



Postmarketing Surveillance for Product Safety in Pregnancy

Meghna Alimchandani, M.D.

Deputy Director, Division of Pharmacovigilance
Office of Biostatistics and Pharmacovigilance
CBER | US FDA

Regulatory Education for Industry (REdI): Annual Conference 2024
Small Business & Industry Assistance (SBIA)
May 30, 2024

Objectives

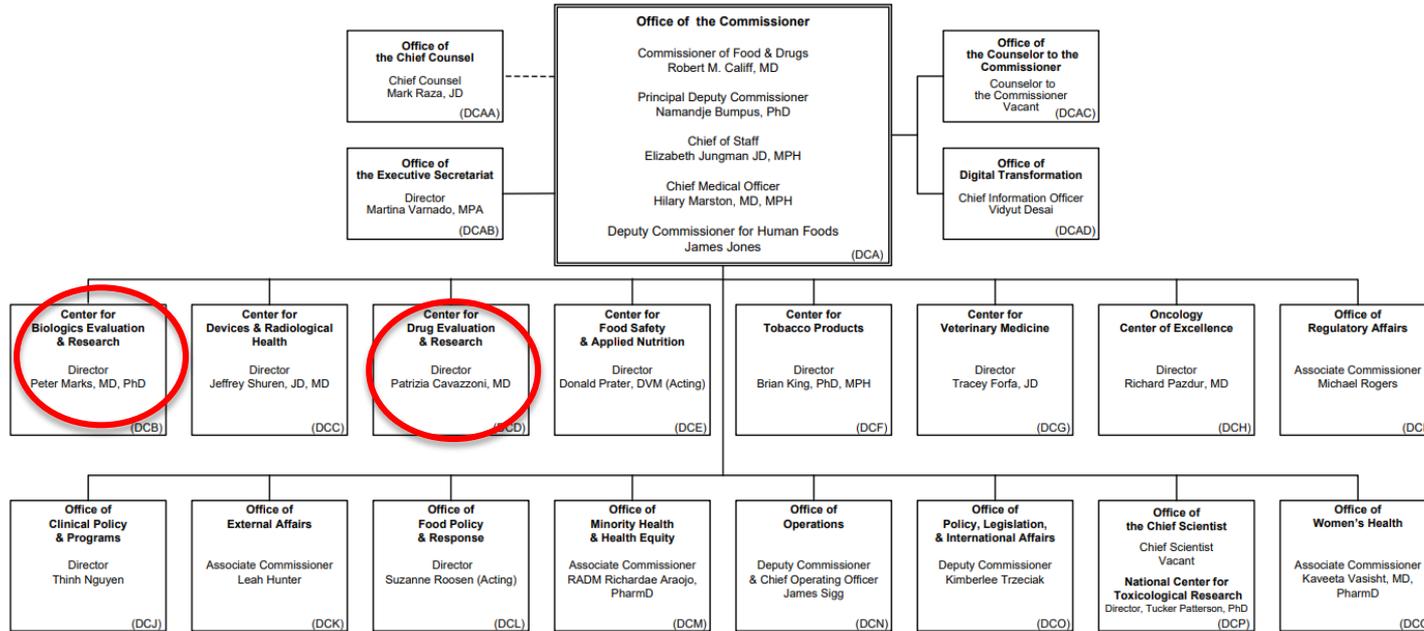
- Describe organization chart
- Describe safety throughout product lifecycle
- Describe postmarketing surveillance for product safety in pregnancy
 - Passive surveillance
 - Active surveillance
- Discuss signal evaluation and risk management
- Describe pregnancy and lactation labeling rule (PLLR)
- Provide examples
- Summarize and provide conclusions

FDA Organization Chart



Department of Health and Human Services Food and Drug Administration

February 2024



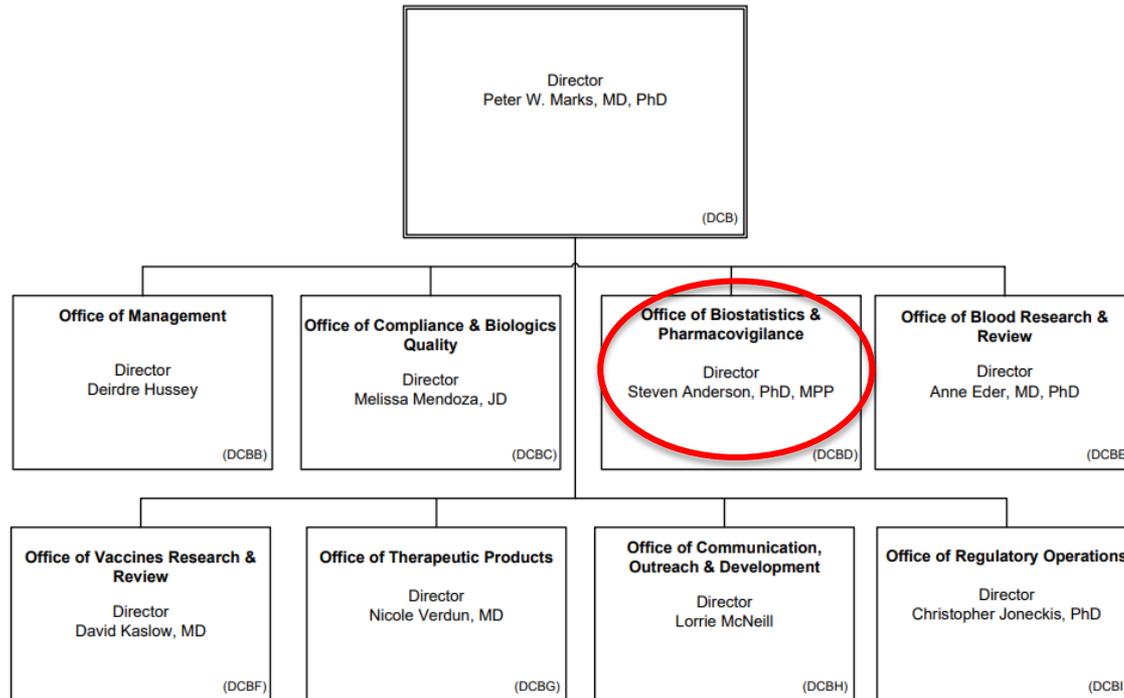
Legend:
--- Direct report to DHHS General Counsel

CBER Organization Chart



February 2024

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

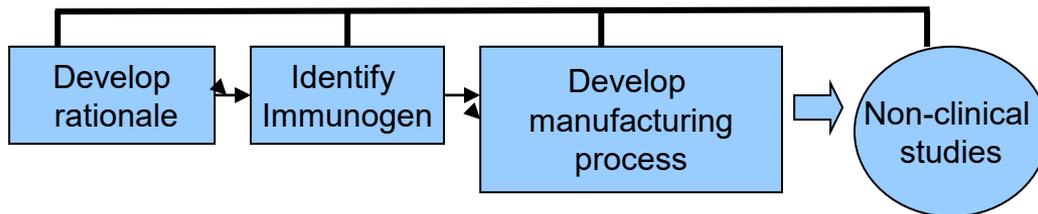


Safety throughout product lifecycle

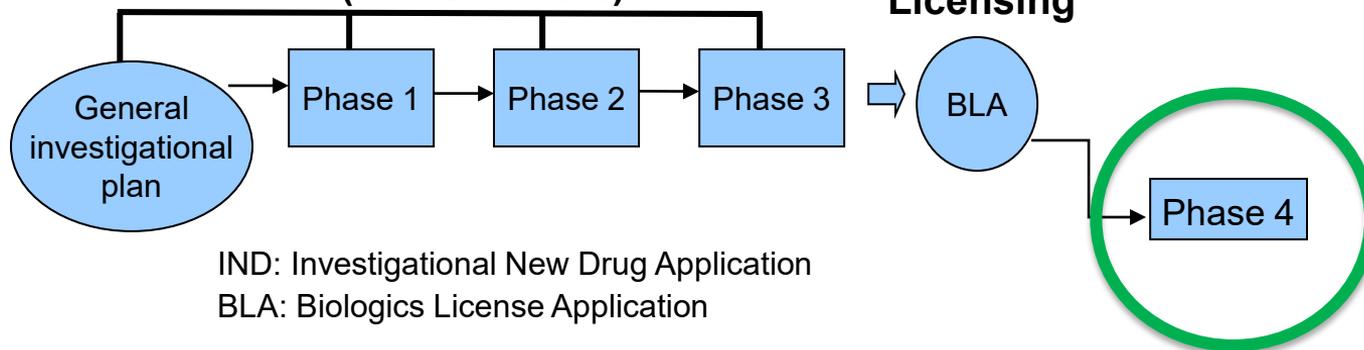
Product Development Lifecycle



Pre-IND (pre-clinical research)



IND (Clinical Trials)



IND: Investigational New Drug Application
BLA: Biologics License Application



Product Safety Throughout Lifecycle

- FDA ensures that products are safe for their intended use
- Product safety activities occur throughout the life cycle
 - Preclinical research (non-human) testing of candidate products
 - Early phase human studies through large phase III clinical trials
 - Inspection of manufacturing facilities
 - Monitoring of lot release
 - Inspection of clinical sites for compliance with Good Clinical Practices
 - [Postmarketing adverse event surveillance](#)
- Monitoring product safety is equally important during development and during the postmarketing period

Why does CBER conduct postmarketing safety surveillance?



- Limitations of premarket safety database
 - May not detect safety issues that arise when products are marketed to the general population (e.g., postmarketing surveillance may reveal interactions with comorbid conditions)
 - May exclude groups within the general population (e.g., pregnant women)
 - Small sample sizes and observation periods limit reliable detection to the most common events with shorter latency to onset
 - Unless a trial has a dedicated safety endpoint, inferences about safety are limited by concerns about post hoc analyses with multiple comparisons
- Postmarketing surveillance further characterizes the safety profile of licensed products



Pregnant women during clinical development

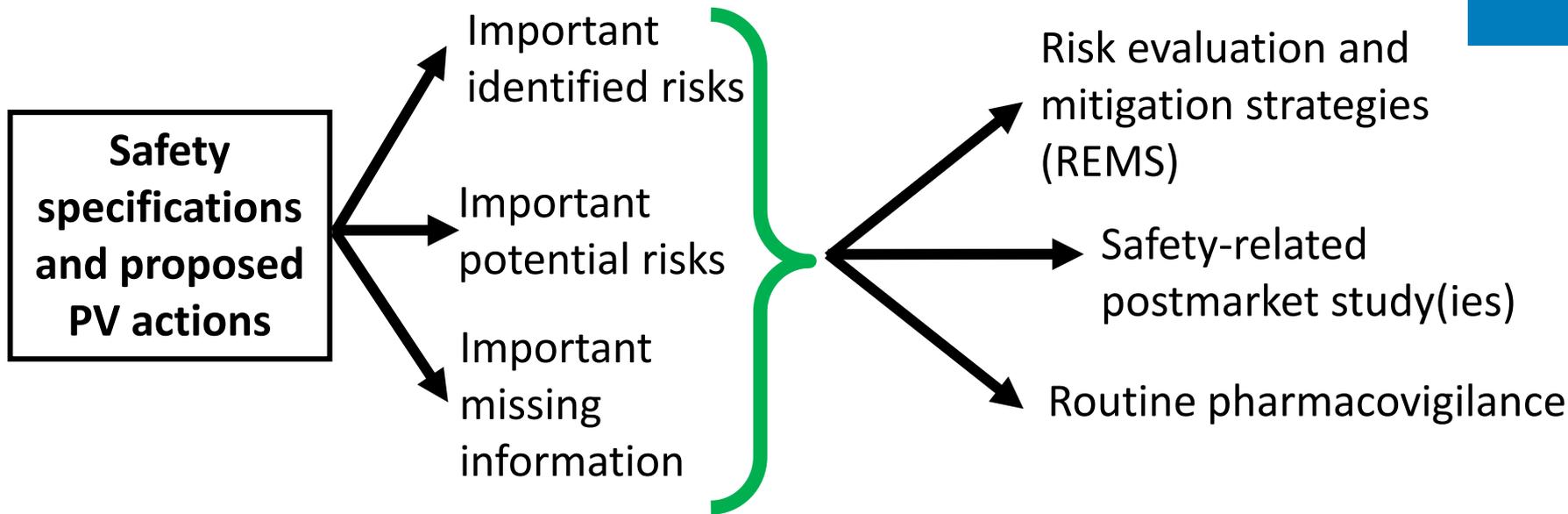
- During clinical development of most drugs and biological products, pregnant women are actively excluded from trials
- If pregnancy does occur during a trial, the usual procedure is to discontinue treatment and monitor the women to assess pregnancy outcomes
- Consequently, at the time of marketing, for most products, there are no or limited human data to inform the safety of a drug or biological product taken during pregnancy.

<https://www.fda.gov/media/124746/download>



Postmarketing surveillance for product safety in pregnancy

Pharmacovigilance Plan (PVP)



FDA Guidance for Industry: E2E Pharmacovigilance Planning (April 2005) available at <https://www.fda.gov/media/71238/download>

FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005) available at <https://www.fda.gov/files/drugs/published/Good-Pharmacovigilance-Practices-and-Pharmacoepidemiologic-Assessment-March-2005.pdf>

Postmarketing Surveillance for Product Safety in Pregnancy

- Use in pregnancy/lactation often categorized as *Important Missing Information* in PVP
- Passive adverse event reporting/enhanced pharmacovigilance
- Active surveillance: postapproval pregnancy safety studies
 - Sponsor conducted studies (postmarketing requirement/commitment or voluntary study)
 - USG conducted studies
 - Academia conducted studies

Pregnancy exposure related AE report

- Factors in evaluating the effects of product exposure in human pregnancies may include, but are not limited to, the following:
 - Adverse outcome description
 - Exposure description
 - Product, the dose, frequency, route of administration, and duration
 - Gestational age at exposure
 - Maternal age, medical and pregnancy history, and use of concomitant medications, supplements, and other substances
 - Exposures to known or suspected environmental teratogen

Passive Surveillance

- Continuous safety monitoring for licensed products
- Spontaneous adverse event (AE) reports
- Reporting regulations:
 - Voluntary AE reporting for healthcare providers and the public
 - Mandatory AE reporting for manufacturers (21 CFR 600.80)
 - Expedited reporting of serious* and unlabeled AEs in 15 days
 - Non-expedited reports
 - Periodic safety reports

**Seriousness*: death, hospitalization, life-threatening, disability, congenital anomaly, other medically important event

Pharmacovigilance (PV) databases

- Vaccine Adverse Event Reporting System (VAERS)
- FDA Adverse Event Reporting System (FAERS)
- Manufacturer's global PV database
- World Health Organization's VigiBase
- Foreign regulatory agency PV database (e.g., EudraVigilance)

Have you had a reaction following a vaccination?

1. Contact your healthcare provider.
2. Report an Adverse Event using the VAERS online form or the downloadable PDF. *New!*

Important: If you are experiencing a medical emergency, seek immediate assistance from a healthcare provider or call 9-1-1. CDC and FDA do not provide individual medical treatment, advice, or diagnosis. If you need individual medical or health care advice, consult a qualified healthcare provider.



Reporting requirements for healthcare providers administering COVID-19 vaccines

About The Vaccine Adverse Event Report

Note: Any use of these data implies consent to abide by the terms of the data use restrictions.

CDC Wonder:
Publicly
available
VAERS data

How to Report Adverse Events to FDA



U.S. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Available at: <https://www.fda.gov/Safety/MedWatch/default.htm>



- How to Report:
 - Online (www.fda.gov/medwatch)
 - Download the form
 - Mail
 - Fax 1–800–332–0178
- For questions about the form:
 - 1–800–332–1088

Source: <https://www.fda.gov/media/169322/download>

Adverse Event Reporting Systems

- Pharmacovigilance databases accept all reports regardless of the plausibility of the product causing the event or the clinical seriousness of the event

Strengths

- Rapidly detects potential safety problems
- Potential detection of rare adverse events
- Open-ended for hypothesis generation
- Geographic diversity
- Capability to monitor production lots



Adverse Event Reporting Systems

- Pharmacovigilance databases accept all reports regardless of the plausibility of the product causing the event or the clinical seriousness of the event

Limitations

- Missing and/or inaccurate data
- Reported diagnoses are not verified
- Under-reporting
- Reporting bias (stimulated reporting)
- Absence of unvaccinated control group
- Inability to assess causation
- Not likely to detect long latency events

Role of Product Utilization Data

- Sponsor distribution data provides context for AE reports
 - Accounts for total amount distributed in US
 - Lot-specific
 - Use in specific age groups, e.g, women of childbearing age (if available)
- Interpret with caution
 - Cannot calculate incidence
 - Not all doses distributed were administered

Possible statement on pregnancy reporting in recent Draft Guideline

- **Reports of exposure** through a parent, such as the use of medicinal products in pregnancy or breastfeeding, **with no associated AE/ADR** in either the parent or the child should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions.
- **AEs/ADRs**, such as abnormal outcome following parental exposure, including congenital anomalies, potential epigenetic responses, developmental disorders in the fetus or child, fetal death/spontaneous abortion, or AEs/ADRs in the mother or new-born, are **subject to ICSR reporting requirements**.

ICH HARMONISED GUIDELINE

E2D(R1) POST-APPROVAL SAFETY DATA: DEFINITIONS AND STANDARDS FOR MANAGEMENT AND REPORTING OF INDIVIDUAL CASE SAFETY REPORTS (Draft version) available at

<https://www.fda.gov/media/176977/download>



Challenge Question #1

Pregnant women are often excluded from clinical trials and use in this population is categorized as missing information in the pharmacovigilance plan.

True or False.

A. TRUE

B. FALSE



Challenge Question #2

Postmarketing surveillance for product safety in pregnancy includes:

- A. Adverse event reporting in accordance with 21 CFR 600.80
- B. Enhanced pharmacovigilance as specified by CBER
- C. Submission of periodic safety reports at quarterly intervals for 3 years postapproval and at annual intervals thereafter
- D. Postapproval pregnancy safety studies
- E. All of the above



Postapproval Pregnancy Safety Studies Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Denise Johnson-Lyles at 301-796-6169 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Clinical/Medical

48826dft.docx
04/30/19

Postmarketing Surveillance for Product Safety in Pregnancy

- *Active surveillance*

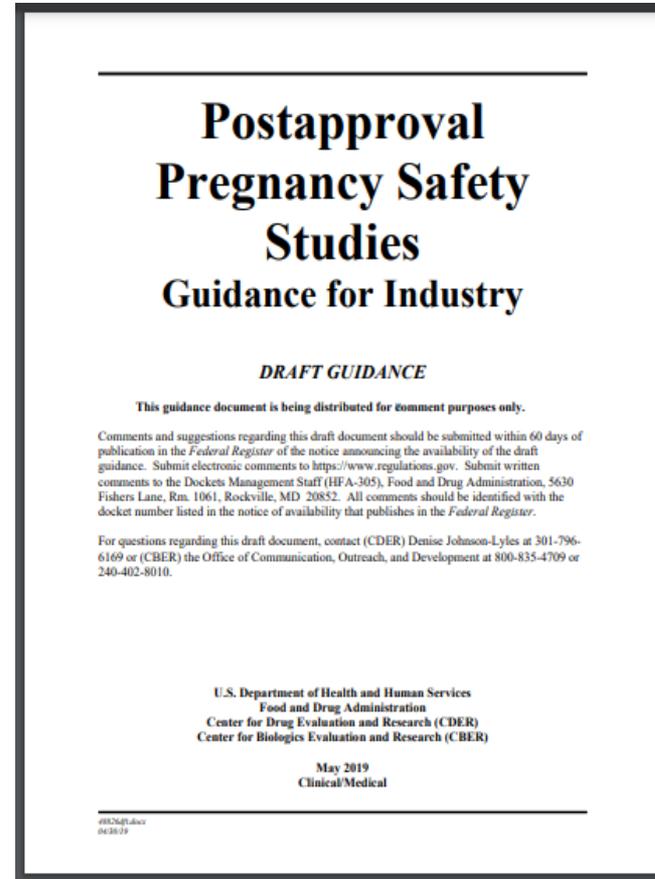
Safety-related postmarketing study

A study being conducted specifically to evaluate safety or further investigate a safety issue(s) associated with a product.

NOTE: A study must have a primary safety endpoint to be considered a safety-related study.

Guidance outlines **3 approaches** to pregnancy safety surveillance:

1. Pharmacovigilance
2. Pregnancy registries
3. Database studies



Study designs



- **Pregnancy registries:** prospective observational cohort studies to collect data on product exposure during pregnancy and associated maternal and infant safety outcomes; comparator group or historical control
 - Pregnant women are enrolled and followed until pregnancy outcome; infants are followed for a specified time period
- **Database studies:** Electronic health care data (administrative claims and electronic health records)
 - Requires mother-infant linkage

Study protocols

- Study protocols should include:
 - Description of study population
 - Outcomes
 - Control/comparator
 - Rationale for sample size
 - Data collection methods
 - Plans for data analysis
 - Study milestone dates

Postapproval pregnancy safety studies

- Sponsor conducted studies
 - Postmarketing requirements (PMRs)
 - Postmarketing commitments (PMCs)
 - Voluntary sponsor studies
- Other
 - USG or academia

<https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>

Types of sponsor conducted safety postmarketing studies

- **Postmarketing requirement (PMR) study**
 - **Required** under Food and Drug Administration Amendments Act of 2007
 - **Targeted safety study** to assess a specific **serious risk** (see next slide for study purposes under FDAAA)
- **Postmarketing commitment (PMC) study**
 - **“Agreed-upon”** study between FDA and Applicant
 - General safety surveillance; studies for AESIs that do not meet FDAAA criteria
- **Voluntary study**

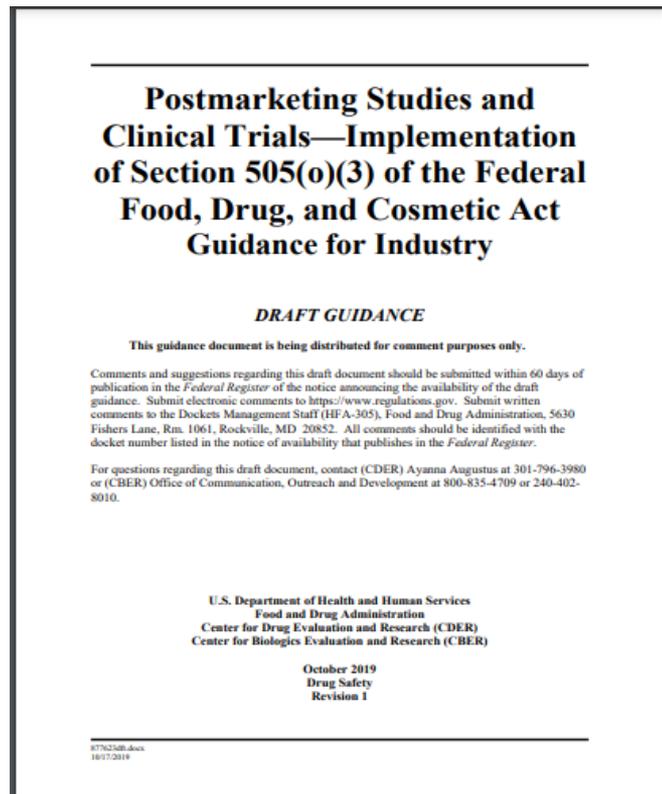
[Postmarketing Studies and Clinical Trials—Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry](#)

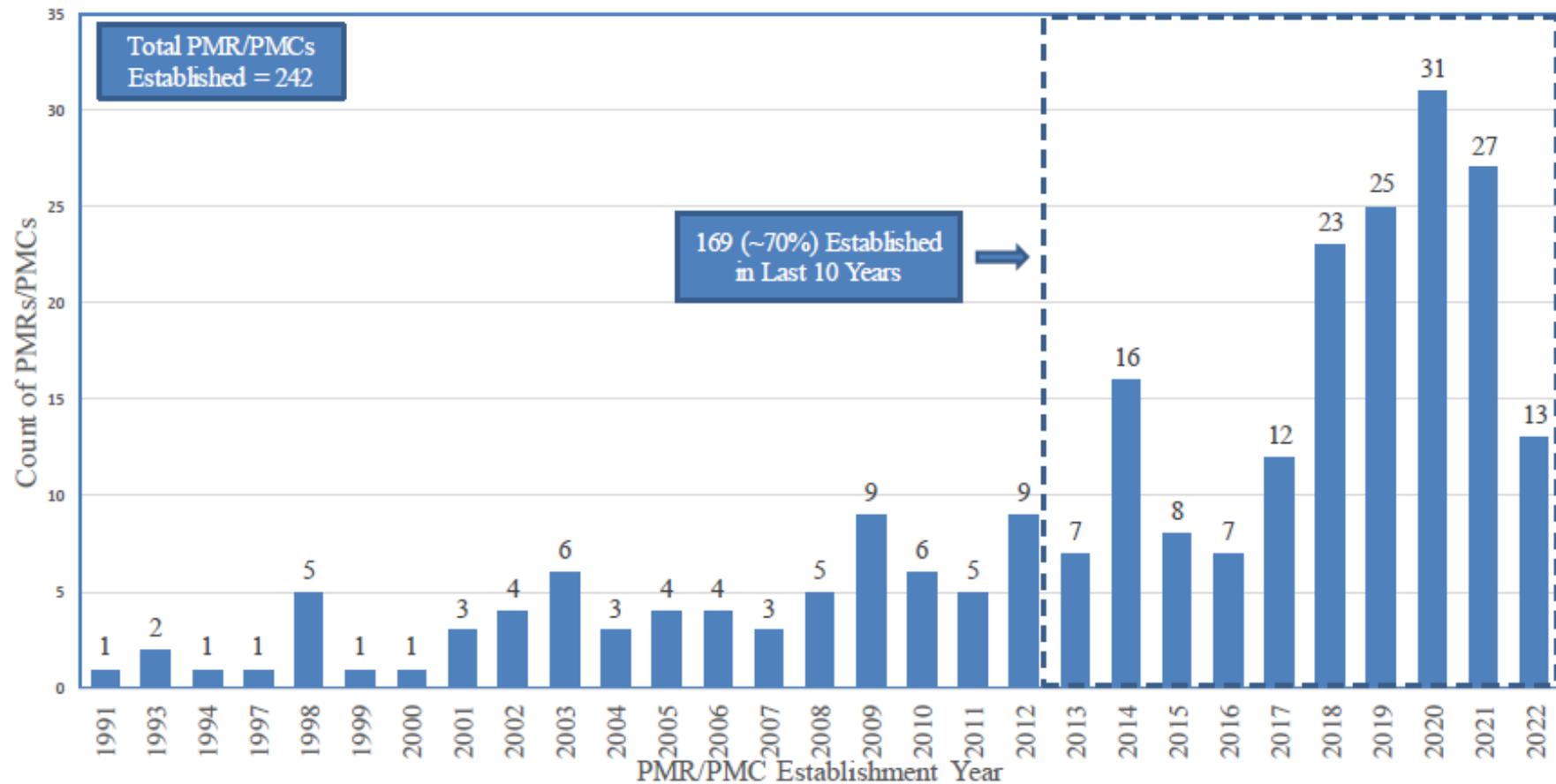
Postmarketing requirement (PMR) to assess a serious risk

Postmarketing studies and clinical trials may be required for any or all of the following three purposes:

- To assess a known ***serious risk*** related to the use of the drug
- To assess ***signals of serious risk*** related to the use of the drug
- To identify an ***unexpected serious risk*** when available data indicate the potential for a serious risk

[Postmarketing Studies and Clinical Trials—Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry](#)







Challenge Question #3

Postapproval pregnancy safety studies may be conducted by:

- A. Sponsor postmarketing requirement study
- B. Sponsor agreed-upon postmarketing commitment study
- C. Sponsor voluntary study
- D. Study conducted by USG or academia
- E. All of the above



Challenge Question #4

Postapproval safety study designs may include:

- A. Observational cohort/registry design
- B. Database studies using electronic health care data (administrative claims and electronic health records)
- C. Spontaneous AE reports
- D. A and B
- E. All of the above

Best Practices for FDA Staff in
the Postmarketing Safety
Surveillance of Human Drug
and Biological Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2024
Drug Safety

Signal Evaluation and Risk Management



Signal Evaluation

- FDA uses the term **signal** to mean information that arises from one or multiple sources (including observations and experiments) that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify **further action to verify**.
- Use all available postmarketing surveillance data sources

Signal Evaluation



- Identification of a product's potential for adverse developmental outcomes, including teratogenicity, is important because product-associated adverse developmental outcomes are potentially preventable.
- Other outcomes of interest include but are not limited to:
 - Preterm delivery
 - Small for gestational age
 - Pregnancy complications
 - Miscarriage
 - Stillbirth
 - Abnormalities of immune system development in neonates, and long-term neurologic outcomes in infants

Signal Detection, Evaluation, and Verification



Sources of Safety Data	
Pre-licensure	Post-licensure
Clinical trials	Spontaneous reporting (VAERS/FAERS)
	Large electronic healthcare database
	Other (Literature, foreign regulatory agencies)

Hypothesis generating	
Signal Detection	Signal Evaluation

Hypothesis Testing
Signal Verification

Regulatory Actions
Communications, Label Changes, Recalls, etc.

Verification Tools
Large electronic healthcare databases
Observational Studies
Clinical Trials

Signal Evaluation

- Individual case review and aggregate review
- Case series analysis
 - Unexpected clinical or demographic clustering
 - Is this event new for this product?
 - Biologic plausibility of causal association
 - “Positive re-challenge” reports
 - Absence of alternative explanations (concomitant medications, co-morbidities)
 - How do reporting rates compare with background rates?
- Aggregate data analysis, including disproportionality analyses
- Review data from other sources (literature, postmarketing studies)

Signal Evaluation and Risk Management

- Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event.
- After a signal is identified it should be further assessed to determine whether it represents a potential risk and whether other action should be taken.
- Regulatory actions include:
 - Communications
 - Label changes
 - Product Withdrawal/Recall
 - Inspections
 - Postmarketing studies and/or additional surveillance activities
 - FDA may require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS) to ensure benefits outweigh risks
 - Professional meeting presentation/abstract; peer-reviewed publication



Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Division of Pediatric and Maternal Health (CDER) at 301-796-2200 or the Office of Communication, Outreach, and Development (CBER) at 240-402-8010.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**July 2020
Labeling
Revision 1**

50762dft.docx
7/15/2020

Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry

Pregnancy and lactation labeling rule (PLLR)

- Goal is to provide the prescriber with relevant information for decision-making when treating pregnant or lactating women
- PLLR format improves presentation of currently available data
- Animal data put in context of human exposure
- **Human data added when available**
 - Data sources may include clinical trials, postmarketing AE data, postmarketing studies
- Explicitly states when no data are available



Examples



Vaccine Safety Datalink infrastructure enhancements for evaluating the safety of maternal vaccination

Allison L. Naleway, Bradley Crane, Stephanie A. Irving , Don Bachman, Kimberly K. Vesco, Matthew F. Daley, Darios Getahun, Sungching C. Glenn, Simon J. Hambidge, Lisa A. Jackson, Nicola P. Klein, Natalie L. McCarthy, David L. McClure, Lakshmi Panagiotakopoulos, Catherine A. Panozzo, Gabriela Vazquez-Benitez, Eric S. Weintraub, Ousseny Zerbo and Elyse O. Kharbanda

Abstract

Background: Identifying pregnancy episodes and accurately estimating their beginning and end dates are imperative for observational maternal vaccine safety studies using electronic health record (EHR) data.

Methods: We modified the Vaccine Safety Datalink (VSD) Pregnancy Episode Algorithm (PEA) to include both the International Classification of Disease, ninth revision (ICD-9 system) and ICD-10 diagnosis codes, incorporated additional gestational age data, and validated this enhanced algorithm with manual medical record review. We also developed the new Dynamic Pregnancy Algorithm (DPA) to identify pregnancy episodes in real time.

Results: Around 75% of the pregnancy episodes identified by the enhanced VSD PEA were live births, 12% were spontaneous abortions (SABs), 10% were induced abortions (IABs), and 0.4% were stillbirths (SBs). Gestational age was identified for 99% of live births, 89% of SBs, 69% of SABs, and 42% of IABs. Agreement between the PEA-assigned and abstractor-identified pregnancy outcome and outcome date was 100% for live births, but was lower for pregnancy losses. When gestational age was available in the medical record, the agreement was higher for live births (97%), but lower for pregnancy losses (75%). The DPA demonstrated strong concordance with the PEA and identified pregnancy episodes ≥ 6 months prior to the outcome date for 89% of live births.

Conclusion: The enhanced VSD PEA is a useful tool for identifying pregnancy episodes in EHR databases. The DPA improves the timeliness of pregnancy identification and can be used for near real-time maternal vaccine safety studies.

Ther Adv Drug Saf

2021, Vol. 12: 1–11

DOI: 10.1177/
20420986211021233

© The Author(s), 2021.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

Allison L. Naleway
Center for Health
Research, Kaiser
Permanente Northwest,
3800 N. Interstate Ave,
Portland, OR 97227, USA
Allison.Naleway@kpchr.org

Bradley Crane
Stephanie A. Irving
Don Bachman
Kimberly K. Vesco
Center for Health
Research, Kaiser
Permanente Northwest,
Portland, OR, USA

Matthew F. Daley
Kaiser Permanente
Colorado, Denver, CO, USA

Darios Getahun
Sungching C. Glenn
Kaiser Permanente
Southern California,
Pasadena, CA, USA

Simon J. Hambidge
Denver Health, Denver,
CO, USA

Lisa A. Jackson
Kaiser Permanente
Washington Health
Research Institute,
Seattle, WA, USA

Nicola P. Klein

Maternal Influenza Vaccine and Risks for Preterm or Small for Gestational Age Birth

James D. Nordin, MD, MPH¹, Elyse Olshen Kharbanda, MD, MPH¹, Gabriela Vazquez Benitez, PhD¹, Heather Lipkind, MD, MS², Claudia Vellozzi, MD, MPH³, and Frank DeStefano, MD, MPH³, on behalf of the Vaccine Safety Datalink*

Objective To study the impact of influenza vaccine administered to pregnant women during all trimesters on the rates of preterm and small for gestational age (SGA) births, evaluating both increased and decreased risk.

Study design This retrospective observational matched cohort study involved 7 Vaccine Safety Datalink sites across the US for the 2004-05 through 2008-09 influenza seasons. Cohort eligibility and outcomes were determined from administrative, claims, medical records, and birth data. In propensity score- and vaccine exposure time-matched analyses, ORs for preterm and SGA births were calculated.

Results Among 57 554 matched vaccinated and unvaccinated pregnant women, including 16 240 women in the first trimester, maternal vaccination was not associated with increased or decreased risk for preterm birth (OR for delivery at <37 weeks gestation, 0.97 [95% CI, 0.93-1.02]; for delivery at ≤32 weeks gestation, 0.98 [95% CI, 0.86-1.12]; and for delivery at ≤34 weeks gestation, 0.96 [95% CI, 0.88-1.04]) or SGA birth (OR for <5th percentile weight for gestational age, 1.02 [95% CI, 0.96-1.09], and for <10th percentile weight for gestational age, 1.00 [95% CI, 0.96-1.04]). Similarly, first trimester vaccination was not associated with increased or decreased risk for preterm or SGA birth.

Conclusion Receipt of trivalent inactivated influenza vaccine during pregnancy was not associated with increased or decreased risk of preterm or SGA birth. These findings support the safety of vaccinating pregnant women against influenza during the first, second, and third trimesters, and suggest that a nonspecific protective effect of the influenza vaccine for these outcomes does not exist. (*J Pediatr* 2014;164:1051-7).

Monitoring the safety of COVID-19 vaccines in pregnancy in the US

Pedro L. Moro, Lakshmi Panagiotakopoulos, Titilope Oduyebo, Christine K. Olson, and Tanya Myers

Immunization Safety Office, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, National Center for Zoonotic and Emerging Infectious Diseases, United States

ABSTRACT

Pregnant persons are at increased risk of severe illness from COVID-19. The first COVID-19 vaccines in the U.S. were authorized for emergency use in December 2020 and pregnant persons were eligible and could get vaccinated despite scarce safety data in this population. To monitor the safety of COVID-19 vaccination during pregnancy, four surveillance systems are used by the Centers for Disease Control and Prevention (CDC). The Vaccine Adverse Event Reporting System is a national, passive system that captures reports of potential adverse events. V-safe is a novel, active system that uses text messaging and web-based surveys to provide health check-ins after vaccination; and enrolls eligible v-safe participants in the v-safe pregnancy registry. The Vaccine Safety Datalink is a collaboration between the CDC and nine integrated health care organizations which performs near-real time surveillance and traditional epidemiologic studies on pregnant vaccine recipients. The CDC is committed to timely and comprehensive monitoring of COVID-19 vaccine safety in pregnancy.

ARTICLE HISTORY

Received 25 June 2021
Revised 30 August 2021
Accepted 16 September 2021

KEYWORDS

Adverse events;
epidemiology; coronavirus;
COVID-19; mRNA vaccines;
SARS-COV-2; adenovirus
type 26; pregnancy;
surveillance; vaccine safety

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8903939/pdf/KHVI_17_1984132.pdf

Protocol: Validating Pregnancy Outcomes and Gestational Age in a Claims-EMR Linked Database
Report: Validating Pregnancy Outcomes and Gestational Age in a Claims-EMR Linked Database

Drug Safety (2021) 44:1151–1164
<https://doi.org/10.1007/s40264-021-01113-8>

ORIGINAL RESEARCH ARTICLE



Validating Claims-Based Algorithms Determining Pregnancy Outcomes and Gestational Age Using a Linked Claims-Electronic Medical Record Database

Keran Moll¹ · Hui Lee Wong² · Kathryn Fingar¹ · Shayan Hobbi² · Minya Sheng¹ · Timothy A. Burrell¹ · Linda O. Eckert⁴ · Flor M. Munoz⁵ · Bethany Baer² · Azadeh Shoaibi² · Steven Anderson²



Contents lists available at [ScienceDirect](#)

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Vaccine exposure during pregnancy among privately and publicly insured women in the United States, 2016–2018



Keran Moll^{a,*}, Hui-Lee Wong^b, Kathryn Fingar^a, Cindy Ke Zhou^b, Michael Lu^c, Mao Hu^c, Shayan Hobbi^d, Timothy Burrell^a, Bethany Baer^b, Julia Simard^e, Joyce Obidi^b, Yoganand Chillarige^c, Thomas MaCurdy^{c,f}, Steve Anderson^b, Azadeh Shoaibi^b

Original Research

Healthcare providers' use of a concise summary to prescribe for lactating patients

Teresa Koenig^a, Cynthia Robins^a, Paula Darby Lipman^a, Miriam Dinatale^{b,*}, Tamara Johnson^b, Leyla Sahin^b, Catherine Roca^b, Jeannie Limpert^b, Kristie Baisden^b, Yeruk Mulugeta^b, Lynne Yao^b, Kerri-Ann Jennings^b, Meghna Alimchandani^b, Darcie Everett^b, Audrey Gassman^b, Christina Chang^b, Christopher Ellis^b, Elimika Pfuma Fletcher^b, Sherbet Samuels^b

^a Westat, United States^b United States Food and Drug Administration, United States

ARTICLE INFO

Keywords:
Pregnancy and lactation labeling rule
Breastfeeding
Prescribing information
Prescription drug labeling
Prescribing/counseling decision making
Risk communication

ABSTRACT

Background: Most breastfeeding individuals take at least one prescription drug, yet limited data from lactation studies are available to inform the safety of these drugs during breastfeeding. As a result, healthcare providers (HCPs) rely on available information about safety of drugs used during pregnancy or on personal experiences to inform prescribing/counseling decisions for breastfeeding individuals. To improve risk communication regarding drugs used during lactation, the U.S. Food and Drug Administration published the Pregnancy and Lactation Labeling Rule (PLLR) in 2015, which added a narrative summary of available risk information to the lactation section of Prescribing Information (PI). Prior studies on labeling in PLLR format revealed that although HCPs found these details valuable, they regarded the narrative as too long to support decision-making during patient encounters.

Objective: This qualitative study's objective was to assess the utility of adding a concise summary to the Lactation subsection of PI to complement the narrative and succinctly communicate to busy HCPs a drug's risks when used during lactation. The concise summary consisted of a bolded headline, bulleted descriptions of available study findings and potential adverse reactions, and recommendations for risk mitigation.

Methods: Twenty-five online focus groups were conducted with five segments of HCPs to obtain their feedback on the concise summary and discuss their prescribing/counseling decisions for four fictitious prescription drugs including one vaccine.

Results: HCPs utilized the concise summary to make initial prescribing/counseling decisions. Many also used the labeling narrative for a comprehensive benefit-risk assessment.

Conclusion: The findings indicate a need to continue to improve communication about safety of drugs used during lactation, and that the concise summary may help facilitate this communication. The study also highlights the need to educate HCPs about PI limitations when clinical data are lacking and the need to encourage clinical studies to be conducted to support actionable recommendations about use of prescription drugs during lactation.

8 USE IN SPECIFIC POPULATIONS

...

8.2 Lactation

▶ **Statement of known risks**

Risk mitigation strategy statement

*Concise
summary*

- Summary of findings of risk in human or animal studies
- Description of potential adverse reactions

Risk Summary – Narrative describing what is known about the presence of the drug in breast milk and, if present, at what concentration; potential adverse effects on the breastfeeding infant; potential adverse impacts on milk production; and risk mitigation recommendations.

Clinical Considerations – Narrative describing steps to reduce the breastfeeding infant's exposure to the drug and, if appropriate, what adverse reactions to monitor for in the infant.

Data – A narrative description of the human and/or animal data that supports the information under the Risk Summary and Clinical Considerations headings.

<https://www.sciencedirect.com/science/article/pii/S1551741124000512?via%3Dihub>

ADVERSE EVENT REPORTING



You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). In addition to the reporting requirements in 21 CFR 600.80, you must submit adverse experience reports for preterm birth and hypertensive disorders of pregnancy as 15-day expedited reports to the Vaccine Adverse Event Reporting System (VAERS) at <https://vaers.hhs.gov/>. Reports of preterm birth and hypertensive disorders of pregnancy must be submitted as 15-day expedited reports for 3 years following the date of product licensure. You must submit distribution reports as described in 21 CFR 600.81. For

...we have determined that you are required to conduct the following studies:

Study titled, “A Rapid Surveillance and Cohort Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO) Exposure During Pregnancy in the United States” (Protocol C3671027).

Study titled, “Post-Marketing Safety Study Using a Pregnancy Registry to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO) Exposure During Pregnancy” (Protocol C3671041).

Study titled, “A Post-Marketing Safety Study to Evaluate the Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO) Exposure During Pregnancy in an Integrated Healthcare System in the United States” (Protocol C3671042).



Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings

- Reviews and evaluates data on safety, effectiveness and use of vaccines
- Also considers quality and relevance of FDA's research program which provides scientific support
- Makes appropriate recommendations to the FDA Commissioner

[Vaccines and Related Biological Products Advisory Committee | FDA](#)



Summary and Conclusions

Summary

- Despite rigorous safety evaluation during premarket phases of clinical development, postmarketing safety monitoring is necessary due to limitations of clinical trials
- Postmarketing surveillance includes many approaches including passive and active surveillance
- FDA may require postmarketing studies by manufacturers
- New databases have expanded population-based surveillance capabilities
- FDA and CDC share many vaccine surveillance activities
- Our goal to ensure safe and effective products in the general U.S. population, including populations of interest, such as pregnant women

Thank you!