Pregnancy & Lactation Labeling Rule (PLLR)

Industry Perspective

Traci J. Lee, PharmD
Director, Labeling
Global Regulatory Affairs

Disclaimer

The views and opinions expressed in the following PowerPoint and accompanying oral presentation should not be construed as official or unofficial GlaxoSmithKline position.

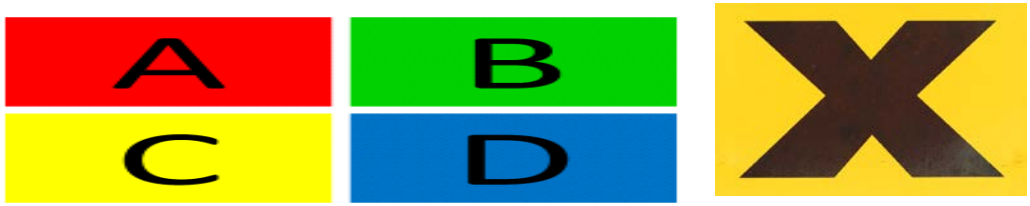
I have a professional relationship with GlaxoSmithKline and have GSK financial holdings. I receive financial compensation and holdings as part of my employment.

Agenda

- One sponsor's view on the Regulation
- Implementation
  - Approach
  - Timelines
  - Standardization
  - Data evaluation
- Challenges
- Insights

Sponsor View

- Acknowledgement of prior challenges
  - Categories confusing and simplistic
  - Benefit and risk decisions more complex than categories relay
  - Lack of robust risk information related to adverse fetal outcomes
  - Labeling updates with human data did not occur on a regular basis



Sponsor View

- Agreement with New Regulation
  - Provides consistent framework and format to communicate benefits and risks of using a drug during pregnancy and lactation

  - Requires integrated summaries of risks and a more complex synthesis of data
  - Incorporates risk of untreated disease
  - Includes information on females and males of reproductive potential

Sponsor Implementation

- Exciting but extensive effort acknowledged
- Large undertaking to effectively execute

Timeline Considerations with Extensive Product Portfolio

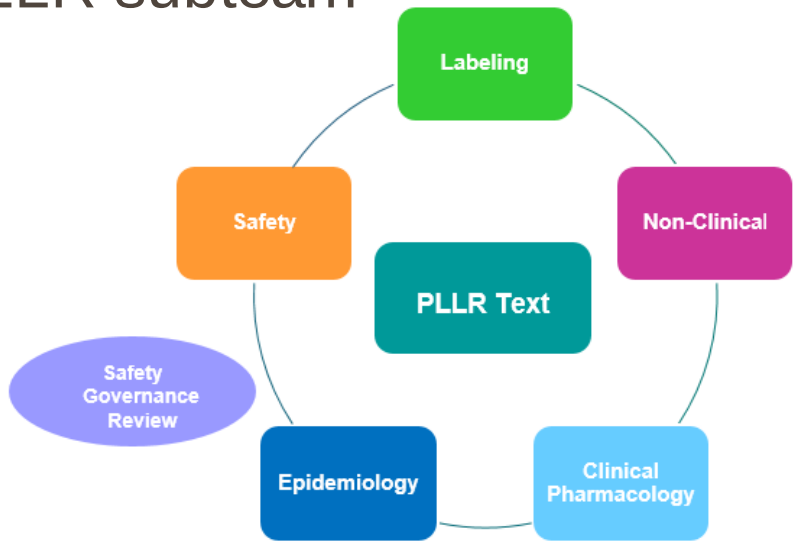
Standardization of Review

Extent of Data Evaluation

- Execution of plans started immediately
  - Considered new product labels vs established PLR labels
  - Very few older non-PLR labels

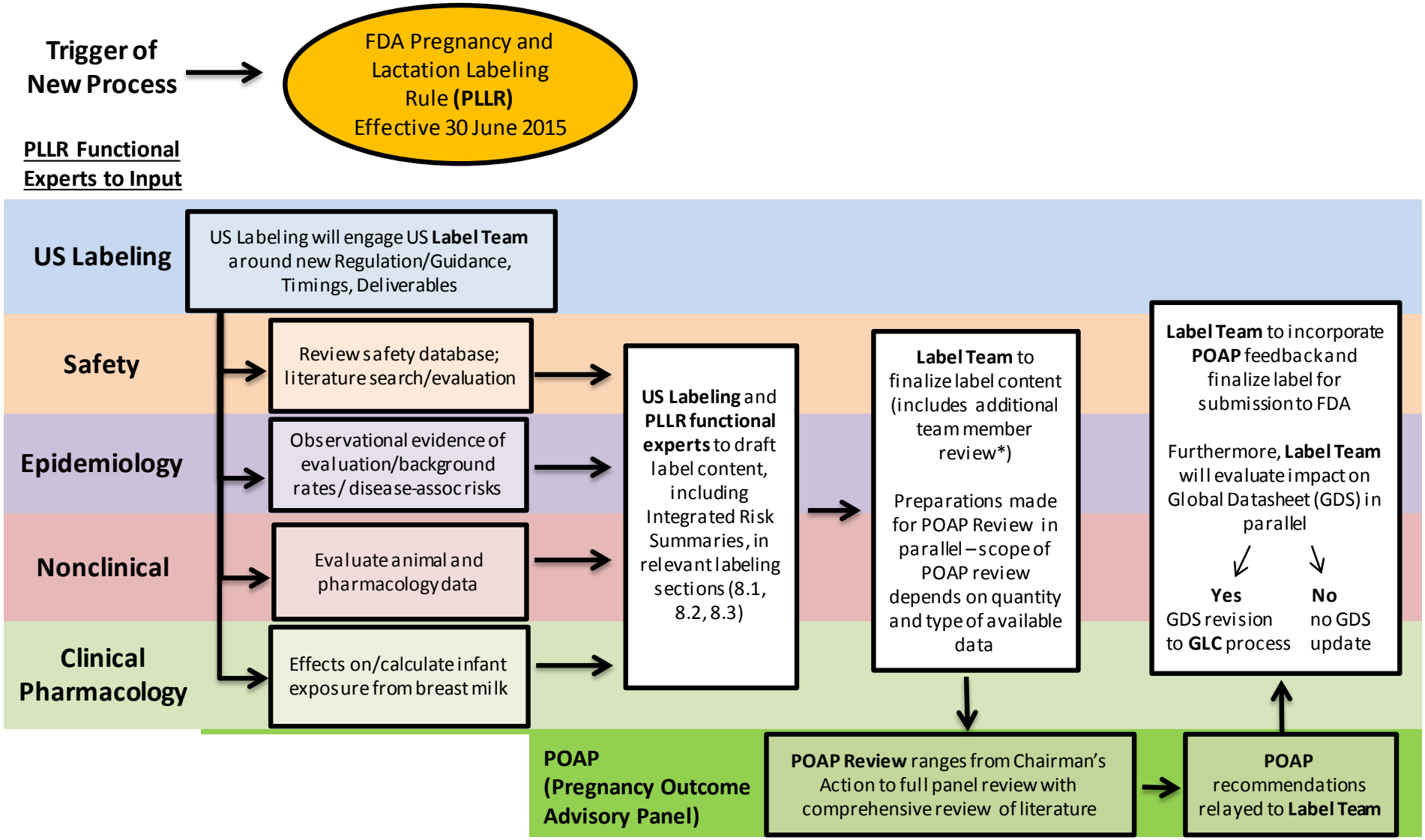
Sponsor Approach

- Established crossfunctional PLLR subteam
  - Labeling
  - Safety
  - Epidemiology
  - Nonclinical
  - Clinical Pharmacology



- Defined an internal process
- Presented proposed plan to management; gained internal Safety Governance Board approval
- Informed relevant internal disciplines
  - Communications with background and resources
  - Presentations to key groups

Schematic of Process



* e.g., Regulatory, Clinical, Legal.

GDS = Company Core Datasheet; POAP = Pregnancy Outcome Advisory Panel (internal safety panel); GLC = internal Global Labeling Committee.

Implementation Timelines

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 or at time of approval, whichever is later
Approved Applications Subject to the Physician's Labeling Rule	
Applications approved any time from June 30, 2001 to June 29, 2002, and from June 30, 2005 to June 29, 2007	3 years after the effective date (30 June 2018)
Applications approved any time from June 30, 2007 to the effective date	4 years after the effective date (30 June 2019)
Applications approved from June 30, 2002 to June 29, 2005	5 years after the effective date (30 June 2020)
*Effective date of final rule is June 30, 2015 **Removal of pregnancy categories is required by June 30, 2018 for non-PLR labels.	

Sponsor PLLR Timelines

- Identified FDA required timelines for the 80+ labels affected

- Most products already in PLR format where significant changes could occur; submitted as prior approval supplements
- Only 5 products NOT in PLR format

Labeling Role

- Created a plan with staggered timelines assigned for extensive product portfolio
  - Quarterly assignments over 3+ years timeline
  - Earlier than FDA implementation timelines
- Identified relevant functional experts
- Held kickoff meetings to explain process
  - Initiated well in advance of regulatory timings
- Worked with each product team to revise labeling and ensure compliance with PLLR and Guidance
  - Many reviews and discussions

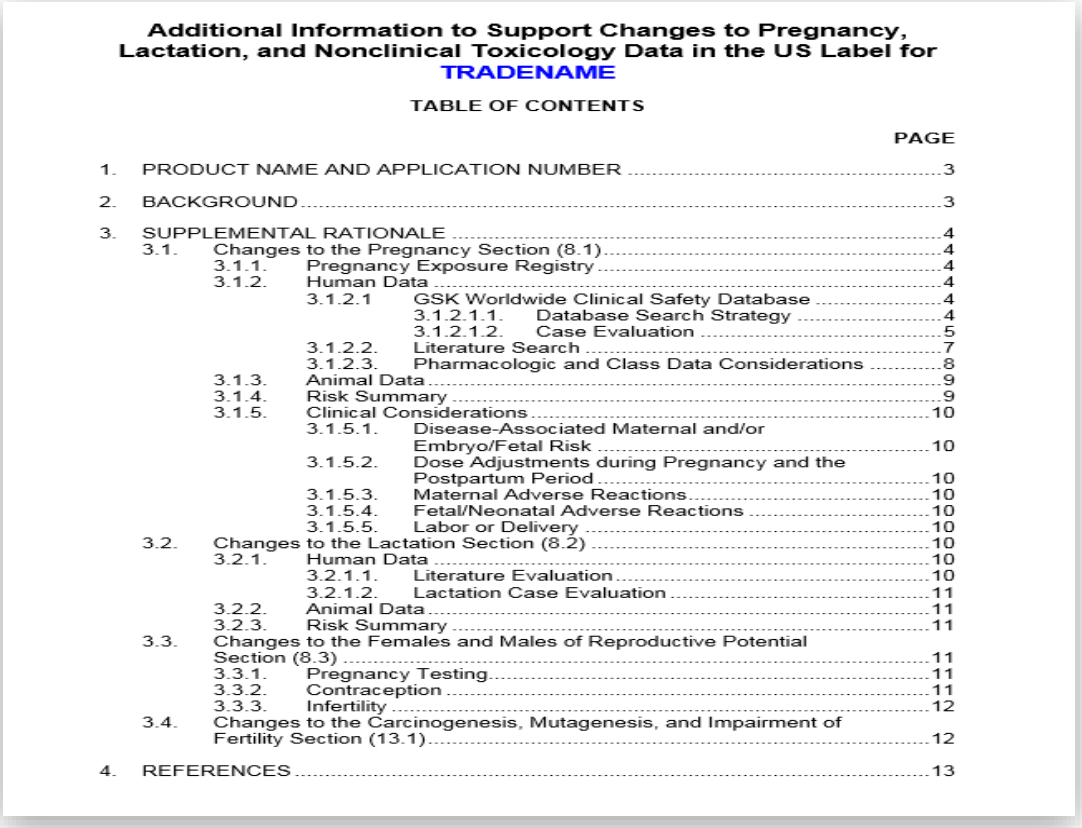
Labeling Role

- Ongoing education of teams about PLLR and process
- Established internal review process after all new or converted PLLR labels drafted
  - Single labeling point of contact review
  - Aid consistency
  - Share experiences across therapy areas
- Review of non-GSK labels approved over time
- Collate GSK experiences and share learnings
  - Internally and externally

DAILYMED

Submissions

- Creation of standardized supporting document template aligned to PLLR sections
- Includes reference to all data supporting label changes
  - Provides clear accountability to functional experts for their contribution to sections



Additional Information to Support Changes to Pregnancy, Lactation, and Nonclinical Toxicology Data in the US Label for TRADENAME

TABLE OF CONTENTS

Training

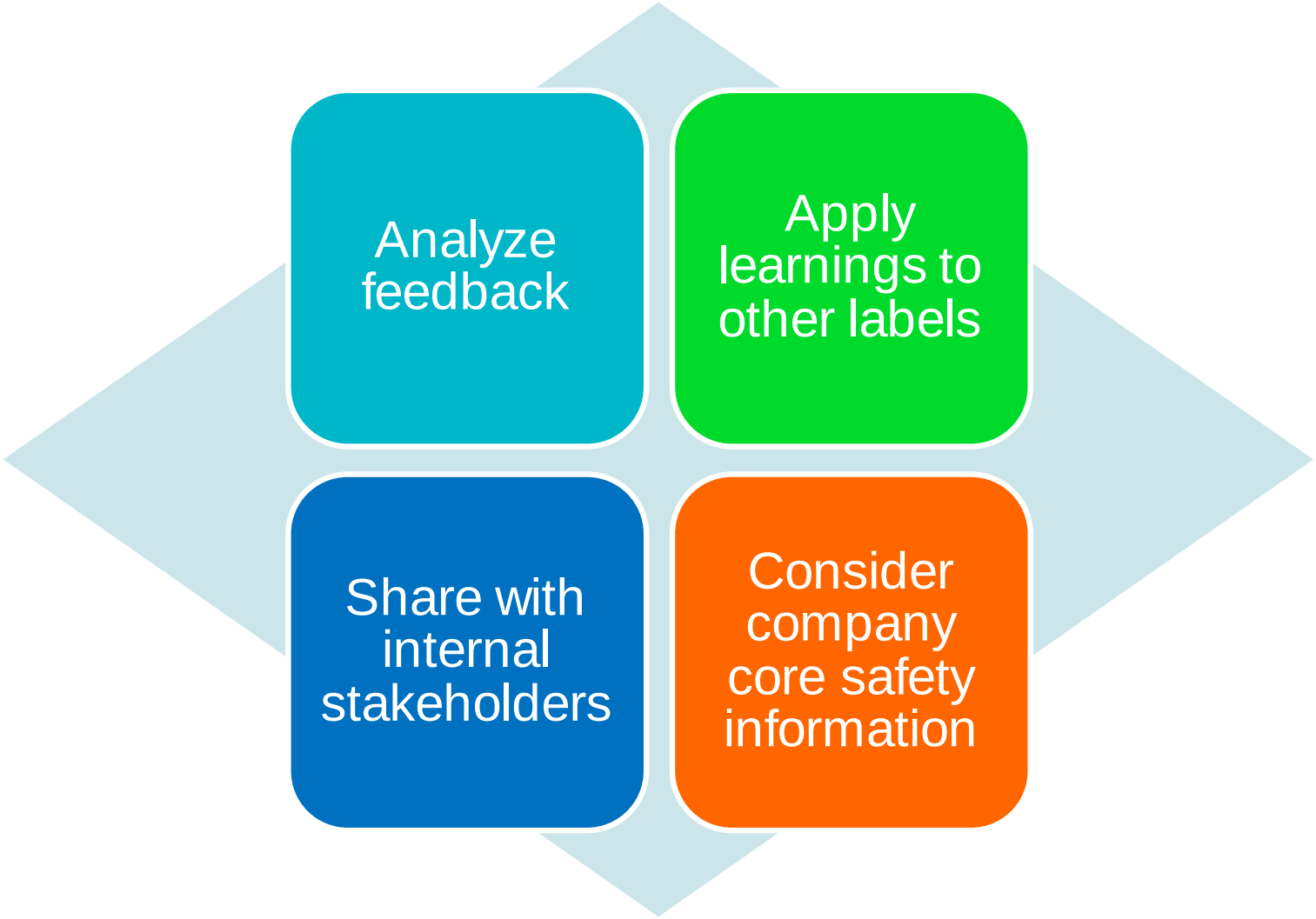
- Initial education and training rolled out
  - Each new team kicking off needed additional review of Regulation and process
- Evaluations take time
  - Searches/review of internal data, published literature
  - Mapping out historical content
- Differing interpretations of data
  - Internally
  - Impact on company core datasheet/global risk statements
  - Sponsor vs. FDA
- Standardization important; difficult with many team members
  - Differing levels of expertise

Internal Resources

- Resource-intensive work
  - Adequate planning to ensure timelines met
- Multiple disciplines involved
  - Pre-work
  - Meetings

- Fewer resources assigned to older, less active projects
  - Adequate resource needed from multiple disciplines
- Some sponsors need to outsource work
  - Increased cost
  - Increased complexity

Gather FDA Feedback



Sponsor Insights

- All published data not appropriate for labeling
  - Data needs to be robust
    - Well designed studies
    - Different methodology expected

- Able to align with “class” PLLR labels in some cases
- Different thresholds for inclusion of data by division
- Limited information in Clinical Considerations accepted
- Original study reports requested
- Requests for original nonclinical presentation of data
- Maternal toxicity information removed

Sponsor Questions

- Can DPMH be consulted more consistently?
  - Consultation appears limited
  - When consulted, more relevant information seems to be accepted
- Can standards around inclusion of data be created?
  - Transparency around acceptable data
  - Thresholds for inclusion of data
  - Consistency across different Review Divisions
- Population based rates vs disease specific rates?
  - Limited success on disease rates
  - How many studies/what sources would produce acceptable data?

Sponsor Summary

- Define and agree a standard process
- Timeline development for portfolio is key
- Internal discussions should start early
  - Complicated process to update labeling
- Appears thinking still evolving with experience
- Final Guidance should clarify some feedback
- Improvement over time
  - Consistently applying learnings
  - Better at evaluating data
  - Better supporting documents

Thank You

Traci J. Lee, PharmD
Director, Labeling
Global Regulatory Affairs
GlaxoSmithKline

Resources for Sponsors

FDA PLLR Website

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm

Pregnancy and Lactation Labeling Final Rule

https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf

DailyMed

http://dailymed.nlm.nih.gov/dailymed/about.cfm

LactMed

http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

List of Pregnancy Exposure Registries

https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm