CLIENT ALERT

ROPES & GRAY

LIFE SCIENCES February 3, 2006

New FDA Rules on Prescription Drug Labeling

On January 24, 2006, the FDA published a final rule revising the requirements for prescription drug and biological product labeling. 71 Fed. Reg. 3922. Although there are some significant changes to the labeling provisions of the regulations, perhaps even more significant are the preemption policies emphatically announced by FDA in the preamble to the regulation. Here we provide a brief overview of the substantive changes to the labeling requirements and summarize the preemption policy.

FDA provides more information on this rule, including links to two draft guidance documents and two final guidance documents discussing specific portions of the rule, at http://www.fda.gov/bbs/topics/news/2005/NEW01272.html.

I. Labeling Revisions

The rule revises the regulations governing the content and format of drug product labeling (often called the "package insert" or "PI") for "newer" drugs - those prescription drugs approved on or after June 30, 2006 (the effective date of the final rule), prescription drugs that had been approved in the five years before June 30, 2006, and older approved drugs for which an efficacy supplement is submitted. These requirements will be found in 21 CFR §§ 201.56 and 201.57.

The rule also makes certain minor changes to the labeling for older prescription drug products (those approved more than five years before June 30, 2006). The revised labeling requirements applicable to older products will be found in § 201.80, and remain largely the same as the requirements in the current § 201.57.

The revisions will need to be implemented in accordance with the following timetable:

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
Application submitted on or after June 30, 2006	Time of submission
Applications pending on June 30, 2006 and applications approved 0 to 1 year before June 30, 2006	June 30, 2009
Applications approved 1 to 2 years before June 30, 2006	June 30, 2010
Applications approved 2 to 3 years before June 30, 2006	June 30, 2011
Applications approved 3 to 4 years before June 30, 2006	June 30, 2012
Applications approved 4 to 5 years before June 30, 2006	June 30, 2013
Applications approved more than 5 years before June 30, 2006	Voluntarily at any time

II. Revisions applicable to newer drugs:

FDA has reordered and reorganized information presented in the PI, with an emphasis on streamlining risk information, eliminating repetition, and increasing usability to health care practitioners. The new contents include:

Highlights of Prescribing Information
- Product Names, Other Required Information
- Boxed Warning
- Recent Major Changes
- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations

Full Prescribing Information: Contents

Full Prescribing Information
Boxed Warning
1 Indications and Usage
2 Dosage and Administration
3 Dosage Forms and Strengths
4 Contraindications
5 Warnings and Precautions
6 Adverse Reactions
- • Listing and Categorization
  - - Clinical Trials Experience
  - - Postmarketing Experience

7 Drug Interactions
8 Use in Specific Populations
- 8.1 Pregnancy
- 8.2 Labor and delivery
- 8.3 Nursing mothers
- 8.4 Pediatric use
- 8.5 Geriatric use

9 Drug Abuse and Dependence
- 9.1 Controlled substance
- 9.2 Abuse
- 9.3 Dependence

10 Overdosage
11 Description
12 Clinical Pharmacology
- 12.1 Mechanism of action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 Nonclinical Toxicology
- 13.1 Carcinogenesis, mutagenesis, impairment of fertility
- 13.2 Animal toxicology and/or pharmacology

14 Clinical Studies
15 References
16 How Supplied/Storage and Handling
17 Patient Counseling Information

The labeling revisions for newer drugs include several general changes. FDA has added a half-page introductory section, "Highlights of Prescribing Information," to the beginning of each label. This section will include the date of initial US approval for the drug product, a subsection titled "Recent Major Changes" that will detail one year's worth of changes to the label, and summaries of the primary labeling sections. Manufacturers will also be required to include the following limitation statement at the end of the Highlights section: "These highlights do not include all the information needed to use [drug] safely and effectively. See full prescribing information for [drug]." FDA's draft guidance document on implementing the new format[1] provides more details regarding the items to be included in the Highlights section.

FDA has also added a Contents section to appear immediately following the Highlights section. The agency envisions that these two sections will serve as a roadmap to the information in the rest of the PI for health care practitioners. Finally, there is now a required Patient Counseling Information section at the conclusion of the PI.

[1] Draft guidance available at http://www.fda.gov/OHRMS/DOCKETS/98fr/05d-0011-gdl0001.pdf.

The labeling revisions also include some more specific changes to certain sections of the document. A brief overview of the more significant of these changes is given below.

Indications and Usage. If there is a common off-label usage for a product but the preponderance of the evidence shows that the drug is ineffective or the risks outweigh the benefits for that usage, FDA may require that this section state that there is a lack of evidence that the drug is safe or effective for that condition. FDA also states very clearly that indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

This theme - that indications and uses must not be implied elsewhere if not included in Indications and Usage - recurs with some frequency throughout the new regulations. This change probably means that companies may no longer promote from the clinical pharmacology portion of the label.

Contraindications. "Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication)." This insistence on not including theoretical possibilities in the PI is another theme repeated throughout the revised regulations. The threat of state products liability lawsuits has pushed companies in recent years to include theoretical risks in a drug's label; the tightening announced should be read in conjunction with FDA's newly announced preemption policy.

Warnings and Precautions. FDA may require a specific warning relating to a common off-label use if that use is associated with a clinically significant risk or hazard.

Adverse Reactions. Adverse reactions that occurred during clinical trials will be listed separately from adverse reactions occurring after approval. FDA states that any comparisons of adverse reactions between drugs must be based on adequate and well-controlled studies. FDA has also modified the adverse reaction definition by "making clear that the section applies only to 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." FDA has made it clear that characterizing adverse events as frequent, infrequent, or rare is no longer permissible, and that adverse events should be expressed by percentages.

Use in Specific Populations. Five different specific populations - pregnancy, labor and delivery, nursing mothers, pediatric use, and geriatric use - must be addressed in each label. The regulations list template language to be used in the pediatric use and geriatric use sections of the label, probably so that the boundaries of the clinical experience in those populations will be clear across products.

Drug Abuse and Dependence. If there is a drug abuse potential for a drug, the PI will need to discuss, among other things, whether the drug is a controlled substance, the types of abuse and resulting adverse reactions that might occur, and methods of recognizing, diagnosing, and treating drug dependence.

Clinical Pharmacology - Pharmacokinetics. Except for anti-infectives, manufacturers may not include data that demonstrate activity or effectiveness in *in vitro* or animal tests and that have not been shown by adequate and well-controlled clinical studies to be pertinent to clinical use unless FDA grants a waiver from this prohibition.

Clinical Studies. This section must discuss in detail any study that is referenced anywhere else in the PI. Any study discussed in the labeling that relates to an indication or use of the drug must not imply or suggest indications or uses or dosing regimens not stated in the Indications and Usage or Dosing sections. Any study discussed that relates to a risk must also refer to the other sections of the labeling where the risk is identified or discussed.

FDA will evaluate whether it is appropriate for a manufacturer to include secondary endpoints, like quality of life or pharmacoeconomic data, in the clinical studies section by using the following criteria:

- Whether the data are from adequate and well-controlled trials that incorporate quality of life or pharmacoeconomic endpoints in their design and carry out appropriate analyses.
- Whether, for pharmacoeconomic studies, the findings are reasonably generalizable to most clinical environments, not just the ones studied.
- Whether the information would be important to a practitioner's understanding of how to use the drug in a clinical setting.

Patient Counseling Information. This section must contain information necessary for patients to use the drug safely and effectively (*e.g.*, precautions concerning driving or the concomitant use of other substances that may have harmful additive effects). The text must reference any FDA-approved patient labeling and that patient labeling must be either printed following this section or accompany the prescription drug labeling.

III. Preemption of state law by FDA regulation

FDA received various comments from manufacturers concerned about possible product liability implications of the revisions of the regulations. In response, and also in addressing the federalism implications of the rule, FDA made a sweeping policy statement regarding federal preemption of state law in the area of drug regulation. Expanding on a position already taken by the government in litigation, the agency states that "FDA believes that under existing preemption principles, FDA approval of labeling under the act . . . preempts conflicting or contrary State law."

The concrete safety and efficacy evaluation performed by FDA prior to approval of any drug - an evaluation that includes both complex clinical issues and practical public health issues - is the basis of the FDA-approved label, which then serves as "the principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use." As stated by the agency,

> If State authorities, including judges and juries applying State law, were permitted to reach conclusions about the safety and effectiveness information disseminated with respect to drugs for which FDA has already made a series of regulatory determinations based on its considerable institutional expertise and comprehensive statutory authority, the federal system for regulation of drugs would be disrupted.

Consistent with its court submissions and existing preemption principles, FDA believes that at least the following claims would be preempted by its regulation of prescription drug labeling:

- Claims that a drug sponsor breached an obligation to warn by failure to put in Highlights or otherwise emphasize any information the substance of which appears anywhere in the labeling;
- 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, in those cases where a drug's sponsor has used Highlights consistently with FDA draft guidance regarding the "brief summary" in direct-to-consumer advertising.
- Claims that a sponsor breached an obligation to warn by failing to include contraindications or warnings that are not supported by evidence that meets the standards set forth in the rule, including the requirement that contraindications reflect "known hazards and not theoretical possibilities;"

- Claims that a drug sponsor breached an obligation to warn by failing to include a statement in labeling or in advertising, when the substance of that statement had been proposed to FDA but was not required to be included in the label by FDA;
- 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
- Claims that a drug's sponsor breached an obligation to plaintiff by making statements that FDA approved for inclusion in the drug's label.

Preemption would include not only claims against manufacturers, but also against health care practitioners for claims related to dissemination of risk information to patients beyond what is included in the labeling. FDA recognizes that not all state law actions will be preempted, such as certain state law requirements that parallel FDA requirements. However, FDA has made a clear statement that, in those product liability situations that are most meaningful to the industry, FDA has occupied the field.

Although preamble statements are not binding, courts do look to preambles to discern the agency's interpretations of its own regulatory power and have recognized preambles as appropriate vehicles for announcing the scope of preemption. As Justice Breyer stated in a concurring opinion in *Medtronic, Inc. v. Lohr*,

> in the absence of a clear congressional command as to pre-emption, courts may infer that the relevant administrative agency possesses a degree of leeway to determine which rules, regulations, or other administrative actions will have pre-emptive effect. . . . It can communicate those intentions [to preempt state law], for example, through statements in 'regulations, preambles, interpretive statements, and responses to comments'. . . .

518 U.S. 470, 505-06 (1996) (concurring in part and concurring in the judgment) (internal citations omitted). The prospect of FDA's preemption of state law precluding the pursuit of products liability lawsuits against drug manufacturers or health care providers for failure-to-warn claims will most likely, however, lead to challenges to FDA's authority to announce preemption of state law.

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