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ASSISTANT GENERAL COUNSEL



September 19, 2000

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

RE: Docket No. 00D-1306; FDA Draft Guidance for Industry on the Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologicals (65 *Federal Register* 38563, June 21, 2000)  
**Need to Modify Existing Regulation, Rather than Issue Guidance**

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing \$26 million in 2000 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

FDA has issued a draft guidance, "Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics." The *Federal Register* notice indicates that this is one of several anticipated guidances that focus on sections of the labeling of prescription drugs. This draft guidance was developed by a CDER committee in conjunction with staff at CBER.

While FDA indicates that the draft guidance is consistent with FDA's Good Guidance Policy, PhRMA believes that FDA is inappropriately using a guidance document to announce what amounts to changes in the current regulations governing the content of physician labeling for prescription drugs. Therefore, PhRMA urges FDA to withdraw the draft guidance, or at least those sections that conflict with the current regulations, and instead proceed through notice and comment rulemaking to modify the existing regulation.

First, some portions of the draft guidance conflict with provisions in the regulation that governs the preparation of the physician labeling, 21 CFR 201.57. The requirements are grounded in the statute, section 502 of the Food, Drug, and Cosmetic Act. For example, the draft guidance sets forth a very specific format for the presentation of adverse event information (Guidance p.2), but that format differs from the format required by the regulation (21 CFR 201.57(g)).

Second, the draft guidance adds some requirements for labeling that are not in the regulation. For example, the draft guidance proposes that the adverse reaction section

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contain an OVERVIEW section that is not required by the existing regulation. In addition, the draft guidance states that "serious adverse reactions that are unusual in the absence of drug therapy ... should be included in labeling even if there are only one or two reported events." (Guidance p. 6) The regulation, however, does not contain any similar requirement. Thus, the draft guidance is adding requirements, rather than setting forth one way by which sponsors can meet existing requirements.

Third, the number of issues raised in PhRMA's substantive comments on the contents of the draft guidance illustrate why these changes should be made through modification of the existing regulation for the incorporation of adverse event information in prescription drug labeling, rather than through a guidance. Some of these issues are highlighted here, but they are all described more fully in comments being submitted today by Alan Goldhammer of PhRMA.

**Class Labeling** – The draft guidance describes information that should be included in prescription drug labeling, but does not address how manufacturers of products with mandatory class labeling are supposed to comply with this draft guidance, if it becomes final, and the requirements of specific class labeling.

**Other Sections of Prescription Drug Labeling** – The draft guidance does not discuss how changes in one section of product labeling that are made to accord with the draft guidance, if it is finalized, will be consistent with, or contradict, other portions of the labeling required by the existing regulation.

**Coordination with Other Proposed Labeling Changes** – The notice announcing the draft guidance indicates that FDA will be proposing other changes to prescription drug labeling, but the draft guidance does not address how manufacturers should coordinate the preparation and printing of revised labeling. Sequential modification of individual sections of drug labeling is inefficient, will present unnecessary burdens for manufacturers and FDA, and may confuse prescribers. Rather than make a series of changes to drug labeling for existing products, PhRMA recommends that FDA provide, through notice and comment rulemaking, information about all proposed changes to prescription drug labeling.

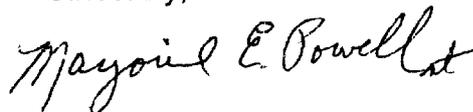
**Need for Consistent Definitions** – The draft guidance uses several terms that are not defined, but sets forth an expectation that manufacturers will make decisions about labeling content based on those definitions. For example, there is no definition of "important," but the draft guidance requires inclusion in Overview section of "important" adverse reactions.

**Inconsistencies with Other Guidances** – The draft guidance is, as noted in the PhRMA substantive comments, inconsistent with other CDER guidances, such as the reviewer guidance for safety reviews.

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For all these reasons, PhRMA urges FDA to withdraw this draft guidance and instead proceed through notice and comment rulemaking to consider changes to required prescription drug product labeling. We would be pleased to discuss any of these comments with FDA.

Sincerely,

A handwritten signature in cursive script that reads "Marjorie E. Powell". The signature is written in black ink and is positioned above the printed name.

Marjorie E. Powell