

January 27, 2006

FDA Final Rule on Prescription Drug Labeling & Statement on Preemption of State Product Liability Laws

On January 24, 2006, FDA published a final rule in the Federal Register setting forth new requirements on the content and format of the approved labeling for prescription drugs and biologics.¹ The final rule will be codified principally at 21 C.F.R. §§ 201.56 and 201.57 and replaces FDA's existing regulations, which have been in effect since 1979. This memorandum provides an overview of the final rule, with emphasis on the significant changes from the prior requirements for prescription drug labeling.

In addition, within the preamble to the final regulation FDA made a number of important statements regarding the preemptive effect of FDA labeling determinations on conflicting state law requirements. The discussion in the preamble represents the agency's most direct and formal statement on the preemptive effect of its labeling regulations. This memorandum will address some of the key elements of FDA's statements on preemption.

I. Background

On December 22, 2000, FDA published a proposed rule to revise the format and certain aspects of the content of the approved labeling for human prescription drugs, also known as the package insert or approved prescribing information.² Because the labeling for many prescription drugs has increased in length and complexity in recent years, FDA proposed a new format intended to make drug labeling more readable and "user friendly" for prescribers.³ FDA's proposed rule was based in part on feedback from surveys, focus groups, and public meetings, and was intended to reduce the amount of time needed for practitioners to locate information in prescription drug labeling, increase the effectiveness of drug treatment, and reduce the potential for drug related errors.⁴

The proposed rule included many changes to the existing format for prescription drugs. Most notably, FDA proposed the addition of an introductory "Highlights" section and index, and proposed reorganizing many of the existing elements included in drug labeling.

In response to FDA's proposal, numerous stakeholders submitted comments. While most comments supported FDA's proposed reordering of the different sections of the labeling, several groups raised concerns about other aspects of the proposed requirements. Several comments emphasized that the Highlights section, the creation of different labeling standards for older and newer products, and other aspects of the proposed rule could have serious product liability implications. For example, by requiring some manufacturers to highlight certain warnings or other safety information, or requiring manufacturers to alter or remove other warnings, manufacturers could be subject to "failure to warn" claims.

¹ 71 Fed. Reg. 3922 (January 24, 2006).

² 65 Fed. Reg. 81082 (December 22, 2000).

³ 71 Fed. Reg. at 3922.

⁴ *Id.* at 3972.

Accordingly, several comments urged FDA to include in connection with any final rule a clear statement that FDA labeling requirements preempt inconsistent requirements under state law, including requirements imposed under state tort law in personal injury cases. Additional concerns voiced by the pharmaceutical industry and others included proposed restrictions on the inclusion of certain in vitro data in labeling, changes to the handling of adverse event information, and FDA's proposed implementation plan.

The proposed rule languished for years without significant FDA activity until the recent publication of the final rule. In its final rule, FDA retained most elements of the proposed rule and responded to the comments that many stakeholders had submitted. In addition to the new rule, FDA issued four guidance documents (some in draft) regarding specific aspects of the final rule and several hypothetical examples of the new labeling format.⁵

II. New Labeling Requirements

A. Effective Date

FDA's new rule applies to any New Drug Application ("NDA"), Biologics License Application ("BLA"), or efficacy supplement⁶ (1) approved between June 30, 2001 and June 30, 2006, (2) pending on June 30, 2006, or (3) submitted on or after June 30, 2006.⁷ The new rule is effective on June 30, 2006, but provides for a phased implementation schedule as follows⁸:

Applications (NDA, BLA, Efficacy Supplement)	Deadline for Submitting Labeling to FDA that Complies with the Final Rule
Submitted on or after June 30, 2006	Time of submission
Pending on June 30, 2006 and approved 0 to 1 year before June 30, 2006	June 30, 2009
Approved 1 to 2 years before June 30, 2006	June 30, 2010
Approved 2 to 3 years before June 30, 2006	June 30, 2011
Approved 3 to 4 years before June 30, 2006	June 30, 2012
Approved 4 to 5 years before June 30, 2006	June 30, 2013

⁵ The guidance documents are available at <http://www.fda.gov/cder/regulatory/physLabel/default.htm> and include the following:

- "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format";
- "Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format";
- "Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements" (Draft);
- "Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format" (Draft).

⁶ An "efficacy supplement" generally describes any supplemental application submitted for an approved product that requires new efficacy data. For example, an application requesting approval for a new indication, new dosage regimen, or new patient population might require clinical data, and thus would have to include labeling for the product that complies with the new rule.

⁷ 21 C.F.R. § 201.56(b)(1).

⁸ *Id.* at § 201.56(c).

For older products not covered by the new rule, the labeling requirements remain largely the same as under the prior regulations.⁹ Although the new rule does not apply to products approved prior to June 30, 2001, manufacturers of such products may voluntarily comply with the new regulation.

B. New Labeling Requirements

The new requirements are detailed and extensive. Some of the key features include the following:

“Highlights” Section: Labeling must include introductory information entitled “Highlights of Prescribing Information,” limited to one-half page (absent an FDA waiver).¹⁰ The Highlights section is intended to be a brief summary of key safety and effectiveness information. Specific rules govern the content and format of the Highlights section. For example, the Highlights must include the year in which the drug was initially approved in the United States, a condensed version of any boxed warning (no more than 20 lines), a section on recent major labeling changes,¹¹ contact information for adverse event reporting, and select information on indications and usage, warnings and precautions, and other sections of the full prescribing information. If a product has a boxed warning, it must appear in both the Highlights (in summary form) and in the full prescribing information.¹² With respect to warnings and precautions, FDA noted that the Highlights section should identify the most clinically significant risks and concisely summarize the salient features of those risks.¹³ The Highlights section must also cross-reference the full prescribing information indicating where more detailed information can be found¹⁴

Although several comments requested that FDA provide specific criteria for selecting information for inclusion in the Highlights section, the agency took the position that “it would not be appropriate, or possible, to specify in the final rule the precise content of Highlights.” Rather, “[j]udgment will continue to be necessary to determine what information” should appear in the Highlights section of the labeling.¹⁵ Prior approval supplements will be required to change the Highlights information except for certain minor changes.

Table of Contents: In addition to cross-references in the Highlights section, the new rule also requires a table of contents for the full prescribing information, entitled “Full Prescribing Information: Contents.”¹⁶ The Contents section is required to list all of the headings and subheadings required under the rule. FDA noted that the “Highlights and Contents both figure prominently in FDA’s plans to convert prescription drug labeling to electronic format.”¹⁷ The agency suggested that once in electronic format, the Contents could provide hyperlinks to the sections of the full prescribing information.¹⁸

⁹ *Id.* at § 201.56(e); labeling requirements for “older” drugs are now codified at 21 C.F.R. § 201.80, which contains the requirements previously found in § 201.57.

¹⁰ 71 Fed. Reg. at 3930; 21 C.F.R. § 201.57(a).

¹¹ The rule requires that labeling changes must be identified by the month and year that the change was incorporated into the labeling. 71 Fed. Reg. at 3938; 21 C.F.R. § 201.57(a)(5). The rule also requires that a reference to a labeling change be deleted at the first reprinting of the labeling after the change has been in the labeling for one year. *Id.*

¹² 71 Fed. Reg. at 3937; 21 C.F.R. §§ 201.57(a)(4), 201.57(c)(1).

¹³ 71 Fed. Reg. at 3939; 21 C.F.R. § 201.57(a)(10).

¹⁴ 21 C.F.R. § 201.56(d)(3).

¹⁵ 71 Fed. Reg. at 3932.

¹⁶ 71 Fed. Reg. at 3941; 21 C.F.R. § 201.57(b).

¹⁷ 71 Fed. Reg. at 3941.

¹⁸ *Id.*

Full Prescribing Information: Although the new rule retains the content of most sections of current prescription drug labeling, the new rule reorders many of the sections and clarifies several issues related to their content. The final rule requires the sections of the labeling to be ordered in the following manner:¹⁹

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

The final rule also makes changes to specific sections of the full prescribing information. For example, Warnings and Precautions will appear as a single section, and Drug Interactions and Use in Specific Populations will appear as distinct sections.²⁰ Other significant aspects of the final rule include the following:

- FDA retained the existing definition of an “adverse reaction” for purposes of labeling, but clarified that adverse reactions include only those adverse events for which there is some basis to believe that there is a causal relationship between the event and the drug.²¹
- The final rule requires that the Warnings and Precautions section include adverse reactions that may not meet the regulatory definition of “serious,”²² but nonetheless have a significant impact on clinical use of the drug. The agency acknowledged that “the inclusion of less serious but clinically significant adverse reactions may add to the overall length of the ‘Warnings and Precautions’ section,” but nevertheless believes that it appropriate to require the inclusion of “nonserious adverse reactions ... that have significant impact on therapeutic decisionmaking.”²³
- FDA dropped its proposed use of special symbols in the labeling such as an inverted black triangle to signal a drug that has been on the market for three years or less, or an exclamation point to call attention to a boxed warning.²⁴
- FDA dropped its proposal to exclude in vitro data from labeling for anti-infectives that are not supported by clinical data, and stated that it will consider the issue further.²⁵
- The Clinical Studies section must describe those studies that facilitate an understanding of how to use a drug safely and effectively. If studies were “appropriately designed,” secondary endpoints such as quality of life and pharmaco-economic data will be permitted in the Clinical Studies section.²⁶

¹⁹ 21 C.F.R. § 201.56(d)(1).

²⁰ 21 C.F.R. §§ 201.57(c)(6), 201.57(c)(8)-(9).

²¹ 71 Fed. Reg. at 3948-49.

²² See 21 C.F.R. § 312.32(a).

²³ 71 Fed. Reg. at 3946.

²⁴ *Id.* at 3925.

²⁵ *Id.* at 3927; 21 C.F.R. § 201.57(c)(13)(ii).

²⁶ 71 Fed. Reg. at 3953.

- The preamble included discussion about when information from clinical studies on indications and dosing that are not consistent with the Indications and Usage or the Dosage and Administration sections of the labeling may be presented, although ambiguity remains. FDA stated that the requirement for substantial evidence “would not preclude discussing in labeling an adequate and well-controlled clinical study, including a dose ranging study that has treatment arms with dosing regimens that are not recommended, if the data for the use of regimens are important to a practitioner’s understanding of how to use the drug safely and effectively.”²⁷ If such data is presented, it must be accompanied by a statement indicating that those dosage regimens have not been found safe and effective by FDA.²⁸

Patient Labeling: FDA revised the proposed requirement that FDA-approved patient labeling must be reprinted at the end of the professional labeling to allow patient labeling to either accompany the professional labeling or to be reprinted at the end of such labeling.²⁹

Formatting: The rule sets forth specific and detailed requirements for the format and font size of labeling. Labeling must use (at minimum) a 6-point font for trade labeling, 8-point for labeling accompanying promotional materials, and 10-point for medication guides to be distributed to patients.³⁰ The rule also has specific requirements for the use of subheadings, bolding, centering, horizontal lines, and vertical lines.³¹ It is likely that these requirements will significantly increase the length of most package inserts.

In addition to the specific requirements set forth in the proposed rule, FDA emphasized that sponsors have an ongoing obligation to act to correct labeling that, in light of new information, has become inaccurate.

III. Preemption and Product Liability

In its proposed rule, FDA specifically requested comments on the product liability implications of the new requirements.³² Several comments expressed a concern that the new requirements could be used by plaintiffs as evidence that labeling in the prior format did not provide adequate warnings. These comments requested that FDA state in the final rule that FDA approval of labeling, whether in the old format or the new, preempts conflicting state law, regulations, or court decisions.³³ In response, the preamble to the final rule contains extensive commentary on product liability issues and sets forth a strong case for the preemptive effect of FDA labeling determinations on conflicting state law requirements, whether arising by statute or administrative rule, or through product liability actions.³⁴ These statements are the most formal and (arguably) far-reaching policy statements by FDA to date on the preemptive effective of its labeling regulations.

FDA emphasized that the views set forth on preemption represent “the government’s long standing views,”³⁵ as set forth in amicus briefs filed in litigation and in prior rulemaking proceedings such as the regulations on tamper-resistant packaging for over-the-counter products³⁶ and the Reye’s Syndrome warning for aspirin.³⁷

²⁷ *Id.*

²⁸ *Id.*

²⁹ 71 Fed. Reg. at 3954; 21 C.F.R. § 201.57(c)(18).

³⁰ 71 Fed. Reg. at 3955; 21 C.F.R. §§ 201.57(c)(18), 201.57(d)(6).

³¹ 71 Fed. Reg. at 3956-58; 21 C.F.R. § 201.57(d).

³² As FDA explained, the agency was required to consider preemption issues under Executive Order 13132, which requires agencies to construe a federal statute to preempt state law only under enumerated circumstances. 71 Fed. Reg. at 3967.

³³ *Id.* at 3933-34

³⁴ *Id.* at 3933-36.

³⁵ *Id.* at 3934.

³⁶ See 47 Fed. Reg. 50442, 50447 (November 5, 1982).

³⁷ See 51 Fed. Reg. 8180, 8181 (March 7, 1986); see also 47 Fed. Reg. 54750 (January 27, 1994) (amending 21 C.F.R. § 20.63 to preempt state requirements for the disclosure of adverse event-related information that is treated as confidential under FDA regulations).

FDA began its discussion by stating unequivocally that “FDA believes that under existing preemption principles, FDA approval of labeling under the act, whether it be in the old or new format, preempts conflicting or contrary State law.”³⁸ The agency emphasized that “FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective.”³⁹ “The centerpiece of risk management for prescription drugs generally is the labeling which reflects thorough FDA review of pertinent scientific evidence and communicates to health care practitioners the agency’s formal, authoritative conclusions regarding the conditions under which product can be used safely and effectively.”⁴⁰ State laws that are inconsistent with FDA labeling decisions have the result of undermining FDA’s public health role. “FDA has learned of several instances in which product liability lawsuits have directly threatened the agency’s ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act.”⁴¹ FDA cited as an example a California case seeking specific warnings that FDA had considered and rejected.⁴² Such state law actions “conflict with the agency’s own interpretations and frustrate the agency’s implementation of its statutory mandate.”⁴³

FDA specifically addressed the argument -- frequently advanced in product liability lawsuits -- that FDA-required warning information represents only a minimum standard and labeling should include additional or stronger warnings in order to warn patients appropriately. FDA rejected this argument, calling such a view a “misunderstanding of the act.”⁴⁴ “In fact, FDA interprets the act to establish both a ‘floor’ and a ‘ceiling,’ such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading.”⁴⁵ State law requirements can create pressure to expand labeling warnings to include speculative risk and thereby undermine the usefulness of the labeling information. Additional warnings required by state law or court decisions “are not necessarily more protective of patients. Instead, they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use.”⁴⁶

FDA also rejected the idea that manufacturers are free to make changes to risk information without FDA approval. Although existing labeling regulations provide that manufacturers can amend warnings in labeling in limited circumstances, FDA must ultimately approve any such changes or they must be immediately removed. For this reason, “in practice manufacturers typically consult with FDA before doing so to avoid implementing labeling changes with which the agency ultimately might disagree (and that therefore might subject the manufacturer to enforcement action).”⁴⁷

Based on these principles, FDA stated that it believes that at least the following claims would be preempted by its regulation of prescription drug labeling:

1. Claims that a drug sponsor breached an obligation to warn by failing to put in Highlights or otherwise emphasize any information the substance of which appears anywhere in the labeling;
2. Claims that a drug sponsor breached an obligation to warn by failing to include in an advertisement any information the substance of which appears anywhere in the labeling (where the sponsor follows FDA guidance on disclosing risk information in direct-to-consumer advertising);

³⁸ 71 Fed. Reg. at 3934.

³⁹ *Id.*

⁴⁰ *Id.*

⁴¹ *Id.*

⁴² *Dowhal v. SmithKline Beecham Consumer Healthcare*, 2002 Cal. App. LEXIS 4384 (Cal. Ct. App. 2002), rev'd, 2004 Cal. LEXIS 3040 (Cal. April 15, 2004).

⁴³ 71 Fed. Reg. at 3934.

⁴⁴ *Id.*

⁴⁵ *Id.* at 3935.

⁴⁶ *Id.*

⁴⁷ *Id.* at 3934.

3. Claims that a sponsor breached an obligation to warn by failing to include contraindications or warnings that are not supported by evidence that satisfies FDA's standards;
4. Claims that a drug sponsor breached an obligation to warn by failing to include a statement in labeling or advertising, the substance of which had been proposed to FDA for inclusion in labeling, if that statement was not required by FDA at the time plaintiff claims the sponsor had an obligation to warn (absent an FDA finding of fraud on the part of the sponsor);
5. Claims that a drug sponsor breached an obligation to warn by failing to include in labeling or in advertising a statement the substance of which FDA has prohibited in labeling or advertising; and
6. Claims that a drug's sponsor breached an obligation to plaintiff by making statements that FDA approved for inclusion in the drug's label (absent an FDA finding of fraud on the part of the sponsor).⁴⁸

Furthermore, FDA stated that preemption extends not only to the drug manufacturers, but also to healthcare practitioners for claims related to the dissemination of risk information to patients beyond what is included in the labeling.

The ultimate legal weight and import of these statements on preemption in product liability cases remains to be seen. FDA has made many of these arguments in amicus briefs in individual cases, but never in the context of formal agency rulemaking. The Supreme Court has stated that a federal agency's views on preemption are entitled to some deference, given that the "agency is likely to have a thorough understanding of its own regulation and its objectives and is 'uniquely qualified' to comprehend the likely impact of state requirements."⁴⁹ Moreover, courts give greater weight to agency policies that are expressed in formal, prospective agency action, rather than in informal policy statements or individual adjudication.⁵⁰

Although FDA's statements on preemption appear in the preamble and not in the regulations, these statements represent a formal statement of agency policy adopted in the context of notice and comment rulemaking.⁵¹ Moreover, FDA's discussion on preemption is extensive and includes a specific legal and policy rationale for why FDA's labeling determinations preempt. Given FDA's scientific expertise and knowledge of the impact of inconsistent state laws, now coupled with a formal policy statement regarding preemption, it is possible that courts will be increasingly receptive to arguments that inconsistent requirements related to drug labeling are preempted.

⁴⁸ *Id.* at 3935-36.

⁴⁹ *Geier v. Am. Honda Motor Co., Inc.*, 529 U.S. 861, 883 (2003), quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 496 (1996).

⁵⁰ *United States v. Mead Corp.*, 533 U.S. 218, 228 (2001) ("The fair measure of deference to an agency administering its own statute has been understood to vary with circumstances, and courts have looked to the degree of the agency's care, its consistency, formality, and relative expertness, and to the persuasiveness of the agency's position...").

⁵¹ Under FDA's regulations, preamble statements constitute advisory opinions and represent the formal position of FDA on a matter. 21 C.F.R. § 10.85(d)(1) & (e). Advisory opinions are not, however, legal requirements. 21 C.F.R. § 10.85(k).

If you would like further information about FDA's new labeling rule or would like to discuss its implications for your company, please contact any of the below attorneys.

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This information is not intended as legal advice, which may often turn on specific facts. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:

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