Including Pregnancy Registry Data in Labeling

Leyla Sahin, MD, FACOG
Division of Pediatric and Maternal Health
Center for Drug Evaluation and Research, Office of New Drugs
US FDA

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Disclaimer

- I do not have any financial disclosures to report
- This presentation represents the views of the speaker, and not the official position of the FDA

Objectives

- New Labeling System and human data
- Approach to inclusion of pregnancy registry data in labeling
- Examples

New Labeling System

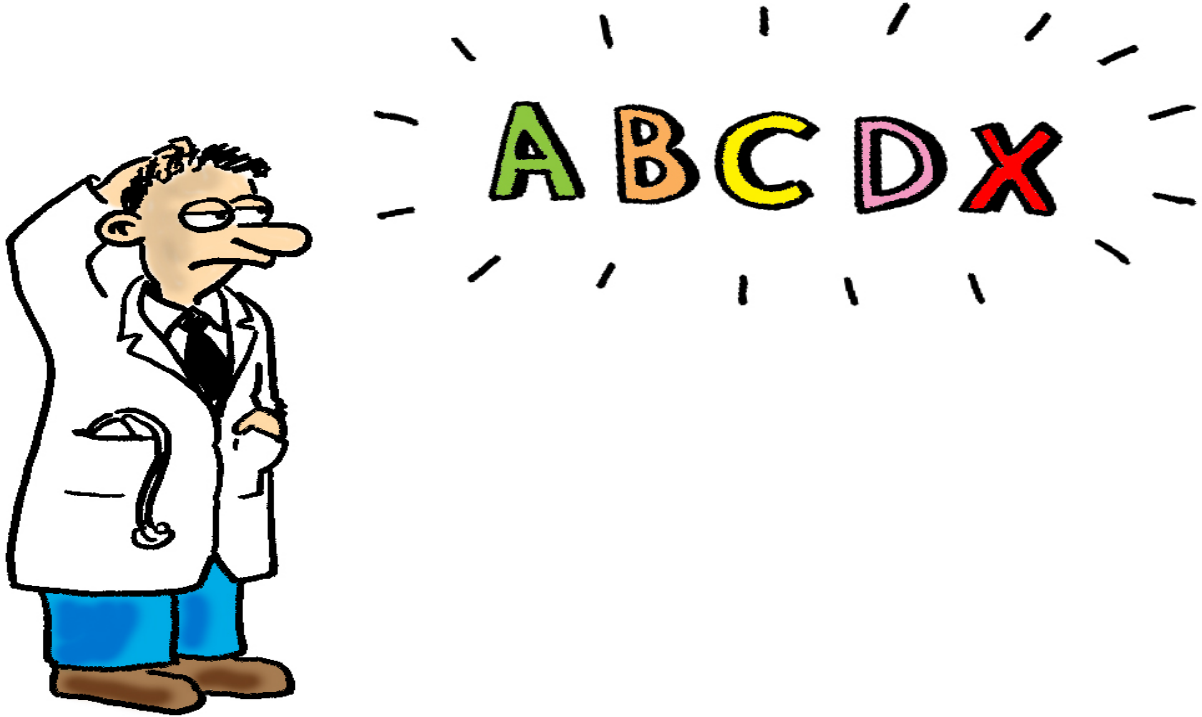
The Pregnancy

and

Lactation

Labeling Rule (PLLR)

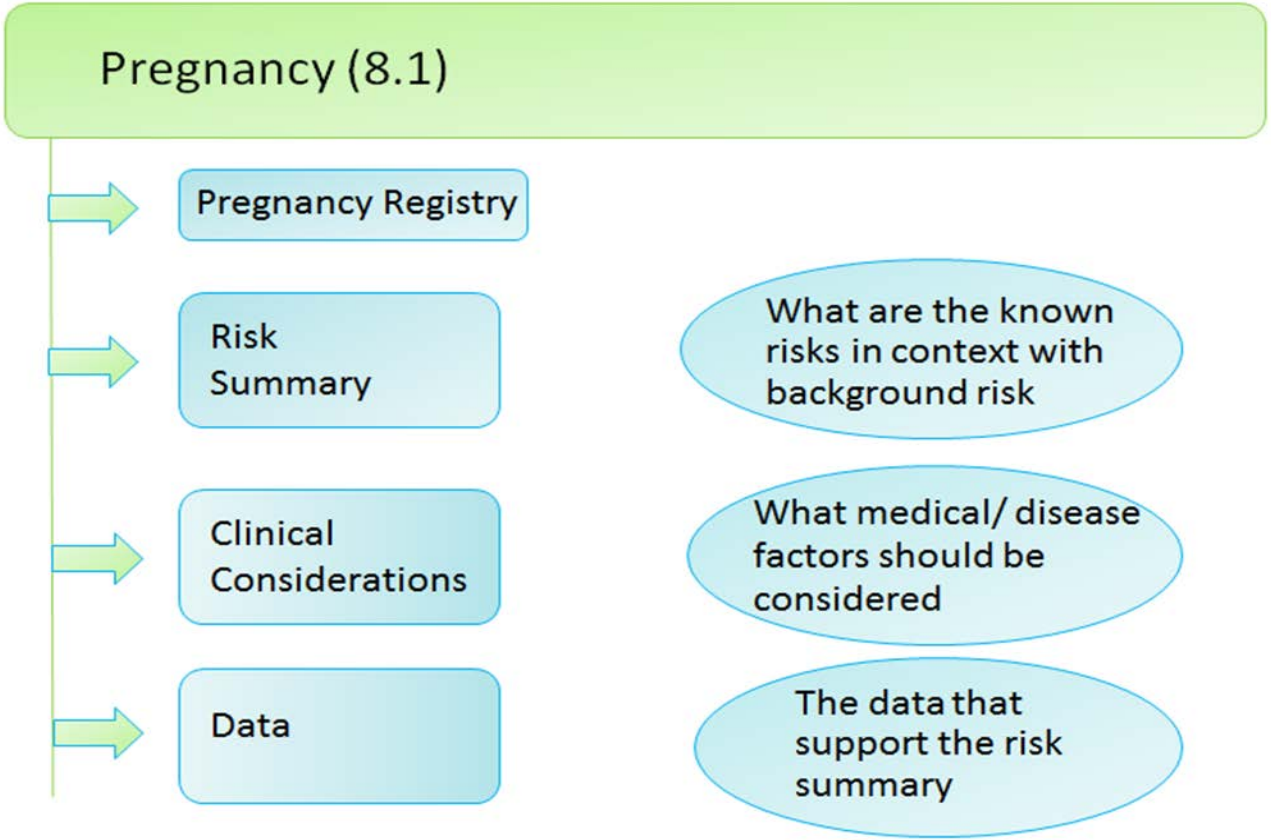
Evidence Based ?



New Labeling System

- Provides the prescriber with relevant information for critical decision-making when treating pregnant or lactating women
- Focus on human data
- More complete statement of the known risks based on the available data
- Considerations of medical/disease factors

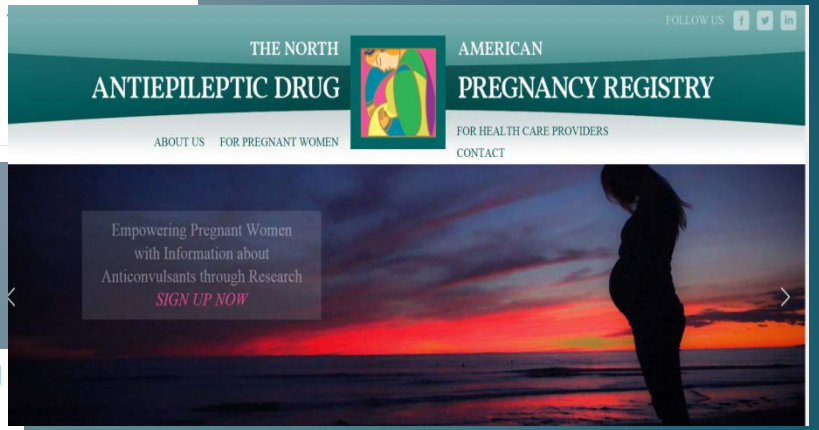
New Format

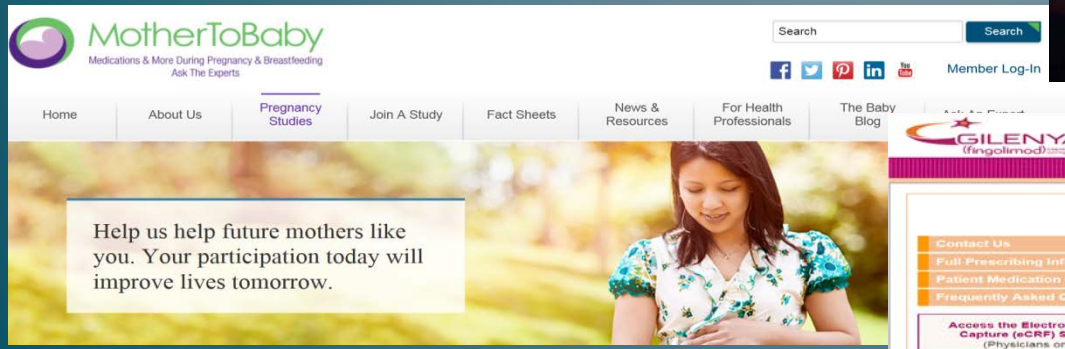

Pregnancy (8.1)
Pregnancy Registry
Risk Summary
What are the known risks in context with background risk
Clinical Considerations
What medical/ disease factors should be considered
Data
The data that support the risk summary

Approach to assessing pregnancy registry data

Menveo® pregnancy registry: an observational study on the safety of Menveo exposure in pregnant women and their offspring

Menveo® pregnancy registry is established to meet a post marketing commitment agreed upon with CBER to establish a pregnancy registry to prospectively collect data on pregnancy exposures to Menveo. This registry is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating health care provider.





Data assessment

- Multidisciplinary review: epidemiologists, medical officers, statisticians
- Considerations
  - Sample size, statistical power
  - Comparators
  - Adjustment for confounders
- Study results
  - Validity
  - Interpretability

Overall safety assessment

- Consideration of other data sources
  - Published data
  - Unpublished data
  - Company safety data, FDA Adverse Event Reporting System data
  - Nonclinical data
- Overall data assessment
  - Cumulative exposures
  - Differences in study designs/methods
  - Consistency of findings across studies
  - Can a risk conclusion be drawn?


communication
noun
1
2 something that commu
sage communicates with the
ate with older ones.
ship; young people
letter or messag

Communicating pregnancy registry data in labeling

- How to communicate the results
  - In a meaningful manner
  - Describe the limitations
  - In the context of other data
  - In the context of the background risk

- Goal is balanced messaging-consideration of treatment benefit and public health impact

Observations

- Multi-product or disease based registries have generally been more successful for collection of data and sustainability of the registry
- Data from studies with different methodologies overcome the limitations of individual study designs and increase confidence in the findings

Example of multiproduct Pregnancy Registry- Antiretroviral Pregnancy Registry (APR)*

	2016
Number of drugs included in the registry	53
Number of sponsors	27
Number of countries participating	70
Number of evaluable prospective cases	17,371
Number of 1st trimester exposures	8,227
U.S. reports	76.6%

*data from December 2016 APR Interim Report

Example of Approved Labeling

Viramune ® (nevirapine) (5-2017)

8.1 Pregnancy

Risk Summary

Available data from the Antiretroviral Pregnancy Registry (APR) show no difference in the risk of overall major birth defects compared to the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP)*(see Data).* The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

Viramune (nevirapine) continued

Data

Human Data

Based on prospective reports to the APR of over 2,600 exposures to nevirapine during pregnancy resulting in live births (including over 1,100 exposed in the first trimester), there was no difference between nevirapine and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.8% (95% CI:1.9, 4%) following first trimester exposure to nevirapine-containing regimens and 3.2% (95%CI 2.4, 4.3%) for second/third trimester exposure to nevirapine-containing regimens.

Labeling Example (2)

Gardasil ® (Human papillomavirus 9-valent) vaccine (10-2016)

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available human data do not demonstrate vaccine-associated increase in risk of major birth defects and miscarriages when Gardasil 9 is administered during pregnancy.

Labeling Example (2) continued Gardasil ®

Human Data

A five-year pregnancy registry enrolled 2,942 women who were inadvertently exposed to GARDASIL within one month prior to the last menstrual period (LMP) or at any time during pregnancy, 2,566 of whom were prospectively followed. After excluding elective terminations (n=107), ectopic pregnancies (n=5) and those lost to follow-up (n=814), there were 1,640 pregnancies with known outcomes. Rates of miscarriage and major birth defects were 6.8% of pregnancies (111/1,640) and 2.4% of live born infants (37/1,527), respectively. These rates of assessed outcomes in the prospective population were consistent with estimated background rates.

Example (2) continued Gardasil® Human Data

In two post-marketing studies of GARDASIL (one conducted in the U.S., and the other in Nordic countries), pregnancy outcomes among subjects who received GARDASIL during pregnancy were evaluated retrospectively. Among the 1,740 pregnancies included in the U.S. study database, outcomes were available to assess the rates of major birth defects and miscarriage. Among the 499 pregnancies included in the Nordic study database, outcomes were available to assess the rates of major birth defects. In both studies, rates of assessed outcomes did not suggest an increased risk with the administration of GARDASIL during pregnancy.

Labeling Example (3)

Humira® (adalimumab) (4-2017)

8.1 Pregnancy

Risk Summary

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data].* The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Labeling Example (3)

Humira® (adalimumab) (4-2017)

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

Summary

- Pregnancy registry data will be included in labeling if it informs or changes the risk profile
- Need to communicate data in a balanced way that is meaningful for the healthcare provider