
Guidance for Industry

Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements

DRAFT GUIDANCE

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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)**

**January 2006
Labeling**

Guidance for Industry

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

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Guidance for Industry¹

Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements²

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 new content and format requirements of labeling for human prescription drug and biological products (21 CFR 201.56(d) and 201.57).³ FDA recognizes the broad scope and complexity of these new regulations and is issuing this guidance to provide recommendations for applicants revising labeling of already approved products and for applicants drafting labeling for new products to be submitted with a new drug application (NDA) or biologics license application (BLA). FDA also recognizes that, as both applicants and the Agency become more familiar with writing labeling that complies with these new regulations, good examples and practices will emerge. FDA has appended a list of Frequently Asked Questions (FAQs) (Appendix A) and has posted illustrative examples of labeling in the new format at www.fda.gov/cder/regulatory/physLabel/default.htm. The information at this Web site will be updated with new examples, if needed, as they become available.

This guidance provides recommendations on the following subjects:

¹ This guidance has been prepared by the Medical Policy Coordinating Committees in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² See the final rule “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products” published in the *Federal Register* in January 2006.

³ 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 biological products that are regulated as drugs.

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- 34 • Issues to consider when revising labeling for approved products to meet the new content
35 and format requirements, including:
- 36 • how to distribute information among newly created sections
- 37 • when it is important to repeat information in varying levels of detail in different
38 sections
- 39 • how to minimize redundancy
- 40 • when to cross-reference
- 41 • Issues to consider when developing “Highlights of Prescribing Information” (Highlights)
- 42 • Procedural information, including:
- 43 • how to determine which applications are covered
- 44 • how to submit labeling
- 45 • how to apply for a waiver
- 46 • information about class labeling
- 47 • information about abbreviated new drug applications (ANDAs)
- 48 • How to format labeling, including the use of subheadings, cross-references, type size, and
49 how to address omitted sections

50 FDA has also made minor amendments to the regulations for labeling of prescription drug and
51 biological products not subject to the new content and format requirements (see 21 CFR
52 201.56(e) and 201.80 and sections V.A and V.B of this document).
53

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

59 60 **II. BACKGROUND**

61
62 In January 2006, the Agency published a final rule that amended the requirements for the content
63 and format of labeling for human prescription drug and biological products. The new regulations
64 are designed to make information in prescription drug labeling easier for health care practitioners
65 to access, read, and use, thereby facilitating practitioners' use of labeling to make prescribing
66 decisions. Changes to the labeling format include the addition of introductory prescribing
67 information, entitled “Highlights of Prescribing Information” (Highlights), and a “Table of
68 Contents” (Contents) for the “Full Prescribing Information” (FPI). Highlights contains selected
69 information from the FPI that health care practitioners most commonly reference and consider
70 most important. The Contents lists the sections and subsections of the FPI. The final rule also
71 reorders and reorganizes the FPI, makes minor changes to the content of the FPI, and sets

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72 minimum graphical requirements for the format of the labeling. For the purpose of this
73 guidance, the term *new format* refers to labeling that meets the content and format requirements
74 at §§ 201.56(d) and 201.57. The term *old format* refers to labeling formatted to meet the
75 requirements of the 1979 final rule (former §§ 201.56 and 201.57).⁴ See Appendix B for a listing
76 of prescription drug labeling sections in the old and new formats.

77
78 This guidance focuses on the major issues applicants may face when developing new labeling or
79 when revising labeling to meet the new requirements and provides procedural information
80 important for implementation. FDA expects that the most challenging aspects of this new
81 regulation will be developing Highlights and distributing information among sections that have
82 been substantially affected by this rule, particularly when the information must be culled from
83 the labeling in the old format. Therefore, the guidance focuses primarily on these issues and not
84 on developing sections that have not been changed by this rule. Additional guidance documents
85 that address content and format for specific FPI sections are available and should be consulted
86 when developing labeling.⁵

III. CONSIDERATIONS FOR REVISING LABELING

A. General Principles

92
93 The FPI in the new format contains substantially the same information as labeling in the
94 old format, typically with reordering and reorganization of the information. For example,
95 new labeling sections (e.g., DRUG INTERACTIONS, USE IN SPECIFIC
96 POPULATIONS, PATIENT COUNSELING INFORMATION) contain information
97 formerly included in the PRECAUTIONS section. Certain sections (e.g., CLINICAL
98 STUDIES, NONCLINICAL TOXICOLOGY) that were previously optional are now
99 required (§ 201.56(d)). Therefore, although labeling in the old format for approved
100 products does not contain the new section headings, most of the content already is
101 included in the labeling under different headings or subheadings. For example,
102 information from the old WARNINGS section and old PRECAUTIONS section is
103 consolidated into a single new section (WARNINGS AND PRECAUTIONS) and
104 information in certain old PRECAUTIONS subsections (e.g., *Information for Patients,*
105 *Drug Interactions, Pregnancy, Labor and Delivery, Nursing Mothers, Pediatric Use,*

⁴ See 44 FR 37434, “Labeling and Prescription Drug Advertising; Content and Format for Human Prescription Drugs,” Final Rule, June 26, 1979.

⁵ See the following FDA guidances for industry: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* and *Clinical Studies Section of Labeling for Human Prescription Drugs and Biological Products — Content and Format*. FDA has issued a draft guidance, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*. Once finalized, it will represent the Agency’s thinking on this topic.

We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/cder/guidance/index.htm>

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106 *Geriatric Use*) is relocated to new labeling sections (e.g., PATIENT COUNSELING
107 INFORMATION, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS).

108
109 FDA recommends following these general principles when revising labeling in the old
110 format.

111 112 1. *Developing New Sections*

113
114 FDA expects that most sections or subsections from labeling in the old format can be
115 moved, with little or no modification, to corresponding sections in the new format. See
116 Appendix C for information on how to reorganize labeling sections and subsections
117 within the new format.

118
119 In some cases, however, the labeling in the old format may not include the information
120 specified by the new regulations or the content of a section may be inadequate. If the
121 information or section in the old format is inadequate, it must be revised (§ 201.56(a)).
122

123 If the labeling in the old format lacks an entire section that is required in the new format,
124 then the section must be developed unless it is clearly inapplicable (§ 201.56(d)). For
125 example, if the labeling in the old format does not contain an *Information for Patients*
126 subsection in the PRECAUTIONS section, the applicant must develop a PATIENT
127 COUNSELING INFORMATION section unless the section is clearly inapplicable to use
128 of the drug.

129 130 2. *Data Analyses*

131
132 FDA recognizes that revising labeling to comply with the new regulations is an excellent
133 opportunity to update labeling content to ensure that it accurately reflects current
134 knowledge. FDA expects that, in most cases, the revisions will involve limited rewriting
135 aimed at clarifying text, eliminating redundancies, and updating outdated terminology.
136 FDA emphasizes that no new data analyses of the information in the old format are
137 required as long as the labeling that is developed is truthful and accurate. However, if
138 new information is available that causes the labeling to be inaccurate, the labeling must
139 be updated to incorporate the new information (§ 201.56(a)(2)). In some cases, new data
140 analyses may be necessary.

141 142 3. *Updating Claims*

143
144 Although the content of information in labeling in the old format will not significantly
145 change when converted to the new format, the process of updating labeling provides a
146 unique opportunity for the applicant to systematically evaluate information in labeling to
147 identify unsubstantiated claims or outdated information and revise it accordingly. By
148 regulation, all express or implied claims in labeling must be supported by substantial

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149 evidence.⁶ If unsubstantiated claims currently exist in labeling, the applicant must revise
150 the labeling to remove such claims (§ 201.56(a)(3)).

B. Distributing Information Among Sections

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152
153
154 When revising labeling in the old format to comply with the new regulations, applicants
155 will face many decisions about where to put information and whether to repeat
156 information in more than one section. Often sections or subsections can be moved with
157 little or no modification (see Appendix C). In some cases, it will be more appropriate to
158 move certain information from a labeling section in the old format to a different labeling
159 section in the new format or to consolidate similar issues under a new subheading. In
160 other cases, it will be appropriate to divide portions of information in a single labeling
161 section among two or more sections. The following general principles and examples are
162 offered to help applicants make decisions about where to locate information in the new
163 format.

1. Creating Hierarchy

164
165
166
167 It is often important to repeat information in varying levels of detail in different labeling
168 sections, based on the type and clinical relevance of the information. Important clinical
169 information relevant to prescribing decisions should be identified, prioritized, and located
170 in the labeling section that most appropriately communicates the type of information
171 being considered.

2. Avoiding Redundancy

172
173
174
175 Detailed information about a particular topic should be consolidated in a single labeling
176 section. Often, other sections of labeling should more briefly describe or refer to the
177 topic, but not repeat the same level of detail. For example, clinically relevant information
178 about a drug interaction that rises to the level of a warning will typically be described in
179 the WARNINGS AND PRECAUTIONS section, with supporting detail in the DRUG
180 INTERACTIONS section and other sections as appropriate (e.g., DOSAGE AND
181 ADMINISTRATION section if a dosage modification is necessary).

182
183 In some instances, information repeated in different sections of labeling in the old format
184 can be combined in the new format. For example, the old WARNINGS and old
185 PRECAUTIONS sections sometimes each contained information about a similar issue;
186 this information can now be consolidated under one subheading in the new WARNINGS
187 AND PRECAUTIONS section. When moving and consolidating information in labeling,
188 optional subheadings can be ordered to reflect the importance and relative public health
189 significance of the information.

⁶ 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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191 3. *Using Cross-References*

192
193 When information about the same topic is contained in more than one section, the section
194 with greatest clinical relevance (i.e., containing the most important information relevant
195 to prescribing) will typically include a succinct description and will cross-reference the
196 related sections that contain additional detail. If the detailed information is appropriately
197 divided into more than one section, those sections should cross-reference each other. In
198 some cases, cross-references are required (e.g., § 201.57(c)(1), (c)(6)(iv), and (c)(15)(ii)).
199

200 4. *Illustrative Example*

201
202 The Agency expects that distributing information among certain sections may present
203 special challenges. Based on our experience in developing mock labeling, we have
204 identified several basic principles. The following discussion of distributing information
205 among labeling sections illustrates these principles. Although drug interaction
206 information has been selected for this example, these principles also apply to other
207 labeling sections.
208

- 209 • Drug interaction information typically appears in the CLINICAL
210 PHARMACOLOGY and DRUG INTERACTIONS sections. Frequently, there is
211 a subset of information that is clinically relevant and essential for prescribing
212 decisions. That subset of information may be distributed among several sections,
213 including the BOXED WARNING, CONTRAINDICATIONS, WARNINGS
214 AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION
215 (§ 201.57(c)(3)(i)(H) and (c)(8)). FDA recommends using a descriptive header of
216 summary concepts preceding a discussion of specific information (e.g., “CYP3A
217 inhibitor”).
218
- 219 • When drug interaction information rises to the level of a warning, precaution, or
220 contraindication or necessitates a dosage adjustment, this information should be
221 discussed briefly in the applicable section(s), with details in the DRUG
222 INTERACTIONS section (§ 201.57(c)(8)).
223
- 224 • The DRUG INTERACTIONS section contains clinically relevant information,
225 such as the need to modify a dose or regimen. It can include information about
226 the observed absence of a drug interaction if that interaction would otherwise be
227 anticipated or is of special concern (e.g., other drugs in the class need a dosage
228 adjustment or if the drugs are commonly coadministered).
229
- 230 • More detail about drug interaction studies, including negative results of drug
231 interaction studies, and any clinically relevant, nonclinical data should be
232 included in the CLINICAL PHARMACOLOGY section.
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235 **IV. HIGHLIGHTS**

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237 **A. General Principles**

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239 The purpose of Highlights is to provide immediate access to the information that
240 practitioners most commonly refer to and view as most important. Highlights is intended
241 to serve as an information tool, drawing attention to this information and guiding the
242 practitioner to the section in the FPI where detailed information can be obtained.

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

249

250 It is critical that the summarized content of Highlights be consistent with the more
251 detailed information in the FPI, but not all of that information will be included in
252 Highlights. Selecting the information to include in Highlights requires judgment about
253 the data in relation to the clinical setting in which the drug is used. The information
254 considered of greatest importance will vary, depending on factors such as differences in
255 safety profiles or dosing considerations for different indications or populations.

256

257 Information about a topic, or similar topics, extracted from the FPI should be grouped
258 together and summarized with a brief, clear statement. For example, several warnings
259 from the FPI about a similar issue could be condensed into one bulleted item under the
260 Warnings and Precautions heading in Highlights.

261

262 Summarized information should be presented in direct language that is succinct and
263 imparts a complete piece of information (e.g., for a warning: a description of the risk, its
264 consequences, and the actions to take to prevent or mitigate it). In some cases, the
265 information can be summarized in a few words, while in others, a few short phrases or
266 sentences are more appropriate. Each summarized statement should be located under the
267 appropriate Highlights heading and must cross-reference the section(s) or subsection(s) of
268 the FPI that contains more detailed information (§ 201.56(d)(3)).

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B. Information in Highlights

1. Initial U.S. Approval (§ 201.57(a)(3))

On the line immediately beneath the established name (or for biologics, the proper name of the product), the verbatim statement “Initial U.S. Approval” must be presented, followed by the four-digit year in which FDA initially approved the new molecular entity, the new biological product, or the new combination of active ingredients (e.g., Initial U.S. Approval: 2004).

Multiple dates should not be listed for products with multiple formulations approved or licensed in different years. For these products, list the initial approval date of the new molecular entity, new biologic product, or new combination of active ingredients.

2. Boxed Warning (§ 201.57(a)(4))

The Boxed Warning in Highlights must contain a concise summary of the information from the BOXED WARNING in the FPI, and is limited in length to 20 lines. Because the BOXED WARNING in the FPI is an abbreviated description of the drug’s most important warnings and contraindications, the Boxed Warning in Highlights serves to emphasize such information, as well as to direct attention to the complete box and to the sections in the FPI that contain more detailed information.

FDA recommends that the information under the Boxed Warning heading in Highlights be summarized in a bulleted format, with each bullet communicating a discrete warning or contraindication. In rare instances, the BOXED WARNING in the FPI may be sufficiently concise to warrant repeating the statement verbatim in the Boxed Warning in Highlights.

3. Recent Major Changes (§ 201.57(a)(5))

When substantive labeling changes are made to any of the following sections of the FPI, the heading(s) of the changed section(s) must be listed in Highlights under the heading Recent Major Changes:

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

Minor corrections, such as typographical errors or grammatical changes, are not considered substantive labeling changes.

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- **What must be included**
 - At a minimum, the section heading, identifying number, and the date on which the change was incorporated in the labeling in month/year format (e.g., 6/2005 or June 2005)
 - If appropriate, the section subheading (e.g., when there are multiple subheading listings for a section)
 - **Multiple labeling changes**
 - If there are changes in more than one section of the labeling, the sections in Recent Major Changes should be listed in the same order as they appear in the FPI.
 - If there is more than one change in the same labeling section during the 1-year period listed and the change is to the content under the same subheading, the date that supersedes the previous one should be listed. For example, if a new indication (hypertension) was added to the labeling in March 2005, and a limitation to the hypertension indication was added in June 2005, the change under the Recent Major Changes heading should be listed as:

Indications and Usage, Hypertension (1.2) 6/2005
 - If there is more than one change in the same labeling section during the 1-year period listed, but the change is to the content under different subheadings, each section heading, subheading, identifying number, and date should be listed separately. For example:

Indications and Usage, Hypertension (1.2) 6/2005
Indications and Usage, Heart Failure (1.3) 9/2005
 - **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, WARNINGS AND PRECAUTIONS, CLINICAL STUDIES). If there are changes in any of the five applicable sections, each changed section should be listed under the Recent Major Changes heading. For example:

Indications and Usage, Hypertension (1.2)	June 2005
Dosage and Administration, Hypertension (2.2)	June 2005
Warnings and Precautions, Hyperkalemia (5.6)	June 2005
 - **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)). It is
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360 unusual for information to be completely deleted from labeling (e.g., removing a
361 warning as opposed to moving the warning to a different section), but if this occurs,
362 the review division will determine how best to identify this change.
363

- **Initial submission of revised labeling in the new format**

364 The Agency acknowledges that whether to include the Recent Major Changes
365 heading when converting labeling to the new format may be unclear because it is
366 difficult to anticipate if the 1-year time period for listing the changed labeling section
367 will elapse before the labeling in the new format is approved. Therefore, applicants
368 should include any substantive labeling changes under the Recent Major Changes
369 heading in the draft labeling submitted for review. At the time of approval, the
370 review division will determine whether the section is still applicable.
371

- **Removing a listing from Recent Major Changes**

372
373 A changed section must be listed under Recent Major Changes for at least 1 year after
374 the date the labeling change was approved and can continue to be listed until the
375 labeling is reprinted for the first time after the 1-year period. When the 1-year time
376 period expires, the applicant can choose (1) to reprint labeling immediately to remove
377 the listing or (2) to wait until the next reprinting to remove the listing. FDA
378 recommends that applicants notify the Agency in their Annual Report about removal
379 of a listing from Recent Major Changes and the corresponding vertical line in the FPI
380 (see 21 CFR 314.70(b)(2)(v)(C)(1) and 601.12(f)(3)(i)(D)(1)).
381
382

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

383
384 Information under the Indications and Usage heading must include a concise statement of
385 each of the drug's indications, briefly noting any major limitations. FDA recommends
386 that the information be presented in a bulleted format. In unusual circumstances, it may
387 be appropriate to present the indications verbatim from the FPI (e.g., when a product has
388 one indication and the statement in the FPI is sufficiently concise). For a product with
389 limitations of use that are applicable to all of the product's indications or with a major
390 safety concern associated with all its uses, it is appropriate to list those limitations or
391 concerns together, under an appropriately titled subheading (e.g., Important Limitations).
392
393

394 If the drug is a member of an established pharmacologic class, the information under
395 Indications and Usage must include the statement “(*Drug*) is a (*name of class*) indicated
396 for (*indication(s)*).” If the drug is not a member of an established pharmacologic class,
397 the statement should be omitted.
398

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

399
400 Information under the Dosage and Administration heading must contain a concise
401 summary of the recommended dosage regimen, starting dose, dose range, critical
402 differences among population subsets, monitoring recommendations, if any, and other
403 clinically significant clinical pharmacology information that affects dosing
404

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405 recommendations (e.g., dosing adjustments recommended for concomitant therapy,
406 specific populations with coexisting conditions, clinically relevant food effects). FDA
407 recommends a tabular format to enhance accessibility of information (e.g., when there are
408 different dosing regimens for different indications). When applicable and important,
409 special storage or handling information can be mentioned under this heading (e.g., special
410 handling of chemotherapeutic agents, need for refrigeration, reconstitution prior to
411 administration of the drug).

412

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

414

415 Information under the Dosage Forms and Strengths heading must include a concise
416 summary of the dosage form and strength and whether the drug product is scored. If a
417 drug product has numerous dosage forms, bulleted subheadings (e.g., capsules, tablets,
418 injectable, suspension) or tabular presentations are recommended.

419

420 7. *Contraindications (§ 201.57(a)(9))*

421

422 Information under the Contraindications heading must include either a concise summary
423 of the situations in which the drug should not be used because the risk clearly outweighs
424 any possible therapeutic benefit or the statement “none” if no contraindicated situations
425 have been identified. “Relative contraindications” (i.e., circumstances under which the
426 drug may be used with caution) are not true contraindications and are not appropriate for
427 inclusion under this heading.

428

429 8. *Warnings and Precautions (§ 201.57(a)(10))*

430

431 Information under the Warnings and Precautions heading must include a concise
432 summary of the most clinically significant safety concerns that affect decisions about
433 whether to prescribe the drug, recommendations for patient monitoring to ensure safe use
434 of the drug, and measures that can be taken to prevent or mitigate harm. Thus, although
435 it is unlikely that all of the safety information listed in the FPI will be included in
436 Highlights, the most clinically significant safety concerns should be addressed.

437

438 9. *Adverse Reactions (§ 201.57(a)(11))*

439

440 • **Most frequently occurring adverse reactions**

441

442 Information under the Adverse Reactions heading must include a listing of the most
443 frequently occurring adverse reactions, even if they are included elsewhere in Highlights,
444 and the criteria used to determine inclusion (e.g., incidence rate). The listing should be
445 concise, not lengthy or comprehensive. This listing may include adverse reactions that
446 are important for reasons other than frequency (e.g., leading to discontinuation or dosage
447 adjustments) unless they are included elsewhere in Highlights (e.g., under Warnings and
448 Precautions or Contraindications).

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450 The adverse reactions listed as *most frequently occurring or most common* should be
451 selected from the table of adverse reactions from clinical trials in the FPI. Rates of most
452 common adverse reactions vary, but should be appropriate to the nature of a drug's
453 adverse reactions profile and the size and composition of the safety database. The criteria
454 for determining inclusion must be identified along with the listing (e.g., >2%). If adverse
455 reaction profiles vary significantly for different indications, list the most common adverse
456 reactions by indication. Also note if different criteria for determining inclusion are used
457 for different indications.
458

- 459 • **Adverse reaction reporting contact information**

460 Highlights must also contain adverse reaction reporting contact information that includes:

- 461 1. The verbatim statement "To report SUSPECTED ADVERSE REACTIONS,
462 contact" followed by the manufacturer's name and phone number for adverse
463 reaction reporting,
464
- 465 2. the manufacturer's Web address of the direct link to its Web site for voluntary
466 reporting of adverse reactions (if available),⁷ and
467
- 468 3. FDA's phone number and Web address for voluntary reporting of adverse
469 reactions (see below).

470 **FDA's phone numbers and Web addresses for voluntary**
471 **reporting of adverse reactions:**

472 MedWatch (for drug products other than vaccines)
473 Phone number – 1-800-FDA-1088
474 Web address – www.fda.gov/medwatch

475
476
477 VAERS (for vaccines)
478 Phone number – 1-800-822-7967
479 Web address – www.fda.gov/vaers⁸

480
481 **10. Drug Interactions (§ 201.57(a)(12))**

482 Information under the Drug Interactions heading includes a concise summary of:

- 483 • a list of other drugs (or classes of drugs) or foods that interact or are predicted
484 to interact in clinically significant ways with the drug
- 485 • practical instructions for preventing or decreasing the likelihood of the
486 interaction
487
488

⁷ If a manufacturer does not have a Web site for voluntary reporting of adverse reactions, the manufacturer is not required to create one.

⁸ For vaccines, this Web address is also used for required reporting by health care providers.

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489 Descriptive subheadings of summary concepts (e.g., CYP3A inhibitor) may precede
490 specific information. In general, drugs that were found not to interact or to interact in a
491 nonclinically relevant way should not be included under this heading, nor should details
492 of drug interaction studies. However, it may be appropriate to include pertinent negative
493 findings of drug interaction studies under this heading if the interaction would otherwise
494 be anticipated or is of special concern (e.g., other drugs in the class need a dosage
495 adjustment or if the drugs are commonly coadministered). A tabular format is
496 recommended for presentation of drug interaction information for drugs with numerous
497 clinically significant interactions.

498
499 Interactions with particularly serious clinical consequences that are summarized under the
500 Contraindications or Warnings and Precautions heading in Highlights would be described
501 in greater detail in the DRUG INTERACTIONS section in the FPI.

502
503 Because some drugs are associated with a large number of clinically significant drug
504 interactions, it may not be possible to concisely summarize all the critical information in
505 Highlights. In these instances, include a statement under the Drug Interactions heading in
506 Highlights that alerts the prescriber to the presence and significance of the drug
507 interaction information in the FPI.

508 509 *11. Use in Specific Populations (§ 201.57(a)(13))*

510
511 Information under the Use in Specific Populations heading includes a concise summary
512 of any clinically important differences in response or recommendations for use of the
513 drug in specific populations (e.g., differences between adult and pediatric responses, need
514 for specific monitoring in patients with hepatic impairment, need for dosing adjustments
515 in patients with renal impairment). Typically, information under this heading includes
516 limitations or precautions for specific populations or established differences in response.

517
518 Ordinarily, the absence of information about the safety and effectiveness of a drug in a
519 specific population (e.g., pregnant women, children) should not be included under this
520 heading. It may be appropriate to include some information about use in specific
521 populations under other headings in Highlights (e.g., Contraindications, Warnings and
522 Precautions, Dosage and Administration) based on the type and clinical relevance of the
523 information.

524

525

526 **V. PROCEDURAL INFORMATION**

527

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

529

530 Section 201.56(b)(1) provides that the final rule applies to prescription drug products
531 with an NDA, BLA, or efficacy supplement that:

- 532 • is submitted on or after the effective date of the final rule,
- 533 • is pending on the effective date of the final rule, or

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- has been approved in the 5 years prior to the effective date of the final rule.

Although FDA recognizes the effort involved in revising labeling, the Agency strongly believes that the new format is a significant advance in communicating drug information. Therefore, we encourage applicants with products to which the final rule does not apply to voluntarily revise the labeling of their products to comply with the new content and format requirements.

1. New NDAs, BLAs, and Efficacy Supplements

After the effective date of the final rule, draft labeling submitted with new NDAs, BLAs, and efficacy supplements must be in the new format. Consistent with current practice, the labeling will be reviewed with the application or supplement.

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

- A new indication or a significant modification of an existing indication, including removal of a major limitation of use
- A new dosage regimen, including an increase or decrease in daily dosage or a change in frequency of administration
- A comparative efficacy or comparative pharmacokinetics claim naming another drug
- A change expected to significantly affect the size of the patient population to be given the drug, either broadening or narrowing the population (e.g., pediatrics, geriatrics)
- Clinical data to verify and describe the clinical benefit for a drug approved based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity (see 21 CFR 314.510 and 601.41)
- A labeling supplement with clinical data⁹

2. Approved and Pending Applications

The timing for submitting labeling in the new format is based on the implementation plan (see § 201.56(c) and Appendix D), but an applicant can voluntarily convert product labeling to the new format prior to the date specified in the implementation plan. For an approved application, the labeling would be submitted as a *prior approval* labeling supplement.¹⁰ Applicants voluntarily revising older labeling would also submit draft labeling as a prior approval labeling supplement. Under § 201.56(c)(2), for applications

⁹ See FDA's draft guidance for industry *Submitting Separate Marketing Applications and Clinical Data for the Purposes of Assessing User Fees* for the definition of clinical data. Once finalized, this guidance will represent the Agency's thinking on this topic.

¹⁰ See §§ 314.70(b) and 601.12(f) about supplements requiring FDA approval before the change is made.

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573 pending when the rule becomes effective, FDA would approve labeling in the old format
574 and the applicant then would have the implementation period to submit a prior approval
575 labeling supplement. When more than one approval for the same product occurred in the
576 5 years prior to the effective date of the final rule (e.g., NDA and efficacy supplement),
577 the date of the most recent approval determines the timing of submission of labeling in
578 the new format according to the implementation plan. After labeling is approved in the
579 new format, any subsequent changes to Highlights, other than identified minor
580 exceptions, require submission of a prior approval supplement (§§ 314.70(b) and (c) and
581 601.12(f)).

582

B. Appending FDA-Approved Patient Labeling

584

585 The final rule requires that, 1 year after the effective date, any FDA-approved patient
586 labeling either accompany the labeling or be reprinted immediately following the last
587 section of the labeling (§§ 201.57(c)(18) and 201.80(f)(2)).¹¹

588

589 Prior to the final rule, the regulations required that any printed patient information or
590 Medication Guide required to be distributed to patients be reprinted at the end of labeling.
591 The final rule changes these requirements as follows:

592

- 593 • Any FDA-approved patient labeling, and not just labeling required by regulation
594 to be distributed to patients, must be reprinted in or accompany the labeling.
595 Because distribution of Medication Guides to patients has always been required
596 (see 21 CFR part 208), the final rule does not change this requirement.
- 597 • This requirement applies to the labeling of all drugs, not just those subject to the
598 new format requirements.
- 599 • The final rule provides the option of either reprinting the FDA-approved patient
600 labeling (including Medication Guides) immediately following the last section of
601 labeling or having the FDA-approved patient labeling accompany the labeling as
602 a separate document.

603

604 When the only change to the labeling is the addition of FDA-approved patient labeling
605 (either reprinted in or accompanying the labeling as a separate document), a labeling
606 supplement is unnecessary. The Agency recommends notifying FDA of this change in
607 the annual report (see §§ 314.81 and 601.12). If there are changes to the labeling other
608 than those listed in the annual report, submit the appropriate labeling supplement (e.g.,
609 changes being effected (CBE) or prior approval).

¹¹ The term *FDA-approved patient labeling* refers to any labeling that has been reviewed and approved by the Agency that provides information for patients and is intended for distribution to patients who are prescribed a drug.

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C. Submitting Electronic Versions of Labeling

For information about submitting labeling electronically, applicants should consult the guidances for industry on *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and *Providing Regulatory Submissions in Electronic Format — Content of Labeling*.¹²

D. Applying for a Waiver from Highlights' One-Half Page Requirement

The new regulations require that Highlights, excluding the boxed warning, be limited in length to one-half page (§ 201.57(d)(8)). FDA recognizes that under certain circumstances, particularly when a product has many indications or many serious warnings 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 can submit a waiver request with the submission (e.g., NDA, BLA, efficacy supplement, or labeling supplement). (See 21 CFR 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 could not be met. The Agency will discuss the waiver request with the applicant during labeling negotiations and will formally document its decision in an action letter.

E. Class Labeling

1. Mandated Statements

In some instances, a statement(s) for a drug or class of drugs is required by regulation to be included in a particular section of the labeling. For example, 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 new format, the statement must be included in the corresponding section in the new format (e.g., a statement required to be included in the BOXED WARNING in the old format must be included in the BOXED WARNING in the new format). For sections that have been altered or eliminated, see Table 1 for the location of the statement in the new format.

¹² We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/cder/guidance/index.htm>.

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Table 1 — Location of Statements Required To Be Included in Labeling

Location in Old Format	Location in FPI of New Format
WARNINGS	WARNINGS AND PRECAUTIONS
PRECAUTIONS (General)	WARNINGS AND PRECAUTIONS
PRECAUTIONS (Drug Interactions)	DRUG INTERACTIONS
PRECAUTIONS (Special Populations)	USE IN SPECIFIC POPULATIONS
PRECAUTIONS (Information for Patients)	PATIENT COUNSELING INFORMATION
HOW SUPPLIED (or after HOW SUPPLIED)	HOW SUPPLIED/STORAGE AND HANDLING

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The Agency will consider, on a case-by-case basis, those instances where statements are required to be included in labeling in the new format, but not in a specific labeling section. Whether a specific statement required by regulation must appear in Highlights will be determined by the Agency.

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, 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, the Agency will determine during the labeling review and approval process: (1) the appropriate location of a class labeling statement in the FPI, (2) whether the information merits inclusion in Highlights, and (3) the content and location of the summarized statement in Highlights. Applicants should propose content and location of class labeling statements in the new format in the draft labeling submitted with their applications or supplements.

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F. 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:

1. differences have been approved under a suitability petition filed under 21 CFR 314.93
2. the ANDA product and the reference listed drug are produced or distributed by different manufacturers
3. aspects of the listed drug's labeling are protected by patent or exclusivity

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

ANDA applicants are encouraged to consult the guidance for industry on revising ANDA labeling following revision of the reference listed drug labeling for information about when and how to submit labeling supplements.¹³

VI. FORMATTING

The final rule includes certain formatting requirements (e.g., ordering, numbering, type size) that were designed to enhance readability and accessibility of labeling information (§ 201.57(d)). Beyond these requirements, the Agency expects that some flexibility in formatting will be necessary because of variability in the type and quantity of labeling information for different drugs. The Agency recommends the use of a two-column format for Highlights and Contents because this format enhances effective communication of the labeling information. Other general recommendations for specific formatting issues are described below.

A. Subheadings

The use of subheadings, in addition to those required by the final rule to help organize information in the FPI, is encouraged (e.g., to identify individual warnings). Each subheading that is used must be assigned a decimal number that corresponds to its placement and order in the FPI (§§ 201.56(d)(2) and 201.57(c)).

B. Omitted Sections (§ 201.56(d)(4))

Any required section, subsection, or specific information that is clearly inapplicable must be omitted from Highlights and the FPI. For example, if a drug is indicated for use only in males, and there are no preclinical or clinical data relevant to women of childbearing

¹³ See FDA's guidance for industry *Revising ANDA Labeling Following Revision of the RLD Labeling*.

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714 potential, the *Pregnancy, Labor and Delivery*, and *Nursing Mothers* subsections would be
715 omitted because they are not applicable.

716
717 When a section or subsection is omitted from the FPI, the section must also be omitted
718 from the Contents (§ 201.56(d)(4)). The heading “Full Prescribing Information:
719 Contents” must be followed by an asterisk and the following statement must appear at the
720 end of the Contents: “*Sections or subsections omitted from the Full Prescribing
721 Information are not listed” (§ 201.56(d)(4)).

722
723 In the example of a drug indicated for use only in males, the Contents heading appears as
724 follows:

FULL PRESCRIBING INFORMATION: CONTENTS*

725
726
727 The numbering in the Contents and FPI appears as follows:

728
729
730 **8 USE IN SPECIFIC POPULATIONS**
731 8.4 Pediatric Use
732 8.5 Geriatric Use
733 **9 DRUG ABUSE AND DEPENDENCE**
734

735 At the end of the Contents, the following statement appears:

736
737 *Sections or subsections omitted from the Full Prescribing Information
738 are not listed.

739
740 In most cases when clinically relevant information about a drug is not available, the
741 section or subsection should be omitted. Infrequently, describing the absence of data will
742 provide important information for the prescriber and, therefore, the section or subsection
743 should be included. For example, if a drug has not been adequately studied in a specific
744 patient population (e.g., hepatically impaired), the labeling should include a *Hepatic*
745 *Impairment* subsection that describes the lack of information.

C. Cross-references

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748
749 Cross-referencing is encouraged, and in some cases required (e.g., § 201.57(c)(1),
750 (c)(6)(iv), and (c)(15)(ii)), because it reduces the need to repeat detailed information
751 about a similar issue in several different sections (see III.B.3 of this guidance for more
752 information). The preferred presentation of cross-references in Highlights is the
753 numerical identifier in parentheses following the summarized labeling information (e.g.,
754 (1.1)). The preferred presentation of cross-references in the FPI is the section heading
755 followed by the numerical identifier (e.g., *see Indications and Usage (1.1)*). Because
756 cross-references are embedded in the text in the FPI, the use of italics to achieve
757 emphasis is encouraged.

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759 **D. Type Size**
760

761 The final rule requires different minimum type sizes for trade labeling (i.e., labeling on or
762 within the package from which the drug is to be dispensed) and for labeling disseminated
763 in other settings (e.g., labeling that accompanies prescription drug promotional
764 materials). (See § 201.57(d)(6).) Appendix E shows minimum type size requirements
765 for labeling in the new format (§ 201.57) and in the old format (§ 201.80), including
766 requirements for FDA-approved patient labeling. The Agency encourages a minimum
767 type size of 10 points for FDA-approved patient labeling.
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APPENDIX A — Frequently Asked Questions

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Where to Locate Information

Q1. Where should microbiology data be presented in the CLINICAL PHARMACOLOGY section?

A1. A subsection in the CLINICAL PHARMACOLOGY section can be created (e.g., 12.4 *Microbiology*) and all of the microbiology information for antimicrobial products consolidated into that subsection.

Q2. Labeling for some products includes disease-specific pathophysiology or epidemiology information. In the new format, where should this information be presented?

A2. In rare cases when a brief description of disease pathophysiology may facilitate understanding of a drug's pharmacology, the information may be included in the *Mechanism of Action* subsection of the CLINICAL PHARMACOLOGY section (§ 201.57(c)(13)(i)(A)). Epidemiologic information is discouraged because it is quickly outdated and will therefore require the applicant to frequently update the product's labeling.

Q3. What section of the labeling should contain animal efficacy data when a drug is approved based on effectiveness data from studies in animals (§§ 314.610 and 601.91)?

A3. In general, the specifics about animal efficacy study results should be presented in the *Animal Toxicology and/or Pharmacology* subsection of the NONCLINICAL TOXICOLOGY section of labeling. However, other sections should disclose that effectiveness was derived solely from animal studies and explain why (e.g., INDICATIONS AND USAGE, CLINICAL STUDIES). For example, the CLINICAL STUDIES section should make it clear that no human efficacy studies were conducted due to ethical considerations and that approval was based solely on evidence of effectiveness in animals. This section should also include a cross-reference to the *Animal Toxicology and/or Pharmacology* subsection. In addition, the labeling provided to patients must explain that the drug's approval was based on efficacy studies conducted in animals alone (§§ 314.610(b)(3) and 601.91(b)(3)).

Q4. Can the proprietary (or proper) and established names be repeated at the beginning of the FPI?

A4. The proprietary and established names, as well as other product identification information must be presented in Highlights (§ 201.57(a)(2)). The proprietary and established names

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814 can be repeated at the beginning of the FPI, or at the beginning of each page of the FPI
815 (e.g., as a header), if this enhances product identification on subsequent pages of labeling.

816
817

Scope

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820 ***Q5. Are combination products subject to this new labeling rule?***

821

822 A5. Combination products that are comprised of a prescription drug and biologic, a
823 prescription drug and device, or a biologic and device that were reviewed under a BLA or
824 NDA are subject to the new labeling rule, if the prescription drug component is subject to
825 the new labeling rule (see § 201.56(b)). Applicants with these products must submit
826 revised labeling to conform with the new requirements to the original NDA or BLA. In
827 addition, applicants with combination products reviewed under device authorities should
828 contact the Office of Combination Products regarding whether the drug or biological
829 product component is subject to the prescription drug labeling rule. (See 21 CFR part 3.)

830

831

Procedural

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834 ***Q6. How should a labeling supplement be submitted for a product reviewed in more than***
835 ***one division?***

836

837 A6. For a product with marketing applications in more than one review division, the applicant
838 should continue to follow the procedures established with the divisions for submitting
839 labeling supplements. If the applicant is uncertain about where to submit a supplement
840 that converts labeling to the new format, the division where the original NDA or BLA
841 was approved should be contacted for assistance.

842

843

844 ***Q7. Does the adverse reaction reporting contact information have to be presented as part of***
845 ***the “fair balance” information in promotional materials?***

846

847 A7. There is no requirement to include the adverse reaction reporting contact information in
848 promotional materials.

849

850

Formatting

851

852

853 ***Q8. Can the proprietary and established (or proper) names be presented on the same line in***
854 ***Highlights?***

855

856 A8. To conserve space in Highlights, the proprietary and established names should be
857 presented on the same line, unless they are too long. In that case, the established name
858 should be presented on the line underneath the proprietary name.

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Q9. Is there a preferred format for the revision date?

A9. The date of the most recent revision must be presented at the end of Highlights (§ 201.57(a)(15)). The preferred format is “Revised: Month Year” or “Revised: Month/Year” (i.e., Revised: June 2003 or Revised: 6/2003).

Q10. Should Latin abbreviations be used in the DOSAGE AND ADMINISTRATION section (e.g., qd versus once daily)?

A10. The Agency recommends that Latin abbreviations be avoided because of the greater potential for medication errors should an abbreviation be misread.

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APPENDIX B — Prescription Drug Labeling Sections

Old Format*	New 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	<p>HIGHLIGHTS OF PRESCRIBING INFORMATION</p> 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
	<p>FULL PRESCRIBING INFORMATION: CONTENTS</p>
	<p>FULL PRESCRIBING INFORMATION</p> 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

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

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

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APPENDIX C — Reorganizing Labeling Sections

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883			
884	Location in Old Format	→	Location in FPI in New Format
885			
886	Boxed Warning	→	Boxed Warning
887	Description	→	Description
888	Clinical Pharmacology	→	Clinical Pharmacology
889	Indications and Usage	→	Indications and Usage
890	Contraindications	→	Contraindications
891	Warnings	→	Warnings and Precautions
892	Precautions		
893	General	→	Warnings and Precautions
894	Information for Patients	→	Patient Counseling Information
895	Laboratory Tests	→	Warnings and Precautions
896	Drug Interactions	→	Drug Interactions
897	Drug/Laboratory Test		
898	Interactions	→	Warnings and Precautions
899	Carcinogenesis, Mutagenesis,		
900	Impairment of Fertility	→	Nonclinical Toxicology (Carcinogenesis,
901			Mutagenesis, Impairment of Fertility)
902	Pregnancy	→	Use in Specific Populations (Pregnancy)
903	Labor and Delivery	→	Use in Specific Populations (Labor and Delivery)
904	Nursing Mothers	→	Use in Specific Populations (Nursing Mothers)
905	Pediatric Use	→	Use in Specific Populations (Pediatric Use)
906	Geriatric Use	→	Use in Specific Populations (Geriatric Use)
907	Adverse Reactions	→	Adverse Reactions
908	Drug Abuse and Dependence	→	Drug Abuse and Dependence
909	Overdosage	→	Overdosage
910	Dosage and Administration	→	Dosage and Administration
911	How Supplied	→	Dosage Forms and Strengths
912		→	How Supplied/Storage and Handling
913	Animal Pharmacology		
914	and/or Animal Toxicology	→	Nonclinical Toxicology (Animal Toxicology and/or
915			Pharmacology)
916	Clinical Studies	→	Clinical Studies
917	References	→	References

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APPENDIX D — Implementation Plan

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Applications (NDAs, BLAs, and Efficacy Supplements) Required to Conform to New Labeling Requirements	Time by Which Conforming Labeling Must Be Submitted to the Agency for Approval
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 E — Type Size Requirements for Labeling and FDA-Approved Patient Labeling Included with Labeling

	Type Size Requirements for Labeling	FDA-Approved Patient Labeling Included with Labeling	Type Size Requirements for FDA-Approved Patient Labeling
New Format (21 CFR 201.57)			
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
Old Format (21 CFR 201.80)			
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

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