Regulatory Education for Industry (REdI) Fall 2016 Conference (September 27th-28th, 2016)

Prescribing Information: Resources and Review Process

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Overview of Presentation

- Prescribing Information: Physician Labeling Rule (PLR) Format vs. Non-PLR Format
- Updating Labeling
- Labeling Resources
- Labeling Review Process

Prescribing Information

Labels vs. Labeling[1]

- Labels: a display of written, printed, or graphic matter upon the immediate container of any article. For example:
  - Container label
- Labeling: all labels and other written, printed, or graphic matters upon any article (or its containers or wrappers) or accompanying the article. Examples include:
  - FDA-approved patient labeling
  - Carton/container labeling
  - Prescribing information

[1] See Section 201, Chapter II, (k) and (m) of Food Drug and Cosmetic Act (FD&C Act)

Prescribing Information (PI)

- Written for healthcare providers and must:[1]
  - Contain a summary of essential scientific information needed for safe and effective use of the **human prescription drug or biological product**
  - Be informative and accurate and neither promotional in tone nor false or misleading
  - Be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading
- Also known as “package insert”; however, FDA recommends using term “prescribing information”

[1] 21 CFR 201.56(a)(1) and (2)

Boxed Warning
Description
Clinical Pharmacology
Indications and Usage
Contraindications
Warnings
Precautions
- General
- Information for Patients
- Laboratory Tests
- Drug Interactions
- Drug/Laboratory Test Interactions
- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Pregnancy
- Labor and Delivery
- Nursing Mothers
- Pediatric Use
- Geriatric Use

Adverse Reactions
Drug Abuse and Dependence
Overdosage
Dosage and Administration
How Supplied

Non-PLR ("Old") Labeling Format[1]

- Limited format requirements
- **Not** included:
  - Concise summary of important information
  - Table of Contents
  - Numbered sections or subsections
- Information **not** ordered according to clinical relevance

[1] See 44 FR 37434 (June 26, 1979); 21 CFR 201.80

Development of the Physician Labeling Rule[1]

- Starting in 1992, FDA organized national physician survey, focus groups, and open public meeting to understand how healthcare prescribers use PI
  - What information is most important
  - How labeling could be improved
  - How labeling information was accessed
- Developed prototype PI
- Published Proposed Rule in 2000
- Published Final Rule in 2006

[1] See 65 FR 81082 (December 22, 2000) and 71 FR 3922 (January 24, 2006)

Physician Labeling Rule (PLR)[1]

January 2006 PLR amended regulations about format and content of PI

Rationale:

- Ensure PI contains necessary information for safe and effective use of product
- Make information easier for healthcare providers to access, read, and use
- Reduce medication errors

[1] Final Rule (PLR) "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" 71 FR 3922 (January 24, 2006)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

PLR Highlights and Table of Contents

PLR Implementation[1]

- Applications subject to PLR labeling requirements:
  - NDA, BLA, or ES approved on or after June 30, 2001*
  - Overall excellent compliance with PLR submission schedule!

- CDER highly encourages submission of voluntary PLR conversion labeling supplements:
  - NDA/BLA approved prior to June 30, 2001 (without an ES approved on or after June 30, 2001)

[1] Final Rule (PLR); 21 CFR 201.56(b and c)
NDA = New Drug Application; BLA = Biologics License Application; ES = efficacy supplement

Prescription Drug and Biological Product Labeling in PLR Format[1]

~ 37% of marketed drug and biological products approved under NDAs/BLAs/ANDAs have labeling in PLR format:

- BLAs = 90% (98/109)
- NDAs = 55% (1325/2430)
- ANDAs = 30% (2075/6833)

56% of branded drugs have PLR format labeling

ANDA = abbreviated new drug application

[1] Analysis does not include vaccine, plasma derivative, allergenic, and cellular therapy products; analysis conducted in December 31, 2015

Updating Labeling

Updating Labeling

Application Holder's Responsibilities

- Should review labeling at least annually for outdated information[1]
- Labeling must be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading[2]
  - "a drug … shall be deemed to be misbranded .. (i)f its labeling is false or misleading in any particular"[3]

Labeling Update Opportunities

- Encourage updates in multiple labeling type submissions (e.g., PLR conversions, efficacy supplements)

[1] Implementing PLR Content and Format Requirements Guidance; [2] 21 CFR 201.56(a)(2)
[3] FD&C Act [section 352(a) of the U.S.C.]

Labeling Resources

PLR Internet Site (1 of 4)

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

Drugs@FDA


A to Z Index | Follow FDA
U.S. Food and Drug Administration
Protecting and Promoting Your Health
Home
Food
Drugs
Medical Devices
Radiation-Emitting Products
Vaccines, Blood & Biologics
Animal & Veterinary
Cosmetics
FDA Home
Drug Databases
Drugs@FDA
Drugs@FDA
FDA Approved Drug Products
FAQ | Instructions | Glossary | Contact Us
Drugs@FDA Demo | What's New in Drugs@FDA
Search by Drug Name, Active Ingredient, or Application Number
Enter at least three characters:
Submit
Clear
Advanced Search
Browse by Drug Name
A B C D E F G H I J K L M N O P Q R S T U V W X Y Z 0-9
Drug Approval Reports by Month
Disclaimer

http://labels.fda.gov/

FDA Online Label Repository

IMPORTANT DISCLAIMER

Please be aware of the following when using information from this Web site:

The drug labels and other drug-specific information on this Web site represent the most recent drug listing information companies have submitted to the Food and Drug Administration (FDA). (See 21 CFR part 207.) The drug labeling and other information has been reformatted to make it easier to read but its content has neither been altered nor verified by FDA. The drug labeling on this Web site may not be the labeling on currently distributed products or identical to the labeling that is approved. Most OTC drugs are not reviewed and approved by FDA, however they may be marketed if they comply with applicable regulations and policies described in monographs. Drugs marked "OTC monograph final" or "OTC monograph not final" are not checked for conformance to the monograph. Drugs marked "unapproved medical gas", "unapproved homeopathic" or "unapproved drug other" on this Web site have not been evaluated by FDA for safety and efficacy and their labeling has not been approved. In addition, FDA is not aware of scientific evidence to support homeopathy as effective.

The device labeling and other device-specific information on this website have been voluntarily submitted to the FDA by device manufacturers. FDA has not reviewed this information prior to posting on this website. The device labeling has been reformatted to make it easier to read but its content has not been altered nor verified by FDA. The device labeling on this website may not be the labeling on currently distributed products.

Proprietary Name Search **NDC Number Search**

Active Ingredient Search **Application Number or Regulatory Citation Search**

Company Search **Proprietary Name and Company Search**

Search for Labels on DailyMed

The labels are also available on the National Library of Medicine's DailyMed web site. You can search for labels by drug name and link to the Library's information resources about marketed drugs.

DailyMed

https://dailymed.nlm.nih.gov/dailymed/index.cfm

ALL DRUGS | HUMAN DRUGS | ANIMAL DRUGS

Enter drug, NDC code, drug class, or Set ID

MORE WAYS TO SEARCH: ADVANCED SEARCH | BROWSE DRUG CLASSES | LABEL ARCHIVES | TABLET/CAPSULE ID TOOL

This website contains **89957** drug listings as submitted to the **Food and Drug Administration (FDA)**.
At the present time, this Web site does not contain a complete listing of labels for approved prescription drugs.

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NEWS

DailyMed Announcements

Posted: September 13, 2016

Update: 2016 DailyMed/RxNorm Jamboree Workshop scheduled for September 27

FDA GUIDANCES & INFORMATION

Drug Guidance, Compliance & Regulatory Information

View FDA Structured Product Labeling Resources
View FDA Drug Labeling Guidances
View All FDA Drug Guidances

How Labeling is Different on Drugs@FDA vs. DailyMed and labels.fda.gov

	Drugs@FDA	DailyMed and Labels.fda.gov
Format	PDF	SPL • Hyperlinks • Allows indexing
Type of PI	Last FDA-approved PI	Most up-to-date labeling submitted to FDA
Includes recent PI updates: • Annual reportable changes • Pending CBE-0 labeling supplements	No	Yes
Includes previously approved labeling, regulatory history, and FDA reviews	Yes	No
Includes other types of labeling	Patient labeling	• Patient labeling • Carton/container labeling
FDA reviews labeling	Always	Generally no

CBE = Changes Being Effected
PDF = Portable Document Format; SPL = Structured Product Labeling

PLR Internet Site (2 of 4)

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) new
- 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) new
- Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (draft) (PDF - 115KB)
- Clinical Pharmacology Section of Labeling (draft) (PDF - 117KB)
- 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) new
- Labeling for Biosimilar Products (draft) (PDF - 143KB) new
- CDER Guidances (Drugs)
  Refer to this page for other guidances that contain labeling recommendations and product-specific guidances.

PLR Internet Site (3 of 4)

New labeling presentations

Sample PLR template now in Word format

Labeling Presentations

- Professional Labeling: The Prescribing Information
- 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)
- Drug Interaction Information in Labeling – Strategies for Enhancing Quality, Utility, and Clarity (PDF - 5.5MB)
- 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)

Sample Templates and Format Labeling Tools

- 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)

Sample Template: Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

Sample Template: Contents

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Sample Template: Full Prescribing Information (1 of 2)

FULL PRESCRIBING INFORMATION

WARNING: TITLE OF WARNING

- **Text** ***[see Contraindications (4)]***
- **Text** ***[see Warnings and Precautions (5.x)]***

1 INDICATIONS AND USAGE
PROPRIETARY NAME is indicated for …

Limitations of Use

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title (e.g., **Administration Instructions**)

2.2 Subsection Title (e.g., **Recommended Dosage**)

3 DOSAGE FORMS AND STRENGTHS
Dosage form(s): strength(s)

4 CONTRAINDICATIONS
*[If no contraindications are known, this section must state "*None.*"*

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title (e.g., **Clinically Significant Adverse Reaction or Risk #1**)

5.2 Subsection Title (e.g., **Clinically Significant Adverse Reaction or Risk #2**)

6 ADVERSE REACTIONS
[If the source of adverse reactions (AR) cannot be determined (e.g., an older drug) consider eliminating numbered subsections (e.g., remove subsection 6.1 Clinical Trials Experience and 6.2 Postmarketing Experience) and including a list of AR preceded by a modified postmarketing caveat statement. For example, "The following adverse reactions associated with the use of drugoxide were identified in clinical trials or postmarketing reports. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency, reliably, or to establish a causal relationship to drug exposure."]

Sample Template: Full Prescribing Information (2 of 2)

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Subsection Title *[see Warnings and Precautions (5.1)]*
- Subsection Title *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.2 Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to [product proper name] in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

6.2 Postmarketing Experience (if no Immunogencity subsection) OR **6.3 Postmarketing Experience** (if 6.2 is Immunogenicity)
The following adverse reactions have been identified during post approval use of drug X. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
The following headings and subheadings are for use for labeling that is required to be in PLLR format.

Pregnancy Exposure Registry (omit if not applicable)

Risk Summary (required heading)

Clinical Considerations (omit if none of the subheadings below are applicable)
Disease-Associated Maternal and/or Embryo/Fetal Risk (omit if not applicable)

Dose Adjustments During Pregnancy and the Postpartum Period (omit if not applicable)

Maternal Adverse Reactions (omit if not applicable)

Fetal/Neonatal Adverse Reactions (omit if not applicable)

PLR Internet Site (3 of 4)

Labeling Presentations

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Format (SRPI) resources

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).

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: FDA 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: FDA 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

Highlights (HL) References vs. Full Prescribing Information (FPI) Cross References

HL References (SRPI Item #6)

Each summarized statement or topic in HL must reference section(s) or subsection(s) of FPI. Preferred format is numerical identifier in parenthesis:

- (1.1)
- (2.2, 5.3)

FPI Cross-References (SRPI Item #32)

Correct: **section** heading followed by numerical identifier (all in italics)

- *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*

Incorrect: (avoid subsection heading)

- [~~*see Dosage Adjustments in Patients with Renal Impairment (2.2) and Pharmacokinetics (12.3)]*~~

PLR Internet Site (4 of 4)

Established Pharmacologic Class (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 August 2016) (PDF - 204KB)
  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).

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 Review Process

How FDA Reviews PI

- In response to application holder questions, FDA provides comments about draft PI before NDA/BLA submission
- Application holder submits an NDA/BLA that includes a draft PI that meets labeling regulatory requirements and is consistent with guidance recommendations
- FDA reviews PI upon submission and throughout review cycle
- FDA and application holder develop final PI
  - Iterative process of communications/discussions with both parties
- Final PI (PDF format) is approved by FDA and attached to approval letter

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

Month	Labeling Process
Pre-Submission	Pre-NDA/sNDA/BLA/sBLA communication to sponsor about labeling requirements
Month 2	• RPM SRPI (format) Review • Identify major labeling issues
Month 3	Include Labeling Issues in 74-Day Letter
Month 5	Labeling Planning Meeting (high-level content issues)
Months 7-8	Internal Labeling Meetings
Months 9-10	Labeling discussions with application holder (3-6 weeks prior to action)

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

Early Labeling Review

Application holder is requested to resubmit labeling that addresses issues

Sections	Issue
DOSAGE AND ADMINISTRATION	• Dosage or administration instructions are disorganized or unclear (e.g., no subsections or tables for complicated dosage or administration) • 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
DRUG INTERACTIONS	• Drug interaction (DI) information is disorganized • Does not include clinical implications or practical instructions for preventing and managing DI
PATIENT COUNSELING INFORMATION	• Section not developed or missing

Middle of Cycle Review[1]: High-Level Issues

Sections	High-Level Content Issue
• BOXED WARNING • INDICATIONS AND USAGE • WARNINGS AND PRECAUTIONS	May contain inappropriate inconsistencies with other relevant PI
DOSAGE AND ADMINISTRATION	May not contain recommended starting dosage, titration, or maximum dosage
ADVERSE REACTIONS	• May not describe appropriate safety database • May include adverse events without any basis for a causal relationship between the drug and event
DRUG INTERACTIONS	Contains negative drug interactions that may not be clinically relevant
CLINICAL STUDIES	• May imply or suggest indications/uses or dosing regimens that are not included in INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections, respectively • May not contain adequate description of study design, results of important baseline disease characteristics, or definitions of endpoints

[1] These items may be discussed at a Labeling Planning Meeting

Who Reviews the PI at FDA?[1]

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

[1] Review of human prescription drug and biological product PI regulated in CDER (different FDA staff review vaccine, plasma derivative, allergenic, and cellular therapy PI)

2 Labeling specialists

ETASU = Elements to Assure Safe Use

Associate Directors for Labeling (ADLs)[1]: Responsibilities

- Oversee and manage labeling review division activities such as review of:
  - PLR conversion labeling
  - NME and new therapeutic biologic product labeling
- Promote consistency in division labeling practices
- Help to ensure division labeling conform with labeling regulations, guidance, and policies and are:
  - Appropriately consistent within and across drug classes
  - Clinically meaningful and scientifically accurate
  - Clear and concise for healthcare providers

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

Labeling Development Team (LDT)[1]

Previously known as SEALD[2] Labeling Team

- Assists in labeling review
- Provides oversight of labeling quality
- Provides labeling review training
- Develops and maintains labeling review resources
- Develops and implements labeling policy initiatives to promote consistency in labeling practices across CDER
- Leads labeling outreach to public

[1] LDT website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm443026.htm
[2] SEALD = Study Endpoints and Labeling Development

Questions for Audience
(choose the single correct answer)

Question #1: Labeling on Drugs@FDA and DailyMed have the following in common:

a. Contain most up-to-date labeling submitted to FDA
b. Include hyperlinks
c. Usually include carton and container labeling
d. Include previously approved labeling
e. None of the above

Question #2: When is an application holder required to update their prescribing information (PI)?:

a. When information in the PI is inaccurate
b. When information in the PI is misleading
c. To include information from a recently completed post-marketing Phase 3 trial
d. (a) and (b)
e. (a), (b), and (c)

Thank you!