

Pregnancy & Lactation Labeling Rule (PLLR)

Industry Perspective

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

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

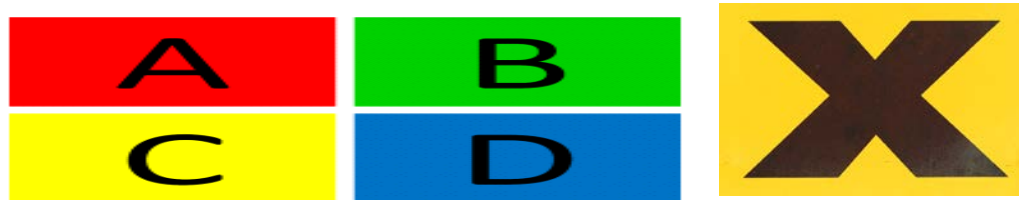
Agenda



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



- 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



- 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**

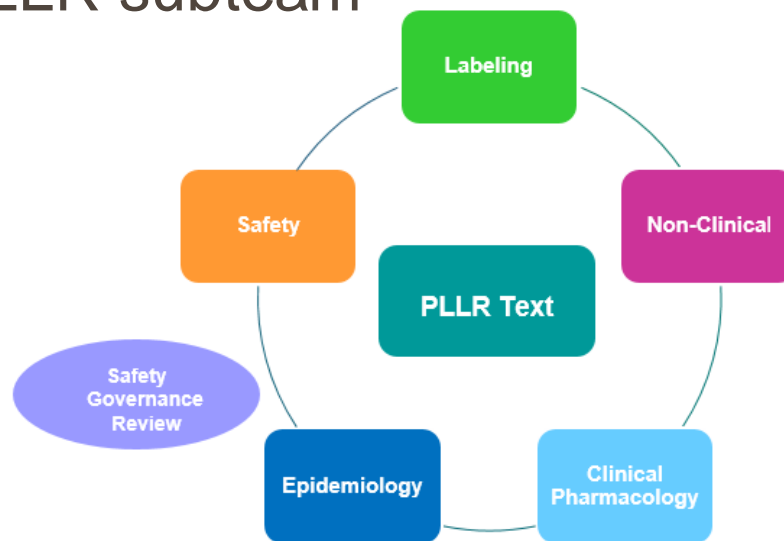
- Execution of plans started immediately
 - Considered new product labels vs established PLR labels
 - Very few older non-PLR labels

Sponsor Approach



- Established crossfunctional PLLR subteam

- Labeling
- Safety
- Epidemiology
- Nonclinical
- Clinical Pharmacology



- Defined an internal process

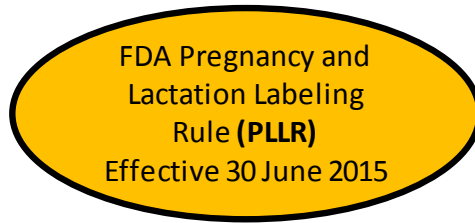
- Presented proposed plan to management; gained internal Safety Governance Board approval

- Informed relevant internal disciplines

- Communications with background and resources
- Presentations to key groups

Schematic of Process

Trigger of New Process →



PLLR Functional Experts to Input

US Labeling

US Labeling will engage US Label Team around new Regulation/Guidance, Timings, Deliverables

Safety

Review safety database; literature search/evaluation

Epidemiology

Observational evidence of evaluation/background rates/disease-assoc risks

Nonclinical

Evaluate animal and pharmacology data

Clinical Pharmacology

Effects on/calculate infant exposure from breast milk

US Labeling and PLLR functional experts to draft label content, including Integrated Risk Summaries, in relevant labeling sections (8.1, 8.2, 8.3)

Label Team to finalize label content (includes additional team member review*)

Preparations made for POAP Review in parallel – scope of POAP review depends on quantity and type of available data

Label Team to incorporate POAP feedback and finalize label for submission to FDA

Furthermore, Label Team will evaluate impact on Global Datasheet (GDS) in parallel

Yes → GDS revision to GLC process

No → no GDS update

POAP (Pregnancy Outcome Advisory Panel)

POAP Review ranges from Chairman's Action to full panel review with comprehensive review of literature

POAP recommendations relayed to Label Team

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

GDS = Company Core Datasheet; POAP = Pregnancy Outcome Advisory Panel (internal safety panel);

GLC = internal Global Labeling Committee.

Implementation Timelines

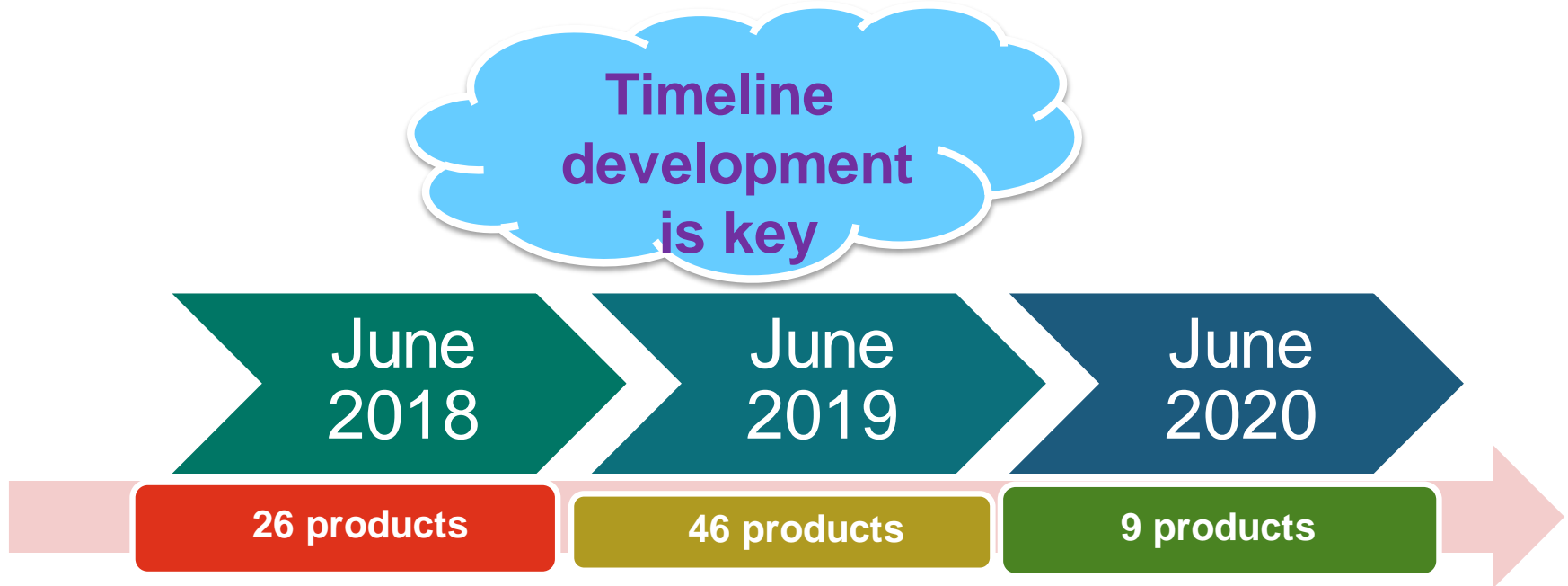


<u>New or Pending Applications</u>	
Applications submitted on or after the effective date* of the final rule	Time of submission
Applications pending on the effective date of the final rule	4 years after the effective date or at time of approval, whichever is later
<u>Approved Applications Subject to the Physician's Labeling Rule</u>	
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



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**

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- 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>
