Regulatory Education for Industry (REdI):

PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

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PLLR: Implementation and Challenges

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Disclaimer

- **The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.**
- **The labeling examples included in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended labeling templates.**

Overview

- Introduction
- Considerations and Emerging Best Practices
  - Supportive Information
  - Process Considerations
  - Content Considerations
- Summary

Introduction

Division of Pediatric and Maternal Health (DPMH)

- **Located within Office of New Drugs/CDER/FDA**
- **Comprised of Maternal Health Team, Pediatrics Team, and Pediatrics Regulatory Team**
- **To develop clinically relevant, evidence-based labeling and other communications that facilitate informed use of medicines in children and females of reproductive potential.**

DPMH's Role

- To raise awareness amongst external and internal stakeholders
  - Participation and outreach at professional conferences and meetings
  - Communication to applicants through regulatory meetings and correspondence
- Collaboration within the Agency for consistency of process
- To assist with review of PLLR labeling conversions
- To track the drug product labeling compliance with PLLR

PLLR Implementation Schedule

	NDAs, BLA, ESs	Required Submission Date of PLLR Format
New Applications (prospective cohort)	Submitted on or after 6/30/2015	At time of submission
Start (6/30/15) ----------		
Older Approved Applications (retrospective cohort)	Approved 6/30/2001 to 6/29/2002 Approved 6/30/2005 to 6/29/2007	6/30/2018
	Approved 6/30/2007 to 6/29/2015 or pending on 6/30/2015	6/30/2019
	Approved 6/30/2002 to 6/29/2005	6/30/2020
	For applications approved prior to 6/30/2001 in old format labeling	Not required to be in PLLR format. However, must remove Pregnancy Category by 6/29/2018

Considerations and Emerging Best Practices

Expectations for Submission of PLLR Compliant Labeling

- **The submitted labeling should:**
  - **comply with the PLLR format**
  - **reflect an integrated assessment of known risks relevant to pregnancy, lactation and infertility based on available information/data**
  - **be accompanied by a summary and review of the available relevant information/data**

Supportive Information (1)

- **FDA recommends an assessment of current available information to provide updated and accurate recommendations for subsections 8.1, 8.2, and 8.3**
- **The majority of experience with drug use during pregnancy and lactation occur during the postmarketing period**
- **There may be new information that is not captured in old labeling**

Supportive Information (2)

- **Assessment should generally include (when applicable):**
  - **A review and summary of the published literature related to drug use during pregnancy and lactation, and drug effects on fertility**
  - **A review and summary of relevant cases reported in the drug pharmacovigilance database**
  - **An interim report of an ongoing pregnancy registry or a report of a closed pregnancy registry**
- **Locate supportive information in Module 1 of submission**

Process Considerations (1)

- **Applicant must be aware of requirement for labeling to comply with PLLR format**
  - **includes new 505 (b)(2) and biosimilar applications**
- **Agency is informing applicants through pre-BLA/pre-NDA meetings, external conferences, FDA website and other methods of communications**
- **<u>No waivers of PLLR requirement</u>**
- **Deferral requests will be reviewed on a case-by-case basis**
- **Potential Refuse to File (RTF) issue**

Process Considerations (2)

- **Submission lacks information/data to support labeling content**
  - **Would not be grounds for RTF by itself**
  - **Review division may issue information request (IR)**
  - **Applicant should consider the amount of supporting information that needs to be prepared and the time needed to respond to the IR**
  - **Response to an IR could be considered a major amendment**

Content Considerations (1)

- ***Risk Summary:***
  - **Remove pregnancy category classification**
  - **Existing data or recommendations should be reviewed and revised or updated based on data**

Content Considerations (2)

- ***Clinical Considerations:***

  Disease-Associated Maternal and/or Embryo/Fetal Risk

  - **This section should not include an exhaustive textbook review of the untreated disease/condition and pregnancy outcomes**
  - **Limit information contained in this subsection to a brief description of any serious known or potential risk of the underlying disease/condition on pregnancy outcomes**

Example of 8.1 Pregnancy, Clinical Considerations

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Pregnant patients with left ventricular ejection fraction less than 35% on maximally tolerated doses of beta-blockers may be particularly heart-rate dependent for augmenting cardiac output. Therefore, pregnant patients who are started on TRADENAME, especially during the first trimester, should be followed closely for destabilization of their congestive heart failure that could result from heart rate slowing. Monitor pregnant women with chronic heart failure in 3rd trimester of pregnancy for preterm birth.

Content Considerations (3)

- ***Data***

***Human Data*:**

- **Describe any potential risk mentioned in Risk Summary**
- **Describe clinical trials, pregnancy exposure registry studies, large epidemiologic studies, or well-described case series**
- **Should not be lengthy**
- **Succinctly describe study design, drug exposure, pregnancy outcomes**
- **Describe any limitations of the data**

Example of 8.1 Pregnancy, Human Data

Data

Human Data

TRADENAME was evaluated in 12 HIV-infected pregnant women in an open-label pharmacokinetic trial *[see Clinical Pharmacology (12.3)]*. No new trends in the safety profile were identified in pregnant women dosed with TRADENAME compared to the safety described in non-pregnant adults, based on the review of these limited data.

Antiretroviral Pregnancy Registry Data: Based on prospective reports from the Antiretroviral Pregnancy Registry (APR) of over 3,000 exposures to [drugcomponent1] containing regimens (including over 1,000 exposed in the first trimester), there was no difference between [drugcomponent1] and overall birth defects compared with the background birth defect rate of 2.7% in the [reference population]. Based on prospective reports from the APR of over 5,000 exposures to [drugcomponent2] containing regimens (including over 2,000 exposures in the first trimester) there was no difference between [drugcomponent2] and overall birth defects compared with the [reference population]. For both [drugcomponent1] and [drugcomponent2], sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5 fold increase in risk of overall birth defects ...

Content Considerations (4)

- ***Data:***

  Animal Data

  - **Describe any potential risk mentioned in Risk Summary**
  - **Describe study type, species, timing of the exposure (i.e., during the period of organogenesis), findings, presence of maternal toxicity, limitations of data**
  - **When expressing animal dose/exposure in terms of multiples of human dose/exposure**
    - **comparisons based on AUC preferred**
    - **comparisons based on BSA may be considered**

Example of 8.1 Pregnancy, Animal Data - AUC

Data

Animal Data

Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7-fold for [drugcomponent1] and 1.8-fold for [drugcomponent2] for males and females that of the exposures in humans at the recommended therapeutic dose. In a peri-and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21) occurred.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6-fold for [drugcomponent1] and 1.0-fold for [drugcomponent2] that of the exposures in humans at the recommended therapeutic dose ...

Content Considerations (5)

- **8.3 Females and Males of Reproductive Potential**
  - **Subsection should be included only when necessary**
  - **If there is Embryo-Fetal Toxicity that supports recommendations for pregnancy testing and contraception use, a Warning & Precaution is generally included**

Example of 8.3 Females and Males of Reproductive Potential

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action and animal data, TRADENAME can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TRADENAME treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with TRADENAME and for at least X months after the last dose.

Males

Drugname is present in semen *[see Clinical Pharmacology (12.3)].* It is not known if the amount of drugname in semen can cause embryo-fetal harm. Advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure to pregnant partners and female partners of reproductive potential during treatment with TRADENAME and for at least X months after the last dose. Advise males not to donate semen during treatment with TRADENAME and for at least X months after the last dose.

Infertility

Based on findings from animal studies, female fertility may be compromised with TRADENAME *[see Nonclinical Toxicology(13.1)].*

Summary

- **The submitted labeling should comply with PLLR requirements and be accompanied by a summary and review of the available relevant information/data**

- **Additional Recommendations:**
  - **Refer to the Draft Guidance for Industry**
  - **Refer to the Selected Requirements of Prescribing Information (SRPI)**
  - **Review recent PLLR conversions, especially those in similar drug class or for similar patient population**

Thank You

Draft Guidance, Appendix B: Implementation Plan

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	Time of submission
Applications pending on the effective date of the final rule	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
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
Applications approved from June 30, 2002, up to and including June 29, 2005	5 years after the effective date of the final rule

Example of 8.1 Pregnancy, Animal Data - BSA

Data

Animal Data

No teratogenic effects were observed when drugname was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m2 basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; these effects were not observed at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits.