Public Citizen's Health Research Group's Comments on Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels
Docket No. 00N-1269
June 22, 2001

In general, Public Citizen strongly supports this Food and Drug Administration (FDA) proposed rule to revise the format and content of the professional product labeling, or "package insert," of new and recently approved drugs. For years, these labels have been difficult to read, often obscuring important information, particularly risk information, in a sea of black ink.

There is an additional reason to improve the professional labeling: patients, in addition to doctors, are starved for accurate information on prescription drugs. In 1981, the pharmaceutical industry, trade groups representing pharmacists and physicians, and the U.S. Congress succeeded in killing the Patient Package Insert Program. The PPI program would have required an objective FDA-approved informational leaflet for patients with all prescriptions. Consequently, there is currently no consistent source of information for patients. The FDA's Medguide program would only be applicable to particular drugs (if the industries don't thwart this initiative as well) and current "voluntary" leaflets by the industry have been shown in both FDA and two Public Citizen research studies to lack essential safety information. (These studies are summarized at http://www.citizen.org/hrg/PUBLICATIONS/1442.htm.)

It is therefore critical that the FDA consider the consumer in designing and drafting the professional labeling. Many patients do (and more should) request the labeling from pharmacists -- it is crucial that, as far as possible, language comprehensible to patients be used.

It is also important that the agency acknowledge the limits of what can be accomplished by professional labeling, however well designed. There is strong evidence that safety labeling changes do not adequately protect patients from the unsafe use of prescription drugs by physicians and pharmacists. In the following three instances, even a black box warning placed prominently at the beginning of labels and one or more "Dear Doctor" letters failed to sufficiently constrain misprescribing:

- Continued prescribing of contraindicated drugs with terfenadine (Seldane).[1,2,3]
- Contraindicated use of cisapride (Propulsid)[4]
- Failure to conduct recommended liver function tests in patients taking

troglitazone (Rezulin), as shown in studies conducted by both the FDA[5] and Public Citizen.[6]

We are also concerned that the FDA's proposed regulation exempts from the labeling changes drugs that have been on the market for more than five years. While this may help the industry to not make expenditures on labels that are a minuscule fraction of their expenses, sales or profits, there is no reasonable public health rationale for this unwarranted "grandfathering." It is noteworthy that when the Congress required standardization of food labels (also regulated by the FDA) there was no analogous grandfathering. We agree that prioritizing new- and recently approved drugs is reasonable, but urge you to move expeditiously to relabel all drugs.

Finally, we believe that the project to relabel drug is a golden opportunity to finally require manufacturers to list all inactive ingredients as well. We now turn to comments on specific aspects of the Proposed Rule.

PROPOSED § 201.57(a) – HIGHLIGHTS OF PRESCRIBING INFORMATION SECTION

Perhaps the most important proposed change in the professional product labeling is a requirement for a "Highlights of Prescribing Information" section. This section would appear at the beginning of the label and consist of selected information that prescribers view as most important.

We strongly support the creation of this section of the professional label. We do, however, recommend some minor modifications in the order in which information is presented. We believe that risk information (other bolded warnings [which are not now necessarily in the "Highlights"], contraindications and drug interactions) should appear higher up in the label, certainly before "Dosage and Administration" and "How Supplied". Physicians (and patients) searching for dosage and formulation information will be looking specifically for that information and will find it regardless of its location because they cannot prescribe without it. On the other hand, placing risk information higher increases the probability that the reader will encounter that information by chance and make a more informed prescribing decision.

INVERTED BLACK TRIANGLE – PROPOSED § 201.57 (a)(2)

Public Citizen supports requiring an inverted black triangle on the labeling of new drugs, similar to what has been done in the United Kingdom for a number of years. This symbol can be used to alert prescribers to the need for intensive surveillance for new and unexpected adverse drug reactions not detected in clinical trials. The symbol would also alert patients that they may have been prescribed a new drug with which, by definition, prescribing experience in the U.S. is limited.

However, we strongly urge that the agency extend the proposed three-year inverted triangle requirement to five years. In our experience, if a drug is going to be withdrawn or require a black box warning or additional safety labeling, it will occur within the first five years of marketing.

INDICATIONS AND USAGE SECTION – PROPOSED § 201.57(c)(2)

We suggest that the FDA, in the interest of clarity, change the name of this section to the "Food and Drug Administration-Approved Uses" section. The phrase "Indications and Usage" is regulatory jargon with a meaning that may not be clear to prescribers and is not understood by patients.

We applaud the FDA for proposed § 201.57(c)(2)(iv)(A) to specify that the label should declare succinctly if evidence is available to support the safety and effectiveness of the drug only in a selected subgroup of the larger population of patients. If the evidence to support the FDA-approved use is based on surrogate endpoints or a *post hoc* subanalysis, the limitations of these data must also be described.

Equally important is the FDA's proposal for § 201.57(c)(2)(iv)(D) which would permit a statement that there is no evidence that a drug is safe (the label can already say that it is ineffective) for a use or condition.

We also suggest that the FDA require a statement in the "Food and Drug Administration- Approved Uses" section of whether the drug was approved on the basis of placebo- or active-controlled trials. If active controls were used, the name(s) of these drugs and their results in the study should be stated.

PROPOSED §201.57 (c)(7) – DRUG INTERACTIONS SECTION

Public Citizen fully supports the proposal to create a full list of drugs associated with interactions with the labeled drug. This is far superior to listing the categories of drugs that might result in interactions. Both physicians and patients may not be adequately familiar with all the drugs in a particular category.

PROPOSED § 201.57(c)(9) – ADVERSE REACTIONS

The current regulations define an adverse reaction (now to be included in the "Comprehensive" portion of the label as opposed to the "Highlights") as an "undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." According to the Proposed Rule, this would be revised to read: "An adverse reaction is a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response." The FDA goes on to say

that "... this change in terminology [is] because the 'reasonably associated' language in the current definition can be and in many cases has been interpreted as meaning that a reaction should be included merely if there is a temporal association, rather than a reasonable causal association, between a response and a drug."

Clearly, this a lowering of the standard of information that must be provided for physicians (and patients). If a manufacturer can convince the FDA that there is not a "reasonable possibility" that the drug "caused" a given reaction, no matter how frequent, it can exclude the reaction from the Adverse Reactions section of the label. In our view, this places too much power in the hands of the company, particularly because convincing evidence of causality can be difficult to generate (particularly for rare events) and may not be apparent for years after a drug is marketed. In the interim, physicians (and patients) will not be warned.

Moreover, the change in definition is intimately connected to the FDA's plans to reduce manufacturers' obligation to *report* adverse reactions. The Federal Register notice states that the language proposed is similar to that (inappropriately) agreed to by the FDA at the International Conference on Harmonisation (ICH) and that "the agency is currently in the process of developing a proposed rule revising its adverse event reporting regulations for drugs and biological products, and the revised definition of 'adverse reaction' ... is consistent with definitions being considered by the agency for inclusion in that rulemaking." Thus, the change in definition in the labeling rule becomes the stalking horse for changing the definition in the reporting rule. Neither is acceptable.

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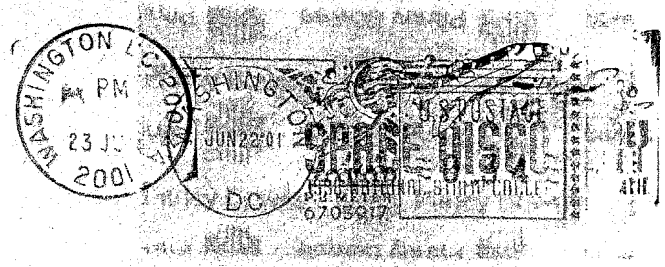

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