

Title 21

EDITORIAL NOTE ON PART 201

Editorial Note: Nomenclature changes to part 201 appear at 69 FR 13717, Mar 24, 2004

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDA-approved patent labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007

- (a) **Highlights of prescribing information.** The following information must appear in a prescription drug labeling
- (1) **Highlights limitation statement.** The verbatim statement "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)"
 - (2) **Drug names, dosage form, route of administration, and controlled substance symbol.** The proprietary name and the established name of the drug, if any, as defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (the act) or, for biological products, the proper name (as defined in § 600.3 of this chapter) including any appropriate descriptors. This information must be followed by the drug's dosage form and route of administration. For controlled substances, the controlled substance symbol designating the schedule in which the controlled substance is listed must be included as required by § 1302.04 of this chapter
 - (3) **Initial U.S. approval.** The verbatim statement "Not a U.S. Approval" followed by the four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients. The statement must be placed on the immediate label beneath the established name or, for biological products, proper name of the product
 - (4) **Boxed warning.** A concise summary of any boxed warning required by paragraph (c)(1) of this section, not to exceed a length of 20 lines. The summary must be preceded by a heading, in upper-case letters, containing the word "WARNING" and other words that are appropriate to identify the subject of the warning. The heading and the summary must be contained within a box and boxed. The following verbatim statement must be placed immediately following the heading of the boxed warning "See full prescribing information for complete boxed warning"
 - (5) **Recent major changes.** A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period
 - (6) **Indications and usage.** A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effectiveness in particular subsets of the population, or second-line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner "(Drug) is a (name of class) indicated for (indication(s))"
 - (7) **Dosage and administration.** A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information
 - (8) **Dosage forms and strengths.** A concise summary of the information required under paragraph (c)(4) of this section, with any appropriate subheadings (e.g., tablets, capsules, injectable, suspension), including the strength or potency of the dosage form in metric system (e.g., 10-mg tablets) and whether the product is scored
 - (9) **Contraindications.** A concise statement of each of the product's contraindications, as required under paragraph (c)(5) of this section, with any appropriate subheadings
 - (10) **Warnings and precautions.** A concise summary of the most clinically significant information required under paragraph (c)(6) of this section, with any appropriate subheadings, including information that would affect decisions about whether to prescribe a drug,

- (11) **Adverse reactions.**
- () A list of the most frequently occurring adverse reactions, as described in paragraph (c)(7) of this section, along with the criteria used to determine inclusion (e.g., incidence rate) Adverse reactions important for other reasons (e.g., because they are serious or frequently lead to discontinuation or dosage adjustment) must not be repeated under this heading in headings if they are included elsewhere in headings (e.g., Warnings and Precautions, Contraindications)
 - () For drug products other than vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number and Web address for voluntary reporting of adverse reactions)"
 - () For vaccines, the verbatim statement "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or VAERS at (insert the current VAERS phone number and Web address for voluntary reporting of adverse reactions)"
 - (v) For manufacturers with a Website for voluntary reporting of adverse reactions, the Web address of the direct link to the site
- (12) **Drug interactions.** A concise summary of the information required under paragraph (c)(8) of this section, with any appropriate subheadings
- (13) **Use in specific populations.** A concise summary of the information required under paragraph (c)(9) of this section, with any appropriate subheadings
- (14) **Patient counseling information statement.** The verbatim statement "See 17 for Patient Counseling information" or, if the product has FDA-approved patient labeling, the verbatim statement "See 17 for Patient Counseling information and (insert either FDA-approved patient labeling or Medication Guide)"
- (15) **Revision date.** The date of the most recent revision of the labeling, identified as such, placed at the end of headings
- (b) **Full prescribing information: Contents.** Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1)
- (1) Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2)
- (c) **Full prescribing information.** The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4) If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2)
- (1) **Boxed warning.** Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data The box must contain, in uppercase letters, a heading inside the box that includes the word "WARNING" and conveys the general focus of the information in the box The box must briefly explain the risk and refer to more detailed information in the "Contraindications" or "Warnings and Precautions" section, accompanied by the identifying number for the section or subsection containing the detailed information
 - (2) **1 Indications and usage.** This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition
 - () This section must include the following information when the conditions listed are applicable
 - (A) If the drug is used for an indication on a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy
 - (B) If evidence is available to support the safety and effectiveness of the drug or biological product on a selected subgroup of the larger population (e.g., patients with mild disease or patients in a specific age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section for a discussion of the available evidence
 - (C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbiology susceptibility tests), the identity of such tests
 - (D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the "Dosage and Administration" section
 - (E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information

- (F) If there are specific conditions that should be met before the drug is used on a long-term basis (e.g., demonstration of responsiveness to the drug in a short-term trial in a given patient), a statement of the conditions; or, if the indications for long-term use are different from those for short-term use, a statement of the specific indications for each use
 - () If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition
 - () Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biologic products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biologic products, such statements must be supported by substantial evidence
 - (v) For drug products other than biologic products, a indication stated in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section
 - (v) For biologic products, a indication stated in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section
- (3) **2 Dosage and administration.**
- () This section must state the recommended dose and, as appropriate
 - (A) The dosage range,
 - (B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increased effectiveness,
 - (C) Dosages for each indication and subpopulation,
 - (D) The intervals recommended between doses,
 - (E) The optimal method of treating dosage,
 - (F) The usual duration of treatment when treatment duration should be limited,
 - (G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),
 - (H) Modification of dosage needed because of drug interactions or in specific patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),
 - () Important considerations concerning compliance with the dosage regimen,
 - (J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary
 - () Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section
 - () Radionuclide dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it
 - (v) This section must also contain specific directions on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")
- (4) **3 Dosage forms and strengths.** This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including
- () The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and
 - () A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section
- (5) **4 Contraindications.** This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of the nature of the disease, have a condition that, if not treated, could be fatal or life-threatening.

risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be stated (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be stated as a contraindication) if no contraindications are known, this section must state "None"

(6) **5 Warnings and precautions.**

- () **General.** This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacologic class or those resulting from drug/drug interactions), manifestations imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of a clinically significant adverse reaction and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section in accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.
- () **Other special care precautions.** This section must contain information regarding any special care to be exercised by the practitioner for safe and effective use of the drug (e.g., precautions not required under any other specific section or subsection).
- () **Monitoring: Laboratory tests.** This section must identify any laboratory tests helpful in following the patient's response or identifying possible adverse reactions. If appropriate, information must be provided on such factors as the range of normal and abnormal values expected in the particular situation and the recommended frequency with which tests should be performed before, during, and after therapy.
- (v) **Interference with laboratory tests.** This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

(7) **6 Adverse reactions.** This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacologic action of the drug or may be unpredictable in its occurrence. This definition does not include 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.

- () **Listing of adverse reactions.** This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologic category and chemically related class, if applicable. The list items must be preceded by the information necessary to interpret the adverse reactions (e.g., for contraindications, total number exposed, extent and nature of exposure).
- () **Categorization of adverse reactions.** Within a listing, adverse reactions must be categorized by body system, by severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency information cannot be readily determined, adverse reactions must be listed in decreasing order of severity.
 - (A) **Clinical trials experience.** This section must list the adverse reactions identified in contraindications that occurred at or above a specified rate appropriate to the safety database. The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading. If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing. If comparative rates of occurrence cannot be readily determined (e.g., adverse reactions were observed only in the uncontrolled trial portion of the overall safety database), adverse reactions must be grouped within specified frequency ranges as appropriate to the safety database for the drug (e.g., adverse reactions occurring at a rate of less than 1/100, adverse reactions occurring at a rate of less than 1/500) or descriptively identified. If frequency ranges cannot be determined. For adverse reactions with significant contraindications, the listings must be supplemented with additional details about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important.
 - (B) **Postmarketing experience.** This section of the labeling must list the adverse reactions, as defined in paragraph (c)(7) of this section, that are identified from domestic and foreign spontaneous reports. This listing must be separate from the listing of adverse reactions identified in contraindications.
- () **Comparisons of adverse reactions between drugs.** For drug products other than biologic products, any claim comparing the drug to which the labeling applies with other drugs in terms of frequency, severity, or character of adverse reactions must be based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biologic products, any such claim must be based on substantial evidence.

(8) **7 Drug interactions.**

- () This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the interaction, if known, must be briefly described. Interactions that are described in the "Contraindications" or "Warnings and Precautions" sections must be discussed in more detail under this section. Details of drug interaction pharmacokinetic studies that are included in the "Clinical Pharmacology" section that are pertinent to clinical use of the drug must not be repeated in this section.
- () This section must also contain practical guidance on known interference of the drug with laboratory tests.
- (9) **8 Use in specific populations.** This section must contain the following subsections:
- () **8.1 Pregnancy.** This subsection of the labeling must contain the following information in the following order under the subheadings "Pregnancy Exposure Registry," "Risk Summary," "Clinical Considerations," and "Data":
- (A) **Pregnancy exposure registry.** If there is a scientifically acceptable pregnancy exposure registry for the drug, contact information needed to enroll in the registry or to obtain information about the registry must be provided following the statement "There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (name of drug) during pregnancy."
- (B) **Risk summary.** The Risk Summary must contain a risk statement(s) based on data from all relevant sources (human, animal, and/or pharmacologic) that describe, for the drug, the risk of adverse developmental outcomes (i.e., structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth). When multiple data sources are available, the statements must be presented in the following order: Human, animal, pharmacologic. The source(s) of the data must be stated. The labeling must state the percentage range of live births in the United States with a major birth defect and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug exposure. If such information is available for the population(s) for which the drug is labeled, it must also be included. When use of a drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary. When applicable, risk statements as described in paragraphs (c)(9)(1)(B)(1) and (2) of this section must include a cross-reference to additional details in the relevant portion of the "Data" subheading in the "Pregnancy" subsection of the labeling. If data demonstrate that a drug is not systemically absorbed following a particular route of administration, the Risk Summary must contain only the following statement: "(Name of drug) is not absorbed systemically following (route of administration), and maternal use is not expected to result in fetal exposure to the drug."
- (1) **Risk statement based on human data.** When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, the Risk Summary must summarize the specific developmental outcome(s); the incidence; and the effects of dose, duration of exposure, and gestational timing of exposure. If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, this risk must be quantitatively compared to the risk for the same outcome in infants born to women who were not exposed to the drug but who have the disease or condition for which the drug is indicated to be used. When risk information is not available for women with the disease or condition for which the drug is indicated, the risk for the specific outcome must be compared to the rate at which the outcome occurs in the general population. The Risk Summary must state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk.
- (2) **Risk statement based on animal data.** When animal data are available, the Risk Summary must summarize the findings in animals and based on these findings, describe, for the drug, the potential risk of any adverse developmental outcome(s) in humans. This statement must include: The number and type(s) of species affected, timing of exposure, animal doses expressed in terms of human dose or exposure equivalents, and outcomes for pregnant animals and offspring. When animal studies do not meet current standards for nonclinical developmental toxicology studies, the Risk Summary must so state. When there are no animal data, the Risk Summary must so state.
- (3) **Risk statement based on pharmacology.** When the drug has a well-understood mechanism of action that may result in adverse developmental outcome(s), the Risk Summary must explain the mechanism of action and the potential associated risks.
- (C) **Clinical considerations.** Under the subheading "Clinical Considerations," the labeling must provide relevant information, to the extent it is available, under the headings "Disease-associated maternal and/or embryo/fetal risk," "Dose adjustments during pregnancy and the postpartum period," "Maternal adverse reactions," "Fetal/Neonatal adverse reactions," and "Labor or delivery":
- (1) **Disease-associated maternal and/or embryo/fetal risk.** If there is a serious known or potential risk to the pregnant woman and/or the embryo/fetus associated with the disease or condition for which the drug is indicated to be used, the labeling must describe the risk.
- (2) **Dose adjustments during pregnancy and the postpartum period.** If there are pharmacokinetic data that support dose adjustment(s) during pregnancy and the postpartum period, a summary of this information must be provided.
- (3) **Maternal adverse reactions.** If use of the drug is associated with a maternal adverse reaction that is unique to

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.