FDA's new drug labeling format: opportunity and challenge

For the first time in more than 25 years, the Food and Drug Administration (FDA) is overhauling the format and content of prescription drug labels. Since the 1970s, drug labels – often referred to as the package insert – have expanded in length, detail and complexity. FDA concluded that the increasingly cluttered label hampered communication of risk information and suffered from 'over-warning' of clinically insignificant and often unsubstantiated risks.

By **Jayne Bultena**

Billed as a move to make drug labeling more readable, concise and useful for healthcare practitioners and patients, January 2006 saw the agency issue a final rule requiring companies to dramatically reorganize current elements of the package insert, include new information and eliminate unnecessary or redundant information. Key provisions of the new rule include allowing voluntary and phased-in compliance for many products, adding a 'highlights' section at the beginning of the package insert summarizing key safety and effectiveness information, and modifying the definition of 'adverse reaction' to pare down unnecessary information. These changes apply immediately to new drugs and on a staggered schedule over the next seven years for recently approved drugs (those approved within the last five years), but are voluntary for older products. Submission of an efficacy supplement (whether for a recently approved or older drug) triggers immediate compliance with the new format and content requirements.

In response to industry concerns about increased product liability risk caused by the new rule's requirement to select information for inclusion in the highlights section and trim the exhaustive lists of adverse reactions, FDA included in the preamble a statement asserting that failure-to-warn claims should be preempted. Because preamble language is considered merely 'advisory', the agency's preemption statement does not have binding legal effect. Nonetheless, courts are expected to take notice of the agency's opinion, but it is unclear what deference it will receive.

As drug and biologic companies begin to grapple with the nuances of these new requirements, they will find that the labeling rule presents both opportunities and challenges. Some of these opportunities and challenges are described below.

Choice of format and timing of conformance

Except for products submitted after June 30, 2006 (the rule's effective date), the long implementation phase-in allows at least three years for conformance to the new format. This lag will allow manufacturers to evaluate the merits of retaining the old format versus conforming with the new format sooner than required. It will also allow time to test the preemption provision in litigation.

In addition, submission of an efficacy supplement that triggers compliance with the new format might create format distinctions within a class of products. For example, 'old' products with mature labeling may continue to use existing labeling while newer competitors submitting supplements to 'catch up' to the labeling of others in a class will need to use the new format.

Finally, manufacturers of approved products may prefer to retain labeling in the old format as long as possible. For some products, conformance with the new format may emphasize labeled information in a way that creates a competitive disadvantage.

'First mover' advantage

A manufacturer may gain advantage by being the first among competitors to adopt the new format, either by conforming to the new format earlier than required, or voluntarily if not required at all. As with similar labeling initiatives – such as the nutrition label and OTC Drug Facts – the new prescription drug format may gain such acceptance that products without it are at a competitive disadvantage, especially if prescribers and patients make treatment decisions based in part on preference for the new format.

In addition, given that the agency intends many class labeling issues to be determined on a case-by-case basis, a sponsor may gain an advantage by being the first in class to negotiate labeling in the new format. That said, it is not clear how FDA will treat a new application with class labeling that is also found in the labeling of older products. It is possible that this process could result in different treatment of the class labeling depending on the format used.

Impact on labeling negotiations

Developing labeling in the new format – either as part of a new submission or in conforming old labeling to the new requirements – will likely involve protracted negotiations with FDA. Conversion to the new format will necessarily focus agency scrutiny on the sponsor's methods, criteria, data and analysis of risk information, and the sponsor's subsequent decisions concerning inclusion, exclusion, characterization and location of that information in labeling. This situation is likely to prolong labeling negotiations.

Impact on black box warnings

FDA's draft guidance on warnings notes that a boxed warning may still be appropriate even though risk information in the new format will be concentrated in the highlights section. However, recently an FDA advisory committee suggested that the ability to highlight warnings under the new labeling rule might obviate the need for a black box warning.

Committee members and FDA officials reviewing adverse events associated with drugs used to treat ADHD, for example, noted that the motivation to require a black box to ensure that prescribers will see the information 'upfront' is satisfied by inclusion in the highlights section. They also noted that the highlights section allowed this important risk information to be placed in context with other information, such as contra-indications and precautions, necessary to manage risks. If the agency embraces this rationale, sponsors may find support for utilizing this method of conveying certain types of risk information that otherwise would have earned a black box.

Impact on marketing

Despite industry's initial hesitation to support the requirement for a highlights section, it offers an advantage in marketing. FDA advertising guidance suggests that manufacturers use the highlights section as an alternative to the patient package insert in the 'brief summary' in print advertisements.

Changing the content and ordering of risk information to conform to the new format, however, may affect the presentation of risk information in direct-to-consumer advertising. Moreover, in the guidance documents accompanying the labeling rule, FDA suggests avoiding imprecise and vague terms – such as 'rare', 'well-designed' or 'trend' – in describing adverse reactions or clinical trials. This advice may mean that such terms will be viewed as misleading or promotional in tone if used in other contexts, such as advertisements, press releases and SEC statements. Finally, it is not clear whether or how information on unapproved uses included in the clinical studies section of labeling can be used, and whether any reference to it must be accompanied by the disclaimer that the use is not approved by FDA.

Implications of preamble statement on preemption

It is too early to predict the implications of FDA's preamble statement on preemption. Generally, courts have been unwilling to find preemption absent an explicit statutory provision or clear conflict between state and federal requirements. FDA's preamble statement will need to be tested in litigation to determine its impact.

Until then, the impact on the product liability risk of manufacturers who choose to modify existing labeling to conform to the new format is unclear. While there may be additional liability in that plaintiffs may bring failure-to-warn cases based on information deleted or given less emphasis in accordance with the new requirements, it is clear there may also be benefits from moving to a state-of-the-art labeling format. ■

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