



Office of  
General Counsel

One Johnson & Johnson Plaza  
New Brunswick, N. J. 08933-7002

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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

**Re: Dockets Nos. 2005D-0011 and 2000N-1269**

On January 24, 2006, FDA released its final rule on Content and Format of Labeling for Human Prescription Drug and Biological Products. That rule called for further comments to be filed on related FDA draft guidances, including: "Implementing the New Content and Format Requirements" and "Warnings and Precautions, Contraindications, and Boxed Warnings." On behalf of the Johnson & Johnson Family of Companies ("J&J"), comments on those guidances are attached.

J&J is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical and medical devices and diagnostics markets. J&J has more than 200 operating companies in 54 countries around the world employing approximately 110,600 employees and selling products in more than 175 countries. The fundamental objective of J&J is to provide scientifically sound, high quality products and services to help heal, cure disease and improve the quality of life.

Before turning to the specific attached comments to the guidances, J&J would like to applaud FDA on its publication of the new labeling rule for prescription drug products. The core substance of the rule – the reordering and reorganization of information presented in pharmaceutical product information labeling – clearly accomplishes the stated goals of streamlining risk information, eliminating repetition, and increasing useability to health care practitioners. Additionally, FDA has addressed certain issues related to labeling in the preamble to the rule, in particular preemption, in a manner that makes the issues both more predictable and more rational for patients, health-care providers, and manufacturers alike. In short, J&J is highly supportive of the new rule and the newly announced accompanying policies. Below are comments on items the company considers especially timely or relevant.

Highlights. The new organization for prescription drug information is more coherent and more useful than the previous regulations, and echoes the positive changes that the Agency has already made for both OTC drug and food labels – more specifically, these new labeling

requirements serve the same informational needs as the “Drug Facts” and “Nutrition Facts” boxes found on OTC drug and food products. In particular, the inclusion of the “Highlights of Prescribing Information” section at the beginning of the labeling will – as the name suggests – ensure that the most important information from the labeling is presented up front for the health care practitioner.

Furthermore, inclusion of the Highlights section should serve to continue to ensure appropriate use of boxed warnings. In effect, the Highlights - by providing a new vehicle to present important information first in summarized form – represents an additional option in terms of risk communication in the appropriate circumstances. This provides more opportunity for boxed warnings to be used only when they are needed, which is an important public health benefit.

Balancing of Benefits and Risks. As FDA has long known, no prescription drug is either 100% safe or 100% effective. The balancing of benefits and risks is at the heart of every approval decision by the Agency and, indeed, at the heart of every prescribing decision by a health care practitioner. The new labeling rule not only embodies this important concept but also facilitates it in practice. In prescribing any drug, health care practitioners must weigh not only the benefits against the risks of the drug in the context of a particular patient but also undertake a similar balance with respect to alternative therapies or even non-treatment. The new regulations structure the labeling to facilitate this weighing of benefits and risks by presenting the information most relevant to that analysis early on in the labeling. First, as discussed above, the Highlights section is an excellent addition to the labeling that will facilitate the benefit-risk analysis. Second, in the body of the labeling, practitioners will first see indication and dosage information, then review warnings, precautions, adverse reactions and drug interactions – the items of most significance to health care practitioners in gauging what the benefits and risks of the drug might be for any particular patient.

In its Federal Register notice, FDA emphasizes that the risks stated in the labeling, in the contraindications section in particular, should be real and demonstrated risks, not theoretical ones. J&J agrees that limiting the risk and contraindication information included in the labeling to “known hazards and not theoretical possibilities” assists health care practitioners by giving them more accurate risk information to use in their balancing of benefits and risks. When manufacturers are obligated to include theoretical risks in their labeling, the theoretical risks may serve to obscure and minimize the known risks associated with the product, which could affect the practitioner’s benefit-risk analysis.

In re-structuring the labeling to emphasize the information that must be used in balancing benefit and risk, FDA has made a positive step towards a more realistic perspective on prescription drugs generally. The terms “safety” and “efficacy” are less useful in the context of a practitioner’s decision whether or not to prescribe a certain drug or to a patient’s understanding of that decision, because no drug is completely safe. The restructuring of the labeling appropriately moves the focus towards the balancing of benefits and risks, and away from the more absolute language of “safety.”

Inclusion of ‘Off-Label’ Prompts or Information in the Labeling. In several places in the new regulation, it appears that FDA may be attempting to provide guidance that bears on claims that might be considered off-label or misleading. For example, FDA notes that no indication or use for a prescription product may be implied anywhere else in the labeling if it does not appear in the “indications and usage” section of the labeling. Additionally, FDA notes that data demonstrating efficacy *in vitro* or in animals may not be included in the labeling unless FDA grants a waiver. And finally, FDA sets out criteria for determining whether it is appropriate for manufacturers to include secondary endpoints in the labeling. In applying these criteria, FDA should consider the importance of providing the most complete, accurate, and meaningful scientific evidence for the prescriber. The topic of off-label use has become fraught with uncertainty given the numerous state and federal entities outside of FDA that continue to stake positions on the subject in a variety of contexts, including enforcement. J&J urges FDA as the expert public health agency charged with regulating prescription drugs to authoritatively provide further clarity in this area. And that in doing so it take into account the public health benefits of the availability of complete and accurate information regarding prescription drugs.

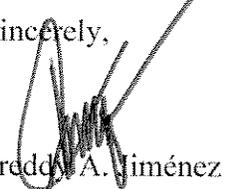
For drugs that are often prescribed for off-label uses by health care practitioners, FDA may require that information related to that off-label use be included in the package insert. FDA notes that it may require that the indications and usage section state that there is a lack of evidence that a drug is safe or effective for a particular, common off-label use if a preponderance of the evidence demonstrates that the risks outweigh the benefit for that usage. FDA also notes that the Agency may require a specific warning related to a common off-label use if that use is associated with a clinically significant risk or hazard. While these are reasonable goals, it is important to note that all of the other information included in an innovator’s labeling stems from data scrutinized by the innovator; the data that FDA uses to conclude that these statements are necessary may not be available to the innovator. Although each of these statements may serve a useful purpose in informing prescribers, the Agency should implement these requirements in a very considered and consistent manner, again taking into account the public health benefits of the availability of complete and accurate information regarding prescription drugs. In particular, FDA should consult early and extensively with the innovator when considering inclusion of this kind of statement in a labeling.

Patient Counseling Information and DTC Advertising. The new labeling requirements set forth quite clearly the set of information that must be conveyed to health care practitioners via the labeling; the regulations also include a section on patient counseling information, denoting that information that it is most important for a prescriber to convey to a patient. In this context, it is worth noting that current FDA guidance on direct-to-consumer advertising is less concise, allowing companies a number of different options for satisfying the requirement that a company make “adequate provision . . . for dissemination of the approved or permitted package labeling.” 21 § C.F.R. 202.1. Now that the labeling has been revised, and is becoming a much more useful tool to consumers, J&J respectfully suggests that FDA consider amending its regulations to identify with specificity the best way or ways to provide the labeling information directly to consumers, in particular with regard to the “adequate provision” requirements for DTC ads. If FDA requires dissemination of the labeling to consumers in a consistent and effective manner,

the better techniques of communicating important information set forth in the rule will be enhanced even further.

In summary, J&J believes FDA's new labeling regulations are a positive development for prescribers, consumers, and manufacturers alike.

Sincerely,



Freddy A. Jiménez  
Assistant General Counsel  
Johnson & Johnson

Attachments