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ASSOCIATE VICE PRESIDENT
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PhRMA

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BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
rm. 1061
Rockville, Maryland 20857

Re: Proposed Rule on Prescription Drug Labeling -- Docket No. 00N-1269; 65 Federal Register 81082 (December 22, 2000).

Dear Sir or Madam:

Enclosed for submission to the above-referenced docket are comments of the Pharmaceutical Research and Manufacturers of America (PhRMA) on FDA's proposed rule to amend the regulations governing the format and content of labeling for human prescription drugs and biologic products. 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 over $30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures. PhRMA companies are the source of nearly all new drugs that are discovered, made, and used worldwide, and will therefore bear the primary responsibility for implementing any new prescription drug labeling requirements.

As explained in more detail in the accompanying comments, PhRMA supports the basic goals of the proposed rule, to make approved product labeling more "user friendly" and to make the comprehensive prescribing information more accessible to health care practitioners. These important objectives are best served by the proposed reordering of the comprehensive portion of the labeling. This reordering will improve the ability of health care practitioners to locate the information they deem most useful within the labeling.

Other proposed changes raise serious concerns, and would not promote the goal of better transmitting important information to health care practitioners about the safe and effective use of a drug. PhRMA strongly opposes the addition of a "Highlights" section. A "Highlights" section would inappropriately emphasize a subset of summary information and discourage health care practitioners from consulting vital information in the comprehensive portion of the labeling, which itself is already a distillation of complex data and information. A "Highlights" section would also raise significant product liability issues.

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PhRMA also does not support the proposed restrictions on the inclusion of *in vitro* data and other data on indications, uses, and dosing, or the proposed changes to the definition of adverse reactions. The restrictions on *in vitro* and other data would serve to deprive practitioners of scientifically valid information that often assists in prescribing decisions. The new criteria proposed for inclusion of information about adverse reactions are not adequately defined and would create further product liability concerns.

The proposed format requirements and the implementation plan are of concern. The new format requirements would impose substantial implementation costs on industry and the FDA. Companies have determined that the requirements would double the length of labeling for most products, and would require new trade packaging for some products to accommodate the added text. FDA will be inundated with labeling supplements and requests for waivers from aspects of the new rule. Over 1,800 products would require relabeling in the first year that the rule becomes effective under the proposed implementation plan. As noted in the detailed comments, PhRMA does not support this implementation plan.

A more prudent course would be to adopt a step-wise approach to implementation of new requirements. As a first step, FDA should require only those aspects of the proposed rule on which there is a consensus, such as the reorganization of the comprehensive prescribing information. These agreed changes should be required only for new applications and effectiveness supplements. There are considerable benefits to this more cautious approach. It would allow sponsors and the agency to focus resources on implementing changes to newer products, which are the products for which health care practitioners are most likely to consult the approved labeling. It would also allow for evaluation of real-world experience with the less controversial changes before determining whether additional and more sweeping and burdensome new requirements are needed.

PhRMA appreciates the opportunity to submit these comments and looks forward to continuing to work collaboratively with the agency on this important initiative to enhance approved product labeling.

Sincerely,

Allen Goldhamer

Enclosure

COMMENTS OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

ON

THE FOOD AND DRUG ADMINISTRATION'S PROPOSED RULE ON REQUIREMENTS ON CONTENT AND FORMAT OF LABELING FOR HUMAN PRESCRIPTION DRUGS AND BIOLOGICS; REQUIREMENTS FOR PRESCRIPTION DRUG PRODUCT LABELS

[65 Fed. Reg. 81082 (December 22, 2000)]

DOCKET NO. 00N-1269

Introduction and General Comments

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over $30 billion a year in discovering and developing new treatments, PhRMA companies are leading the way in the search for cures. These companies are the source of nearly all new drugs that are discovered, manufactured, and used worldwide. PhRMA members will bear the primary responsibility for implementing any changes to the content and format of approved prescription drug labeling, and thus have a direct stake in FDA's proposed rule on product labeling and product labels.

As a general matter, the proposed rule reflects the considerable attention that FDA has devoted to improving the readability and usefulness of the approved product labeling for prescribing physicians and other health care practitioners. PhRMA agrees with the agency's stated objectives of making labeling more "user friendly" and accessible. Key aspects of the proposed rule would promote these goals, including most notably the reorganization of the

comprehensive prescribing information. At the same time, some of the proposed changes risk undermining the fundamental function of the approved labeling as a source of essential information for practitioners to prescribe a product safely and effectively for individual patients.

The proposed "Highlights" section, for example, emphasizes a subset of summary information and would potentially discourage healthcare practitioners from consulting vital information in the comprehensive portion of the labeling. Physicians' focus on the "Highlights" section would directly undercut the intent of the labeling redesign to transmit important prescribing information to practitioners more effectively, and would also lead to significant product liability concerns. Other proposed changes also are at odds with the basic goal of improving the usefulness of labeling for health care practitioners, because they would remove significant scientific information in existing labeling or impose unclear new requirements (e.g., removal of *in vitro* data and clinical data on other uses and dosing, and adoption of a new standard for adverse reactions).

PhRMA agrees with views Dr. Janet Woodcock, director of the Center for Drug Evaluation and Research, expressed on the Drug Information Association sponsored CDER Live telecast on April 28 that the printed drug label is becoming an anachronism. New computer technologies allow for the storage and dissemination of electronic versions of the drug label. Presentations can be indexed to permit rapid access to specific sections. Updating labels with new prescribing information will be easier, getting important safety information out to health care providers more quickly. PhRMA believes that this is the best long term solution to dealing with the issues that FDA has outlined in this proposed rule.

PhRMA does not support the proposed implementation plan. As a first step, requirements for newly and more recently approved products should only apply to original NDAs/BLAs and effectiveness supplements. This would focus the resources of sponsors and the agency on the most important labeling to revise, and would provide additional experience with the new labeling rules before broader changes are required. The proposal to require certain changes in all products within one year is also not workable. Enormous industry and agency resources would have to be devoted to such changes, and there would be a real risk that the FDA's attention to drug reviews and approvals would be compromised.

Many of the proposed changes would impose unjustified implementation costs, as well as possible environmental impacts, without any meaningful corresponding benefit to health care practitioners. In estimating the practical impact of the proposed requirements, it is important to keep in mind that package inserts are typically printed in multi-column format on paper sized to contain the text yet allow for manipulation (e.g., folding) for inclusion in or on the package. Multiple packaging lines may be used for packaging different presentations of a given product, and the configuration and size of paper used is determined by the equipment used on different lines. Companies have determined that the new requirements would double the length of labeling for most products, and may require new trade packaging to accommodate the added text (e.g., use of a carton to hold the product and labeling instead of a bottle with the labeling adhered to the outside). Packaging lines and ancillary equipment would have to be reengineered and redesigned. The administrative and financial burdens would be significant, especially for a large company with multiple packaging facilities and third party manufacturers. For example, the cost to renovate one packaging line to accommodate the larger paper that would be required

could exceed $700,000. One company has determined that over 50 packaging lines could be affected (with multiple packaging lines affected per product) at a total cost approaching $40 million.

Given the substantial costs that any new requirements will impose, it is imperative that the agency continue to act in a deliberate and thoughtful fashion as it institutes the first sweeping overhaul of the approved product labeling since the current rules were put into place in 1979. PhRMA urges the agency to consider as a first step finalizing only those portions of the proposed rule on which there is a consensus that the changes will improve the clarity and usefulness of the labeling, such as the reorganization of the comprehensive prescribing information. The agency could then consider whether there is a genuine need for more sweeping changes.

At a minimum, PhRMA urges that any aspects of the proposed rule that have not yet been field tested be subjected to further scrutiny on a pilot basis before adoption. Additional focus groups and surveys should also be considered. Further market research should probe whether there is a real need for a new "Highlights" section in light of the other proposed changes to the labeling, and whether the new labeling will result in desired behavioral changes by health care practitioners in the way they use approved prescribing information. The prior surveys and focus groups primarily provided the views of office-based physicians on the addition of highlights compared to the existing labeling template. The new template for the comprehensive labeling should be used as a comparator to probe the value of also adding highlights. In addition, health care practitioners other than office-based physicians should be canvassed, along with other groups of professionals who use the information in drug labels (e.g., pharmacists). All of

the past market research, as well as any new market research, should be made available for public review.

Because all of the proposed changes to drug labels and labeling present product liability concerns, PhRMA urges FDA to incorporate into FDA's rule a statement that FDA approval of labels and labeling preempts conflicting or contrary state law, regulations, or decisions of a court of law for purposes of product liability litigation. FDA has defined the types of information necessary for practitioners as they consider whether to prescribe a specific drug, and has in all instances worked with the product sponsor to determine the language that will communicate that information to prescribers. State court juries are not qualified to make decisions about whether the FDA-approved labeling information is adequate for the practitioner. Indeed, juries have sometimes determined that the sponsor should have included information that FDA affirmatively decided should not be included in the drug labeling. Thus, FDA's goal of consistent and user-friendly labeling may be hampered by inconsistent state court jury determinations of adequacy. The agency can avoid this by a statement that FDA-approved labeling preempts inconsistent decisions in individual personal injury litigation.

More detailed comments on specific features of the proposed rule follow. The detailed comments are organized to track the headings and sections of the preamble to the proposed rule, starting with the proposed new "Highlights of Prescribing Information." FDA specifically requested comments on 15 issues in the proposed rule. PhRMA's comments on these issues are included below within its comments on the various sections and subsections of the proposed rule.

Detailed Comments

I. Highlights of Prescribing Information [proposed §§ 201.56(d) & 201.57(a)]

A. Appropriateness of Including a "Highlights" Section

PhRMA strongly opposes the addition of a "Highlights" section to the approved product labeling. The basic intent of the proposed rule is best and most appropriately served by the reorganization of the labeling sections to place critical and most often read information first. This change alone will enable a prescriber to find specific information readily and discern the material he or she deems most useful. Including a distilled summary of important prescribing information in an additional "Highlights" section would not contribute to the appropriate use of the package insert. To the contrary, it would only encourage practitioners to rely improperly on the highlights section and not consult the additional information in the comprehensive labeling.

The approved labeling is already a distillation of complex data and information. The way to make the labeling a more valuable and useful tool for health care practitioners is not to distill it further, but to reorganize it and make it easier to access. The agency itself acknowledges in its proposed "highlights reminder" that highlights do not include all of the information needed to prescribe a drug safely and effectively. Yet the proposed rule would structure labeling in a manner that would inevitably distract from the full prescribing information and lead practitioners not to read the comprehensive information that is needed for safe and effective prescribing.

Additional difficulties would arise. Most significantly, there would be unavoidable inconsistencies in the approach used by different companies to develop the "Highlights" section. Deciding what to include in the section would necessarily entail an element of judgment and choice on the part of manufacturers. For example, proposed section

201.57(a)(10) would require that the heading "Warnings/Precautions" be followed by a concise summary of the "most clinically significant" aspects of that section of the comprehensive prescribing information. In the preamble to the proposed regulations, FDA states that "[t]he cautionary information chosen from the comprehensive prescribing information for inclusion in this section should be that which is most relevant to clinical prescribing situations."[1] Clearly, such a decision involves a significant level of judgment and choice on the part of the manufacturer as to what is most relevant to clinical prescribing situations. Discrepancies and inconsistencies could, and likely would, arise as different companies and different reviewing divisions within FDA pick and choose information from the comprehensive prescribing information to include in the highlights section.

Inconsistencies would be particularly troubling for products with class labeling. Unless the agency designates the precise information that should be contained in the "Highlights" section for a particular therapeutic class, different manufacturers will make different decisions in selecting information from the comprehensive labeling for the "Highlights" section. If these variances develop, the benefits of uniformity across the labeling for a class would be lost.

The substantive flaws in the proposed "Highlights" section are exacerbated by the significant administrative costs that would be incurred to add such a section to labeling. Incorporating this entirely new feature in labeling would expand the already lengthy package insert. It would also require more extensive negotiations with the agency over labeling, for

[1] 65 Fed. Reg. at 81089.

example to determine where the appropriate threshold should be set for products with significant adverse event information.

The "Highlights" section, then, presents numerous potential problems and few countervailing virtues, if any. Further concerns arise due to product liability issues, discussed next.

B. Product Liability Concerns

The preamble to the proposed rule states that concerns about increased product liability risks from the new highlights requirement are "highly speculative."[2] There is simply no basis for FDA's off-hand dismissal of this critical issue. Suits would inevitably arise based on the alleged inadequacy of the "Highlights" section and purported inconsistencies between the information condensed for that section and the comprehensive information. This concern is far from speculative. Every pharmaceutical product liability case involves allegations regarding the adequacy of the information disclosed about the product, including allegations that important information is missing or that risk or other information disclosed was not sufficiently prominent. Plaintiffs have specifically brought actions that assert liability based on product summaries that are argued to be incomplete or otherwise flawed.

The only way to resolve these liability risks would be for FDA to mandate the precise content of the "Highlights" section for a particular product and for FDA's determination to preempt any possible tort liability. Preemption should extend to the entire label, not just the "Highlights" section. Even if the "Highlights" section were preemptive, plaintiffs might cite the

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[2] 65 Fed. Reg. at 81087.

fact that newer products have a "Highlights" section as evidence that the labeling for an older product is inadequate in its disclosure of risk information. Plaintiffs might also cite the contrasts between the new "Highlights" section of a new dosage form as alleged evidence of the inadequacy of the labeling of an older dosage form. These risks would increase the product liability exposure presented by older products, unless compliance with FDA labeling requirements were broadly to preempt state law tort claims.

C. "Highlights Reminder" [proposed § 201.57(a)(15)]

There are compelling reasons to eliminate the requirement of a "Highlights" section, as explained above. If the new section is nevertheless retained in a final rule, PhRMA asserts that the proposed "highlights reminder" statement must be revised significantly to act as a better disclaimer concerning the limits of the highlights information. First, the statement should be moved to the front of the "Highlights" section. This would inform health care practitioners immediately that the material that follows is not a reflection of the entire package insert, and that it is necessary to refer to the comprehensive labeling for complete information. Second, the statement should be bolded and underlined to make it more conspicuous. Third, the statement should be worded more strongly, as follows: "These highlights do not include all the information needed to prescribe [drug] safely and effectively. For more complete safety and effectiveness information, health care practitioners must review the comprehensive prescribing information provided below in its entirety."

D. One-Half Page Limit [proposed § 201.57(d)(8)]

It is not feasible to create a meaningful "Highlights" section that is a half-page long or less. Companies have tried in good faith to create mock-ups of "Highlights" sections for actual products and have been unable to satisfy the half-page limitation. At the same time, health

care practitioners clearly will not find a highlights section that is longer than a half page useful, as the survey information cited in the preamble to the proposed rule demonstrates.[3] This conflict is irreconcilable, and demonstrates why the proposed "Highlights" section is not feasible. In order to create a highlights section that is acceptable to physicians, critical safety and effectiveness information would be omitted. The expedience gained by creating a highlights section for health care practitioners does not justify adoption of a label format that deters health care practitioners from reviewing the full labeling.

E. Inverted Black Triangle ("▼") [proposed § 201.57(a)(2)]

Use of an inverted black triangle ("▼") in the United States to identify significant new products would likely create confusion while producing few benefits. This symbol is used in the United Kingdom as part of a broader system designed to capture adverse events reports for new products where there is any conceivable link to the drug, notwithstanding uncertainty about the causal relationship, whether the reaction is well recognized, or whether other drugs have been given concurrently.[4] In order to have similar utility here, the meaning and function of the symbol in labeling would have to be better defined, and an extensive education campaign conducted for physicians and other health care practitioners.

In addition, use of the symbol could create problems with the software that is used to generate text, print labeling, and prepare electronic label files. Therefore, PhRMA urges that the agency drop the proposed use of the inverted black triangle.

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[3] 65 Fed. Reg. at 81084.
[4] ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000, Datapharm Publications Ltd., 1999, pps. iii, iv.

F. Boxed Warning [proposed § 201.57(a)(4)]

1. Boxed Warning with Text Exceeding 20 Lines

The need to shorten boxed warnings with longer text in order to keep the "Highlights" section from growing in length is another example of why the concept of the "Highlights" section is flawed. If information is sufficiently important that it is required to be captured in a boxed warning, then it should be fully presented and not summarized, no matter its length. Boxed warning language is crafted with care and negotiated with the agency to be as succinct as possible. Further shortening the text could result in misinterpretation of the warning or omission of pertinent information deemed necessary for the safe and correct use of the product. This concern is not resolved by cross-referencing the full boxed warning in the comprehensive section of the label. It is just not realistic to expect the average prescriber to review a partial warning in one portion of the labeling and then check another portion of the labeling for the remainder of the text. Therefore, PhRMA recommends that the agency drop the proposed use of the shortened boxed warning.

2. Boxed Warning Icon ("!")

Including an exclamation point ("!") as a special icon to identify a boxed warning is superfluous. Practitioners are already familiar with the single black line warning box and that formatting alone calls sufficient attention to the warning. In addition, health care practitioners would have to be educated about the meaning of the "!" symbol, and even then the symbol could be confused with a "1," especially when a smaller type size is used. A square or octagon could be used as an alternative, but symbols can create problems with the software that is used to generate text, print labeling, and prepare electronic label files. Accordingly, PhRMA asserts that the preferred alternative remains no special icon. If no symbol is adopted for the boxed warning,

the warning could still be listed in an index. Given the prominence of the boxed warning, health care practitioners should not have difficulty locating it within the labeling.

G. Recent Labeling Changes [proposed § 201.57(a)(5)]

Where "recent labeling changes" are included for a product and the labeling is not revised for more than a year, there should be no fixed time limitation set by which the labeling must be revised to remove the "recent labeling changes." There is no basis to require an entire labeling revision where it would not otherwise occur.

H. Indications and Usage [proposed § 201.57(a)(6)]

If a "Highlights" section remains, PhRMA recommends that sponsors be given flexibility to repeat the indications and usage from the comprehensive information verbatim or to use a bulleted format. For products with less extensive indications and usage information, the material could be provided verbatim. For products with longer text, a bulleted list might be used. Alternatively, the text might be repeated verbatim even for products with longer narratives where summarizing the information would present concerns.

I. Contacts for ADR Reporting [proposed § 201.57(a)(11)]

There is no need to repeat the contact information for ADR reporting in two portions of the labeling. The clearest approach would be to include the information only once near the name and address of the manufacturer, packager, or distributor. It is not intuitive to look in the warnings and precautions section for a phone number. In addition, only the name and phone number of the manufacturer should be listed.

II. Index to Comprehensive Prescribing Information [proposed § 201.57(b)]

The real value of including an index to the comprehensive prescribing information would be for electronic labeling where hypertext links can be provided from the

index to the body of the labeling. For paper labeling, the index may serve a somewhat helpful function by providing an overview of the labeling and assisting health care practitioners in searching for relevant information, at least during the transition period when health care practitioners are adjusting to the new organization of the labeling. At the same time, the index would add to the length of the labeling. This would be more problematic if other proposed requirements are retained that would also add to the labeling length, such as the inclusion of a "Highlights" section and the need to use 8-point type for text. PhRMA recommends that labels include an index, but only if other proposed highlights section and other format requirements are dropped, in keeping with other PhRMA recommendations.

III. Comprehensive Prescribing Information [proposed §§ 201.56(d) & 201.57(c)]

A. General Comments

Reordering the sections of the comprehensive portion of the labeling provides an effective means for enabling health care practitioners to locate the information they deem most useful within the labeling. Other proposed changes to the comprehensive prescribing information should be reconsidered. PhRMA does not support the proposed restrictions on the inclusion of *in vitro* data and other data on indications, uses, and dosing that are not included in the "Indications and Usage" and "Dosage and Administration" sections, as these restrictions would serve to deprive practitioners of scientifically valid information that could help contribute to informed prescribing decisions. PhRMA also does not support the proposed change to the definition of adverse reactions, because the new criteria are not well defined and would create significant product liability concerns. These concerns arise from both the potential for comparisons of labeling for newer and older drugs, and the potential inconsistencies resulting from the inadequacies of the new definition of adverse reactions.

B. Boxed Warning [proposed § 201.57(c)(1)]

As stated above (section I.F.2), there is not a need for an icon ("!") to signal the boxed warning. In addition, if the "Highlights" section is retained, it would be redundant to include the boxed warning both in the "Highlights" and at the beginning of the comprehensive prescribing information. The boxed warning should only be printed once. If the requirement is retained that the boxed warning be included twice, notwithstanding the redundancy, it should be moved to the "Warnings/Precautions" section. It would seem intuitive that health care practitioners would check the "Warnings/Precautions" section for all warnings, including the boxed warning.

C. Implied/Suggested Indications, Uses, or Dosing Outside "Indications and Usage" and "Dosage and Administration" Sections [proposed §§ 201.57(c)(2), (3), (13) & and (15)]

The agency should reconsider the proposal to bar the inclusion of data on indications, uses, and dosing that are not included in the "Indications and Usage" and "Dosage and Administration" sections. The package insert should present information intended to foster the understanding of a product's clinical and safety profile, as well as information intended to communicate a product's FDA-approved indication. Studies that are scientifically sound and provide medically relevant information to the prescriber should be included in labeling, as they are now. This information (e.g., reports of supportive clinical studies in the clinical pharmacology section) may be valuable to practitioners and patients, and the language describing the data would be carefully negotiated between FDA and the sponsor, along with the rest of the labeling. This proposed change also poses product liability concerns, because of the loss of information that may be relevant to prescribing practitioners. The exclusion of such valuable

and clinically significant information in the labeling would run counter to FDA's stated goal of providing more informative labeling for practitioners and patients.

This is especially true in the case of Patient Reported Outcomes (a.k.a. Quality of Life) where this information may be presented in the clinical studies section but not in the indications section. These studies very often contribute to the understanding of the product's profile, and excluding such information may hinder a practitioner's access to information which could help support the use and understanding of the product. Similarly, presentation of dosing information that reflects doses higher than the top dose in the "Dosage and Administration" section is often very valuable to health care practitioners. This information allows for a better understanding of the product safety profile and communicates that there is an established "margin of safety" between the top doses and what has been presented in the "Dosage and Administration" section, and PhRMA recommends that FDA not adopt the proposed regulation excluding it from drug labels.

To the extent FDA is concerned about the use of these data in promotion, the agency can address the issue through its existing legal authority. If the proposed restrictions are retained, FDA could find itself inundated with requests for waivers under proposed section 201.58. The need for companies to seek numerous waivers would place an unnecessary burden on both industry and FDA.

With respect to the inclusion of effectiveness and/or toxic drug and/or metabolite concentration ranges and therapeutic concentration windows, PhRMA believes that information other than therapeutic drug concentration monitoring (TDM) information would more

appropriately be placed in the "Clinical Pharmacology" section. If safety were an issue, then the "Warnings/Precautions" section would be the appropriate place for that information.

D. Warnings/Precautions [proposed § 201.57(c)(6)]

Combining the "Warnings" information with the "Precautions" information makes good sense. However, the use of mandatory standardized subheadings within the "Warnings/Precautions" section is not appropriate. It may often be more informative to provide specific information tailored to a particular issue than to try to combine precautions of varying seriousness under a single subheading. PhRMA urges that sponsors be given flexibility in this regard to determine the proper way to present information on warnings and precautions. It would be both extremely difficult and potentially counterproductive to try to develop standard subheadings to address all the areas of concern that might arise across therapeutic groups.

In addition, there appears to be an inconsistency between the proposed inclusion of "clinically significant adverse reactions" in the Warnings section and the proposed change in the definition of an adverse reaction. Under the proposed "Warnings" section requirement, an adverse reaction that is not necessarily "noxious/injurious to health" would be required to be included in the "Warnings" section if it could adversely affect compliance (i.e., it is "clinically significant"). Such reactions do not rise to the level of a warning or precaution, and inclusion of them in the "Warnings" section will dilute the impact of this section. Further, such a reaction would not even qualify as an adverse reaction under the proposed definition. This inconsistency helps demonstrate how the proposed definition of "adverse reaction" (as discussed below) is not only unclear but could apparently lead to the exclusion from the adverse reaction section of the labeling of adverse reactions that are "clinically significant," even if they are not "noxious." For a reaction to be clinically significant enough to be put in the "Warnings" section, and yet not

qualify as an adverse reaction, will undoubtedly lead to confusion and misunderstanding. PhRMA believes that FDA must reconcile these definitions.

E. Drug Interactions [proposed § 201.57(c)(7)]

PhRMA urges that this section be expanded beyond providing information on clinically significant drug interactions. All valid data, clinical or *in vitro*, should be permitted to appear in the labeling, including positive and negative findings (that is, information on interactions or the lack of interactions). Interaction studies often are performed with drugs commonly administered by health care practitioners, and they want information as to whether these drugs are safe to co-prescribe with a new molecular entity (e.g., drugs commonly given to heart failure patients like coumadin, digoxin, ACE inhibitors, diuretics). PhRMA believes that it would be best to provide such information under "Drug Interactions," but if not, it should be presented in the prescribing information as a subset of the clinical pharmacology section.

PhRMA also recommends that FDA clarify the proposed requirement that information on the mechanism of drug/drug or drug/food interaction be included. There are instances where the mechanism is not clearly understood (e.g., a food effect which might be related to stomach emptying, a drug that potentiates sedation caused by other drugs (such as oxycodone, lorazepam, or ethanol), but where the exact mechanism is unknown). The proposed rule should be modified to state that the mechanism(s) of the interaction will be described if understood.

F. Use in Specific Subpopulations [proposed § 201.57(c)(8)]

PhRMA recommends that the proposed rule make clear that information on use under conditions of hepatic impairment and renal impairment may be included in this section, in addition to the subpopulations already identified.

G. Adverse Reactions [proposed § 201.57(c)(9)]

PhRMA does not believe that there are any good grounds to alter the definition of adverse reactions and require retroactive changes to existing labeling. FDA can address new products on a case-by-case basis under its existing authority where the agency determines that excessive adverse event information is presented. However, adoption of the new proposed criteria for labeling that is already approved would cause confusion and raise acute product liability concerns.

As an initial matter, the new proposed criteria for determining what adverse reaction information to include in labeling are not workable in their current form because key facets of the criteria are not defined. The proposed rule would limit the items to be listed in the adverse drug reactions section to those that are "noxious (i.e., injurious to health) and unintended" and those for which there is a "reasonable possibility that the product caused the response." In its May 2000 Draft Guidance for Industry on the adverse reactions section of labeling,[5] FDA distinguished "adverse reactions" from "adverse events" and stated that not all adverse event information should be included in labeling. The new proposed definition would apparently add a further filter and exclude adverse reactions that are not "noxious", "injurious to health," or "unintended." It is not clear what these terms mean or how they would be applied. For example, what does it mean for a response to be "noxious" or "injurious to health," as opposed to merely an "undesirable effect?" The agency would have to publish extensive additional clarification for these concepts to be implemented in practice.

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[5] Draft Guidance for Industry: Content and Format for the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (May 2000).

Even with additional clarification, the proposed rule, with its proposed implementation plan, would be extremely difficult to satisfy for previously approved drugs. For marketed products, compliance with the new and more restrictive definition would require reevaluation of prior clinical trial data, and some data may not be available in clinical trial databases. Where appropriate data exist, there would be significant practical difficulties and burdens in reevaluating the data in order to make appropriate decisions about what information to include and what information to exclude. Meanwhile, numerous labeling supplements would have to be submitted to the agency, adding to its already high workload.

If labeling is changed in material ways for products that have been on the market for some period of time, the changes could prompt substantial confusion among health care practitioners. An extensive educational program would have to be initiated to explain the meaning and significance of the labeling changes.

Adoption of a new definition of adverse reactions creates serious product liability concerns. For example, discrepancies most certainly will arise between products in the same therapeutic class, because labels for older products will include adverse reactions that do not meet the new criteria and thus are not listed in labeling for newer products. Plaintiffs' attorneys would attempt to use this discrepancy in labeling to attack the adequacy of the risk disclosures in the less-inclusive labeling for newer products. As noted above (section I.B), the only real solution to these product liability concerns is to make the federal requirements for the entire label preemptive so that the FDA-approved labeling is deemed an adequate disclosure in a product liability lawsuit. Otherwise, the agency must be extremely wary of changing features of the

labeling, like the standard for including adverse reactions, that are critical for both prescribing and product liability reasons.

Therefore, PhRMA recommends that FDA drop the proposed change to the definition of adverse reactions.

H. *In Vitro* Data [proposed § 201.57(c)(13)]

PhRMA recommends that sponsors be permitted to retain *in vitro* data in labeling for anti-infective products without the need to obtain a waiver. Elimination of *in vitro* susceptibility data from labeling would withhold important information from health care practitioners, information that contributes to the choice of the appropriate antibiotic in a particular setting. This could result in an increase, rather than a decrease, in inappropriate antibiotic use. Physicians often must rely on their experience and clinical practice to prescribe anti-infective products due to the absence of susceptibility data and rapid diagnostic tests at the point of care. When microbiological data are not available, decisions to prescribe an antibiotic should be based on the clinician's assessment of the most likely etiology and optimal therapy, including available clinical, pharmacodynamic, and *in vitro* data from clinical trials and post-marketing experience with antimicrobial agents.

Professional guidelines from reputable organizations such as the American Thoracic Society indicate use of *in vitro* susceptibility data to make educated empirical judgments based on both the patient's symptoms and the *in vitro* susceptibility spectra of the suspected organism in choosing an antibiotic. In their March 21 comments to the FDA, the Infectious Diseases Society of America concurs, stating,

> . . . it is important that all relevant data be available to them (physicians). Removing *in vitro* data from PIs poses problems that our member physicians believe, ultimately, will impact negatively

> on physician decision-making and patient care. Of particular concern, our members believe that FDA's action will impede physicans' ability to determine appropriate anti-infective therapy for patients with drug resistant or unusual infections.

It is not appropriate for FDA to selectively require that sponsors remove such scientifically important information from the labeling, which inhibits health care professionals' access to this valuable information. Furthermore, it is not clear how FDA would determine testing limits for automated *in vitro* susceptibility testing devices for new drugs without the inclusion of *in vitro* data in the labeling.

Beyond the case of antibiotics, the definition of mechanism of action, and therefore the definition of a drug class, is due to *in vitro* as well as animal data. Although a receptor binding study might not give an indication of a drug's effectiveness in a controlled clinical setting, it may well indicate why the drug worked, and give an indication of which drugs can be used together, or which should not be used at all, according to the practitioner's understanding of the mechanism of the disease being treated.

For these reasons, PhRMA recommends that the existing guidelines on inclusion of *in vitro* data in product labeling not be changed.

I. Waiver Process

Although PhRMA strongly believes that *in vitro* and animal data should be retained in labeling, as discussed above, should the agency implement the proposal to exclude such data absent a waiver, PhRMA urges that the final rule explain in detail the process by which sponsors apply for a waiver. This description should address whether revised labeling is submitted with the waiver, or if waiver issues must be resolved prior to submitting revised labeling by means of a changes being effected (CBE) supplement.

J. Clinical Studies [proposed § 201.57(c)(15)]

PhRMA supports the revisions to the "Clinical Studies" section. Also, PhRMA believes that the labeling would flow more logically if all the clinical data (clinical pharmacology and clinical trials) were in close proximity.

K. References [proposed § 201.57(c)(16)]

The proposed rule requiring that all information contained in "References" be based on adequate and well-controlled trials will omit many references for anti-infective products. Examples include standardized test methodology and *in vitro* studies. These references are important, and PhRMA urges that they be permitted.

L. Patient Counseling Information [proposed § 201.57(c)(17)]

The proposed rule would require that any approved printed patient labeling or Medication Guide be reprinted at the end of the package insert. PhRMA urges that the agency clarify this requirement to make clear that patient labeling need not be printed twice for trade packages. That is, there should not be a requirement to include the full patient labeling in the package insert intended for the practitioner and also to include the full patient labeling separately for distribution to the patient. Such double printing would be wasteful and unnecessary.

IV. New Format Requirements [proposed § 201.57(d)]

A. Bolding Information [proposed § 201.57(d)(5)]

The use of bolding is an appropriate way to ensure the visual prominence of the targeted information. PhRMA believes that capitalization, italics, and underlining, which are currently used in package inserts to order and/or add prominence to certain text, should also be considered.

B. Use of Color and Additional Symbols

Use of color in a package insert would likely be lost through photocopying and printing from an electronic source. Color might also be lost to health care practitioners receiving labeling through a source other than the manufacturer or the PDR. The benefits of using color are thus not clear. Adding color would substantially increase printing costs. Accordingly, PhRMA believes that FDA should not require the use of color.

FDA should also exercise care in considering adoption of any additional symbols. Symbols can be difficult to print, and can be lost if presented in electronic labeling and then printed.

C. Vertical Line

The proposed use of a vertical line to highlight recent changes in the comprehensive prescribing information, without any explanatory text, would likely cause confusion and would not clearly delineate a recent change. This would be particularly true for labeling with extensive revisions. Use of a vertical line would also add an unnecessary measure of complexity to the printing process, as companies would have to determine how to incorporate vertical lines on the multi-column format that is used for printed package inserts. PhRMA recommends that FDA not adopt this approach. Instead, revised sections or subsections should be identified in a narrative manner by citing the sections affected, e.g., in a section dedicated to labeling changes.

D. Type Size

PhRMA does not expect that the proposed requirement that all text be in 8-point type will produce meaningful benefits for health care practitioners. Furthermore, it will impose substantial printing and other logistical costs on manufacturers. Current type sizes range from

4.5 to 7 point. Use of 8-point type will produce a significant increase in the size of labeling (from 75 to 100 per cent), contrary to the agency's estimates. This change alone will present significant logistical problems, as new equipment will be needed for printing and packaging, and as many labels will become too large to attach to bottles and will have to be included in cartons. FDA itself has adopted use of 6-point type for OTC drug labeling in the recently revised Drug Facts box.[6] If 6-point type is adequate for consumers who are self-medicating, it should be adequate for health care practitioners. A larger type-size may be used for headings, but there is no need to expand the size of the labeling by requiring that all text appear in 8-point type. PhRMA recommends that FDA drop this proposed change.

V. Revisions to Labeling for Older Drugs

A. *In Vitro* and Animal Data [proposed § 201.80(b)(2)]

As explained above (section III.H), PhRMA believes that the current rules for the inclusion of *in vitro* and animal data should be retained. The same reasons that support retention of this data for newer products apply to older drugs.

B. Implied/Suggested Indications, Uses, or Dosing Outside "Indications and Usage" and "Dosage and Administration" Sections [proposed §§ 201.80(c)(2), (j) & (m)(1)]

As explained above (section III.C), PhRMA believes that there is not a good basis for the proposed restrictions on clinical information on indications, uses, or dosing not specifically referenced in the "Indications and Usage" and "Dosage and Administration" sections. The same grounds that exist for revising this aspect of the proposed rule for newer products apply to older products.

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[6] *See* 21 C.F.R. § 201.323.

C. Information for Patients [proposed § 201.80(f)(2)]

As explained above (section III.K), PhRMA believes that where there is approved patient labeling or a Medication Guide there should not be a requirement that the patient labeling or Medication Guide be printed twice to accompany trade packages.

VI. Proposed Implementation Plan

A. Requirements for Newly and More Recently Approved Drugs

PhRMA does not agree with the proposed implementation requirements for newly and more recently approved prescription drug products. A more prudent course would be to adopt a step-wise implementation plan, beginning with only original NDAs/BLAs and effectiveness supplements. This would allow sponsors and the agency to gain experience with the relabeling process, and would also focus resources to revise the newest products. Physicians are simply more likely to consult labeling for new products, as they are already generally familiar with the labeling for existing products.

After the agency and sponsors gain experience with the new labeling rules, and after additional data are collected about the real world utility and value of the changes, consideration could be given to extending the requirements to other products.

B. Labeling Changes for All Approved Prescription Drug Products

Under the proposed rule, approximately 1,838 products would require relabeling the first year after the rule becomes effective. Implementing the rule as proposed will increase the number of supplements requiring review and thus impose a significant burden on the agency. Given this burden, PhRMA is concerned that this initiative might compromise the agency's attention to the drug review and drug approval process. It would not be feasible to make the

proposed changes to existing product labels in one year. PhRMA recommends the requirements under this section be dropped.

C. Relationship of Proposed Requirements to Other Prescription Drug Labeling Initiatives

PhRMA recommends that the proposed rule include additional information on how implementation of the prior draft guidance on adverse reactions and other labeling initiatives (e.g., pediatric, geriatric, pregnancy, and antibiotic resistance) will be coordinated with this proposed rule. In addition, it is not clear how the paperless labeling initiative (i.e., electronic labeling) will be affected by the proposed rule. Industry is concerned that various ongoing labeling initiatives will not be coordinated and will force sponsors to revise a package insert for an individual program several times in the span of a few years.

VII. Revisions to Prescription Drug Labels -- Inactive Ingredient Information [proposed § 201.57(c)(12)(i)(D)]

PhRMA recommends that companies be permitted to list inactive ingredient information on product labels where appropriate. For example, information on potential allergens is potentially critical to proper medical treatment, and companies should be able to include such information on product labels as they determine proper.

PhRMA also urges that companies remain able to state on the label or carton the type of dispensing container that should be used when special conditions apply (e.g., light-resistant dispensing container necessary). Placing this information only in the insert is not adequate. It should be included in a conspicuous location such as the immediate container, label, or carton.

VIII. Economic Impacts -- Cost-Benefit Analysis

FDA's projected benefit of the proposed rule of $296 million in present value over ten years appears to be based on conclusory and unsupported assumptions. For example, the estimate for physician time saved as a result of the proposed labeling changes is based on a conclusion that the revised label format will save 15 seconds of reading time per physician per insert. There is no support for this conclusion. In fact, given that the proposed "Highlights" section is an incomplete summary of information that is already in the insert, and given the assurances by FDA that physicians will still need to read the full prescribing information before prescribing a drug, it seems clear that addition of the "Highlights" section would lengthen, rather than shorten, the time health care practitioners would need to read the labeling. Thus, contrary to FDA's conclusion that the new labeling will result in time savings, it is likely that the opposite will occur. The only way that would not be the case is if physicians save time because the "Highlights" section induces them to skip significant information in the full prescribing section of the labeling. This of course would be a dangerous result, would be a great disservice to better patient care, and is contrary to FDA's stated purpose for the proposed rule.

PhRMA is skeptical about the claimed benefits that FDA estimates would result from decreases in avoidable adverse events. The agency points out that some studies show that certain ADRs may be caused by incorrect product use and are thus avoidable. PhRMA supports FDA's well-intentioned goal of reducing avoidable adverse drug events. However, issues surrounding medication errors are complex and are only minimally addressed through this proposal. In addition to overstating the benefits of this proposal, FDA understates the costs. FDA estimates that the present value of the total implementation costs will be $94.53 million. This estimate is based on an incorrect assumption about how much longer package inserts would

become if the proposed requirements were implemented, and does not reflect the full attendant costs for retooling packaging lines. The cost estimates also do not reflect the indirect costs that will be incurred as the result of the agency resources that would be diverted to process the flood of labeling supplements and waiver requests that would be triggered.

Potential environmental costs also are not adequately considered. These costs could be significant. Additional paper, larger shipping containers, and cartons will be required for products to accommodate the longer labeling, and these costs should be weighed. This will also have ramifications for pharmacies, as they may be forced to purchase larger packaging units complicating inventory control.

Before imposing these new rules on the industry, especially since it is not at all clear that the benefits of the proposal will in fact be realized, PhRMA urges that FDA continue to work with the industry to develop proposals that will more effectively address the important concerns raised by the proposal.