Improving Pregnancy Safety in the Postmarket Setting: Regulatory Perspective

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Authority to Require Postmarket Safety Studies

Under section 505(o)(3) of the Federal Food, Drug, & Cosmetic Act (FD&C Act)

- Require studies or trials *at the time of approval* to:
  - Assess a known serious risk related to the use of the drug
  - Assess a signal of serious risk related to the use of the drug
  - Identify an unexpected serious risk when available data indicates the potential for a serious risk

- Require such studies or trials *after approval* if FDA becomes aware of new safety information

FDA Guidance: Postmarketing Studies and Clinical Trials
FDA Draft Guidance: Postapproval Pregnancy Safety Studies

General Postmarket Approaches

Three general approaches to assessing the occurrence of major congenital malformations (MCMs) and other pregnancy outcomes:

- **Pharmacovigilance**
  - Spontaneous reports, case reports or case series from medical literature, etc.
  - A series of similar reports of a distinct abnormality or a group of similar abnormalities can suggest a signal
- **Pregnancy registries**
  - Remain an important tool for safety data collection in the postmarketing setting because of the prospective design and the ability to collect detailed patient level data
  - However, patient recruitment and retention often challenging, generally not sufficient by themselves
- **Complementary data sources**
  - May help address the limitations inherent to a pregnancy registry-based study
  - Electronic healthcare data (e.g., insurance claims and electronic health record databases) are commonly used

FDA Draft Guidance: Postapproval Pregnancy Safety Studies

Considerations for Postmarket Pregnancy Safety Studies Using Electronic Healthcare Data

- Factors that can impact the validity of study

Identification of pregnancy episodes	Linkage to external vital statistics and registries
Mapping of mothers and infants	Key covariates, competing risks
Estimate of gestational age and pregnancy start	Length of follow-up
Exposure assessment for critical periods	Ability to conduct chart review
Maternal, pregnancy, infant outcome assessment	Others

- A wealth of methods development and validation studies in medical literature
  - However, concerns remain for the validated methods given suboptimal validation approach and results
- Data and methodological challenges differ by the purpose of study, study question, type of medication, nature of outcome, characteristics of data source, type of study, etc.
- Rigorous studies are desired to inform regulatory decision making

FDA Continues to Evaluate and Develop Methods and Data Sources to Improve Capabilities for Drug Safety Assessment in Pregnancy

- FDA's Sentinel System
  - FDA's congressionally mandated distributed data network for drug safety surveillance
  - One focus is to define and refine methods to assess medical product utilization, safety, and effectiveness during pregnancy
- Medicaid
  - Develop the capability of using national Medicaid data for FDA post-marketing active surveillance to assess medication safety during pregnancy
- PDUFA VII Pregnancy Safety Commitment
  - Prescription Drug User Fee Act (PDUFA) reauthorization for FYs 2023-2027
  - Advance analytic capabilities and develop a consistent approach to pregnancy safety post-market requirements (PMRs) and commitments (PMCs) PDUFA VII Commitment Letter

Thank You