

# Including Pregnancy Registry Data in Labeling

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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)

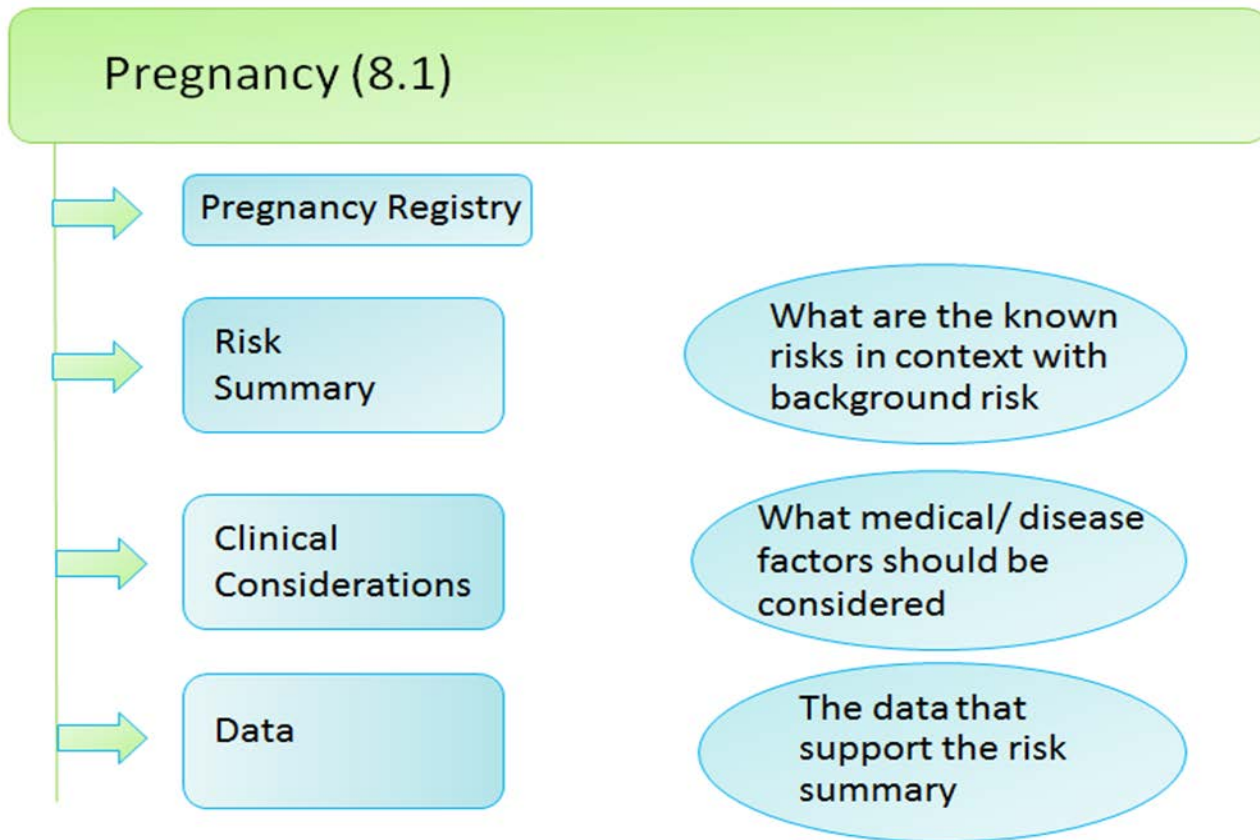
# Evidence Based ?



# 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



# **Approach to assessing pregnancy registry data**





Science & Research

Home > Science & Research > Science and Research Special Topics > Women's Health Research

Women's Health Research

OWH Research and Development Program

OWH Public



Pregnancy Registry Information Professionals

NUVIGIL Pregnancy Registry

WELCOME

Welcome to the NUVIGIL Pregnancy Registry Web site. The NUVIGIL Pregnancy Registry has been established to evaluate the safety of NUVIGIL use during pregnancy. To learn more about the NUVIGIL Pregnancy Registry, contact a Registry representative at 1-866-404-4106 (toll-free).

How to enroll?

- BY PHONE—Call the Pregnancy Registry at 1-866-404-4106
- ONLINE—“Click” on the Registration Request Button provide your contact information. Someone from the Pregnancy Registry will then contact you to confirm necessary information to complete the registration process.

Registration Request

If you are pregnant and have taken at least one NUVIGIL tablet within 6 weeks of becoming pregnant or at any time during your pregnancy, you may be eligible to participate in the Registry. To learn more about the Registry, including how to participate, please click the “Patients” button below.

If you are a healthcare professional treating a patient who is taking NUVIGIL, and has become pregnant, you are encouraged to enroll the patient in the Registry. Please click the “Healthcare Professionals” button below for more information.

Patients

Healthcare Professionals



Medications & More During Pregnancy & Breastfeeding  
Ask The Experts



Help us help future mothers like you. Your participation today will improve lives tomorrow.



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.

THE NORTH AMERICAN  
ANTIEPILEPTIC DRUG PREGNANCY REGISTRY

ABOUT US FOR PREGNANT WOMEN FOR HEALTH CARE PROVIDERS CONTACT

Empowering Pregnant Women with Information about Anticonvulsants through Research  
*SIGN UP NOW*



GILENYA Pregnancy Registry

Physicians

Patients

Contact Us

Full Prescribing Information

Patient Medication Guide

Frequently Asked Questions

Access the Electronic Data Capture (eCRF) System (Physicians only)

For more information on GILENYA, please click here.

Novartis Pharmaceuticals Corporation, the marketer of GILENYA, has established an FDA-mandated pregnancy registry to collect information about the effect of GILENYA use during pregnancy from voluntary participants.

Quintiles, a leading research provider for patient registries, will manage the registry on behalf of Novartis Pharmaceuticals Corporation and collect information related to GILENYA exposure and maternal, fetal and infant outcomes.

The findings from the registry will be used to give health care providers important information for treating and counseling patients who are pregnant or may become pregnant and are treated, or plan to be treated with GILENYA.

If you are a physician treating a patient with GILENYA who has become pregnant, you are encouraged to enroll the patient into the registry. Please click the “physician” tab.

If you are a patient who has taken at least one dose of GILENYA around the time of conception or while pregnant, please click the “patient” tab.

# 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?



# 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 1 <sup>st</sup> trimester exposures	8,227
U.S. reports	76.6%

\*data from December 2016 APR Interim Report

# Example of Approved Labeling



Viramune<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup>



### *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