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March 20, 2001

To: Food and Drug Administration
United States Government

Re: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics: Proposed Rule.

Docket number: 00N-1269

On December 22, 2000, the Food and Drug Administration proposed revisions for the package inserts of prescription drugs. The proposal has many merits. However, other aspects of the FDA's proposal raise several concerns.

1. The new regulations propose a succinct summary of information at the beginning of each package insert. The general idea of a summary is useful, but its "Dosage and Administration" category in the summary section contains only the usual recommended dosages. This section should also contain a "Range of Effective Doses" listed just below the usual recommended doses. A range of effective doses is important, because many patients respond to doses substantially lower than those recommended by drug companies. If given the usual recommended doses, these patients often develop side effects. Therefore, information about the range of effective doses will allow physicians and patients greater dosage flexibility for specific situations. This is particularly important because 76.2% of all adverse drug reactions are dose-related phenomena -- in other words, lower doses may have prevented many of these adverse reactions.

2. Of greatest concern is the FDA's proposed changes in how adverse drug effects are defined. The current definition of an adverse drug effect requires that the effect is "reasonably associated with the use of the drug." In contrast, the new definition will only include adverse effects "for which there is reasonable possibility that the product caused the response." The key word is "caused." This is a poorly conceived, potentially harmful change for several reasons:

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A. The biological actions of new drugs are often not fully known. The actions of some approved drugs, such as Neurontin and Elmiron, are still not clear. The FDA's proposal would require "a reasonably plausible causal relationship" between a drug and a side effect, but the limited knowledge about a new drug' actions might not offer a plausible explanation. Indeed, many adverse effects occur during pre-marketing research that are not explainable, but after marketing become better understood.

B. The new definition would allow drug companies to interpret the significance of adverse reactions. If a cause for an adverse effect was not readily apparent, a drug company could choose not to list it in the product information. However, drug companies have well-known conflicts of interests in interpreting research data. Articles in the scientific literature have shown that drug companies have suppressed unfavorable information or pressured researchers from reporting important adverse reactions. A recent *Los Angeles Times* investigation involving Rezulin, withdrawn after more than 80 deaths, suggests that important side-effect data were kept from the FDA. Allowing drug companies or researchers with conflicts of interest to decide whether adverse effects might "reasonably be caused" by new drugs creates a giant loophole for discounting potentially important findings.

C. If adverse reactions are not listed in package inserts and the Physicians' Desk Reference (PDR), physicians tend to discount the complaints of patients. This has led to misdiagnosis and improper treatment.

D. The FDA states the new definition "will result in a more focused," i.e. smaller, section. However, physicians and patients searching for an explanation for an unusual reaction need comprehensive, not curtailed, information. Indeed, the information about adverse effects is not comprehensive enough. With 51% of approved drugs, serious adverse effects are discovered after approval -- and many of these side effects are not listed in package inserts. For example, in the minutes of a June 29, 2000, FDA advisory committee meeting, testimony was provided about the death of a 48 year old woman from the cholesterol-lowering drug, Zocor. Her death resulted from a rare pulmonary reaction that, although reported in the medical literature, was not listed in the package insert and PDR. The lack of ready availability of this information impeded treatment of this woman.

E. The FDA states that the current definition has led to "the inclusion of information... that is not meaningful to prescribers." Yet, how can the FDA anticipate which

information will be meaningful to 600,000 physicians or 100,000,000 patients receiving medications? Sometimes, the mere listing of an adverse effect enables the identification of a problem. Patients and physicians have a right to informed consent -- which includes knowing if an adverse reaction occurred in association with a drug during early research, whether or not the cause of the reaction was understood.

F. Drug manufacturers already have ample opportunity in package inserts to explain that an adverse reaction was infrequent or rare, or that it occurred no more often than a placebo, and that the reaction might have been coincidental.

3. The FDA proposed change in definition of an adverse drug reaction begins with: "a noxious and unintended response to any dose of a drug product...." However, the term "noxious" is not a precise medical term and may be interpreted differently by a drug company researcher, an office physician, and a patient. Noxious can mean "harmful" or "destructive," but there are many adverse reactions that aren't harmful but still bother patients and affect treatment. The previous definition of an adverse drug reactions as "an undesirable effect" is more accurate and more likely to lead to accurate reporting of adverse effects.

The inclusion of all important drug information is important because, as the FDA states, the package insert "is the primary mechanism through which FDA and drug manufacturers communicate essential, science-based prescribing information to health care professionals." Dose-response information is vital to the proper treatment of patients. As Dr. Carl Peck has noted in several published articles, the failure of useful dose-response information has led to suboptimal care and unnecessary adverse effects. The introductory summary of package inserts should contain a line with the full range of effective dosages (e.g., "Range of effective doses: 5-80 mg/day.) placed directly beneath the manufacturer suggested doses.

Also, the proposed new definition for adverse effects is too restrictive and will lead to the omission of important information. The decision whether an adverse effect is related to medication treatment belongs to practicing physicians and patients, not drug companies or paid consultants. With ten drug withdrawals in recent years, drug safety is already being questioned. Inappropriately allowing researchers to decide whether an adverse effect is "noxious" or to exclude possible adverse effects because of the lack of full understanding of drug mechanisms will lead to the exclusion of important adverse effects from package inserts, which will further reduce drug safety, erode public confidence, and hinder patient care. The

FDA's new definition for adverse drug effects should be rejected, and the previous definition should be retained.

Sincerely,

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