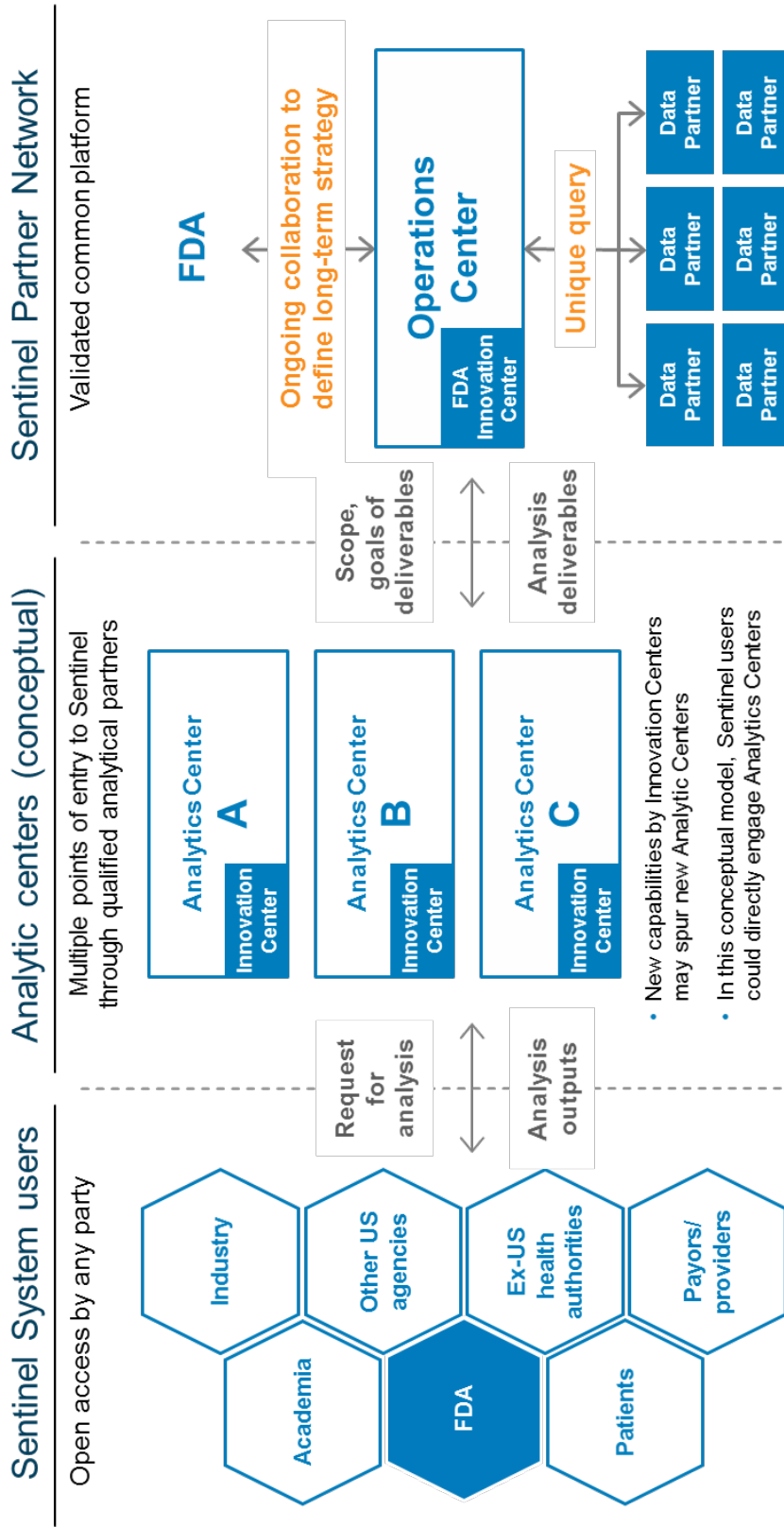
Exhibit 6. Conceptual vision for Sentinel System network structure.

3.5 Strategic Aim E: Disseminate knowledge and advance regulatory science to enable innovation

Across all potential Sentinel System use cases, FDA will continue to position the Agency as a collaborative curator of the Sentinel System. That will include convening stakeholder groups across the learning healthcare ecosystem, publishing results and sharing insights, and conducting demonstration projects. One goal of these activities is shaping guidance and policy, based on FDA's experience with the Sentinel System, and gathering feedback from stakeholders. Over the course of this five-year strategy, FDA will aim to:

1. **Convene public working sessions with active and potential Sentinel System users** such as pharmaceutical industry stakeholders, healthcare payors and providers, and academicians, to better understand how they interact with the Sentinel System. As the Agency engages these stakeholders, it should:

    i. Communicate the unique value proposition and expanding capabilities of the Sentinel System

    ii. Identify common aims across all user groups, including capabilities and data standards

    iii. Identify gaps and opportunities related to data linkages and methods that would support new stakeholder-sourced use cases

    iv. Obtain feedback on user experience.

2. **Shape the discussion and participate as a thought leader in the learning healthcare community.** Throughout the Sentinel Initiative's history, FDA has played a crucial convening role through webinars, training events and the annual public workshop. These venues bring stakeholders together across the learning healthcare ecosystem, providing opportunities to share insights and exchange ideas that might be addressed at a community level. Exchanges facilitated through these events provide important feedback to FDA staff and Sentinel Initiative leadership. For example, in August 2018, the Duke-Margolis Center for Health Policy hosted a public webinar during which Sentinel System capability development projects were presented and discussed in the context of broadening ARIA sufficiency, and in terms of active collaborations with Sentinel System data partners to improve outcome validation activities. These types of venues will continue to bring leaders together to align perspectives across healthcare ecosystem stakeholder groups. In the near term, FDA has or will conduct events to:

    i. Solicit feedback on the five-year FDA Sentinel System strategy

    ii. Obtain input on proposals to enhance active signal detection capabilities

    iii. Obtain input on standards for utilizing new forms of RWD for effectiveness demonstrations

    iv. Obtain expert input and shape approaches to explore high-priority innovation use cases, such as NLP of unstructured data analysis.

3. **Communicate Sentinel System results and insights.** FDA disseminates insights from the Sentinel System, including the underlying methods and analytics, via the Sentinel Initiative website. Contributing to the peer-reviewed scientific literature will further support innovation and knowledge-sharing. FDA will continue to make the growing knowledge from project results, both positive and negative, publicly available wherever possible. This is particularly

relevant as the Sentinel System makes progress on strategic initiatives related to RWE demonstration projects under the FDA-Catalyst banner and beyond. Analyses and interpretation of data, particularly as they relate to establishing novel methodologies, analytical approaches and health outcomes, should be published in open-access peer-reviewed journals. FDA will encourage staff and the broader group of Sentinel System project team members to present their work at scientific meetings, and to participate in and establish new venues for knowledge transfer. These activities can support the generation of new draft guidance for investigators and sponsors involved in drug development.

Section 4 – Summary

From 2019 through 2023, FDA will prioritize activities that will help transform the Sentinel System across several dimensions to achieve its vision of establishing itself as a national resource used to capture real-world medical product performance. The scope of initiatives described in this strategy are feasible over the next five years, but the time and resources required to achieve these strategic aims will vary based on the progress of implementation, learnings from actions taken, underlying foundational capabilities, and overarching Agency-level priorities.

To enable the strategy, FDA will use a strategic portfolio-based funding mechanism that encourages demonstration projects. This approach will provide greater flexibility for project management as new capabilities emerge, and link project delivery to realized value, such as based on the achievement of discrete project milestones. This will enable better tracking of resource use, and ensure that outputs remain relevant given continuous innovation and disruption in the broader technology ecosystem. In general, the activities will be staged over three periods: the near term of the next 12-18 months, the mid-term of two to three years, and the long term of three to five years. **Exhibit 7** illustrates the approximate sequence of activities over the lifespan of the Sentinel System strategy.

Near-term initiatives will establish a foundation for the next evolution of the Sentinel System, with a focus on activities that strengthen the data platform, enhance infrastructure and methods, and upgrade operational elements of the Sentinel System. As progress is made on building the future foundation of safety signal detection and RWD-driven effectiveness capabilities, the more complex strategic aims related to future safety and effectiveness capabilities may be pursued. Critical development milestones must be carefully sequenced to develop next-generation Sentinel System capabilities, such as establishing EHR validation methods in anticipation of RWE generation for post-market safety surveillance. In the long term, FDA will help broaden external access to the Sentinel System, and continue its role in shaping the learning healthcare ecosystem. Finally, FDA will continuously incorporate improvements into the Sentinel System, disseminate knowledge externally, and explore promising technologies to drive innovation.

By implementing this strategy, FDA has a remarkable opportunity not only to continue to expand the Sentinel System's robust safety surveillance capabilities but also to establish it as a suitable platform for the generation of RWE and explore the universe of addressable effectiveness questions in the future.
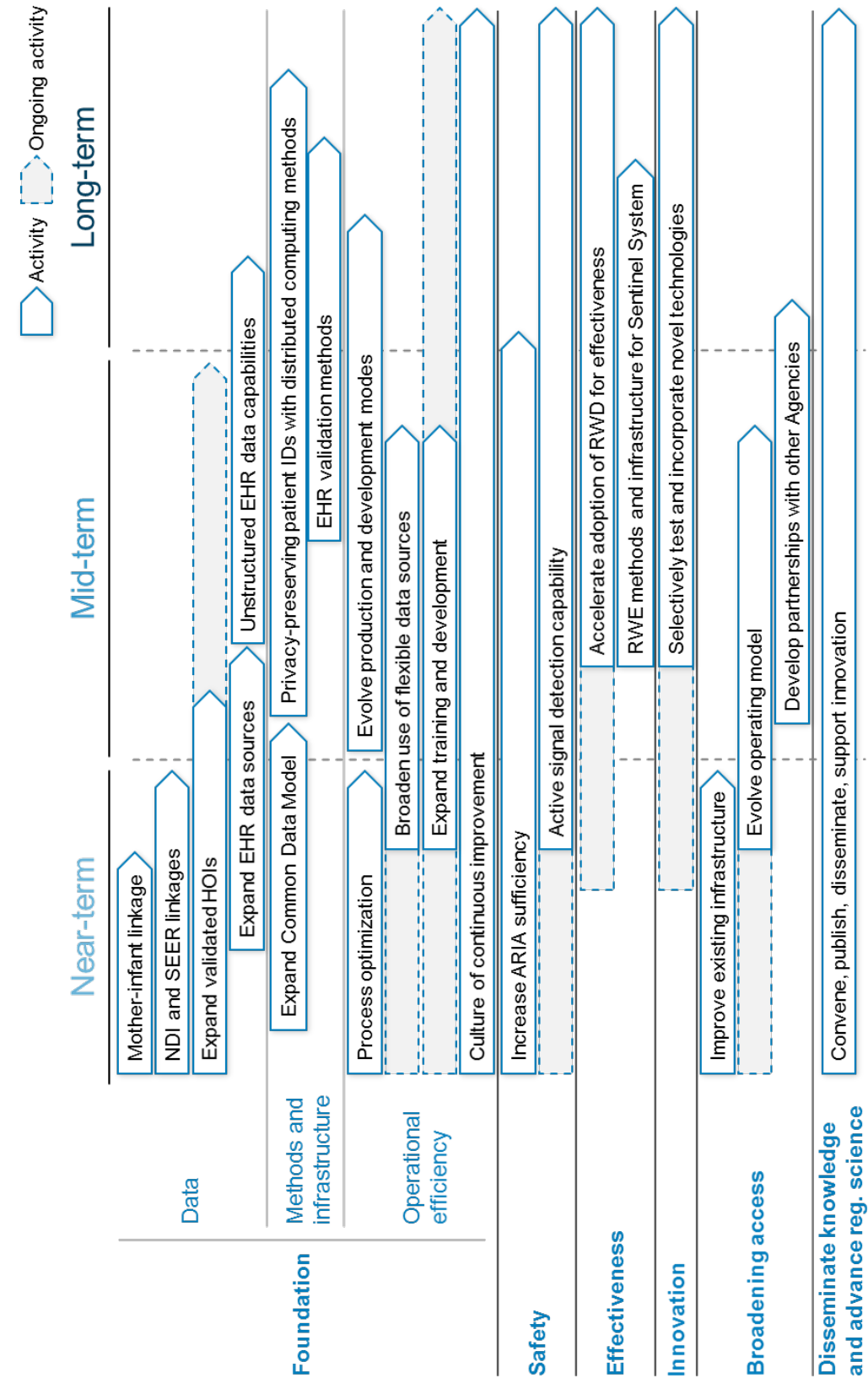
Exhibit 7. Strategic roadmap

Appendix

Table 1. Sentinel System strategy in support of PDUFA VI goals[10]

PDUFA VI goals		Related section in this plan	Sentinel strategy in support of goal
(1)	Expand the Sentinel System's sources of data and enhance the system's core capabilities	Section 3.1 (1)	Expand data sources and linkages
		Section 3.1 (2)	Enhance data infrastructure and methods development
		Section 3.1 (3)	Make operational efficiency improvements
		Section 3.2 (1)	Increase ARIA sufficiency
		Section 3.2 (2)	Enhance the Sentinel System's active signal detection capability
(2)	Enhance communication with sponsors and the public regarding general methodologies, including appropriate ways to query and use Sentinel data	Section 3.5 (1)	Convene public working sessions with active and potential Sentinel System users
		Section 3.5 (2)	Shape the discussion and participate as a thought leader in the learning healthcare community
		Section 3.5 (3)	Communicate results and the growing knowledge associated with Sentinel System use and insights
(3)	Evaluate additional ways to facilitate public and sponsor access to Sentinel's distributed data network to conduct safety surveillance	Section 3.4 (1)	Improve operations and procedures for accessing existing Sentinel System tools, methods, and results
		Section 3.4 (2a)	Implement a new operating model
		Section 3.5 (1)	Convene public working sessions with active and potential Sentinel System users
(4)	By end of FY 2019, hold or support a public meeting to discuss and seek feedback on current and emerging Sentinel projects to improve Sentinel and Active Risk Identification and Analysis (ARIA)	Completed	Workshops held, including on 7/26/18: *Planned Next Steps to Advance the Sentinel System* to provide insight into the specific challenges surrounding ARIA insufficiency, and highlight key solution approaches

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10 "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018-2022"
Section K "enhancement and modernization of the FDA drug safety system" (pages 34-36), Website accessed 12-01-2018.

(5)	By end of FY 2020, establish policies and procedures (MAPPs and SOPPs) to inform sponsors about the planned use of Sentinel to evaluate a safety signal involving their products	Section 3.1 (3e)	Reinforce a culture of continuous improvement (including establishing or updating MAPPs as appropriate)
(6)	By end of FY 2020, facilitate integration of Sentinel into the human drug review program through staff development and updates to SOPPs and MAPPs	Section 3.1 (3d)	Continue to expand training and development opportunities among FDA staff
		Section 3.1 (3e)	Reinforce a culture of continuous improvement, including updates to relevant MAPPs as appropriate
(7)	By end of FY 2020, develop training for review staff to given them a working knowledge of Sentinel and allow them to participate in its use for safety evaluations	Section 3.1 (3d)	Continue to expand training and development opportunities among FDA staff
(8)	By end of FY 2022, analyze and report on the impact of Sentinel expansion and integration on FDA's use of Sentinel for regulatory purposes	Section 3.1 (3e)	Reinforce a culture of continuous improvement, including formal after-action reviews for major projects, and institution of a quality monitoring and performance management program

Table 2. Sentinel System strategy in support of recommendations from the Sentinel Final Assessment Report (2017)[11]

	Sentinel Final Assessment Report Recommendation	Related section in this plan	Sentinel strategy in support of commitment
(1)	Clearly articulate a long-term strategy for Sentinel, building from the PDUFA VI commitments and including an operational roadmap and plan to deliver, to align stakeholders on the overall vision for Sentinel, the associated strategic priorities and the actions needed to achieve the vision	n/a	The development of this strategy satisfies this recommendation
(2)	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 post-marketing context when a formal PMR is pursued)	Section 3.5 (1)	Convene public working sessions with active and potential Sentinel System users
		Section 3.5 (2)	Shape the discussion and participate as a thought leader in the learning healthcare community
		Section 3.5 (3)	Communicate results and the growing knowledge associated with Sentinel System use and insights
(3)	Create more systematized Sentinel training curriculum, with more regular trainings, with the Operations Center providing regular updates to current users	Section 3.1 (3d)	Continue to expand training and development opportunities among FDA staff
(4)	Continue to foster closer scientific collaboration with Operations Center researchers and relevant data partners	Section 3.1 (3a)	Streamline the Sentinel System query intake and scoping process
		Section 3.1 (3b)	Promote flexible use of potential data sources
		Section 3.1 (3c)	Evolve specialization of production and development modes of the Sentinel System

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[11] "Sentinel Initiative Final Assessment Report" *Sentinel Initiative.* September 2017. Website accessed 12-01-2018.

Table 3. Sentinel System strategic initiatives relevant to the RWE provisions in the 21st Century Cures Act[12]

	21st Century Cures Act mandates (Section 3022)	Related section in this plan	Sentinel strategy in support of mandate
(1)	Establish a program to evaluate the potential use of real-world evidence (1) to support the approval of a new indication for an approved drug and (2) support or satisfy post-approval study requirements	Section 3.3 (1)	Continue to establish standards for high quality RWD and evaluating RWE
		Section 3.2 (1)	Increase ARIA sufficiency to help support post-approval study requirements
(2)	Include in a framework for the RWE program: (1) the sources of real-world evidence, including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities; (2) the gaps in data collection activities; (3) standards and methodologies for collection and analysis of real-world evidence; and (4) the priority areas, remaining challenges, and potential pilot opportunities	Section 3.1 (1)	Expand data sources and linkages so that the Sentinel System can answer a broader range of questions
		Section 3.1 (2)	Enhance data infrastructure and methods development to improve the utility of available data sources
		Section 3.3 (1i-iii)	Enhance linkages to a narrow set of data sources most relevant to effectiveness demonstration projects, use new data sources to enhance clinical trials and, expand and validate HOIs relevant for effectiveness
		Section 3.3 (1v)	Continue to establish standards for high quality RWD and evaluating RWE, including methods for determining causality
(3)	Develop the RWE framework in consultation with stakeholders in public workshops	Section 3.5 (1)	Convene public working sessions with active and potential users
		Section 3.5 (2)	Shape the discussion and participate as a thought leader in the learning healthcare community
(4)	Establish guidance for the industry on circumstances when sponsors of drugs may rely on real-world evidence for regulatory purposes and the appropriate standards and methodologies for collection and analysis of RWE	Section 3.5 (3)	Communicate results and the growing knowledge associated with Sentinel System use and insights and contributing to new draft guidance for investigators and sponsors involved in drug development

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[12] United States. *21st Century Cures Act*. H.R. 34, 114th Cong. (2015-16). Section 3022 "Real World Evidence" (pages 1096-1098)