PLR Implementation, CDER Staff for Labeling Review, and Labeling Resources

Eric Brodsky, MD
Associate Director, Labeling Development Team
Office of New Drugs
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)
Disclaimer

• The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.

• Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.
Overview

• Physician Labeling Rule (PLR) vs. non-PLR format
• CDER staff involved in prescribing information (PI) review
• Labeling resources
PLR vs. Non-PLR ("old") Format

**PLR Format**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
- Product Names, Other Required Information
- Boxed Warning
- Recent Major Changes
- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations

**FULL PRESCRIBING INFORMATION: CONTENTS**

**FULL PRESCRIBING INFORMATION**
- Boxed Warning
- 1 Indications and Usage
- 2 Dosage and Administration
- 3 Dosage Forms and Strengths
- 4 Contraindications
- 5 Warnings and Precautions
- 6 Adverse Reactions
- 7 Drug Interactions
- 8 Use in Specific Populations
- 9 Drug Abuse and Dependence
- 10 Overdosage
- 11 Description
- 12 Clinical Pharmacology
- 13 Nonclinical Toxicology
- 14 Clinical Studies
- 15 References
- 16 How Supplied/Storage and Handling
- 17 Patient Counseling Information

**Old Format**

- Description
- Clinical Pharmacology
- Indications and Usage
- Contraindications
- Warnings
- Precautions
- Adverse Reactions
- Drug Abuse and Dependence
- Overdosage
- Dosage and Administration
- How Supplied

Optional sections:
- Animal Pharmacology
  - and/or Animal Toxicology
- Clinical Studies
- References
CDER Prescription Drug and Biological Product Labeling in PLR Format
(NDAs/BLAs only)¹

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>Proportion of CDER Prescription Drug and Biological Product Labeling in PLR Format (NDAs/BLAs only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2014</td>
<td>~ 45%</td>
</tr>
<tr>
<td>January 2016</td>
<td>~ 56%</td>
</tr>
<tr>
<td>January 2017</td>
<td>~ 61%</td>
</tr>
<tr>
<td>September 2017</td>
<td>~ 64%</td>
</tr>
</tbody>
</table>

CDER labeling in PLR format:
• BLAs (93%), NDAs (62%), ANDAs (38%)

NDAs = New Drug Applications; BLAs = Biologics License Applications
¹ September 2017 analysis based on Structured Product Labeling (SPL) files generally only includes marketed products and excludes repackers, relabelers, and redistributor labeling
Labeling in PLR Format (Required and Voluntary)\(^1\)

FDA appreciates industry’s hard work on the PLR conversions!

<table>
<thead>
<tr>
<th>NDAs, BLAs, and ESs</th>
<th>Applications with Labeling in PLR Format (September 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required: NDAs, BLAs, ES submitted and approved on or after 6/30/2006</td>
<td>100%</td>
</tr>
<tr>
<td>PLR Rule Effective Start Date (6/30/2006)</td>
<td></td>
</tr>
<tr>
<td>Required: NDAs, BLAs, ES approved 6/30/2001 to 6/30/2006 or pending on 6/30/2006</td>
<td>96%</td>
</tr>
<tr>
<td>Voluntary: NDAs/BLAs approved from 1938 to 6/29/2001 (without an ES approved on or after 6/30/2001)</td>
<td>~15%</td>
</tr>
</tbody>
</table>

\(^1\) Data in table as of September 2017; 21 CFR 201.56(b) and (c); ESs = efficacy supplements
Submitted PLR Conversions Labeling Supplements to Date¹

Required and voluntary PLR conversions are part of efforts to update labeling

<table>
<thead>
<tr>
<th></th>
<th>Submitted PLR Conversions to Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Voluntary (n=218)</td>
</tr>
<tr>
<td>Number Approved</td>
<td>186</td>
</tr>
<tr>
<td>Number Pending</td>
<td>32</td>
</tr>
<tr>
<td>(under review in CDER)</td>
<td></td>
</tr>
</tbody>
</table>

¹ Based on number of PLR conversion labeling supplements submitted (NDAs/BLAs); excludes efficacy supplements and original NDAs/BLAs
CDER Staff Involved in Labeling Review
# CDER Staff Who May be Involved in PI Review

<table>
<thead>
<tr>
<th>CDER Staff that Typically Review PI</th>
<th>Additional CDER staff that Review PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Division Management</td>
<td>Deputy Director for Safety</td>
</tr>
<tr>
<td>Clinical (medical officers)</td>
<td>Clinical Microbiology (antimicrobial products)</td>
</tr>
<tr>
<td>Regulatory Project Managers</td>
<td>Office Management</td>
</tr>
<tr>
<td>Pharmacology/Toxicology</td>
<td>Labeling Development Team(^2)</td>
</tr>
<tr>
<td>Associate Directors for Labeling(^2)</td>
<td>Office of New Drugs</td>
</tr>
<tr>
<td>Division of Pediatric and Maternal Health</td>
<td></td>
</tr>
<tr>
<td>Office of Clinical Pharmacology (includes Labeling and Health Communications staff(^2))</td>
<td>Office of Biostatistics</td>
</tr>
<tr>
<td>Office of Pharmaceutical Quality</td>
<td>Office of Translational Sciences</td>
</tr>
<tr>
<td>Division of Medication Error Prevention and Analysis</td>
<td>Office of Biotechnology Products Labeling Reviewer(^2)</td>
</tr>
<tr>
<td>Office of Prescription Drug Promotion</td>
<td></td>
</tr>
<tr>
<td>Division of Medical Policy Programs (patient labeling)</td>
<td>Office of Medical Policy</td>
</tr>
<tr>
<td>Division of Risk Management</td>
<td>Division of Pharmacovigilance</td>
</tr>
<tr>
<td>Controlled Substance Staff (controlled substances)</td>
<td>Office of Center Director (CDER)</td>
</tr>
</tbody>
</table>

\(^1\) Involvement depends on labeling type and review division

\(^2\) Labeling specialists (each color represents a different CDER office)
Associate Directors for Labeling: Roles and Responsibilities

• ADL positions created in summer of 2015
• One ADL in each prescription drug review division (16 total ADLs)
• Serves as principal senior labeling advisor for division
• Ensures that division labeling:
  – Meets regulations and is appropriately consistent with labeling guidances and FDA policies
  – Is appropriately consistent within and across drug classes and indications
  – Is clear and concise for healthcare providers
Labeling Review Resources
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.

1 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
PLR Requirements for Prescribing Information Website

- PLR Final Rule and Labeling Requirements
- Labeling Guidances
- Labeling Presentations – Labeling Content
- Articles with Labeling Content
- Labeling Presentations – Labeling Review Process and Resources
- Sample Templates and Format Labeling Tools
- Product Quality-Related Resources for Prescribing Information
- ANDA Labeling
- Established Pharmacologic Class Resources
- Additional Labeling Resources

1 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
<table>
<thead>
<tr>
<th>No.</th>
<th>Drug Name</th>
<th>Active Ingredient</th>
<th>Approval Date</th>
<th>FDA-approved use on approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Verzenio</td>
<td>abemaciclib</td>
<td>9/28/2017</td>
<td>To treat certain advanced or metastatic breast cancers Press Release</td>
</tr>
<tr>
<td>33</td>
<td>Solosec</td>
<td>secnidazole</td>
<td>9/15/2017</td>
<td>To treat bacterial vaginosis</td>
</tr>
<tr>
<td>32</td>
<td>Aliqopa</td>
<td>copanlisib</td>
<td>9/14/2017</td>
<td>To treat adults with relapsed follicular lymphoma Press Release Drug Trials Snapshot</td>
</tr>
<tr>
<td>31</td>
<td>benznidazole</td>
<td>benznidazole</td>
<td>8/29/2017</td>
<td>To treat children ages 2 to 12 years old with Chagas disease Press Release Drug Trials Snapshot</td>
</tr>
<tr>
<td>30</td>
<td>Vabomere</td>
<td>meropenem and vaborbactam</td>
<td>8/29/2017</td>
<td>To treat adults with complicated urinary tract infections Press Release Drug Trials Snapshot</td>
</tr>
<tr>
<td>29</td>
<td>Besponsa</td>
<td>inotuzumab ozogamicin</td>
<td>8/17/2017</td>
<td>To treat adults with relapsed or refractory acute lymphoblastic leukemia Press Release Drug Trials Snapshot</td>
</tr>
<tr>
<td>28</td>
<td>Mavyret</td>
<td>glecaprevir and pibrentasvir</td>
<td>8/3/2017</td>
<td>To treat adults with chronic hepatitis C virus Press Release Drug Trials Snapshot</td>
</tr>
</tbody>
</table>