Maternal Immunization Working Group Phase II

June 9, 2015
NVAC

Chairs:
Richard Beigi, MD
Saad Omer, PhD

Maternal Immunizations Facts

- Pregnant women and young infants are at a higher risk for morbidity and mortality from various vaccine-preventable diseases
- A provider recommendation and vaccine offering during pregnancy are key factors that help increase vaccination coverage
- Maternal immunization can help foster positive attitudes towards vaccines in pregnant women that may result in greater awareness, acceptance, and demand for vaccines for both themselves and their children

NVAC CHARGE FOR THE MIWG

CHARGE

The Assistant Secretary for Health charges the NVAC to:

Part 1:

- Review the current state of maternal immunization and existing best practices
- Identify programmatic barriers to the implementation of current recommendations related to maternal immunization and make recommendations to overcome these barriers [1]

Part 2:

- **Identify barriers to and opportunities for developing vaccines for pregnant women and make recommendations to overcome these barriers**

[1] Reducing Patient and Provider Barriers to Maternal Immunizations, Public Health Reports, Jan-Feb 2015

MEMBERSHIP MIWGII

NVAC	Rich Beigi (Co-chair), Saad Omer(Co-chair) Walt Orenstein, Ruth Lynfield, Seth Hetherington
NVPO leads	Jennifer Gordon Karin Bok
Subject Matter Experts	Ajoke Sobanjo-ter Meulen, Steven Black, Mary Healy, Cindy Pellegrini, Flor Muñoz, Jan Bonhoeffer, D. Tomianovic, Geeta Swamy, Kathy Edwards, Leonard Friedland, Debra Hawks, Jeanne Sheffield, N.Bhat, Debbie Higgins, Fernando Polack, Cheryl Broussard, Gina Burns, Sharon Humiston, Amina White, Carol Baker
Ex Officio Federal Liaisons	Karen Broder (CDC) Jennifer Liang (CDC) Stacey Martin (CDC) Pedro Moro (CDC) Marion Gruber (FDA) Jeff Roberts (FDA) Valerie Marshall (FDA) Avril Houston (HRSA) Emily Levine (HHS/OGC) Barbara Mulach (NIH) Mirjana Nesin (NIH) Jennifer Read (NIH) Margaret Jacovone (DoD) Fran Cunningham (VA) Richard Martinello (VA)
Special Assistant	Katy Seib

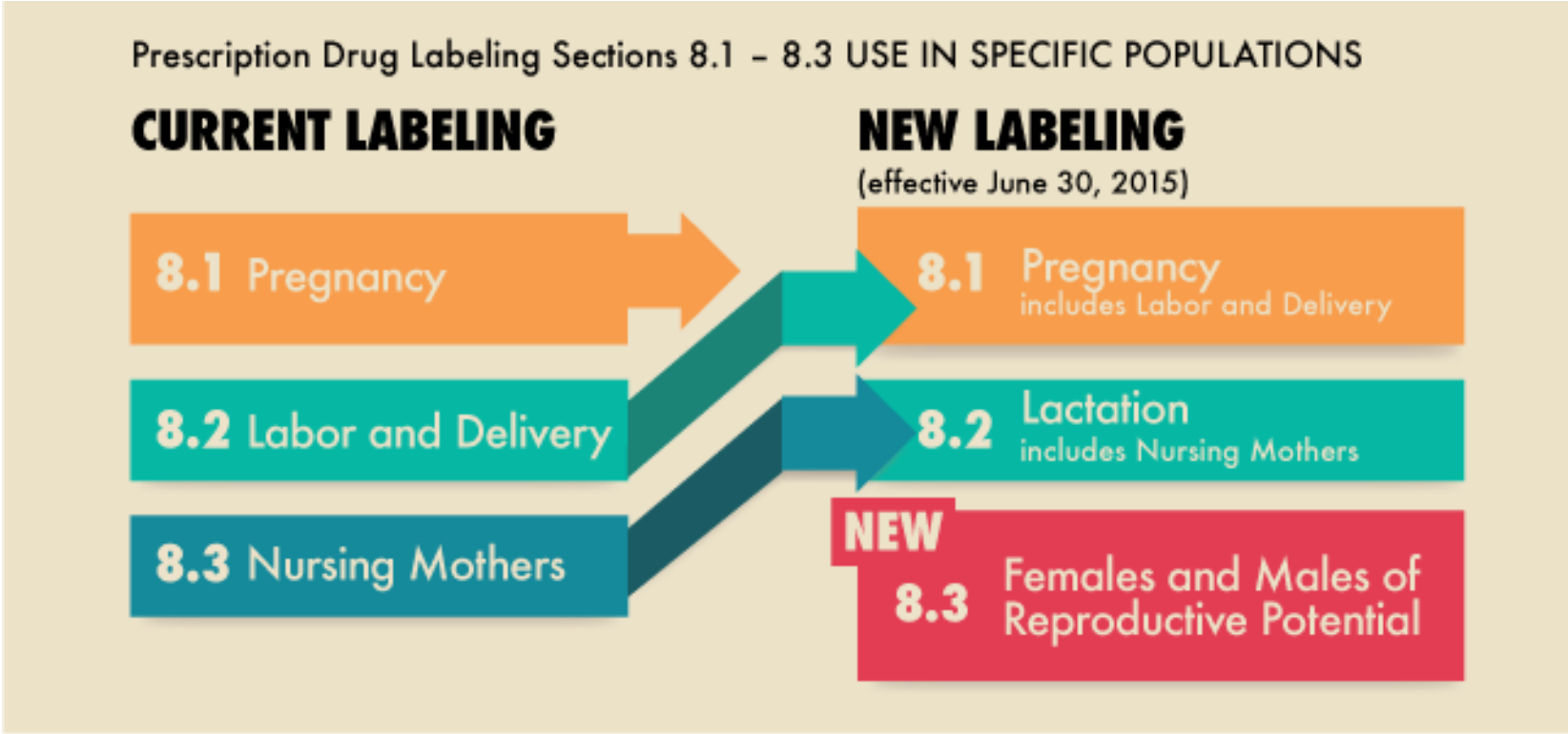
MIWG II Meetings

- January 2015: Updates on Vaccines Administered During Pregnancy (Dr. Nesin)
- March 2015: Epidemiology and Vaccine Research of GBS and RSV (Dr. Polack and Dr. Baker)
- May 2015: Best Pharmaceuticals for Children Act implementation by NIH (Dr. Zajicek)
- June 2015: Pregnancy and Lactation Labeling Rule (Dr. Gruber)

Upcoming MIWG II Meetings

- August 2015: GlaxoSmithKline Maternal Immunization Program (Dr. Friedland)
- October 2015: Novavax Maternal Immunization Program

NVAC Feedback on **Pregnancy and Lactation Labeling Rule** Implementation



The PLLR removes pregnancy letter categories – A, B, C, D and X. The PLLR also requires the label to be updated when information becomes outdated [1]

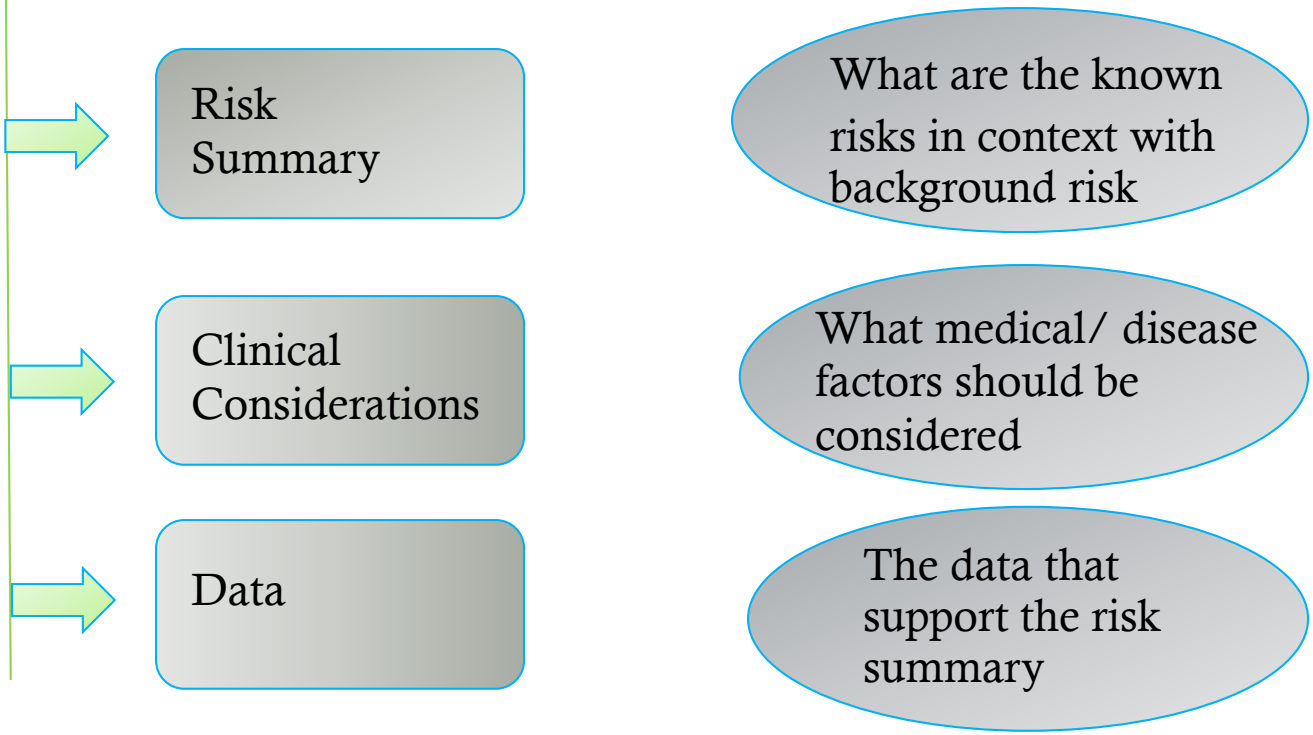
[1] Roberts and Gruber, Regulatory considerations in the clinical development of vaccines indicated for use during pregnancy . Vaccine. January 2015

PLLR Final Rule

- Published on December 4, 2014
- Amends the Physician Labeling Rule (PLR) of 2006
  - Pregnancy and Lactation labeling subsection revisions were deferred when PLR was published in 2006
- Creates consistent format for providing information about the risks and benefits of product use during pregnancy and lactation, and by females and males of reproductive potential
- Requires the removal of the pregnancy categories from all human prescription drug and biological product labeling
- Replaces the letter categories with three subsections that provide details about use of the product in "Pregnancy," "Lactation" and by "Females and Males of Reproductive Potential"
- Seeks to make product labeling a better communication tool in order to present the scientific information available for each drug and biological product

Revised Format Under Section 8

Pregnancy (8.1) and Lactation (8.2)



PLLR: Required Labeling Elements

8.1 Pregnancy

- Pregnancy Exposure Registry Contact Info
- Background risk statement
- Risk Summary
  - Human data*
  - Animal data
- Clinical considerations
  - Disease-associated maternal/embryo/fetal risk
  - Dose adjustments during pregnancy a
  - Maternal/fetal/neonatal adverse reactions
  - Labor or delivery
- Data: Human, * Animal

8.2 Lactation

- Risk summary
  - Effects on milk production
  - Presence of drug in milk
  - Adverse effects in breast-fed child
- Clinical considerations
- Data

8.3 Females and Males of Reproductive Potential

- *Human data may come from clinical trials, pregnancy exposure registries, other large scale epidemiologic studies, or case series reporting a rare event

PLLR Implementation Schedule

Applications Required To Conform to New Pregnancy/Lactation Content Requirements	Time by Which Labeling with New Pregnancy/Lactation Content Must Be Submitted to FDA for Approval
New or Pending Applications:*	
Applications submitted on or after the effective date of the final rule (June 30, 2015)	Time of submission
Applications pending on the effective date of the final rule (June 30, 2015)	4 years after the effective date of the final rule or at time of approval, whichever is later
Approved Applications Subject to the Physician Labeling Rule:	
Applications approved any time from June 30, 2001, up to and including June 29, 2002, and from June 30, 2005, up to and including June 29, 2007	3 years after the effective date of the final rule (June 30, 2018)
Applications approved any time from June 30, 2007, up to and including the effective date of the final rule	4 years after the effective date of the final rule (June 30, 2019)
Applications approved from June 30, 2002, up to and including June 29, 2005	5 years after the effective date of the final rule (June 30, 2020)

*"Applications" includes NDAs, BLAs, and efficacy supplements.

PLLR – Implications for Vaccine Labeling

- Manufacturers are required to evaluate existing labeling to ensure it accurately reflects current knowledge about use of the product during pregnancy; need to update label when new information becomes available
- In general, data from use of vaccines in pregnancy derived from post-marketing studies or published maternal immunization studies, e.g.,
  - Clinical trials, pregnancy exposure registries, observational postlicensure studies, case series, etc
- No requirement for the manufacturer to conduct additional studies
- Current thinking is that data should be derived from studies conducted with the specific product unless evidence of risk apparent from data accrued using a closely related product(s)

PLLR – Implications for Vaccine Labeling

- Licensed vaccines recommended by ACIP for use in pregnancy (e.g., influenza, TdaP)
  - No expected impact on existing recommendations
  - No requirement for additional studies
- Investigational vaccines specifically developed for use in pregnancy (e.g., GBS, RSV vaccines)
  - PLLR does not impact the requirement for demonstration of "substantial evidence" of effectiveness and safety in order to support usage and claims specific to pregnancy
    - e. g., GBS vaccine to prevent early onset disease in neonates
  - Such evidence is based on adequate and well-controlled studies
  - Data would be included in Section 6 ("Adverse reactions") and Section 14 ("Clinical studies") of product labeling

PLLR – Next Steps

- PLLR requires an evaluation of available information about a vaccine's use in pregnancy
  - Moving forward, manufacturers whose products are subject to the final rule will be responsible for regularly reviewing information and data that become available regarding the use of their product by pregnant and lactating women
- Provides an opportunity to update labeling to ensure they are informative and accurate
- Draft Guidance Published

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf

PLLR - Next Steps

- Implementation of PLLR provisions , as they apply to vaccine labeling, will require close collaboration between OVRR and vaccine manufacturers in accordance with published guidance
- What data can/should be included in Section 8.1 – 8.3?
  - Rule states data can come for clinical trials, pregnancy exposure registries, large scale epidemiologic studies, case series reporting
  - BIO-CBER Roundtable of March 2015: Industry requested guidance
  - Establishment of CBER Internal Working Group
  - Vaccine 'Mock" labeling? - CBER website?
  - Outreach to CDC?
  - Recommendations by NVAC MIWG?

PLLR Discussion Topics

- Overall feedback/comments
- Outreach activities that FDA should engage in (dissemination and education)
- Additional studies in pregnant women: which vaccines should be studied and entity that should conduct the study (government to enhance data and information that could be included in section 8.1/8.2)

THANK YOU

PLLR Implementation Schedule (cont.)

- Drugs approved **prior to** June 30, 2001 are required to remove the pregnancy letter category by June 30, 2018 (3 years after PLLR goes into effect)
- Labeling for these products is not required to conform to the Physician Labeling Rule (PLR)
  - Consequently are not required to revise the Pregnancy and Nursing Mothers sections under PLLR
- Agency efforts underway to encourage, or in some cases require, conversion of the older labeling to the PLR (and PLLR) format

PLLR – Implications for Vaccine Labeling

- Prescribing information for most US licensed vaccines carry either
  - Category B (no human data & animal data reassuring)
  - Category C (no human data & no animal data)
    - 21 CFR 201.57(c)(9)(i)
- Category B & C allow vaccination of pregnant women if the benefits from the use of the vaccine in pregnant women may be acceptable despite its potential risk & there is determination that the vaccine is clearly needed
- US licensed vaccines with letter category B or C not contraindicated for use in pregnant women
- PLLR removes the letter categories but does not change the considerations for vaccination of pregnant women