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Optimizing the Use of Postapproval Pregnancy Safety Studies
September 18-19, 2023, Workshop Report

Introduction

Pregnant individuals have historically been excluded from drug and biological product development trials.[1] As a result, the pregnancy information in the labeling for many of these drug products is based on only nonclinical reproductive toxicology data at the time of approval. The human safety data in pregnant individuals needed to inform labeling and clinical care has often come from postapproval registries, observational studies, spontaneous or published case reports, and case series. Adequate data on individuals who use drug product(s) during pregnancy (i.e., exposed pregnancies) for observational studies often take years to accumulate, especially for drugs that are not routinely used during pregnancy. Overall, the lack of data and the length of time needed to generate adequate data create challenges for providers and patients when making decisions about optimal treatment during pregnancy. In the United States alone, approximately 5.5 million pregnancies occur each year, and half of these pregnant individuals use at least one drug or biological product to treat various chronic (e.g., depression) or acute (e.g., nausea and vomiting in pregnancy) medical conditions.[2,3]

To advance optimal approaches to efficient generation of high-quality human safety data for drug products used during pregnancy, the U.S. Food and Drug Administration (FDA) made a commitment, under the latest reauthorization of the Prescription Drug User Fee Act (PDUFA VII),[4,5] to develop a framework describing how to optimally use data from different types of postapproval pregnancy safety studies. To inform the development of this framework, the Duke-Margolis Institute for Health Policy, working with the FDA, convened a public workshop on September 18-19, 2023.[6]

The workshop brought together interested parties – including patients, providers, researchers, and drug industry representatives – to provide information and facilitate discussions. Topics covered included the need for human pregnancy safety data, possibilities for access to high-quality data, and optimal design and implementation of postapproval pregnancy safety studies. Participants provided feedback on FDA's

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[1] Use of the terms 'drug' or 'drug product' in this report include drug products regulated under section 505 of the Federal Food, Drug, and Cosmetic Act and biological products regulated under section 351 of the Public Health Service Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act.

[2] U.S. Centers for Disease Control and Prevention, National Center for Health Statistics. U.S. Pregnancy Rates Drop During Last Decade [Press Release] Hyattsville (MD); 2023 April 12, Available from: https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2023/20230412.htm

[3] Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol 2011;205:51.e1-8.

[4] PDUFA VII: Fiscal Years 2023 – 2027, https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027, accessed 12/13/2023

[5] Prescription Drug User Fee Act Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027 Commitment Letter, Available from https://www.fda.gov/media/151712/download.

[6] Additional information from the workshop proceedings is available at https://healthpolicy.duke.edu/events/optimizing-use-postapproval-pregnancy-safety-studies

preliminary work on developing a consistent and transparent approach to help decide when and what types of postapproval pregnancy safety studies might optimally be used to obtain timely evidence for regulatory decision-making.[7]

The workshop covered several key areas, including:

- Interested parties' perspectives on opportunities to optimize postapproval pregnancy safety study types and designs;
- FDA's considerations for constructing a draft framework to help identify the most appropriate study type(s) to assess drug safety in pregnancy in a timely manner;
- Potential approaches to bridge knowledge gaps in developing the framework including how FDA's Sentinel Initiative[8] (i.e., Sentinel System and Biologics Effectiveness and Safety (BEST)) may address these gaps; and
- Interested parties' perspectives on FDA's considerations for the proposed framework.

As a next step, FDA will conduct five Sentinel Initiative demonstration projects to address gaps in knowledge about performance characteristics of different study designs (four by FDA's Center for Drug Evaluation and Research (CDER) and one by FDA's Center for Biologics Evaluation and Research (CBER)).[9] The projects' findings will contribute to the ongoing development of the draft framework. In addition, input from workshop attendees (in-person and virtual) and comments to a public docket (Docket No. FDA- 2023-N-3104[10]) will be used to further develop the framework.

Prescription Drug User Fee Act (PDUFA VII) Deliverables

- By September 30, 2023:
  - Hold a public workshop on postapproval safety studies in pregnant individuals to facilitate the determination of optimal postapproval study design(s).
- By September 30, 2024:
  - Publish a workshop report describing the proposed framework.
  - Initiate five demonstration projects.
- By September 30, 2027:
  - Update the proposed framework based on the results of the demonstration projects.
  - Develop a guidance, Manual of Administrative Policies and Procedures (MAPP), and/or Standard Operating Procedures and Policies (SOPP) as appropriate to implement a standardized process for determining necessity and type of pregnancy postapproval studies including postmarketing requirements.

[7] This document summarizes workshop presentations and discussions. It does not necessarily reflect consensus on the topics covered.

[8] FDA's Sentinel Initiative comprises the Sentinel System, FDA-Catalyst, and the CBER Biologics and Safety (BEST) Initiative. For more information, visit https://www.sentinelinitiative.org/about.

[9] Additional information on FDA's demonstration projects to inform development of a pregnancy safety study framework is available at https://www.fda.gov/safety/fdas-sentinel-initiative/fda-demonstration-projects-inform-development-pregnancy-safety-study-framework.

[10] Docket FDA-2023-N-3104. Optimizing the Use of Postapproval Pregnancy Safety Studies; Public Workshop; Request for Comments closed on November 30, 2023. Comments available at: https://www.regulations.gov/document/FDA-2023-N-3104-0001.

When posted, this report meets FDA's PDUFA VII commitment of publishing a workshop report describing the proposed framework. Below, we provide summaries of each session of the public workshop, including a diagram of the framework.

Session 1: Stakeholder Perspectives on the Impact of Postapproval Pregnancy Safety Studies

Objectives: For stakeholders to discuss the impact of and considerations for pregnancy safety studies and to identify potential opportunities to meet stakeholder needs.[11]

A patient, a provider, and a drug industry representative shared their perspectives on the impact of postapproval pregnancy safety studies and the availability of pregnancy safety data. This discussion was largely focused on the complexities of balancing maternal health, medication safety, and the challenges of limited data when making decisions about medication use during pregnancy. Participants emphasized the importance of empowering pregnant individuals and their healthcare providers with the information and support needed to make informed choices. However, limited data on medication safety during pregnancy can introduce uncertainty into this decision-making process, particularly for those managing chronic conditions. Pregnant people with medical conditions must balance the risks of discontinuing medications needed for their health with the potential risks of the medications to the developing fetus. The discussion emphasized the need for preconception counseling and for healthcare providers to work collaboratively with pregnant individuals to navigate this uncertainty carefully, avoiding both undue caution and unfounded reassurance.

The drug industry representative also discussed challenges in achieving sufficient sample size for pregnancy registries studying the risks of birth defects. Other limitations raised by the drug industry representative include challenges with reporting as well as the need to promote retention of study participants for time sufficient to assess pregnancy outcomes. Some panelists and participants acknowledged variability both across activities by industry and in whether there is support for obtaining pregnancy safety data. Some drug companies are beginning to work together and are considering disease-based pregnancy registries to obtain better data.

Session 2: Stakeholder Perspectives on Challenges and Opportunities to Optimize Postapproval Safety Study Types and Designs

Objectives: For stakeholders to share their thoughts on the key factors to enhance the generation of robust and timely drug/biologic safety data for pregnant individuals as part of the drug/biologic development process.

The panelists specifically focused on opportunities to optimize postapproval pregnancy study types and designs. Panelists and participants acknowledged the value of pregnancy registries and database studies and discussed opportunities to address challenges and limitations. Drawing meaningful conclusions on risk associated with drug use during pregnancy based on small numbers of cases in registries or

[11] For consistency, language was primarily used from the workshop's agenda to capture the title and objectives of each session. Since September 2024 the language has continued to evolve and updated terms, e.g., interested parties, are used elsewhere in this report. The workshop's agenda available from: https://healthpolicy.duke.edu/sites/default/files/2023-09/Pregnancy%20Safety%20Study%20Workshop%20Agenda%209.15.23.pdf

database studies was identified as one of the biggest challenges. The panel of experts provided thoughts on how to address this central challenge including designing studies with longer follow-up times and studies that evaluate a spectrum of potential outcomes throughout the lifecycle of a drug product. A disease-based (or multi-product) pregnancy registry may confer the following efficiency and quality benefits:

- Save time and resources in registry setup and maintenance;
- Pool budget and expertise from multiple interested parties;
- Yield greater number of cases because there is less competition for eligible patients and healthcare providers;
- Streamline patient enrollment data gathering and reporting; and
- Provide a central source of information that can be analyzed and used to communicate potential risk(s) consistently and effectively to a wider audience.

Other suggestions for optimizing postapproval safety studies related to drug and biological products included:

- Developing strategies to enhance pregnant individuals' participation and retention by leveraging prenatal care visits;
- Reducing patient and provider burden during participation;
- Simplifying and standardizing protocols and coding of outcomes across studies; and
- Enhancing data coding to facilitate data collection and validation.

Lastly, panelists highlighted the importance of developing analytic approaches that minimize bias and establish study timelines that account for the time needed for the drug to be used and pregnancy outcomes to manifest. The aforementioned suggestions for strategies apply to postapproval surveillance and evaluation for vaccines and other biological products as well as for drug products.

Session 3: FDA's Considerations for Constructing a Pregnancy Safety Study Framework

Objectives: For FDA presenters to provide information on recent work, including: a landscape analysis of postapproval pregnancy safety studies that informed FDA's decision making; a review of postapproval pregnancy safety studies that informed product labeling in compliance with the Pregnancy and Lactation Labeling Rule (PLLR); and an analysis characterizing product utilization during pregnancy that helped form key considerations for the construction of a pregnancy safety study framework.

Overall, FDA's analyses indicate that a wide variety of approaches have been used to assess the safety of medical products during pregnancy and to inform product labeling. Among different types of studies, pregnancy registry studies are used most frequently and have primarily contributed to safety signal detection and to informing labeling. Study approaches and key findings from FDA's analyses that were presented at the workshop are summarized below.

- A landscape analysis of postapproval pregnancy safety studies and their impact on FDA safety-related labeling changes identified 333 such studies. The majority of the studies (n=242) were from an FDA database of postmarketing requirements and commitments (PMR/PMC) of which 169 (70%) were established in the last 10 years and 65 (27%) were completed. Of the completed studies, 30 (46%) led to a labeling update. The average time from establishment of the PMR or PMC to labeling update was 11 years. Slow enrollment resulting in low data accrual seems to be

a common issue and can lead to delays in obtaining information that may lead to labeling updates.

- A cross-sectional descriptive study of the sources and characteristics of quantitative human pregnancy safety data contained in the "*Human Data*" subsection of PLLR-compliant drug labeling from 2015 to 2021 identified 145 unique labelings with 198 quantitative human pregnancy safety statements from 177 unique studies. Some labelings had multiple quantitative statements supported by multiple study types. The most frequently identified study type supporting quantitative safety data statements in PLLR-compliant labeling was pregnancy exposure registries (66 of 145, 46%), followed by database studies with a prespecified outcome (51 of 145, 35%), clinical trials (37 of 145, 26%), expert opinions, guidelines, or systematic literature reviews (29 of 145, 20%), and case-reports/case series (15 of 145, 10%). More than half of pregnancy exposure registries in labeling (38 of 51, 75%) were from the Antiretroviral Pregnancy Registry.[12] Many different study types and data sources have supported quantitative human data statements in the Pregnancy subsection in PLLR labeling.

- A preliminary descriptive analysis measured product utilization during pregnancy across six data partners from the Sentinel Distributed Database (SDD) from January 1, 2008 to January 31, 2023. A total of 249 products associated with a post-marketing pregnancy safety study were considered for this analysis. Very low exposure products were excluded from the analysis because they are not likely to be suitable for comparative studies in administrative healthcare data systems that are the focus of the PDUFA VII demonstration projects. A convenience sample of 28 products with pregnancy exposures <2,500 was included to represent low exposure products to inform the framework development. Of the total 72 products included in the final analysis, 44 products had high exposure (≥2,500 pregnancy exposures) and 28 had low (<2,500). Overall, 80% of the 72 products had 10+ years of utilization data to characterize use during pregnancy. Although sedatives/hypnotics and antidepressants had the highest exposure during pregnancy of the assessed therapeutic classes, drug utilization in pregnant individuals overall was low, especially for newly approved drugs. The pattern of drug utilization cannot be solely explained by the number of years on the market, however. Other factors, such as those related to patient and product characteristics and treatment considerations, should be further explored.

FDA concluded that these observations emphasize the need for a consistent approach to help determine the optimal use of postapproval pregnancy safety studies. Building on these findings, considerations for choosing type(s) of postapproval pregnancy safety study(ies) include the ability to detect and evaluate safety signals, and how early these signals can be identified. Four key factors were identified for consideration when selecting study type(s):

1) Pregnancy-related maternal, fetal, and infant outcome(s) of interest that are relevant to a specific medical product and the gestational age at the time of drug exposure in pregnancy that may impact the outcomes;
2) Study goal, such as signal detection or signal evaluation, which is determined by existing knowledge about the drug's risk profile and determines the required level of evidence;

[12] Antiretroviral Pregnancy Safety Registry. For more information, visit https://www.apregistry.com/

3) Technical capability of the study including study design and data collection methods to manage bias and confounding; and
4) Magnitude of drug exposure because the prevalence of use of the drug of interest during pregnancy can influence the feasibility and speed of accruing an adequate study population.

Session 4: Design of the Pregnancy Safety Study Framework

Objectives: For FDA presenters to describe important study characteristics and factors that are essential to include in the framework. These study characteristics include considerations to determine the amount of potential exposure, timeliness of signal identification, and validation. In addition, the proposed decision schematic for the framework was discussed.

Building upon groundwork presented in session 3, FDA presented a preliminary pregnancy safety study framework. The goal of FDA's framework, as part of the PDUFA VII commitment, is to establish a systematic and transparent approach to determine viable and optimal types of postapproval pregnancy safety studies to gather timely evidence for regulatory decisions. The framework primarily considers non-interventional or observational studies alongside other safety surveillance methods such as routine pharmacovigilance.[13] These studies can include pregnancy registry studies, healthcare database studies, and single-arm descriptive studies, each with its own data collection methods, sources, and analytical approaches. The selection of a particular study type is based on the specific circumstances and depends on whether the study goal is signal detection (hypothesis generation) or signal evaluation (hypothesis testing). The proposed framework outlines considerations to determine viable and optimal non-interventional pregnancy safety studies. The framework is not designed for a specific therapeutic area. However, it provides flexibility to apply lessons learned across drug classes that may be considered in future use of the framework to enhance the consistency and comparability of safety studies.

FDA presenters and panelists showed how distinct aspects of the framework fit together (Figure 1) and provided details on important study characteristics. The six distinct aspects of the framework are:

- **Determine Available Information on the Drug**
  Initially, the framework focuses on assessing the available information on the drug from various sources such as nonclinical data, clinical trials, routine pharmacovigilance, observational studies, and medical literature, if applicable.

- **Determine Outcomes of Interest and Study Goal**
  The framework calls for identifying the regulatory questions related to information that is needed to ultimately label a drug product and other regulatory actions regarding the safety of using the product during pregnancy. The regulatory questions determine both the outcomes of interest and the study goal (e.g., signal detection, signal evaluation).

- **Assess Technical Capabilities of Potential Study**
  The next step is to delve into the technical capability of the potential study under consideration. This assessment involves evaluating the internal validity and minimum sample size. In

[13] Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff available at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-office-surveillance-and-epidemiology

epidemiologic studies, internal validity is a priority when evaluating the suitability of a study. Suboptimal study design, data, and methods can introduce bias. Since there is no perfect study, it is important to understand what potential bias a study may have, the impact of bias, and how the bias may change the interpretation of the study results. For a given study, the necessary level of evidence depends on study goals, for example, to identify a risk versus to quantify a risk; therefore, the extent of uncertainty that can be accepted is determined on a case-by-case basis. The study goal and direction and extent of potential bias also affect the minimum sample size required for a study.

- **Assess Magnitude of Drug Exposure and Exposure Capture of Potential Study**
  In addition to assessing the technical capabilities, it is also important to assess the magnitude of drug exposure. The magnitude of exposure is estimated by patient and treatment factors and reflects the total pregnancy exposures in the U.S. population. A study's capture of exposure can be thought of as a fraction of the magnitude of the drug exposure, primarily depending on how exposed patients are enrolled or accrued in a potential study. Time factors can also influence the fraction that a study can capture, especially in the first few years of approval.

- **Identify Viable Study(ies)**
  Taken together, these considerations and assessments should provide a shortlist of potential candidate studies informed by the factors outlined above that can be further analyzed to reach an optimal study design.

- **Select the Optimal Study Among the Viable Study Options**
  One or more studies can be selected from a shortlist of viable studies and conducted alone, simultaneously, or sequentially. Selecting the optimal study(ies) is a determination that considers additional factors like timeliness, resource requirements, patient burden, and any tradeoffs between these or other factors.

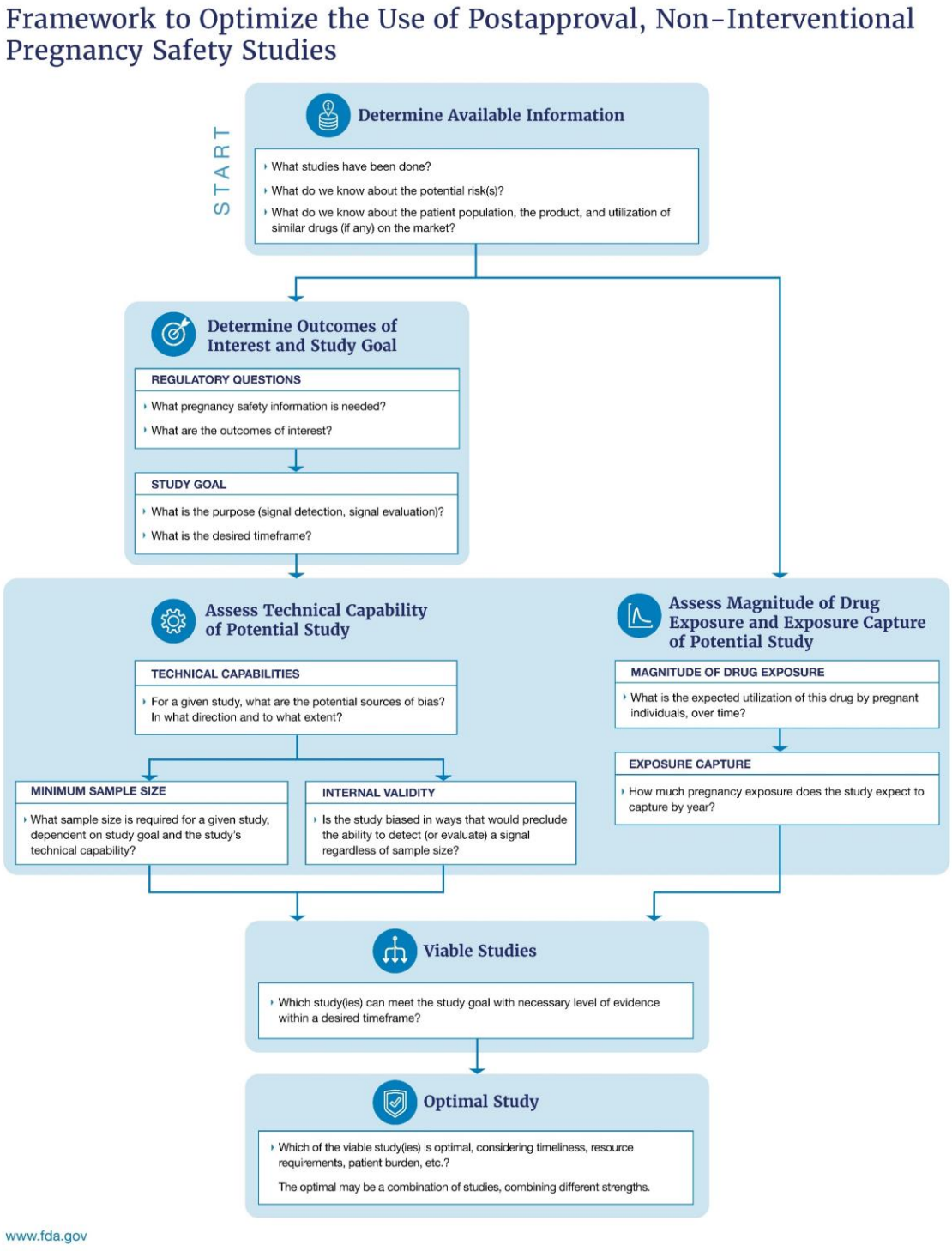

Figure 1. The framework for determining viable and optimal non-interventional studies comprises six distinct aspects, each of which has specific questions to consider.

Open Public Comment Session

Objective: For individuals to provide oral public comments during this workshop.

In addition to the opportunity for interested parties to submit comments to the open public docket, a brief oral public comment session yielded additional interested parties input on pregnancy safety studies and the planned framework. One key theme raised in the public comment session was the real-world complexity of medication use during pregnancy because many pregnant individuals may take multiple medications. This factor, known as polypharmacy should be taken into consideration when designing pregnancy safety studies. Additional factors that require consideration during pregnancy include timing of different exposures, dosage forms and strengths, and drug-drug interactions. Understanding these factors is crucial for assessing their effects on fetal and neonatal outcomes.

Another highlighted issue was the challenges faced by pregnant and breastfeeding individuals, as well as healthcare providers, in accessing and interpreting information about medication safety.[14] As noted above, there is a need for human safety data on medications used during pregnancy. Lack of pregnancy safety data can lead patients to discontinue necessary medications, potentially having a negative impact on the pregnancy and on maternal health. Speakers emphasized the significance of continued funding and expanded research studies to provide answers and prevent adverse outcomes for pregnant individuals and their children.

Advocates also stressed the importance of policy and regulatory actions to include pregnant and lactating populations in clinical research. Key aspects of this theme included integration of research needs into the approval and postapproval surveillance processes, along with a focus on maternal impacts and potential risks to the developing fetus. Defining clear safety and efficacy endpoints in research and including diverse perspectives in discussions are essential for making informed decisions.

Lastly, it was noted that evidence generation from a pregnancy registry is gradual and risk assessment in medication use during pregnancy is complex with no decision being risk-free or perfect. Such challenges further emphasize the importance of manufacturers' participation and support of registries and other reproductive surveillance initiatives to be incorporated into the framework. A mix of methods using all data sources available will need to be employed with greater support from pharmaceutical companies to ensure patients and clinicians can be better informed as they weigh risks and benefits.

Session 5: Filling the Known Gaps for a Comprehensive Pregnancy Safety Study Framework

Objectives: For FDA presenters to discuss plans, per the PDUFA VII commitment, to develop and conduct demonstration projects that will address identified knowledge gaps in the design and performance of different pregnancy safety study types to better inform the development of the framework. In addition, the capabilities of the Sentinel System and the CBER BEST Initiative for safety research were discussed.

[14] Although participants commented on breastfeeding and lactation, the focus of this workshop report is on pregnancy. More information can be found in FDA's draft Guidance for Industry on *Clinical Lactation Studies: Considerations for Study Design*.

The Sentinel Initiative has two systems to monitor drug and biological product safety in pregnancy: 1) the Active Risk Identification and Analysis (ARIA) system within the Sentinel System, which is comprised of a common data model and analytic tools that are predefined, parametrized, and reusable; and 2) the BEST Initiative, which links administrative claims, electronic health records (EHR), and public health immunization information systems with flexible analytic capabilities to quickly respond to public health priorities (Figure 2).[15]

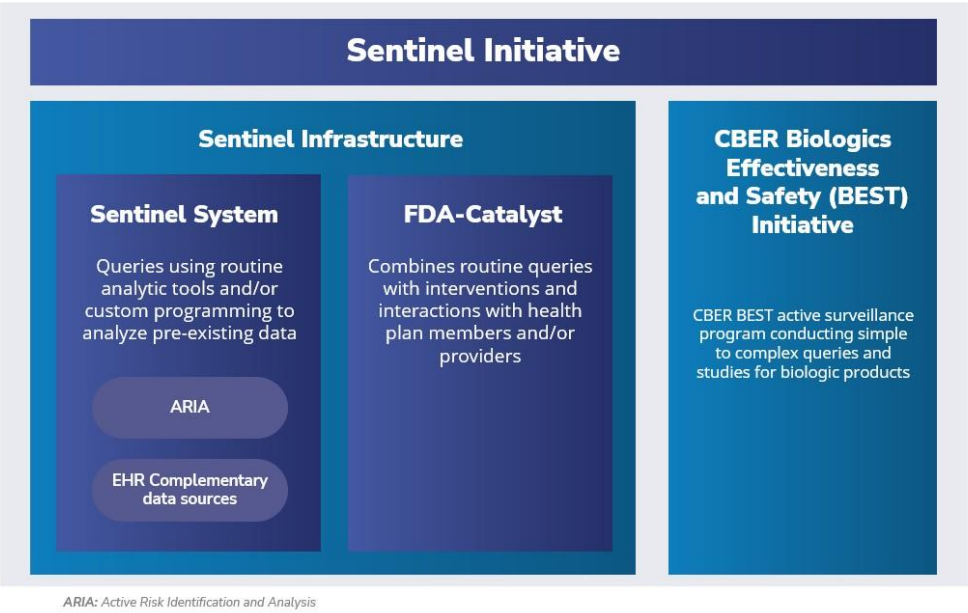

Figure 2. Structure of the Sentinel Initiative.

The demonstration projects were defined to refine the pregnancy safety study framework by assessing the performance of various study approaches (e.g., registry study vs. database study) based on contextual factors such as prevalence of drug exposure during pregnancy. Additionally, ongoing drug utilization data analysis and the development of new methods for estimating drug exposure will complement the demonstration projects.

Meeting attendees added that work was needed to address important data quality challenges given the different systems and coverage across regions and states and lack of standardization in medical and drug coding. The challenges include inconsistent capture of exposures, and issues with medication adherence. In addition, meeting attendees noted the importance of integrating different data streams (claims, registry, and data held by industry) to achieve more comprehensive assessments, although such data integration can also be challenging.

Lastly, attendees highlighted the need for outcome selection that considers both maternal and fetal concerns. Maternal health outcomes (e.g., preeclampsia) in safety studies are essential for a comprehensive understanding of drug safety during pregnancy. For newborns, assessing the

[15] FDA's Sentinel Initiative comprises the Sentinel System, FDA-Catalyst, and the CBER Biologics and Safety (BEST) Initiative. For more information, visit https://www.sentinelinitiative.org/about.

developmental impacts of medications taken during pregnancy was recognized as a major gap in current research methods and data collection strategies.

Session 6: Stakeholder Perspectives on the FDA's Proposed Pregnancy Safety Study Framework

Objectives: For stakeholders to provide feedback on the FDA's proposed framework and discuss additional potential opportunities to enhance the framework to ultimately optimize pregnancy safety studies.

In the final session of the meeting, experts were engaged in a discussion to provide feedback on the pregnancy safety study framework. The panel raised the importance of a nuanced understanding of risk that considers both the effects of medications on the developing fetus and the consequences of uncontrolled maternal diseases on both the pregnant individual and the fetus. Because many pregnant individuals discontinue medications upon pregnancy detection, a small sample size for studying exposure and outcomes remains a significant challenge. Additionally, the potential of the ARIA system and other tools such as software that implements the tree-based scan statistic for identifying major congenital malformations was acknowledged. However, concerns were raised regarding this system and tools, specifically about the risk of missing a true signal due to insufficient sample sizes and low statistical power. There might also be a need to identify more than one source to conduct a sequential or concurrent safety evaluation, potentially requiring the exploration of additional domestic and international data, which may be challenging.

The evolution of data sources in pregnancy safety studies was also noted, highlighting the availability of database studies to complement pregnancy registries. Initially, registries were considered the primary source of pregnancy safety data, offering detailed information on medication exposures and outcomes. However, enrolling participants in registries can be challenging, particularly when trying to detect rare, specific malformations.

Databases were introduced as a secondary data source, focusing on detecting the effects of moderate teratogens and ruling out strong risks as data accumulated. It was recommended that the framework for pregnancy safety studies adopt a dynamic and adaptive design to accommodate accumulating data. The demonstration projects should be based on realistic examples from literature or postapproval surveillance data with sufficient exposure levels. Recognizing the evolving nature of pregnancy studies, participants suggested that any future iterations of the framework emphasize flexibility in study design, and predefined criteria to adjust approaches as utilization and outcome data accrue. Built-in milestones for feasibility assessments may allow for timely adjustments in research strategies.

In addition, using more than one study type to assess drug safety during pregnancy was emphasized, acknowledging each study type's inherent limitations, including confounding factors, misclassification of exposure, outcomes, or both. Despite these concerns, estimating the magnitude of a drug's effect and its uncertainty should include quantitative bias analysis rather than solely considering statistical significance. The required sample size and the number of exposed pregnancies depend on the specific outcome within a particular time frame. Given the limitations with the translation of nonclinical data to applications in clinical practice, a range of potential outcomes was suggested to provide a more comprehensive understanding of a product's risks. In selecting outcomes of interest, a panelist suggested that quantitative bias analysis can facilitate understanding of the impact of systematic errors on the point estimate and the confidence interval.

A panelist suggested a standard set of common outcomes for potential maternal and neonatal risks be used for studying all drugs to more easily compare these findings among drugs within a therapeutic area. Multiple panelists suggested an array of study approaches integrating different methods and data sources can provide a more holistic understanding of a drug's safety in pregnancy. Also, the value of a dynamic, adaptive study approach that can respond as data become more accessible was reiterated, where study approach decisions are based on established case thresholds.

Workshop participants voiced concerns about the underrepresentation of underserved and minority communities in many databases. Multiple participants acknowledged the need for diverse study populations to enhance the quality and relevance of research findings. One suggestion was use of digital technologies as a possible way to improve study diversity (e.g., by expanding recruitment).

Some panelists suggested another important area of focus in pregnancy safety studies would be risk communication to help providers and patients navigate uncertainty and potentially conflicting information associated with the use of the drug. Using best practices in health communication[16] is important to clearly communicate information about risks and robustness of scientific evidence. To increase the certainty of findings, study replication using a different data source or method to confirm the signal may be necessary. In cases where the results of a study are ambiguous, it may still be valuable to communicate the results of those studies to patients and providers.

The meeting closed with a final encouragement for interested parties to submit feedback on the draft framework to the public docket for FDA consideration by November 30, 2023. Per the PDUFA VII commitment, FDA is publishing this workshop report describing the proposed framework. FDA committed to initiating the five demonstration projects by September 30, 2024. Results of those projects will inform updates to the framework, if needed, and development of guidance or Manual of Policies and Procedures/Standard Operating Procedures and Policies as appropriate by September 30, 2027.

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[16] See: Health Communication Strategies and Resources, Centers for Disease Control and Prevention, National Prevention Information Network, https://npin.cdc.gov/pages/health-communication-strategies-and-resources. Accessed March 5, 2024.