CDER's Review of Prescribing Information

March 2, 2017

Eric Brodsky, M.D.

Associate Director, Labeling Development Team (LDT), Office of New Drugs, Center for Drug Evaluation and Research (CDER), FDA

Disclaimer

- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position
- CDER's process for review and development of prescribing information (PI) is evolving
  - CDER does not have a Labeling Review MAPP

Overview of Presentation

- CDER staff involved in PI review
  - Roles and responsibilities of ADLs and LDT
- Labeling milestones during NDA/BLA review
- Format/style/appearance of PI
- PLR resources
- FDA labeling guidances under development
- CDER labeling outreach
- Questions

ADLs = Associate Directors for Labeling; LDT = Labeling Development Team

CDER Staff Involved in PI Review

CDER Staff Who May be Involved in PI Review[1]

(1 of 3)

Box = OND staff in prescription drug review division

Yellow = OND staff

CDER Staff that Typically Review PI	Additional CDER staff that Review PI
Division management	Deputy Director for Safety
Clinical (medical officers)	Clinical Microbiology (antimicrobial products)
Regulatory project managers	Office management
Pharmacology/toxicology[2]	Labeling Development Team[3]
Associate Directors for Labeling[3]	
Division of Pediatric and Maternal Health	
Office of Clinical Pharmacology (includes Labeling and Health Communications staff[3])	Office of Biostatistics
Office of Pharmaceutical Quality	Office of Biotechnology Products labeling reviewer (for biological products)[3]
Division of Medication Error Prevention and Analysis	Division of Risk Management (products with ETASU)
	Division of Pharmacovigilance
Office of Prescription Drug Promotion	Controlled Substance Staff (controlled substances)

[1] Involvement depends on labeling type and review division
[2] OHOP pharm/tox staff are in a separate division
[3] Labeling specialists

CDER Staff Who May be Involved in PI Review[1]

(2 of 3)

Orange = Office of Translational Sciences staff

Purple = OPQ staff

CDER Staff that Typically Review PI	Additional CDER staff that Review PI
Division management	Deputy Director for Safety
Clinical (medical officers)	Clinical Microbiology (antimicrobial products)
Regulatory project managers	Office management
Pharmacology/toxicology	Labeling Development Team[2]
Associate Directors for Labeling[2]	
Division of Pediatric and Maternal Health	
Office of Clinical Pharmacology (includes Labeling and Health Communications staff[2])	Office of Biostatistics
Office of Pharmaceutical Quality	Office of Biotechnology Products labeling reviewer[2] (for biological products)
Division of Medication Error Prevention and Analysis	Division of Risk Management (products with ETASU)
	Division of Pharmacovigilance
Office of Prescription Drug Promotion	Controlled Substance Staff (controlled substances)

[1] Involvement depends on labeling type and review division; [2] Labeling specialists

CDER Staff Who May be Involved in PI Review[1]

(3 of 3)

Blue = Office of Surveillance and Epidemiology (OSE) staff

CDER Staff that Typically Review PI	Additional CDER staff that Review PI
Division management	Deputy Director for Safety
Clinical (medical officers)	Clinical Microbiology (antimicrobial products)
Regulatory project managers	Office management
Pharmacology/toxicology	Labeling Development Team
Associate Directors for Labeling	
Division of Pediatric and Maternal Health	
Office of Clinical Pharmacology (includes Labeling and Health Communications staff)	Office of Biostatistics
Office of Pharmaceutical Quality	Office of Biotechnology Products labeling reviewer (for biological products)
Division of Medication Error Prevention and Analysis	Division of Risk Management (products with ETASU)
	Division of Pharmacovigilance
Office of Prescription Drug Promotion	Controlled Substance Staff (controlled substances)

Brown = Office of Medical Policy staff

Green = Office of Center Director staff

[1] Center for Devices and Radiological Heath (CDRH) may also be involved in PI review for drug-device combination products or drug/biological products with a companion diagnostic device

ADL[1] Roles and Responsibilities (1 of 2)

- ADL positions created in summer of 2015
- One ADL in each prescription drug review division (16 total ADLs)
- Oversees and manages review division labeling activities, such as:
  - NME labeling
  - PLR labeling conversions
- Promotes consistency in division labeling review practices

[1] Prescription drug review division ADLs; NME = new molecular entity

ADL[1] Roles and Responsibilities (2 of 2)

- Helps ensure division labeling conforms with labeling regulations, guidance, and policies and are:
  - Appropriately consistent within and across drug classes and indications
  - Clinically meaningful and scientifically accurate
  - Clear and concise for healthcare providers

[1] Prescription drug review division ADLs; NME = new molecular entity

LDT[1] Responsibilities in CDER

- Develops and implements labeling policy initiatives to promote consistency in and improve labeling review practices (across review divisions)
- Assists in labeling review (consultative role)
- Provides oversight of labeling quality
- Provides labeling review training
- Develops and maintains labeling review resources
- Leads labeling outreach to external stakeholders

[1] LDT website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm443026.htm

Administrative and Content Ownership of PI

Administrative:

- Review division RPMs have administrative responsibility of PI (e.g., schedule labeling meetings, version control, set timelines, manage communications with application holders)

Content:

- Multiple disciplines throughout CDER propose changes to application holder draft labeling
- Different staff from prescription drug review division oversee/manage labeling content (e.g., division management, CDTL, ADL)
- Wording in PI is an agreement between FDA signatory and application holder

Labeling Milestones During NDA/BLA Review

Labeling Milestones: 10-Month Review Cycle for NDAs, BLAs, and ESs[1] (1 of 3)

Month	Labeling Process
Month 2	• RPM SRPI review (format) • High-level content review to identify major labeling issues before a detailed review of PI is possible • Consult requests typically sent to offices/divisions routinely involved in PI review (e.g., OPDP, DMEPA, DPMH) and other disciplines if needed
Month 3	Include labeling issues in 74-day or advice letter
Month 5	Labeling Planning Meeting (LPM) (high-level content issues)

[1] Derived from "CDER 21st Century Review Process: Desk Reference Guide"; review cycle length depends on priority vs. standard and PDUFA V Program status

Selected Requirements of Prescribing Information (SRPI) Review

The Selected Requirements of Prescribing Information (SRPI) is a 41-item checklist of important format prescribing information (PI) items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO**: The PI does not meet the requirement for this item (**deficiency**).
- **YES**: The PI meets the requirement for this item (**no deficiency**).
- **N/A**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

   Comment:

2. The length of HL must be one-half page or less unless (the HL Boxed Warning does not count against the one-half page requirement).

   Comment:

3. A horizontal line must separate:
   - HL from the Table of Contents (TOC), **and**
   - TOC from the Full Prescribing Information (FPI).

Early Labeling Review

Application holder may be requested to resubmit labeling that addresses issues such as the following:

Sections	Issue
DOSAGE AND ADMINISTRATION	• Dosage or administration instructions are disorganized or unclear • Includes information not related to dosage or administration
WARNINGS AND PRECAUTIONS	• Does not include adequate description of warning • Does not include steps to prevent, reduce, or monitor risk or adverse reaction (if known)
ADVERSE REACTIONS	• Includes a "laundry" list of events that are not likely related to drug
DRUG INTERACTIONS	• Poorly presents multiple drug interactions (DI) • Does not include clinical implications or practical instructions for preventing and managing DI (if known)
USE IN SPECIFIC POPULATIONS	• Required PLLR format not submitted

Labeling Milestones: 10-Month Review Cycle for NDAs, BLAs, and ESs[1] (2 of 3)

Month	Labeling Process
Months 7-8	• Internal labeling meetings (detailed review and development of labeling) • Substantially complete labeling sent to OPDP and Patient Labeling Team

[1] Derived from "CDER 21st Century Review Process: Desk Reference Guide"; review cycle length depends on priority vs. standard and PDUFA V Program status

Labeling Milestones: 10-Month Review Cycle for NDAs, BLAs, and ESs[1] (3 of 3)

Month	Labeling Process
Months 7-10	• Labeling discussions with application holder and FDA (4-7 weeks prior to action) • FDA labeling comments should include a rationale for substantive revisions to application holder's draft labeling • Labeling finalization: After application holder and FDA agree on labeling wording, annotations removed, formatting corrected, appropriate dates for Initial U.S. Approval, Recent Major Changes, and Revision Date in Highlights included

[1] Derived from "CDER 21st Century Review Process: Desk Reference Guide"; review cycle length depends on priority vs. standard and PDUFA V Program status

LPM: High-Level Issues (1 of 2)

- Occurs 1 to 3 weeks after mid-cycle meeting (when applicable)
- Objective: discuss high-level labeling issues
- Outcomes: communicate to application holder, obtain additional consultation, plan to address issues

Sections	High-Level Content Issue
General	• Labeling claims or suggestions of safety and/or efficacy advantages over other treatments that are not supported • Implied or suggested indications/uses or dosing regimens that are not included in INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections, respectively
• BOXED WARNING • INDICATIONS AND USAGE • WARNINGS AND PRECAUTIONS	Inappropriate inconsistencies with PI for related products
DOSAGE AND ADMINISTRATION	Does not contain recommended starting dosage, titration, or maximum dosage

LPM: High-Level Issues (2 of 2)

Sections	High-Level Content Issue
WARNINGS AND PRECAUTIONS	• Does not identify and describe clinically significant AR or risks with use of the drug • Inappropriately minimizes association between use of the drug and clinically significant AR or risks • Does not include important steps to prevent, reduce, monitor, and manage clinically significant AR or risks
ADVERSE REACTIONS	• Lacks information on population and extent/nature of drug exposures needed to interpret AR data • Includes a laundry list of events without reasonable association between use of drug and occurrence of adverse event
DRUG INTERACTIONS	Contains negative drug interactions that are not clinically relevant
CLINICAL STUDIES	Does not contain adequate description of study designs, results of important baseline disease characteristics, or definitions of endpoints

Format/Appearance/Style of PI

Format/Appearance/Style of PI (1 of 2)

- Physician Labeling Rule includes formatting requirements
- FDA labeling guidances contain additional format recommendations
- Format requirements/recommendations may change/evolve:
  - New regulations (e.g., PLLR) and new guidances (e.g., Clinical Pharmacology section of labeling guidance)
  - New product types (e.g., increase in number of biological products – new Immunogenicity subsection in ADVERSE REACTIONS section)
  - Revisions to Institute for Safe Medication Practices guidelines for abbreviations, symbols, and dose designations

Format/Appearance/Style of PI (2 of 2)

- Formatting/appearance/style of PI outside regulations and guidances:
  - "Beyond these requirements and recommendations, FDA expects that some flexibility in formatting will be necessary because of variability in the type and quantity of labeling information for different drugs"[1]
  - Sometimes application holders have certain formatting preferences

[1] 2013 Implementing the PLR Content and Format Requirements guidance

PLR Resources for Industry

PLR Internet Site (1 of 5)

U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs > Guidance, Compliance & Regulatory Information > Laws, Acts, and Rules

Laws, Acts, and Rules

- Complete Response Letter Final Rule
- Metered-Dose Inhalers Clean Air Act Information
- **PLR Requirements for Prescribing Information**

Resources for You

- Drugs@FDA
- FDA Online Label Repository
- Labeling Development Team

PLR Requirements for Prescribing Information

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

link

On January 24, 2006, the U.S. Food and Drug Administration (FDA) issued final regulations governing the content and format of prescribing information (PI) for human drug and biological products. The rule is commonly referred to as the "**Physician Labeling Rule**" (PLR) because it addresses prescription drug labeling that is used by prescribers and other health care providers.

The goal of the PLR content and format requirements as described at 21 CFR 201.56 and 201.57 is to enhance the safe and effective use of prescription drug products by providing health care providers with clear and concise PI that is easier to access, read, and use. The PLR format also makes PI more accessible for use with electronic prescribing tools and other electronic information resources.

PI submitted with new drug applications (NDAs), biologic license applications (BLAs), and efficacy supplements must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. The Labeling Development Team works with review divisions to ensure PI conforms with the PLR. This page includes links to the Final Rule, regulations, related guidance documents, and additional labeling resources.

On December 3, 2014, the FDA published the Pregnancy and Lactation Labeling Rule (PLLR). The goal of the PLLR is to enhance the safe and effective use of prescription drug products in pregnant women, lactating women, and females and males of reproductive potential.

PLR Final Rule and Labeling Requirements

- Physician Labeling Rule
  Requirements on content and format of labeling for human prescription drug and biological products, January 24, 2006 (Federal Register Notice)
- 21 CFR 201.56
  Requirements on content and format of labeling for human prescription drug and biological products
- 21 CFR 201.57
  PLR Labeling: Specific requirements on content and format of PLR labeling for human prescription drug and biological products described in § 201.56(b)(1)
- 21 CFR 201.80
  Older drugs: Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1)

PLR and PLR regulations

Labeling databases

PLR Internet Site: Labeling Guidances (2 of 5)

Labeling Guidances

- Implementing the PLR Content and Format Requirements (PDF - 527KB)
- Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway (draft) (PDF - 169KB)
- Dosage and Administration Section of Labeling (PDF - 163KB)
- Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling (PDF - 102KB)
- Adverse Reactions Section of Labeling (PDF - 52KB)
- Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (draft) (PDF - 827KB)
- Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format (draft) (PDF - 208KB)
- Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (draft) (PDF - 115KB)
- Clinical Pharmacology Section of Labeling (PDF - 144KB) new
- Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (draft) (PDF - 319KB)
- Clinical Studies Section of Labeling (PDF - 127KB)
- Patient Counseling Information Section of Labeling (PDF - 91KB)
- Labeling for Biosimilar Products (draft) (PDF - 143KB) new
- Updating ANDA Labeling After the Marketing Application for the RLD Has Been Withdrawn (draft) (PDF - 94KB) new

PLR Internet Site (3 of 5)

Labeling Presentations

- Professional Labeling: The Prescribing Information
- Prescribing Information – Resources and Review Process (PDF - 1.5MB)
- Highlights of Prescribing Information (PDF - 2.7MB)
- Indications and Usage Section (PDF - 1.7MB)
- Dosage and Administration Section (PDF - 2.3MB)
- Safety-Related Information in the Prescribing Information (PDF - 3.7MB)
- Describing Clinically Significant Drug Interactions in the Warnings and Precautions Section (PDF - 616KB)
- Clinical Pharmacology Information in Labeling - Enhancing Quality, Utility, and Clarity (PDF - 4MB)
- Distributing Specific Population Information in Labeling (PDF - 809KB)
- Clinical Studies Section (PDF - 1.2MB)
- Patient Counseling Information Section (PDF - 1.2MB)
- Prescribing Information Potpourri (PDF - 1.7MB)

New labeling presentations for stakeholders

PLR Internet Site (4 of 5)

Sample Templates and Format Labeling Tools

Sample PLR template

- Sample PLR Template – Highlights, Contents, and Full Prescribing Information (DOCX - 80KB)
  Sample tool for developing the Highlights, Contents, and the Full Prescribing Information that includes sections, subsections, headings, and subheadings.
- Selected Requirements of Prescribing Information (SRPI) (PDF - 754KB)
  The SRPI is a checklist review of 41 important format items from labeling regulations and guidances. The following two video presentations provide SRPI examples for items in the (1) Highlights, and (2) Table of Contents and Full Prescribing Information:
- SRPI Review of Highlights (PDF - 10.9MB)
- SRPI Review of Table of Contents and Full Prescribing Information (PDF - 9.8MB)

Format (SRPI) resources

Established Pharmacologic Class (EPC) Resources

EPC resources

- Determining the EPC for Use in Highlights MAPP (PDF - 147KB)
- Determining the EPC for Use in Highlights Guidance (PDF - 65KB)
- FDA EPC Text Phrases for Indications and Usage heading in Highlights (updated December 2016) (PDF - 249KB)
  Search for EPC of approved drugs (EPCs are terms or phrases associated with an approved indication of an active moiety, which FDA has determined to be scientifically valid and clinically meaningful).

PLR Internet Site (5 of 5)

Additional Labeling Resources

- Pregnancy and Lactation Labeling Final Rule
  FDA published the final rule on providing information for the use of prescription drugs and biological products during pregnancy, during lactation, and in females and males of reproductive potential.
- Structured Product Labeling Resources
  SPL is the standard format for electronic submission of the content of labeling.

How to Find FDA EPC Text Phrases

Active Moiety Name	FDA Established Pharmacologic Class (EPC) Text Phrase PLR regulations require that the following statement is included in the Highlights Indications and Usage heading if a drug is a member of an EPC [see 21 CFR 201.57(a)(6)]: "(Drug) is a (FDA EPC Text Phrase) indicated for [indication(s)]." For each listed active moiety, the associated FDA EPC text phrase is included in this document. For more information about how FDA determines the EPC Text Phrase, see the 2009 "Determining EPC for Use in the Highlights" guidance and 2013 "Determining EPC for Use in the Highlights" MAPP 7400.13.
dutasteride	5-alpha reductase inhibitor
finasteride	5-alpha reductase inhibitor
zileuton	5-lipoxygenase inhibitor
botulinum toxin type a	acetylcholine release inhibitor
rimabotulinumtoxinb	acetylcholine release inhibitor
guanidine	acetylcholine releasing agent
dactinomycin	actinomycin
regadenoson anhydrous	adenosine receptor agonist
adenosine	adenosine receptor agonist
regadenoson	adenosine receptor agonist
aminoglutethimide	adrenal steroid synthesis inhibitor
metyrapone	adrenal steroid synthesis inhibitor
hydroxyamphetamine	adrenergic agonist
dipivefrin	adrenergic agonist
epinastine	adrenergic agonist
cosyntropin	adrenocorticotropic hormone
corticotropin	adrenocorticotropic hormone
disulfiram	aldehyde dehydrogenase inhibitor
eplerenone	aldosterone antagonist
spironolactone	aldosterone antagonist

Labeling Guidances Under Development

FDA Labeling Guidances Under Development (1 of 2)[1]

- Indications and Usage Section of Labeling for Human Prescription Drugs and Biological Products – Content and Format (new draft)
- Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (new draft)
- Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products – Content and Format (new draft)

[1] see http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm417290.pdf

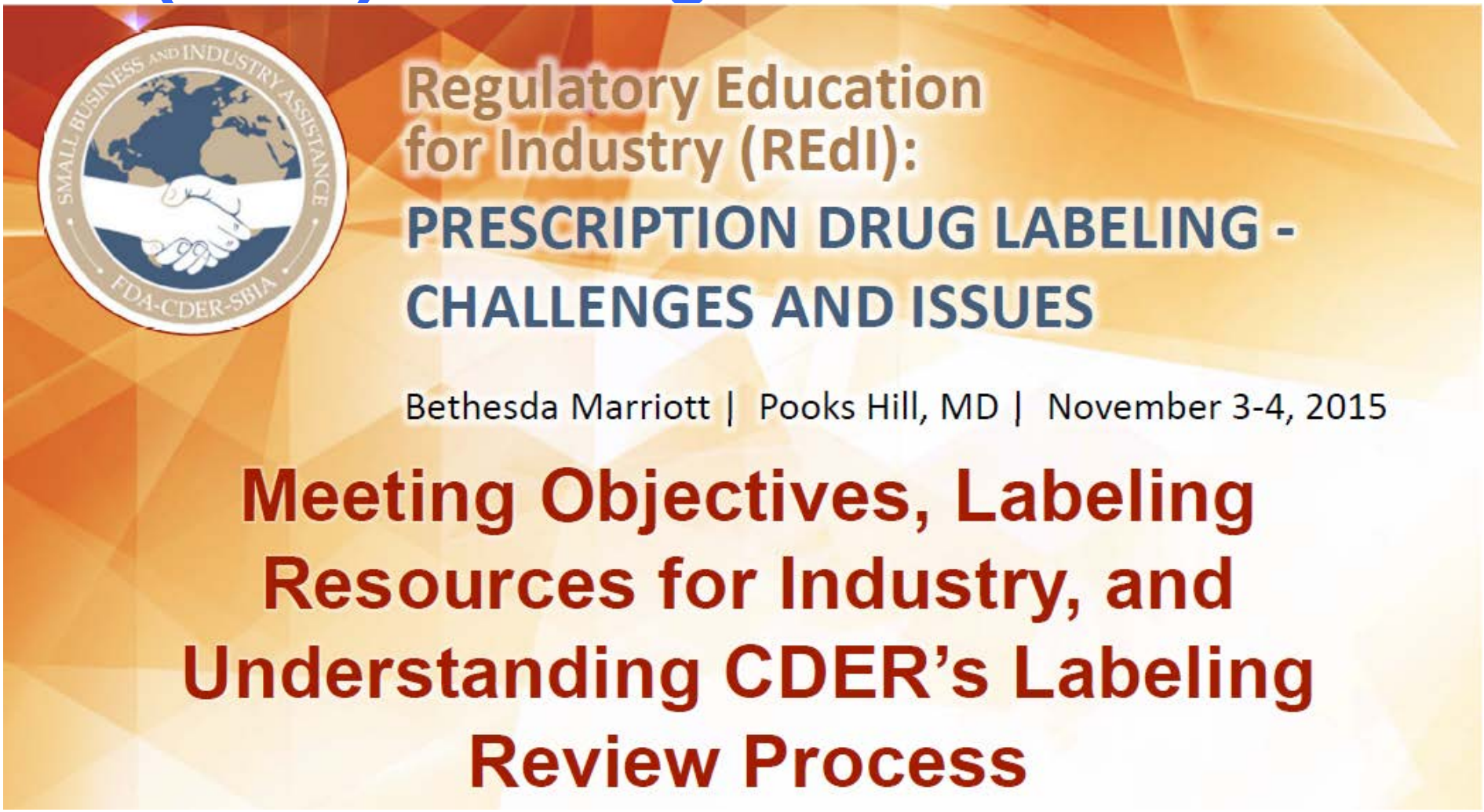
FDA Labeling Guidances Under Development (2 of 2)[1]

- Clinical Drug Interactions Studies: Study, Design, Data Analysis, Implications for Dosing and Labeling Recommendations (revised draft)
- Pharmacokinetics in Patients with Impaired Hepatic Function - Study Design, Data Analysis and Impact on Dosing and Labeling (revised draft)
- Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling (revised draft)

[1] see http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm417290.pdf

Labeling Outreach

November 2015 Two-Day CDER (SBIA) Labeling Conference[1]



1 Thanks to Amy Ebel for presenting and moderating the "Patient Labeling and Patient Counseling Information Section" session

Questions

Questions (1 of 2)

- What labeling topics should CDER address during the November 2017 Labeling Conference?
- Are there additional PLR resources/outreach that would be useful?
- What can FDA do to encourage more voluntary PLR conversions?
- How do you determine the appropriate steps to prevent, reduce, or monitor clinically significant adverse reactions or risks in the WARNINGS AND PRECAUTIONS section?
- How do you determine the clinical implications or practical instructions for preventing or managing drug interactions in the DRUG INTERACTIONS section?

Questions (2 of 2)

- When do you typically receive CDER comments about your labeling (e.g., 74-day letter, mid-cycle, end-of-cycle)?
- What percentage of time does CDER include a rationale for CDER-proposed substantial revisions to your draft labeling?
- Do you routinely review accuracy of your PLR labeling and non-PLR labeling (e.g., once yearly)?
- What parts of labeling do you routinely review for updating (e.g., CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, OVERDOSAGE sections)?
- Do you routinely remove line numbers and headers/footers before submitting “almost” final labeling?

Thank you!

Back-Up Slides

SRPI Review (1 of 2)

- 41 format items from regulations[1] and guidances
  - Items in Highlights, Table of Contents (TOC), and Full Prescribing Information (FPI)

- Prior to Submission: CDER correspondences recommend, **application holders**:
  - *"Use SRPI checklist to ensure PI conforms with format items in regulations and guidances"*

[1] 21 CFR 201.56 and 21 CFR 201.57

SRPI Review (2 of 2)

- Beginning of Cycle SRPI: Performed by **CDER division** (e.g., RPM), within:
  - 74 days of submission of NDA, BLA, ES[1]
  - 60 days of receipt of PLR conversions

- End of Cycle SRPI: CDER correspondences recommend, **application holders**:
  - *"Use SRPI checklist to ensure PI conforms with format items in regulations and guidances"*

[1] CDER 21st Century Review Process – Desk Reference Guide
RPM = Regulatory Project Manager