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# Guidance for Industry

## **Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**February 2013  
Labeling**

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## Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**February 2013  
Labeling**

*Contains Nonbinding Recommendations*

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## **Guidance for Industry<sup>1</sup>**

# **Labeling for Human Prescription Drug and Biological Products<sup>2</sup> — Implementing the PLR Content and Format Requirements<sup>3</sup>**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

## **I. INTRODUCTION**

This guidance is intended to assist applicants in complying with the content and format requirements of labeling for human prescription drug and biological products under 21 CFR 201.56(d) and 201.57. FDA is issuing this guidance to provide recommendations for applicants developing labeling for new prescription drugs and revising labeling for already approved prescription drugs. This guidance also provides recommendations on developing *Highlights of Prescribing Information* (Highlights), formatting labeling, and procedural information.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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<sup>1</sup> This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

<sup>2</sup> This guidance applies to drugs, including biological drug products. For the purposes of this guidance, *drug* or *drug product* will be used to refer to human prescription drug and human prescription biological products that are regulated as drugs.

<sup>3</sup> See the final rule Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 FR 3922, January 24, 2006. This 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 professionals.

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### **II. BACKGROUND**

On January 24, 2006, FDA published a final rule that amended the requirements for the content and format of labeling for human prescription 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 practitioners. The rule was designed to make information in prescription drug labeling easier for health care practitioners to access, read, and use to facilitate practitioners' use of labeling to make prescribing decisions. Labeling includes three sections: Highlights of Prescribing Information (Highlights), a Table of Contents (Contents), and the Full Prescribing Information (FPI). Highlights contains selected information from the FPI that health care practitioners most commonly reference and consider most important. Contents lists the sections and subsections of the FPI. FPI contains the detailed prescribing information necessary for safe and effective use of the drug. The final rule also reordered and reorganized the FPI, made minor changes to the content of the FPI, and set minimum graphic requirements for the format of the labeling.

Not all drugs are subject to the labeling requirements under §§ 201.56(d) and 201.57. The final rule is being implemented on a staged implementation schedule that, based on approval date or application status, requires new and recently approved prescription drugs to comply with these labeling requirements by a particular date (see § 201.56(b) and Appendix A). Prescription drugs that are not subject to §§ 201.56(d) and 201.57 are subject to the labeling requirements under §§ 201.56(e) and 201.80. The final rule also made minor changes to these regulations.

For the purpose of this guidance, the term *PLR format* refers to labeling that meets the content and format requirements at §§ 201.56(d) and 201.57. The term *old format* refers to labeling that meets the requirements at §§ 201.56(e) and 201.80. See Appendix B for a listing of prescription drug labeling sections in the old and PLR formats.

In general, the most challenging aspects of this regulation are developing Highlights and distributing information among sections that have been substantially affected by the rule, particularly when the information originates from the labeling in the old format. Therefore, the guidance focuses primarily on these issues. Additional guidance documents that address content and format for specific FPI sections are available and should be consulted when developing labeling (see section VIII of this document).

### **III. CONSIDERATIONS FOR REVISING LABELING**

The FPI in the PLR format contains substantially the same information as labeling in the old format, typically with reordering and reorganization of the information. For example, new labeling sections (e.g., DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, PATIENT COUNSELING INFORMATION) contain information formerly included in the PRECAUTIONS section. Certain sections (e.g., CLINICAL STUDIES, NONCLINICAL TOXICOLOGY) that were previously optional are now required if applicable (§ 201.56(d)). Therefore, although labeling in the old format for approved products does not contain the new section headings, most of the content already is included in the labeling under different headings

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or subheadings. For example, information from the old WARNINGS section and old PRECAUTIONS section is consolidated into a single new section (WARNINGS AND PRECAUTIONS) and information in certain old PRECAUTIONS subsections (e.g., *Information for Patients, Drug Interactions, Pregnancy, Labor and Delivery, Nursing Mothers, Pediatric Use, Geriatric Use*) is relocated to new labeling sections (e.g., PATIENT COUNSELING INFORMATION, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS).

Making the transition to the PLR format provides an ideal opportunity to review the labeling content for general quality (e.g. format, organization, and readability) and to make it a better communication tool. FDA recommends following these general principles when converting labeling in the old format to the PLR format.

### **A. Developing New Sections**

FDA expects that most sections or subsections from labeling in the old format can be moved, with little or no modification, to corresponding sections in the PLR format (see Appendix C). However, the labeling in the old format may not include the information specified by the new regulations, or the content of a section may not adequately reflect scientific information needed for safe and effective use of the drug. In this case, the labeling must be updated (§ 201.56(a)).

If the labeling in the old format lacks an entire section that is required in the PLR format, the section must be developed unless it is clearly inapplicable (§ 201.56(d)). For example, if the labeling in the old format does not contain an *Information for Patients* subsection in the PRECAUTIONS section, the applicant must develop a PATIENT COUNSELING INFORMATION section because, with only limited exceptions, there will be important information about a drug for the prescriber to convey to the patient or caregiver. In another example, it may not be necessary to develop a CLINICAL STUDIES section for certain older products (e.g., when data are not readily available).

### **B. Data Analyses or New Studies**

FDA recognizes that revising labeling to comply with the PLR regulations is an excellent opportunity to update labeling content to ensure that it accurately reflects current knowledge. FDA expects that, in most cases, the revisions will involve limited rewriting aimed at clarifying text, eliminating redundancies, and updating outdated terminology. Generally, no new data analyses of the information in the old format are required if the labeling is truthful and accurate. However, if new information is available that causes the labeling to be inaccurate, the labeling must be updated to incorporate the new information (§ 201.56(a)(2)). In some cases, a re-analysis of the data may be necessary.

Furthermore, if essential information is missing from the labeling (e.g., new information about a class drug interaction), this information must be included (§ 201.56(a)(2)). In this case, the review division would determine the need for a new study, a decision that would be made independent of the labeling conversion process.

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### **C. Updating Information in Labeling**

By regulation, all express or implied claims in labeling must be supported by substantial evidence.<sup>4</sup> If unsubstantiated claims currently exist in labeling, the applicant must revise the labeling to remove such claims (§ 201.56(a)(3)). Although the content of labeling in the old format will not substantially change when converted to PLR format, the applicant should systematically evaluate information in labeling to identify unsubstantiated claims or outdated information and revise it accordingly.

Revisions to the content requirements in certain sections may result in the need to review and revise those sections. For example, consider the ADVERSE REACTIONS section. For the purposes of prescription drug labeling, the definition of adverse reaction in § 201.57(c)(7) was revised to clarify that it does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. When updating labeling, the applicant should review the ADVERSE REACTIONS section to ensure all events appropriately fall under that section and delete those events unlikely to have been caused by the drug (i.e., usually a lengthy listing commonly referred to as the *laundry list*). Because such a list is not essential to the safe and effective use of the drug, it should simply be omitted.

The OVERDOSAGE section is another example of a labeling section that is typically not revisited after initial approval. However, postmarket experience with overdose may inform new management recommendations for the drug product and the labeling content should be updated to reflect current knowledge.

### **IV. DISTRIBUTING INFORMATION AMONG SECTIONS**

When creating labeling in PLR format or converting labeling in the old format to the PLR format, applicants face many decisions about how to distribute information among labeling sections. Often sections or subsections can be moved with little or no modification (see Appendix C). In some cases, it will be more appropriate to move certain information from a labeling section in the old format to a different labeling section in the PLR format or to consolidate similar issues in one place. In other cases, it will be appropriate to divide portions of information in a single labeling section among two or more sections. The following general principles and examples are offered to help applicants make decisions about how to organize information. These considerations apply whether revising labeling from the old format or creating new labeling.

#### **A. Organizing Information to Avoid Redundancy**

Clinical information pertinent to prescribing decisions should be identified, prioritized, and located in the labeling section that most appropriately communicates the type of information. Detailed information about a particular topic should be consolidated in a single labeling section.

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<sup>4</sup> See § 201.56(a)(3). See also §§ 201.57(c)(2)(iii), (c)(2)(iv), (c)(2)(v), (c)(7)(iii), and (c)(15)(i), and 201.80(c)(2)(i), (c)(2)(ii), (g)(4), and (m)(1)(i).



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Other sections of labeling may more briefly describe or refer to the topic, but not repeat the same content or level of detail. For example, information about a drug interaction that rises to the level of a warning will be described in the WARNINGS AND PRECAUTIONS section, with supporting detail in the DRUG INTERACTIONS section and other sections as appropriate (e.g., DOSAGE AND ADMINISTRATION section if a dosage modification is necessary).

In some instances, information discussed in multiple sections of labeling in the old format can be consolidated in the PLR format. For example, if the old WARNINGS and old PRECAUTIONS sections each contained information about a similar topic, this information should now be consolidated under one subsection in the new WARNINGS AND PRECAUTIONS section. When consolidating information, subsections can be created and should be put in an order that reflects the content's importance and relative public health significance.

In addition, information may need to be reordered to enhance labeling organization, presentation, and ease of use (e.g., information in the DOSAGE AND ADMINISTRATION section should be reordered to correspond to the order of the presentation of the indications in the INDICATIONS AND USAGE section).

### **B. Using Cross-References**

When a topic is discussed in more than one section of labeling, the section containing the most important information relevant to prescribing should typically include a succinct description and should cross-reference sections that contain additional detail. If the detailed information is divided appropriately into more than one section, those sections should cross-reference each other. Cross-references from the more detailed discussion to the less detailed discussion should generally not be necessary (e.g., a succinct BOXED WARNING should reference the fuller discussion of the risk in WARNINGS AND PRECAUTIONS, but the WARNINGS AND PRECAUTIONS section should not refer back to the BOXED WARNING). In some cases, cross-references are required (e.g., §§ 201.57(c)(1), (c)(6)(iv), and (c)(15)(ii)).

### **C. Example of the Distribution of Information Among Labeling Sections**

Several basic principles are illustrated in the following example. Although drug interaction information has been selected for this example, these principles also apply to other labeling sections.

- Drug interaction information should typically appear in the DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections. If there is a subset of information that is essential for prescribing decisions, that subset of information can be distributed among several sections, including the BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections (e.g., §§ 201.57(c)(3)(i)(H) and (c)(8)).
- When drug interaction information rises to the level of a contraindication, or a warning or precaution that necessitates a dosage adjustment, this information should be presented

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succinctly in the applicable section(s), with details in the DRUG INTERACTIONS section (§ 201.57(c)(8)).

- The DRUG INTERACTIONS section contains clinically relevant information, such as the need to modify a dose or regimen. FDA recommends using a descriptive header of summary concepts preceding a discussion of specific information (e.g., CYP3A Inhibitors).
- More detail about drug interaction studies, including those demonstrating no drug interaction (i.e., pertinent negatives), and any clinically relevant, nonclinical data should be included in the CLINICAL PHARMACOLOGY section.

## **V. HIGHLIGHTS**

The purpose of Highlights is to provide immediate access to the information to which practitioners most commonly refer and regard as most important. Highlights also helps guide the practitioner to the section in the FPI where details can be obtained about a specific topic. The following information is intended to help applicants develop Highlights.

### **A. General Principles**

Highlights should be a concise, informative summary of crucial prescribing information, not a verbatim repetition of selected material from the FPI, or a repetition of the Contents. Rarely, it may be appropriate to repeat content verbatim from the FPI (e.g., a succinct boxed warning statement or short indication statement), but in most cases, the information should be summarized and presented in an easily accessible format (e.g., bulleted, tabular).

The information in Highlights is derived from the FPI. Selecting the material to include in Highlights requires judgment about the importance of the data in relation to the clinical setting in which the drug is used.

When information about a risk appears in more than one section of the FPI, the information should typically be presented once in Highlights under the most appropriate heading. For example, if a drug interaction is described under Warnings and Precautions in Highlights, it should not be repeated under Drug Interactions in Highlights.

Summarized information should be presented in clear language that is succinct and imparts the most relevant and complete information. For example, under Warnings and Precautions, the statement in Highlights should, as appropriate, identify the risk, its consequences, and the actions to take to prevent or mitigate it. Directive language is preferable, because it conveys explicit information most concisely (e.g., “Discontinue,” as opposed to “You should discontinue”). Each summarized statement should be located under the appropriate Highlights heading and must cross-reference the section(s) or subsection(s) of the FPI that contains more detailed information (§ 201.56(d)(3)). If new information is to be added to Highlights, the existing information should be evaluated and combined so that the new information can be added while maintaining the required half page length.

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### **B. Information in Highlights**

The following recommendations focus on the content that should be included in Highlights. Because of the importance of the information in Highlights and the space limitations, there are specific formatting requirements applicable to Highlights that were designed to enhance readability and accessibility of labeling information (see § 201.57(d) and section VI of this document).

#### *1. Highlights Title and Limitation Statement (§§ 201.56(d)(1) and 201.57(a)(1))*

The title **HIGHLIGHTS OF PRESCRIBING INFORMATION** must be presented at the beginning of Highlights (§ 201.56(d)(1)). On the first line under the title, the following Highlights Limitation Statement must be presented verbatim in bold: ***These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)*** (§§ 201.57(a)(1) and 201.57(d)(5)). We recommend that the name of the drug product be presented in upper case letters to improve its prominence.

#### *2. Product Title: Drug Names, Dosage Form, Route of Administration, and Controlled Substance Symbol (§ 201.57(a)(2))*

The bolded product title consisting of the proprietary name and the established name of the drug, if any, or, for biological products, the proper name must be presented,<sup>5</sup> followed by the dosage form, and route of administration (§§ 201.57(a)(2) and 201.57(d)(5)). For controlled substances, the symbol for the assigned controlled substance schedule must be included at the end of the line (§§ 201.57(a)(2) and 201.57(d)(5)).

#### *3. Initial U.S. Approval (§ 201.57(a)(3))*

On the line immediately beneath the product title line, the verbatim statement: **Initial U.S. Approval** must be presented, followed by the bolded four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients (§§ 201.57(a)(3) and 201.57(d)(5)), regardless of dosage form or indication (i.e., multiple dates should not be listed for different dosage forms or indications).

#### *4. Boxed Warning (§ 201.57(a)(4))*

The Boxed Warning in Highlights must contain a concise summary of all of the risks described in the BOXED WARNING in the FPI (§ 201.57(a)(4)) and is limited in length to 20 lines, not including the title and required reference to the complete boxed warning in the FPI. The title of the Boxed Warning must appear after the word **WARNING:** and must identify the subject(s) of the warning contained in the box (e.g., **WARNING: ACUTE HEPATIC FAILURE and INFUSION REACTIONS**) (§ 201.57(a)(4)). The

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<sup>5</sup> For drugs, see section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). For biological products, see 21 CFR 600.3.

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italicized verbatim statement: *See full prescribing information for complete boxed warning* must be placed immediately following the title of the boxed warning (§ 201.57(a)(4)). FDA recommends that both the title and the verbatim statement be centered within the box, and all text within the box must be in bold (§ 201.57(d)(5)).

The information summarized under the Boxed Warning heading in Highlights should emphasize the information contained in the BOXED WARNING section of the FPI and direct attention to the complete box and to the sections in the FPI that contain more detailed information. Because the Boxed Warning in Highlights must be a concise summary of the information from the complete BOXED WARNING in the FPI, no information should be presented in the Highlights box that does not appear in the FPI box (§ 201.57(a)(4)). There should be only one box in the FPI and one summarized box in Highlights, even when multiple topics are presented.

FDA recommends that the information under the Boxed Warning heading in Highlights be summarized in a bulleted format. Formatting should facilitate the clear presentation of complex information and risks. For example, each bullet should communicate a discrete warning, clinical indication, or contraindication. In rare instances, the BOXED WARNING in the FPI may be sufficiently concise to warrant repeating the text verbatim under the Boxed Warning heading in Highlights.

### *5. Recent Major Changes (§ 201.57(a)(5))*

When substantive labeling changes have been made to any of the following sections of the FPI within the preceding 12 months, the heading(s) of the changed section(s) must be listed in Highlights under the heading Recent Major Changes (§ 201.57(a)(5)):

- Boxed Warning
- Indications and Usage
- Dosage and Administration
- Contraindications
- Warnings and Precautions

Changes that must not be listed in Recent Major Changes include:

- Changes to sections other than the five listed above
- Changes that are not substantive (i.e., minor revisions such as correcting typographical errors or grammatical changes)
- Changes resulting from converting to the PLR format alone

#### *a. What must be included*

Each listing must include the section heading, the subsection heading (if appropriate), identifying number of the corresponding changed section or subsection, and the date on which the change was incorporated in the labeling (i.e., date the supplement was approved) in month/year format (e.g., 6/2010 or Jun 2010) (§ 201.57(a)(5)).

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### b. Multiple labeling changes

If there are changes to more than one section of the labeling, the listings in Recent Major Changes must be presented in the order in which they appear in the FPI (§ 201.57(a)(5)), and not ordered by dates of the changes.

If there is more than one change in the same labeling section or subsection in the preceding 12 months, only the newest date should be listed. For example, if a new indication (hypertension) was added to the labeling in March 2011, and a limitation to the hypertension indication was added in June 2011, the change under the Recent Major Changes heading should be listed as:

Indications and Usage, Hypertension (1.2) 6/2011

Only when space in Highlights permits, if there are changes within a section to more than one subsection during the 1-year period listed, each section heading, subsection heading, identifying number, and date should be listed separately. For example:

Indications and Usage, Hypertension (1.2) 6/2011  
Indications and Usage, Heart Failure (1.3) 9/2011

If there are changes within a section to more than one subsection during the 1-year period listed and listing subsection headings separately as above would cause Highlights to be greater than one-half page in length, only the main section heading should be listed, with the date of the most recent change. For example:

Indications and Usage (1) 9/2011

Experience has shown that listing each changed subsection on a separate line when multiple changes have occurred often leads to Highlights that is longer than one-half page. Despite not listing each subsection individually in Recent Major Changes, the labeling will still enable the reader to readily identify the changes through the use of the vertical lines adjacent to the new or modified text in the FPI required by § 201.57(d)(9).

### c. Listing related information from different FPI sections

When a drug product is approved for a new indication, new information is often added to other sections of labeling (e.g., DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS, CLINICAL STUDIES). If there are changes to any of the five applicable sections, each changed section must be listed under the Recent Major Changes heading (§ 201.57(a)(5)). For example:

Indications and Usage, Hypertension (1.2) 6/2011  
Dosage and Administration, Hypertension (2.2) 6/2011

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### d. Marking text in the FPI with a vertical line

The corresponding new or modified text in the FPI sections listed under Recent Major Changes must be marked with a vertical line on the left edge (§ 201.57(d)(9)) to alert the reader to the new information. If new text in the FPI is very brief (e.g., 1-2 lines long), it may be appropriate to use spacing to extend the vertical line by 1-2 additional lines (e.g., mark the blank line before and after the new text) to make it more visible. Similarly, if a new sentence has been added to an existing paragraph, it may be appropriate to mark the entire paragraph.

### e. Deletions from labeling

Although it is unusual for information to be completely deleted from labeling (e.g., removing a warning as opposed to revising it or moving the discussion to a different section), if such a situation occurs, the applicant should propose labeling that identifies the change in both Recent Major Changes in Highlights and in the FPI. In some cases, the deletion may best be addressed by adding new text elsewhere in the FPI; in other cases, the Agency will determine how best to identify the change.

### f. Initial submission of revised labeling in the PLR format

Applicants should list under the Recent Major Changes heading any substantive labeling changes to the relevant sections that were approved within 1 year of submission of the draft labeling for review in the PLR format.

### g. Removing a listing from Recent Major Changes

A changed section must be listed under Recent Major Changes for at least 1 year after the date the labeling change was approved and can continue to be listed until the labeling is reprinted for the first time after the 1-year period expires (§ 201.57(a)(5)). When the 1-year time period expires, the applicant can choose (1) to reprint labeling immediately to remove the listing or (2) to wait until the next reprinting to remove the listing. Whenever a supplemental application is submitted, the applicant should review the labeling changes listed under the Recent Major Changes heading and delete any listings that are over 1 year old. FDA recommends that applicants notify the Agency in an Annual Report about removal of a listing from Recent Major Changes and the corresponding vertical line in the FPI (see 21 CFR 314.70(b)(2)(v)(C)(I) and 601.12(f)(3)(i)(D)(I)).

### h. Listing Recent Major Changes for Changes Being Effected (CBE) Supplements<sup>6</sup>

For labeling changes made through a CBE supplement that meet the criteria for listing in Recent Major Changes, the change must be listed under Recent Major Changes for at least 1 year after the date the labeling change is made and can continue to be listed until the labeling is reprinted for the first time after the 1-year period expires (§ 201.57(a)(5)).

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<sup>6</sup> See §§ 314.70(c)(6) and 601.12(f)(2).

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If a further change is made to the labeling when the Agency approves the CBE supplement, the date of approval becomes the new date from which the 1-year period is calculated. As above, when the 1-year time period expires, the applicant can choose to (1) reprint labeling immediately to remove the listing or (2) wait until the next reprinting to remove the listing.

### ***6. Indications and Usage (§ 201.57(a)(6))***

Information under the Indications and Usage heading in Highlights must include a concise statement of each of the drug's indications from the FPI, briefly noting any major limitations of use (§ 201.57(a)(6)). FDA recommends that the information be presented in a bulleted format if multiple indications exist. In some circumstances, it may be appropriate to present the indications with the same wording as in the FPI (e.g., when a product has one indication and the statement in the FPI is sufficiently concise).

If the FPI includes any limitations of use, the presentation in Highlights needs to be clear as to whether the limitation applies to all indications or only certain indications. For a product with limitations of use that are applicable to all of the product's indications, it is appropriate to list those limitations or concerns together, under an appropriately titled subheading (e.g., Limitations of Use). If the drug is approved under §§ 314.510 or 601.41 (i.e., an accelerated approval), a statement regarding the basis for approval should be included.

If the drug is a member of an established pharmacologic class, the information under Indications and Usage must include the statement “(*Drug*) is a (*name of class*) indicated for (*indication(s)*)” (§ 201.57(a)(6)). If the drug is not a member of an established pharmacologic class, the applicant should propose one.<sup>7</sup> The FDA will then determine whether to assign a new or existing pharmacologic class to the drug or to omit a pharmacologic class entirely.

### ***7. Dosage and Administration (§ 201.57(a)(7))***

Information under the Dosage and Administration heading must contain a concise summary of the recommended dosage regimen (e.g., starting dose, dose range, titration regimens, route of administration), critical differences among population subsets, monitoring recommendations, if any, and other clinically significant clinical pharmacology information that affects dosing recommendations (e.g., dosing adjustments recommended for concomitant therapy, specific populations with coexisting conditions, clinically relevant food effects) (§ 201.57(a)(7)). FDA recommends a tabular format to

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<sup>7</sup> See FDA Guidance for Industry: *Labeling for Human Prescription Drug and Biological Products – Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information* and the web page on pharmacologic class at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web site at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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enhance accessibility of information as appropriate (e.g., when there are complex dosage regimens or different dosing regimens for different indications).

In general, every attempt should be made to include the critical dosing and administration information in Highlights. However, there may be instances when a cross-reference to the FPI for detailed information may be necessary for a product with complex dosing and administration information. In such instances, a statement should be included under the Dosage and Administration heading in Highlights to alert the prescriber that additional important information is in the FPI.

### 8. *Dosage Forms and Strengths (§ 201.57(a)(8))*

Information under the Dosage Forms and Strengths heading must include all available dosage forms and strengths (see § 201.57(a)(8)) to assist the prescriber in product selection. If a solid oral dosage form is functionally scored, such information must be included<sup>8</sup> (§ 201.57(a)(8)). If a drug product has numerous dosage forms, bulleted subheadings (e.g., capsules, suspension, injection) or tabular presentations are recommended. For some products, including limited information on packaging can facilitate prescribing (e.g., noting that a 0.5% topical cream is available in both 15 g and 30 g tubes). Because of space constraints in Highlights, multiple strengths for a dosage form should be listed on one line (e.g., Tablets: 25 mg, 50 mg, 100 mg, and 200 mg). Descriptors of the product appearance (e.g., tablet color, shape, embossing) that appear in DOSAGE FORMS AND STRENGTHS in the FPI should not appear in Highlights.

### 9. *Contraindications (§ 201.57(a)(9))*

Information under the Contraindications heading must include a list of all the contraindicated situations described in the FPI or the word “None” if no contraindicated situations have been identified (§ 201.57(a)(9)). FDA recommends that each contraindication be identified in a bulleted list.

As in the FPI, *theoretical* contraindications should not be included in Highlights. For example, some labeling has included a contraindication in patients with hypersensitivity to any of the drug product’s components, despite there being no such reports and no basis upon which to believe such a risk exists. For labeling being converted to PLR format, these *theoretical* contraindications should be removed. If such data do exist, Highlights should include the hypersensitivity contraindication, and the CONTRAINDICATIONS section in the FPI should, in addition, describe the type and nature of the reactions that have been reported. Similarly, circumstances under which the drug may be used with caution are not contraindications and are not appropriate for inclusion.

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<sup>8</sup> A draft guidance is available on this issue. See *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* for FDA’s current thinking on this topic. Once finalized, this guidance will represent the Agency’s perspective on this issue



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### ***10. Warnings and Precautions (§ 201.57(a)(10))***

Information under the Warnings and Precautions heading must include a concise summary of the most clinically significant safety concerns from the FPI that affect decisions about whether to prescribe the drug, recommendations for patient monitoring to ensure safe use of the drug, and measures that can be taken to prevent or mitigate harm (§ 201.57(a)(10)). Individual risk topics should be presented in a bulleted format, with each imparting a complete piece of information (e.g., identify the risk, its consequences, and recommendations for the clinician to prevent or mitigate it, as appropriate). For example:

- Infusion reactions: Severe reactions have been reported. Discontinue DRUG-X for severe reactions; consider pre-treatment for cycles subsequent to milder reactions. (5.X).

The presentation should not merely be a list of subsection headings from Contents. Ambiguous and uninformative information (e.g., use with caution) and terminology that describes a contraindication (e.g., “do not use...”) should be avoided.

The most clinically significant safety concerns should be presented in Highlights; however, not all of the safety information from the FPI will always be included in Highlights. The order of the information should be the same as that of the FPI WARNINGS AND PRECAUTIONS section, reflecting the nature and severity of the risks. As previously stated, it is generally not necessary or useful to repeat information if it appears in other sections of Highlights.

### ***11. Adverse Reactions (§ 201.57(a)(11))***

#### ***a. Most frequently occurring adverse reactions***

Information under the Adverse Reactions heading must include (1) a listing of the most frequently occurring adverse reactions, even if one or more are included elsewhere in Highlights (e.g., under the Warnings and Precautions heading) and (2) the criteria used to determine inclusion (e.g., frequency cutoff rate) (§ 201.57(a)(11)(i)). The listing should be concise, not lengthy or comprehensive, and reactions should be presented in decreasing order of frequency. Specific terms should be used (e.g., neutropenia rather than hematologic) because general terms may not adequately describe the risk.

The list of adverse reactions identified as *most frequently occurring or most common* is usually generated from a table of adverse reactions from clinical trials in the FPI. Rates of most common adverse reactions vary, but should be appropriate to the nature of a drug’s adverse reactions profile and the size and composition of the safety database. If adverse reaction profiles vary significantly for different indications, the most common adverse reactions should be presented separately for each indication.

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### b. Adverse reaction reporting contact information

Highlights must also contain adverse reaction reporting contact information, in bold type, that includes the following (§§ 201.57(a)(11)(ii), (iii), (iv) and 201.57(d)(5)):

- The verbatim statement “**To report SUSPECTED ADVERSE REACTIONS, contact**” followed by the manufacturer’s name and phone number for adverse reaction reporting
- The address of a manufacturer’s web site for voluntary reporting of adverse reactions (only if such a web site exists)<sup>9</sup>
- FDA’s phone number and web address for voluntary reporting of adverse reactions (see below).

#### **FDA’s phone numbers and web addresses for voluntary reporting of adverse reactions:**

##### For drug and biological products (other than vaccines)

MedWatch

Phone number: 1-800-FDA-1088

Web address: [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

##### For vaccines

VAERS

Phone number: 1-800-822-7967

Web address: [www.vaers.hhs.gov](http://www.vaers.hhs.gov)<sup>10</sup>

For example, the completed adverse reaction reporting contact information statement for a drug product would read:

**To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [manufacturer’s phone number] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

The intent of this requirement is to encourage reporting of suspected adverse reactions. The rule specifically requires the inclusion of a phone number and, if available, the web address of the direct link to a site dedicated to adverse reaction reporting. Such dedicated web sites and phone lines provide a structured process for reporting adverse reactions (i.e., telephone interview, a form, or instructions for reporting), whereas an e-mail address or link to a company or product web site does not. An e-mail address or a link to the homepage of a company’s web site cannot be used to meet the requirement for adverse reactions reporting contact information in Highlights (§ 201.57(a)(11)(iv)). Although not specifically required in these labeling regulations, the phone number

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<sup>9</sup> If a manufacturer does not have a web site for voluntary reporting of adverse reactions, the manufacturer is not required to create one.

<sup>10</sup> For vaccines, this web address is also used for reporting required by health care professionals.

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provided should be a toll-free number to encourage reporting by practitioners and consumers.

If more than one entity is responsible for the product (e.g., the product is manufactured by one company and marketed by another, or the product is co-marketed), only one contact should be listed (e.g., the name of the entity identified by agreement between the companies as the recipient of safety information).

### *12. Drug Interactions (§ 201.57(a)(12))*

Information under the Drug Interactions heading must include a concise summary of those drugs (or classes of drugs) or foods that interact or are predicted to interact in clinically significant ways with the subject drug, and practical instructions for preventing or managing the interaction (§ 201.57(a)(12)).

Interaction information in Highlights should reflect the ordering of the DRUG INTERACTIONS section in the FPI, which is based on the relative clinical significance of the information. Descriptive subheadings of summary concepts (e.g., CYP3A inhibitors) can precede specific information. Rarely, it may be appropriate to include pertinent negative findings of drug interaction studies under this heading if the interaction would otherwise be anticipated or is of special concern.

If there are no clinically significant drug interactions, the heading should be omitted from Highlights. Information about lack of drug interactions or drug interactions that are not clinically relevant should not be included in Highlights.

Interactions with serious clinical consequences that are summarized elsewhere in Highlights (e.g., in the Boxed Warning or under the Contraindications or Warnings and Precautions heading) should be described in greater detail in the DRUG INTERACTIONS section in the FPI and need not be repeated under the Drug Interactions heading in Highlights.

Because some drugs have numerous clinically significant drug interactions, it may not be possible to concisely summarize all the critical information in Highlights. In these instances, a statement can be included under the Drug Interactions heading in Highlights that alerts the prescriber to the presence and significance of the drug interaction information in the FPI.

### *13. Use in Specific Populations (§ 201.57(a)(13))*

Information under the Use in Specific Populations heading must include a concise summary of any clinically important differences in response or recommendations for use of the drug in specific populations from the FPI (e.g., differences between adult and pediatric responses, need for specific monitoring in patients with hepatic impairment) (§ 201.57(a)(13)). If multiple populations are described under this heading, they should be presented in the same order in which they appear in the FPI.

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If there are no clinically important differences in response or recommendations for use of the drug in specific populations, the heading should be omitted from Highlights. Ordinarily, the absence of information about the safety and effectiveness of a drug in a specific population (e.g., pregnant women, children) should not be included under this heading. In unusual circumstances, if describing the absence of data provides important information for the prescriber, the heading should be retained. For example, if a drug has not been adequately studied in a specific patient population (e.g., those with hepatic impairment), Highlights may include a bullet describing the lack of information if deemed essential for prescribing decisions in that specific population.

The pregnancy category designation is not appropriate for inclusion in Highlights because, in isolation, it tends to oversimplify the risks of drugs in pregnancy and, as a result, may be confusing. Decisions about use of a drug in pregnancy should be based on careful consideration of available data, not simply on a reference to the pregnancy category. Information about the availability of a pregnancy registry and enrollment information should not appear in Highlights because it is not essential information and does not affect prescribing decisions. Registry information should be included in the Pregnancy subsection of the USE IN SPECIFIC POPULATIONS section of the FPI.

If information about use in specific populations is included under other headings in Highlights (e.g., Contraindications, Warnings and Precautions, Dosage and Administration), it should not be repeated under this heading.

### *14. Patient Counseling Information Statement (§ 201.57(a)(14))*

Highlights must contain the statement **See 17 for PATIENT COUNSELING INFORMATION** in bold or, if the product has FDA-approved patient labeling, **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**, or if the product has a Medication Guide, **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide** (§§ 201.57(a)(14) and 201.57(d)(5)). If the product has both a Medication Guide and another type of FDA-approved patient labeling (e.g., Instructions for Use), the statement should refer only to the Medication Guide. If the product has more than one type of FDA-approved patient labeling other than a Medication Guide (e.g., Patient Package Insert, Patient Information, Instructions for Use), the statement should refer only to FDA-approved patient labeling.

### *15. Revision Date (§ 201.57(a)(15))*

At the end of Highlights, the date of the most recent revision of the labeling must be presented (§ 201.57(a)(15)). The preferred format is **Revised: Month Year** or **Revised: Month/Year** in bold type (i.e., **Revised: Apr 2011** or **Revised: 4/2011**). In PLR format, this statement replaces the revision date that appears at the end of labeling in the old format (§ 201.56(e)(5)). A new approval or changes to the approved labeling will trigger a new revision date. FDA-approved patient labeling or Medication Guides can

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have revision dates that differ from the revision date at the end of Highlights, if appropriate.

- For labeling requiring prior approval (e.g., original applications, efficacy supplements, prior approval labeling supplements), the revision date would be the date of application approval. Manufacturers should leave this field blank and FDA will populate it at the time of approval.
- For CBE supplement labeling (§§ 314.70(c)(6) and 601.12(f)(2)), the revision date generally is the date of application receipt. Manufacturers should populate the revision date field with the date they anticipate FDA will receive the supplement. If the labeling text is changed by FDA, the revision date will be changed to the date of CBE approval.
- For annual report labeling, the revision date should reflect the date that the revised labeling is submitted to FDA. If all such changes are bundled and submitted once a year with the annual report, the revision date should be the date of the receipt of the annual report.

## **VI. FORMATTING**

The final rule includes formatting requirements (e.g., ordering, numbering, type size) that were designed to enhance readability and accessibility of labeling information (§ 201.57(d)). Attention to the formatting requirements of Highlights is particularly important because the most important prescribing information is presented in limited space (see Appendix E, which illustrates a sample Highlights and Contents). Although Appendix E illustrates every possible section and subsection, it is only an example, and not all drugs will have entries for all sections or subsections presented. FDA recommends the use of a two-column format for Highlights and Contents and use of adequate white space in Highlights (e.g., between each section) because these formatting techniques enhance effective communication of the labeling information. 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. Other recommendations for formatting issues are described below.

### **A. Subsection Headings**

Some subsections are required (e.g., 8.1 Pregnancy, 12.1 Mechanism of Action) (§ 201.56(d)(1)). The use of additional subsection headings is encouraged to help organize and identify the content of the information in the FPI (e.g., to identify individual warnings). Subsection headings that are not useful for signaling the content of the subsection, such as *General* or *Miscellaneous* should be avoided. Each subsection heading must be assigned a decimal number that corresponds to its placement in the FPI (§§ 201.56(d)(2) and 201.57(c)).

Subheadings under a subsection may be used to help organize information within a subsection, but they should not be assigned a numerical identifier with an additional decimal point (e.g.,

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12.3.1) nor should they appear in Contents. Instead, other formatting techniques (e.g., italics or underlining) can be used to achieve emphasis.

### **B. Omitted Sections (§ 201.56(d)(4))**

Any section, subsection, or specific information that is clearly inapplicable must be omitted from labeling (§ 201.56(d)(4)). Additionally, in most cases, when clinically relevant information about a drug is not available, the section or subsection should be omitted. Examples of appropriate omissions include the following:

- The DRUG ABUSE AND DEPENDENCE section should be omitted for a drug that is not a controlled substance and has no potential for abuse or dependence.
- The subsection Geriatric Use in the USE IN SPECIFIC POPULATIONS section should be omitted for a drug indicated only in neonates.

When a section or subsection is omitted from the FPI, it must also be omitted from the Contents (§ 201.56(d)(4)). The heading Full Prescribing Information: Contents must be followed by an asterisk and the following statement must appear at the end of the Contents: \*Sections or subsections omitted from the full prescribing information are not listed (§ 201.56(d)(4)). When there is an omission from the labeling, the numbering outlined in § 201.56(d)(1) should be preserved (i.e., subsequent sections and subsections are not renumbered).

In most cases when clinically relevant information about a drug is not available, the section or subsection should be omitted. In a few cases, describing the absence of data can provide important information for the prescriber, and, in these instances, the section or subsection should be included. For example, if a drug has not been adequately studied in a patient population with renal impairment, the labeling should typically include a Renal Impairment subsection under USE IN SPECIFIC POPULATIONS stating the lack of information.

### **C. Cross-References**

Cross-referencing is encouraged, and in some cases required (e.g., §§ 201.57(c)(1), (c)(6)(iv) and (c)(15)(ii)) because it refers the reader to more or related information on the topic and reduces the need to repeat detailed information about a similar issue in several different sections (see IV.B of this guidance for more information).

The preferred presentation of cross-references in Highlights is the numerical identifier in parentheses following the summarized labeling information (e.g., (5.1)). The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier (e.g., [*see Warnings and Precautions (5.1)*]). Because cross-references are embedded in the text in the FPI, we encourage the use of italics to achieve emphasis.

### **D. Type Size and Font Type**

The final rule requires different minimum type sizes for trade labeling (i.e., labeling on or within the package from which the drug is to be dispensed, including product samples) and for labeling

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disseminated in other settings (e.g., labeling that accompanies prescription drug promotional materials) (see § 201.57(d)(6)). Appendix D shows minimum type size requirements for labeling in the PLR format (§ 201.57) and in the old format (§ 201.80), including requirements for FDA-approved patient labeling (§§ 201.57(c)(18) and 201.80(f)(2)). FDA encourages a minimum type size of 10 points for all FDA-approved patient labeling.

There is no requirement for a specific font type (or typeface) for labeling, but the font type should be clear and legible. For example, narrow font types (e.g., Arial Narrow) are not recommended because they are difficult to read and may render the labeling illegible.

### **E. Use of Abbreviations**

Once an abbreviation for a term is defined in Highlights, FDA recommends redefining it the first time it is used in the FPI. Because labeling is frequently used to find a specific piece of information and the labeling may not be read from beginning to end, an acronym may be several pages away from where it was first defined in Highlights.

Unambiguous, commonly understood abbreviations (e.g., mg for milligrams) do not need to be defined. Abbreviations for units of measure (e.g., mg, mL) should be consistent within container and carton labeling. FDA recommends that Latin abbreviations (e.g., QD, QID) be avoided because of the greater potential for medication errors should an abbreviation be misread.<sup>11</sup>

## **VII. PROCEDURAL INFORMATION**

### **A. Applications Covered by the Final Rule**

Section 201.56(b)(1) provides that the final rule applies to prescription drug products with a new drug application (NDA), biologics license application (BLA), or efficacy supplement that

- is submitted on or after June 30, 2006 (the effective date of the final rule),
- is pending with the Agency on June 30, 2006, or
- was approved in the 5 years prior to June 30, 2006.

Although FDA recognizes the effort involved in revising labeling, the Agency strongly believes that the PLR format is an important advance in communicating drug information. Therefore, we encourage applicants with products to which the final rule does not apply to voluntarily convert the labeling of their products to the PLR format.

#### *1. New NDAs, BLAs, and Efficacy Supplements*

Draft labeling for new NDAs, BLAs, and efficacy supplements must be submitted in the PLR format (§ 201.56(c)(1)).

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<sup>11</sup> For additional information on abbreviations and dose designations that can lead to medication errors, see the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

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The following efficacy supplements trigger the requirement to revise labeling to the PLR format:

- Adding or modifying an indication or claim
- Revising the dose or dose regimen
- Providing for a new route of administration
- Making a comparative efficacy claim naming another product
- Significantly altering the intended patient population
- Providing for, or providing evidence of effectiveness necessary for, the traditional approval of a product originally approved under subpart H of part 314 or part 601
- Incorporating other information based on at least one adequate and well-controlled clinical study
- Pediatric supplements in response to written requests and the Pediatric Research Equity Act (PREA) of 2007<sup>12</sup>

Examples of supplements that do not trigger the requirements to revise labeling to the PLR format include NDA supplements for a new tablet strength; supplements that provide bioequivalence information, chemistry, manufacturing, and controls, also known as a “CMC” supplement, including one that contains clinical data but for which the data do not affect labeling (e.g., reformulation); and supplements that add new risk information (e.g., a new contraindication, warning).

### *2. Approved Applications*

The timing for submitting labeling in the PLR format is based on the implementation plan (see § 201.56(c) and Appendix A), but an applicant can voluntarily convert product labeling to the PLR format before the date specified in the implementation plan and is encouraged to do so. When more than one approval for the same product occurred in the 5 years prior to the effective date of the final rule (e.g., NDA and efficacy supplement), the date of the most recent approval determines the timing of submission of labeling in the PLR format according to the implementation plan.

The labeling must be submitted as a *prior approval* labeling supplement.<sup>13</sup> After labeling is approved in the PLR format, any subsequent changes to Highlights, other than identified minor exceptions, require submission of a prior approval supplement (§§ 314.70(b), (c), and (d) and 601.12(f)).

### *3. Submitting Draft Labeling to FDA for Review*

To facilitate FDA’s review of labeling, when a significant amount of new information is being added to the labeling at the same time that the labeling is being converted to the

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<sup>12</sup> Section 505A and 505B of the Federal Food, Drug & Cosmetic Act, as amended by the Food and Drug Administration Amendments Act of 2007 (P. L. 110-85)

<sup>13</sup> See §§ 314.70(b) and 601.12(f) about supplements requiring FDA approval before the change is made.



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PLR format (e.g., an efficacy supplement that also converts labeling to the PLR format), we recommend that the following versions of labeling be submitted as appropriate:

- Labeling in the old format
- Annotated labeling in the old format explaining how existing text was incorporated into the PLR format
- A *clean* version (no redline/strikeout) in the PLR format *without* the new information
- The above *clean* version in the PLR format *with* the new information (in redline/strikeout)

For the example listed above, if the efficacy supplement is to be reviewed in a division other than the one that managed the original application, two supplements should be submitted (i.e., a labeling supplement and an efficacy supplement).

Applicants should explain significant or notable changes in wording or content, or relocation of information to a different section, and how the decisions to make those changes were made. For submissions covering only a conversion of existing labeling to PLR format (without adding new information), the applicant should mark clearly on the cover letter, **Labeling/PLR Conversion** to facilitate identification of the type of submission for FDA.

### **B. Changes to the Regulations for Applications Not Covered by the Final Rule**

FDA has also made minor amendments to the labeling regulations for prescription drug and biological products not subject to the PLR content and format requirements (see §§ 201.56(e) and 201.80). Section 201.80 remains largely unchanged from previous labeling regulations, except for minor revisions to the REFERENCES section and the requirement to append FDA-approved patient labeling to the prescribing information by June 30, 2007. As always, labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular (§ 201.56(a)(3)). Therefore, the applicant should review the labeling at least annually for outdated information. Removing outdated references could be submitted in the Annual Report.

### **C. Appending FDA-Approved Patient Labeling**

The final rule required that by June 30, 2007, any FDA-approved patient labeling either accompany the labeling or be reprinted immediately following the last section of the labeling (§§ 201.56(e)(6), 201.57(c)(18) and 201.80(f)(2)).<sup>14</sup> This requirement applies to the labeling of all drugs, not just those subject to the PLR format requirements. The final rule provides the option of either reprinting the FDA-approved patient labeling (including Medication Guides) immediately following the last section of labeling or having the FDA-approved patient labeling accompany the labeling as a separate document (e.g., included in the carton with the drug).

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<sup>14</sup> The term *FDA-approved patient labeling* refers to any labeling that has been reviewed and approved by FDA that provides information for patients and is intended for distribution to patients who are prescribed a drug.

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In addition, any FDA-approved patient labeling must be referenced in the PATIENT COUNSELING INFORMATION section (§ 201.57(c)(18) in the PLR format or in the Information for Patients subsection (§ 201.80(f)(2) in the old format). A statement referring the reader to FDA-approved patient labeling should appear at the beginning of the section or subsection.

The FDA-approved patient labeling should not be a numbered subsection under the PATIENT COUNSELING INFORMATION section in the FPI or listed in Contents, but appended or reprinted after the last section of labeling.

Including only the FDA-approved patient labeling as the content of the PATIENT COUNSELING INFORMATION section does not meet the requirements of the final rule (§§ 201.57(c)(18) and 201.80(f)(2)). FDA-approved patient labeling and the information in the PATIENT COUNSELING INFORMATION section have distinct purposes. The PATIENT COUNSELING INFORMATION section of the FPI is written for health care professionals and contains the information that is important to convey to patients when the drug is being prescribed, dispensed, or administered. The FDA-approved patient labeling is written for patients to provide them with information about the drug that has been prescribed. FDA believes that both of these are important tools for providing information to patients.

### **D. Submitting Electronic Versions of Labeling**

For information about submitting labeling electronically, applicants should consult the information and guidances for industry on FDA's web site on Structured Product Labeling Resources.<sup>15</sup>

### **E. Waivers and CBE Supplements**

- **Waivers:** Requests to waive a labeling requirement under §§ 314.90(a) or 201.58 should be submitted directly to the application with any related communication directed to the responsible review division. A waiver request may pertain to a labeling requirement described in §§ 201.56, 201.57, 201.80, or 314.50(l)(i). The applicant should clearly identify the submission as a request for a waiver.
- **Waivers of the one-half page Highlights requirement:** The PLR regulations require that Highlights, excluding the boxed warning, be limited in length to one-half page (§ 201.57(d)(8)). Applicants should strive for this one-half page limit, using recommendations included in this guidance (e.g., avoiding redundancy of information, use of directive language, and inclusion of succinct bulleted lists). However, FDA recognizes that under certain circumstances, particularly when a product has many indications or many serious warnings and precautions that merit inclusion in Highlights, it may not be possible to accommodate all the required information within one-half page. In this case, the applicant

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<sup>15</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

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can submit a waiver request with the submission (e.g., NDA, BLA, efficacy supplement, or labeling supplement) (see § 201.58.).

The applicant should prominently identify the submission as one that includes a waiver request. In the waiver request, the applicant should explain why the one-half page requirement cannot be met. FDA will discuss the waiver request with the applicant during the review process and will formally document its decision in an action letter to the applicant.

- Changes to Highlights through a CBE supplement: With minor exceptions, changes to Highlights require a prior approval supplement (§§ 314.70 and 601.12). If the labeling is already approved in the PLR format and the proposed change(s) qualify for a CBE supplement under §§ 314.70(c) and 601.12(f), a prior approval supplement is not needed as long as the change does not warrant inclusion in Highlights (e.g., addition of an adverse reaction to the ADVERSE REACTIONS section in the FPI). If, in the opinion of the applicant, the new information warrants inclusion in Highlights or will be listed under Recent Major Changes in Highlights (i.e., a change to the BOXED WARNING, CONTRAINDICATIONS, OR WARNINGS AND PRECAUTIONS sections), the applicant should notify the appropriate review division about the proposed change to the labeling. The review division may permit changes to Highlights through a CBE supplement after consideration of the new information.

### **F. Class Labeling**

#### *1. Mandated Statements*

In some instances, a statement for a drug or class of drugs is required by regulation to be included in a particular section of the labeling (e.g., 21 CFR 310.517 requires that labeling for oral hypoglycemics of the sulfonylurea class include a statement in the WARNINGS section). When converting labeling to the PLR format, any required statement should be included in the corresponding section in the PLR format (e.g., a statement required to be included in the BOXED WARNING in the old format should be included in the BOXED WARNING in the PLR format). For sections that have been altered or eliminated, see Appendix C for the location of the statement in the PLR format.

In cases where the regulation requires a statement, but the rule does not specify where the statement should appear, FDA will consider, on a case-by-case basis where those statements should appear in the PLR format. Whether a specific statement required by regulation must appear in Highlights will be determined by FDA.

#### *2. Class Labeling Statements That Are Not Mandated by Regulation*

In some cases, the labeling of all members of a class of drugs includes identical statements, even though they are not mandated by regulation. These class labeling statements describe a risk or effect that is typically associated with members of the class, based on what is known about the pharmacology or chemistry of the drugs. For example,

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the boxed warning about the risk of using an ACE inhibitor during the second and third trimesters of pregnancy is uniformly presented in all labeling for this class of drugs.

To ensure consistent presentation of class labeling statements within drug classes, FDA will determine the appropriate content and location of a class labeling statement in Highlights and the FPI.

### **G. Abbreviated New Drug Application (ANDA) Products**

Under 21 CFR 314.94(a)(8), the labeling of a drug product submitted for approval under an ANDA must be the same as the labeling of the listed drug referenced in the ANDA, except for changes required because of the following:

- Differences have been approved under a suitability petition filed under 21 CFR 314.93.
- The ANDA product and the reference listed drug are produced or distributed by different manufacturers.
- Aspects of the listed drug's labeling are protected by patent or exclusivity.

Thus, if the labeling of the reference listed drug is converted to the PLR format, the labeling of the ANDA product must also be revised in accordance with 21 CFR 314.127(a)(7).

### **H. 505(b)(2) NDA Products**

In general, the applicant submitting an application under section 505(b)(2) of the FD&C Act need not wait for changes to be made to the referenced product's labeling to convert its labeling to the PLR format. For specific cases when an applicant may feel such a delay is warranted, a waiver from the requirements for the PLR format can be requested. If the section 505(b)(2) product labeling is converted to the PLR format before the referenced product, and substantial changes are made to sections referenced by the section 505(b)(2) product when the referenced product labeling is converted, FDA may request additional changes to the labeling of the section 505(b)(2) product in accordance with existing regulations and policies.

### **I. Manufacturer Information**

Under § 201.1, labeling must include the name and place of business of the manufacturer, packer, or distributor. Traditionally, this has been printed at the end of the labeling (after the HOW SUPPLIED section). In the PLR format, manufacturer information should be located at the end of the labeling, after the PATIENT COUNSELING INFORMATION section. If the product has FDA-approved patient labeling that is not a separate document or not intended to be detached and distributed to patients, the manufacturer information should be located at the end of the labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document or is to be detached and distributed to patients, the manufacturer information should be located both after the PATIENT COUSELING INFORMATION section and after the FDA-approved patient labeling.

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**VIII. ADDITIONAL LABELING GUIDANCES**

FDA has issued several additional guidances for industry on prescription drug labeling. FDA guidances are available on FDA's guidance web site.

(<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm>.) The web site is updated regularly as new or revised guidances are published.

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**APPENDIX A — Implementation Plan**

| <b>Applications (NDAs, BLAs, and Efficacy Supplements) Required to Conform to PLR Labeling Requirements</b>                     | <b>Time by Which Conforming Labeling Must Be Submitted to the Agency for Approval</b> |
|---|---|
| Applications submitted on or after June 30, 2006  | Time of submission  |
| Applications pending on June 30, 2006, and applications approved any time from June 30, 2005, up to and including June 30, 2006 | June 30, 2009   |
| Applications approved any time from June 30, 2004, up to and including June 29, 2005  | June 30, 2010   |
| Applications approved any time from June 30, 2003, up to and including June 29, 2004  | June 30, 2011   |
| Applications approved any time from June 30, 2002, up to and including June 29, 2003  | June 30, 2012   |
| Applications approved any time from June 30, 2001, up to and including June 29, 2002  | June 30, 2013   |
| Applications approved prior to June 30, 2001  | Voluntarily at any time   |

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**APPENDIX B — Prescription Drug Labeling Sections**

| <b>Old Format*</b>  | <b>PLR Format**</b>   |
|---|---|
| Description<br>Clinical Pharmacology<br>Indications and Usage<br>Contraindications<br>Warnings<br>Precautions<br>Adverse Reactions<br>Drug Abuse and Dependence<br>Overdosage<br>Dosage and Administration<br>How Supplied<br><br>Optional sections:<br>Animal Pharmacology<br>and/or Animal Toxicology<br>Clinical Studies<br>References | <p><b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b></p> Product Names, Other Required Information<br>Boxed Warning<br>Recent Major Changes<br>Indications and Usage<br>Dosage and Administration<br>Dosage Forms and Strengths<br>Contraindications<br>Warnings and Precautions<br>Adverse Reactions<br>Drug Interactions<br>Use in Specific Populations  |
|   | <p><b>FULL PRESCRIBING INFORMATION: CONTENTS</b></p> <p><b>FULL PRESCRIBING INFORMATION</b></p> Boxed Warning<br>1 Indications and Usage<br>2 Dosage and Administration<br>3 Dosage Forms and Strengths<br>4 Contraindications<br>5 Warnings and Precautions<br>6 Adverse Reactions<br>7 Drug Interactions<br>8 Use in Specific Populations<br>9 Drug Abuse and Dependence<br>10 Overdosage<br>11 Description<br>12 Clinical Pharmacology<br>13 Nonclinical Toxicology<br>14 Clinical Studies<br>15 References<br>16 How Supplied/Storage and Handling<br>17 Patient Counseling Information |

\* As required by 21 CFR 201.56(e) and 201.80.

\*\*As required by 21 CFR 201.56(d) and 201.57

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**APPENDIX C — Reorganizing Labeling Sections**

| <b>Location in Old Format</b>                           | → | <b>Location in FPI in PLR Format</b>   |
|---|---|--|
| Boxed Warning   | → | Boxed Warning  |
| Description   | → | Description  |
| Clinical Pharmacology                                   | → | Clinical Pharmacology  |
| Indications and Usage                                   | → | Indications and Usage  |
| Contraindications                                       | → | Contraindications  |
| Warnings  | → | Warnings and Precautions   |
| Precautions   |   |  |
| General   | → | Warnings and Precautions   |
| Information for Patients                                | → | Patient Counseling Information   |
| Laboratory Tests  | → | Warnings and Precautions   |
| Drug Interactions                                       | → | Drug Interactions  |
| Drug/Laboratory Test<br>Interactions                    | → | Warnings and Precautions   |
| Carcinogenesis, Mutagenesis,<br>Impairment of Fertility | → | Nonclinical Toxicology (Carcinogenesis,<br>Mutagenesis, Impairment of Fertility) |
| Pregnancy   | → | Use in Specific Populations (Pregnancy)  |
| Labor and Delivery                                      | → | Use in Specific Populations (Labor and Delivery)                                 |
| Nursing Mothers   | → | Use in Specific Populations (Nursing Mothers)                                    |
| Pediatric Use   | → | Use in Specific Populations (Pediatric Use)                                      |
| Geriatric Use   | → | Use in Specific Populations (Geriatric Use)                                      |
| Adverse Reactions                                       | → | Adverse Reactions  |
| Drug Abuse and Dependence                               | → | Drug Abuse and Dependence  |
| Overdosage  | → | Overdosage   |
| Dosage and Administration                               | → | Dosage and Administration  |
| How Supplied  | → | Dosage Forms and Strengths   |
|   | → | How Supplied/Storage and Handling  |
| Animal Pharmacology<br>and/or Animal Toxicology         | → | Nonclinical Toxicology (Animal Toxicology and/or<br>Pharmacology)                |
| Clinical Studies  | → | Clinical Studies   |
| References  | → | References   |



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**APPENDIX D — Type Size Requirements for Labeling and FDA-Approved Patient Labeling Included with Labeling**

|   | <b>Type Size Requirements for Labeling</b> | <b>FDA-Approved Patient Labeling Included with Labeling</b>  | <b>Type Size Requirements for FDA-Approved Patient Labeling</b> |
|---|--|--|---|
| <b>PLR Format (21 CFR 201.57)</b>   |  |  |   |
| Trade Labeling (i.e., labeling on or within the package from which the drug is to be dispensed) | Minimum 6-point type                       | FDA-approved patient labeling that is not for distribution to patients                             | Minimum 6-point type  |
|   |  | Any FDA-approved patient labeling (except a Medication Guide) that is for distribution to patients | Minimum 6-point type*   |
|   |  | Medication Guide that is for distribution to patients  | Minimum 10-point type   |
| Other Labeling (e.g., labeling accompanying promotional materials)                              | Minimum 8-point type                       | FDA-approved patient labeling that is not for distribution to patients                             | Minimum 8-point type  |
|   |  | Any FDA-approved patient labeling (except a Medication Guide) that is for distribution to patients | Minimum 8-point type*   |
|   |  | Medication Guide that is for distribution to patients  | Minimum 10-point type   |
| <b>Old Format (21 CFR 201.80)</b>   |  |  |   |
| Trade Labeling and Other Labeling   | No minimum requirement                     | FDA-approved patient labeling that is not for distribution to patients                             | No minimum requirement  |
|   |  | Any FDA-approved patient labeling (except a Medication Guide) that is for distribution to patients | No minimum requirement*   |
|   |  | Medication Guide that is for distribution to patients  | Minimum 10-point type   |

\* FDA does not require, but encourages a minimum type size of 10 points for this information.

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### APPENDIX E —HIGHLIGHTS AND CONTENTS FORMAT SAMPLE

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

- [text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

#### FULL PRESCRIBING INFORMATION: CONTENTS\*

##### WARNING: [SUBJECT OF WARNING]

##### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

##### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

##### 3 DOSAGE FORMS AND STRENGTHS

##### 4 CONTRAINDICATIONS

##### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

##### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

##### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

##### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

##### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

##### 10 OVERDOSAGE

##### 11 DESCRIPTION

##### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

##### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

##### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

##### 15 REFERENCES

##### 16 HOW SUPPLIED/STORAGE AND HANDLING

##### 17 PATIENT COUNSELING INFORMATION

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