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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: Docket No. 00N-1269
Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Products Labels; Proposed Rule

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Merck & Co., Inc. is a leading worldwide human health product company. Merck's corporate strategy — to discover new medicines through breakthrough research — encourages us to spend nearly $3 billion annually on worldwide Research and Development (R&D). Through a combination of the best science and state-of-the-art medicine, Merck's R&D pipeline has produced many of the important pharmaceutical and biological products on the market today.

As a leading human health care company responsible for providing health care providers with full and complete prescribing information for our marketed products, Merck is very interested in, and well-qualified to comment on the FDA-proposed rule on the Content and Format of Labeling for Human Prescription Drugs and Biologics and the Requirements for Prescription Drug Product Labels, hereafter referred to as the Proposed Rule. A summary of our concerns follows. Each of these points is discussed in greater detail in the body of this letter.

This Proposed Rule should focus entirely on responding to physician concerns regarding the ease of utilizing prescribing information and be based solely on the results of the physician surveys. It should not be used as a means to incorporate additional labeling proposals not discussed in the focus groups or via physician surveys. Merck supports the reformatting of the Comprehensive Prescribing Information with an Index. Merck does not support the inclusion of a Highlights section. Revision marks and features such as hypertext linking should be reserved for electronic media presentations. The Agency has underestimated resources needed to implement the proposal with regard to the types of submissions, volume of submissions, time, money, and equipment. A Guidance for Industry should be issued simultaneously with the Final Rule to describe implementation, submissions, and review expectations.

The text that follows is divided into: (1) Merck's general comments and recommendations regarding the Proposed Rule, (2) specific comments addressing the questions proposed by FDA, and (3) conclusions. The general comments have been organized, where appropriate, to follow the Federal Register of December 22, 2000.

00N-1269

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(1) General Comments

(1.1) Survey Results

In response to physician surveys, the Agency is proposing to alter the content and format of health care provider labeling to help providers prescribe drugs and biologics safely and effectively, a major undertaking throughout the pharmaceutical industry and within the Agency. Such a major undertaking is justified if it focuses on survey concerns, thereby enabling physicians to find specific information and discern the most critical information through the use of a numbering system. However, in the Proposed Rule, the Agency has also incorporated labeling revisions based on non-survey initiatives. These include redefining the parameters of safety data to be included in labeling, deleting information concerning *in vitro* and preclinical data from labeling, deleting certain clinical study information, and modifying container labeling. The inclusion of these other initiatives within the Proposed Rule extends the scope of the Proposed Rule well beyond the survey concerns.

Recommendation: While the revisions proposed outside of the issues identified in the physician survey also deserve attention, they are better served when addressed in separate initiatives with time for thorough review by industry and other interested parties, independent of the content and format of the package insert. Merck recommends the New Format initiative be limited specifically to the concerns raised in the survey and physician focus groups. Other initiatives described in the proposal should be separated and included, where appropriate, within other Agency initiatives in order to simplify the transition to the new format.

(1.2) Reformat of Package Insert (PI)

- **Comprehensive Prescribing Information and Index**

Merck supports a revised structure for the "Comprehensive Prescribing Information" to provide information in a format identified by physicians as useful to enhance the safe and effective use of prescription products. The inclusion of an Index is appropriate to allow the provider to quickly and easily locate relevant portions of the PI. Reformatting the Comprehensive Prescribing Information to provide information identified by physicians as more important to the beginning should assist physicians in quickly locating needed prescribing information and will result in a more "user-friendly" format .

The Comprehensive Prescribing Information format proposed is very similar to the prescribing information format used by the European Union in professional labeling, the Summary of Product Characteristics (SPC). The SPC is formatted to provide important prescribing information at the beginning of the document. The SPC format uses a numbering system for section and subsection very similar to that in the Proposed Rule.

- **Highlights**

The inclusion of an abbreviated summary of the Comprehensive Prescribing Information, the proposed Highlights section, is inappropriate for many reasons.

All of the safety and dosage information contained in the Comprehensive Prescribing Information is important and cannot (and should not) be condensed into a Highlights section. In addition, despite the language contained in the Proposed Rule, deciding what should be included in the Highlights section will necessarily entail an element of

judgment and choice on the part of the manufacturers[1] and the Agency. Discrepancies and inconsistencies could, and likely will, arise as different companies and different reviewing divisions within FDA select information from the Comprehensive Prescribing Information to include in the Highlights section.

A Highlights section is redundant because the same information would also be contained in the Comprehensive Prescribing Information. Moreover, inclusion of a Highlights section may encourage some providers to not read the Comprehensive Prescribing Information. The Highlights section cannot contain all of the important information set forth in the Comprehensive Prescribing Information. The inclusion of such a section may result in some providers relying solely on the Highlights section, thereby failing to read the additional important information contained in the Comprehensive Prescribing Information.

The addition of the Highlights section would also greatly increase production costs as it adds considerable length to already lengthy PIs while serving no helpful purpose as the same information would be fully described in the Comprehensive Prescribing Information immediately following. (See Section 1.11, Costs to Industry, for a discussion of increased costs associated with the Proposed Rule.)

Finally, inclusion of the Highlights section increases manufacturers' product liability exposure. (See Specific FDA Questions, 2, for a discussion of the product liability issues.)

Recommendation: Merck proposes that the Highlights section not be included and that the information be rearranged within the PI using a numbering system as described under the Comprehensive Prescribing Information section of the Proposed Rule. Placing the information that physicians have identified as most important at the beginning of the Comprehensive Prescribing Information and using a numbering system should allow physicians to quickly and easily find information.

Moreover, having both a half-page Highlights section, which would serve almost as an annotated Index, with the proposed Index is redundant. Merck proposes that the Index would be most appropriate in that it serves the Agency's purpose by allowing the provider to quickly and easily locate relevant portions of the PI. In addition, as providers become familiar with the standard numbering scheme for the Comprehensive Prescribing Information, they will become more proficient in finding the relevant information. In the event that a Highlights section is retained, the Index section should be eliminated.

(1.3) Guidance Document

The Proposed Rule requires extensive revisions to the PI, including: (1) selection of text for the Highlights section (if retained in the Final Rule); (2) reformatting; and (3) proposed deletion of information from sections of the PI to conform with the *Dosage and Administration* and *Indications and Usage* sections. The Proposed Rule also describes

[1] For example, proposed 201.57(a)(10) would require, in the Highlights section, the heading "Warnings/Precautions" 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." 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.

the method of submission when information is deleted from the PI as "Changes being effected without prior approval."

It is important that the Final Rule be consistently implemented across products. Based on the extent to which the Proposed Rule will impact product labeling, consideration should be given to simultaneously issuing a Guidance Document for Industry to help assure consistent application of the Proposed Rule across the industry.

Recommendation: As the Proposed Rule requires extensive revisions to the PI and has wide-reaching impact on the pharmaceutical industry, consideration should be given to the simultaneous issuance of an accompanying Guidance for Industry covering the submission of labeling supplements and the review of such by the FDA.

The FDA should also consider establishing target dates by which sponsors can expect action on labeling supplements submitted under the Proposed Rule.

(1.4) Changes Being Effected Supplements

In addition to the formatting changes required by the Proposed Rule, the Agency is proposing that sponsors delete information from other sections of the PI in order to remove information that is inconsistent with the *Indications and Usage* and *Dosage and Administration* sections [for newer drugs at 201.57(c)(2)(ii),(iii), (c)(3), (c)(13)(ii), and (c)(15)(i) and for older drugs at 201.80(b)(2), (c)(2)(i),(ii),(j) and (m)]. According to the preamble to the Proposed Rule, these deletions may be made without prior FDA approval, and should be submitted as "Changes Being Effected" supplements.

In practice, however, sponsors rarely delete information verbatim. More often, sponsors modify remaining text or add new text. When this occurs, the changes become more complicated and may no longer be considered "moderate" in nature, but rather "major", thus necessitating a "Prior Approval" supplement under 21CFR 314.70(b). In fact, for certain products, sponsors may enter into discussions with FDA when implementing the Final Rule. In such cases, a "Changes Being Effected" supplement may not be feasible or advisable.

Recommendation: The Agency should acknowledge that sponsors must use judgment when classifying labeling supplements to delete information from other sections for older and newer drugs (as cited above). Straightforward deletions should be permitted as "Changes Being Effected." However, more complex changes may require "Prior Approval" supplements.

(1.5) Use of Alternative Communication Media

Many of the proposals outlined in the Proposed Rule [e.g., format, hypertext linking to the Index, font size, highlighting revised sections, and including the text of the Patient Package Insert (PPI) at the end of the PI] would be more appropriate if applied to electronic forms of prescribing information rather than to trade packaging, especially since the physicians does not routinely access trade packaging.

Recommendation: With the advances in electronic communication through industry and FDA web sites and electronic mailings, Merck proposes implementation of the Proposed Rule (i.e., Index followed by Comprehensive Prescribing Information) primarily as an electronic initiative rather than for trade packaging. This "electronic PI" format would allow preparation and rapid dissemination of the PI in a larger print size, hypertext

linking of all sections to the Index, links to sections revised since the previous PI for the product, key word searches to immediately locate necessary prescribing information, and immediate availability of patient information with minimal impact on the paper size of labeling provided with trade packages.

The paper version of the PI used in trade packaging could then be formatted as described in the Proposed Rule including only the Index and Comprehensive Prescribing Information. This would greatly reduce excess use of paper in trade packages and substantially decrease engineering costs to industry while providing information to the prescriber in the most efficient manner.

(1.6) Approved Patient Information

The Proposed Rule describes adding the approved patient information to the end of the PI. In support of this proposal, the Agency stated that it "believes that including this information in professional labeling will facilitate practitioner access to the information and improve their ability to communicate to patients information that the Agency and sponsor believe is important." Physicians, rarely, if ever, access trade packages and it is Merck's understanding that physicians most frequently refer to the Physicians Desk Reference (PDR) and, to a lesser extent, promotional materials with accompanying labeling, as a source of prescribing information for particular products.

Implementing this requirement for trade packages would have little, if any, impact on the Agency's stated purpose, yet would significantly increase the capital costs to industry as well as incur a tremendous environmental impact as a result of the increased size of the PI in trade packages.

Currently, for Merck products with FDA-approved patient information (PPI), Merck attaches a PI and a separate PPI with trade packages. This allows the pharmacist to retain the full PI for his/her own use and to provide the consumer-focused PPI to the patient with the prescription. It is not clear from the Proposed Rule whether FDA contemplated that the proposed combined PI/PPI document would take the place only of the current PI, thus continuing to require a separate PPI or would be a single-document replacement for the current separate PI and PPI.

If it is contemplated that the combined PI/PPI document would replace the two existing separate documents for trade packages, it may make it more difficult for patients to find and read the patient information. In general, it should be easier for a patient to find relevant information in a stand-alone, more consumer-friendly PPI than it would be for a patient to read through a prescriber-oriented PI to find relevant consumer information at the end of the PI. This may be particularly true for elderly patients or for patients with impaired vision.

In addition, the combination of the PI with the PPI would make it more difficult for the patient to receive information at the pharmacy. The pharmacist would either have to provide the patient with the combined document (which would require the patient to read through the lengthy, prescriber-focused PI before getting to the patient information), separate the PPI from a tear-off section of the combined document, or provide the patient with no information. Currently, as noted above, the pharmacist can provide the separate PPI to the patient with his or her prescription while retaining a copy of the PI in the pharmacy.

If it is contemplated that the combined PI/PPI document would be in addition to a separate PPI for trade and sample packages, there will be a tremendous financial and environmental impact on sponsors who currently do not include the full patient information in the PI, but provide it as a separate document included with the trade packaging. In some cases it may necessitate returning to the use of cartons, thus negating many of the efficiencies and environmental savings previously obtained by using cartonless packaging. (See Section 1.11, Costs to Industry, for a discussion on increased costs associated with the Proposed Rule.)

Recommendation: In keeping with the FDA initiatives for improved patient compliance as described in the "Healthy People 2000" program, Merck proposes that for products with a separate approved PPI, manufacturers be permitted to continue to provide the PI and PPI as separate documents with trade packages. This would allow patients to continue to have access to the more consumer-friendly PPI, without having to search for information in the physician-oriented PI, and would allow the pharmacist to easily provide the patient with the information appropriate for the patient, while ensuring that the PI remains available for the pharmacist.

In order to accomplish the Agency's stated goals of facilitating prescriber access to the patient information, the combined PI and PPI could be provided in the PDR, which as noted above is one of the primary sources of prescribing information for the physician, in promotional materials distributed to physicians, and in electronic format. Costs to industry and the environmental impact associated with combining the PI and patient information in the PDR, in promotional materials, and in electronic format would be lower, although still significant, than those associated with making the same change for trade packages.

Merck also proposes that consideration be given to conducting a survey among pharmacists to determine the most cost-effective manner for presentation and distribution of PPIs to patients.

(1.7) Class Labeling

In the proposed rule, FDA does not address class labeling for the Highlights section. Many of the currently approved products affected by the Proposed Rule have class labeling in certain sections of the labeling, predominantly relating to safety issues. If the Final Rule requires a Highlights section, there may be inconsistency among products with class labeling, as the decisions will vary amongst different manufacturers as to what to include in the Highlights section. Additionally, for products within a class where text of the PIs is similar, consideration must be given to whether the FDA will mandate that these products be revised consistently.

Recommendation: For products with class labeling, if the Highlights section is retained, the FDA must designate which class labeling statements must be included to assure consistency across the class.

For products within a class where text of the PIs is similar, FDA should address the information to be included in the Highlights section.

(1.8) Timing for Review of Products to Delete Information

The one-year time limit for implementation of labeling to assure that there is no information within the PI that could imply a different indication or dose regimen is too restrictive for companies with a large number of marketed products. For example, a

company like Merck would need to review labeling for approximately 85 products, requiring the work of several personnel dedicated to the required reviews and submissions to the Agency.

There would also be a need for dedicated personnel at the Agency to review any labeling submitted within that same time frame, as all companies comply with the rule.

Recommendation: A phased-in approach is preferable. For example, within the first year, manufacturers could review labeling for products approved within the prior year. Thereafter, a longer time frame should be allowed for implementation of this requirement to permit a thorough review of information and references. An approach similar to that implemented for geriatric labeling could be used as outlined in the following table.

Approval Date vs Final Rule Date	Timing for Review Completion
Within 1 year	1 year
Within 2-10 years	3 years
11-20 years	5 years
More than 21 years	7 years

(1.9) Timing for Addition of Patient Information to the End of PI

If the Final Rule requires addition of the full text of the PPI to the PI for trade packages, additional time would be required for extensive reconfiguration and replacement of packaging equipment to accommodate the increased paper size of a combined PI and PPI.

Recommendation: Merck proposes that a lead time of 36 months be allowed to make the conversion to a combined document. This would permit the extensive reengineering and validation that will be required to prepare printing and packaging equipment.

(1.10) Use of Symbols/Icons to Designate New Information

Proposed 21 CFR 201.57(a)(2) describes an inverted black triangle to designate a product that has been "approved for less than 3 years in the United States and contains a new molecular entity or new biological product, a new combination of active ingredients, is indicated for a new population, is administered by a new route, or uses a novel drug delivery system." This symbol is intended to provide an easily recognizable way to signal the increased vigilance and reporting of suspected adverse reactions to facilitate faster recognition of events associated with newly marketed products, similar to a system used in the United Kingdom (UK).

According to the UK Medicines Control Agency (MCA), the black triangle symbol is: (1) used to identify new medicines which are under intensive monitoring, (2) well established, and (3) to alert health professionals to the fact that they should report any suspected adverse reaction to the MCA via the Yellow Card Scheme. The following criteria are applied to determine if a product receives "triangle" designation: (i) a new active substance, (ii) a new combination of active substances, (iii) is administered via a new route, significantly different from existing routes, (iv) uses a novel drug delivery system; and, for products that evolve following marketing authorization, (v) is to be given for a significant new indication, where this is likely to result in a significantly different population being exposed to the drug, or where there are potential safety concerns associated with the new indication.

The system in the United Kingdom is designed for reporting adverse events, i.e., doctors and hospital pharmacists are asked to report *all* suspected reactions (i.e., any adverse or any unsuspected event, however minor, which could conceivably be attributed to the drug). Reports should be made despite uncertainty about a causal relationship, irrespective of whether the reaction is well-recognized, and even if other drugs have been given concurrently.[2] This system is well-recognized and understood by health care professionals in the UK.

The use of this symbol in the US has several drawbacks. The symbol as currently described would have limited value to designate products that merit special attention for adverse event reporting as too many products would carry this symbol. Use and meaning of this symbol in US labeling will require an extensive educational effort directed to providers concurrent with efforts to encourage post-marketing reporting of adverse events. Lastly, there would be limited value to adding such a symbol and additional costs to industry to assure that the computer programs used to generate labeling converted the symbol accurately between programs. When printing the two versions (text and PDF versions) of the Federal Register containing this Proposed Rule; one version printed the proposed symbol as an exclamation point and one version printed it as an inverted black triangle.

Recommendation: The use of the inverted triangle symbol must be clearly defined and a major educational effort must be launched by the FDA to educate physicians and other health care professionals about its purpose.

Additionally, the Final Rule should clarify whether the symbol is required only for the first three years of the product's marketing or at any time during the product's life cycle when any of the other listed events may occur. As the Proposed Rule is written, it appears that this symbol is needed only for the listed criteria if the product has been approved for less than three years and any of the other listed criteria apply to the product.

(1.11) Costs to Industry

FDA estimates the capital costs for equipment changes would be about $1 million over ten years and direct costs would range from $8 to 16.9 million per year over ten years.

Based on the extent of the proposed revisions, the existing printing, folding and packaging equipment will, in many cases, not be adequate to accommodate the increased text.

In general, equipment changes require extensive retooling and a long lead time from the equipment manufacturer. Merck estimates that it could cost up to $700,000 per packaging line to accommodate the larger PI, substantially more than the costs estimated in the Proposed Rule. For some of the larger manufacturers, this could have the potential to exceed the FDA's $1 million capital cost estimate many times over. For a company such as Merck, where it may be necessary to convert over 50 packaging lines (within the Company and at toll manufacturers), the cost is projected to reach $40 million.

[2] ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000, Datapharm Publications Ltd., 1999, pps. iii,iv.

This estimate also does not take into consideration the potential increased costs that would be incurred or the environmental concerns that would arise if the new PI, incorporating all of the proposed revisions and the PPI text, would require the use of cartons for products currently packaged without cartons. If the PI becomes too large to adhere to the container, or makes the packaged container too unstable to stand upright during packaging or sales distribution, some products would have to revert to the use of cartons, an additional economic and environmental impact.

Availability of the equipment is also a concern. When the Proposed Rule is implemented across the industry, it will simultaneously impact multiple pharmaceutical and biological companies. A limited number of suppliers provide this type of packaging equipment to the industry.

Recommendation: As previously mentioned (see Section 1.5, Use of Alternative Communication Media and Section 1.6, Approved Patient Information), Merck proposes implementation of the Proposed Rule (i.e., Index followed by Comprehensive Prescribing Information) primarily as an electronic initiative rather than for trade packaging. Trade packaging could be reformatted to be identical to the Comprehensive Prescribing Information. This would eliminate any excess use of paper, avoid the need for returning to the use of cartons and greatly decrease engineering costs to industry while providing information to the provider in the most expeditious way.

(1.12) Substantive Labeling Revisions

In 21CFR 201.57(a)(5), the Agency is requesting that substantive labeling changes should be listed under the "Recent Labeling Changes" subsection of Highlights. However, no definition is provided concerning what constitutes a substantive labeling change. The definition of "substantive changes" should direct the providers' attention to clinically meaningful revisions.

Recommendation: Merck recommends that "substantive changes" be defined, either within the Final Rule or in an accompanying Guidance for Industry.

(1.13) Deletion of *in-vitro data*

FDA is proposing deletion of *in vitro* susceptibility data if not supported by adequate and well-controlled clinical studies. Currently inclusion of this information is allowed for anti-infective drugs if preceded by the statement: "The following *in vitro* data are available but their clinical significance is unknown." FDA is now proposing these data be omitted unless a waiver is granted. This is due to the concern that "...these data create the misleading impression that a product's *in vitro* action represents sufficient information to treat infections with the listed pathogens in humans.... This ultimately would contribute to the inappropriate prescribing of anti-infectives and may also be contributing to the further development of antimicrobial resistance for many drugs."

Recommendation: Merck proposes that *in vitro* data be retained in the Clinical Pharmacology section of the label for anti-infective products. As noted in the PhRMA comments to the recent proposed rule regarding antimicrobial labeling[3], physicians treating patients with serious bacterial infections must often rely on their training, experience and clinical practice to prescribe and initiate therapy with anti-infective

[3] Federal Register, September 19, 2000, Proposed Rule – Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use, pps. 56511-56518.

products prior to the availability of culture results and susceptibility data from clinical specimens. Additionally, there are few rapid diagnostic tests for acute bacterial infections available to aid decision making at the point of care. When patient-specific microbiological data are not available, decisions to prescribe an antibiotic for an approved indication must be based upon a clinical assessment of the most likely etiology and optimal therapy. All available clinical and pharmacodynamic information, including *in vitro* susceptibility data for recent clinical isolates of relevant pathogens contribute to this decision process.

Because physicians use *in vitro* data to decide upon an appropriate antimicrobial therapy, removal of this information about pathogens relevant to the approved indications would be a disservice to the prescriber who often must make immediate decisions on appropriate therapy. These *in vitro* data are clearly not a substitute for the clinical data but, when reviewed in conjunction with the clinical data, provide a better understanding of the attributes of the drug. Availability of the *in vitro* data allows the prescriber to be more fully aware of the spectrum of antibacterial activity of a particular agent, thus enabling more enlightened provisional decision making in initial treatment, pending the availability of culture results and definitive susceptibility data obtained from the patient.

If the FDA's primary intent is to assure proper drug usage, deletion of these data would require physicians to make decisions with even less knowledge about drugs and, rather than decrease, may actually increase misuse or overuse of the anti-infective agent. Deletion of these data would also be counter to the FDA Draft Guidance for Industry, July 1998[4] that recommended *in vitro* data be included with a disclaimer concerning their clinical significance. As stated in the introduction to Labeling for the Microbiology Subsection, "To provide the practicing physician with more complete data to characterize an antimicrobial drug product, the following format should be used in listing microorganisms in the *Microbiology* subsection of the CLINICAL PHARMACOLOGY section of the product labeling..."

Additionally, for approved prophylactic use, e.g., prior to colorectal surgery, these *in vitro* data, combined with the physician experience and clinical practice, provide necessary information to enable the physician to make a more informed decision concerning the appropriateness of the agent being considered for use in this clinical situation.

Based on these concerns, *in vitro* susceptibility data should be retained in the product labeling for antibacterial agents. As suggested in the FDA Draft Guidance for Industry, July 1998,[3] a clear statement can be provided in this section of the label to distinguish organisms in the *in vitro* only list (list #2) from the list of organisms (list #1) which have been studied in sufficient quantities in adequate and well-controlled clinical trials. Additionally, this approach is consistent with the EMEA Committee for Proprietary Medicinal Products (CPMP) Guidance on the Pharmacodynamic Section of the SPC for Anti-bacterial Medicinal Products, June 1997.[5]

(1.14) FDA Proposal – Indications and usage, Dosage and administration

In proposed Sections 201.57(c)(2) – *Indications and Usage,* and 201.57(c)(4) - *Dosage and Administration,* FDA is requiring that indications, uses or dosing regimens must not

[4] Draft Guidance for Industry, July 1998, Developing Antimicrobial Drugs – General Considerations for Clinical Trials, p. 40.

[5] The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP), Note for Guidance on the Pharmacodynamic Section of the SPC for Anti-Bacterial Medicinal Products, 18 June 1997.

be implied or suggested in other sections of the labeling if not included in these sections of the labeling. This is in disagreement with the current 201.57(e) section – *Warnings* and proposed section 201.57(c)(5) section – *Warnings/Precautions*, both of which indicate that a specific warning related to a use not provided for under the *Indications and Usage* section of the labeling may be required by FDA if the drug is commonly prescribed for a disease or condition, there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with clinically significant risk or hazard.

Recommendation: Merck recommends the Proposed Rule be amended to continue to allow inclusion of important information concerning the product, even when those data have not been used to support approved indications, in other sections of the labeling (such as the proposed *Warnings/precautions* section or within the *Clinical studies* section). The results of robust, adequate, and well-controlled clinical trials, even when they were not used to support approved indications, can be highly useful to the physician to determine the course of therapy when presented with an individual patient. Pertinent information, which may have been obtained at doses outside of the recommended dosage range or during clinical trials, and had not been used to support approved indications, may be summarized in these sections since the reported events may have been related to the drug.

In addition, certain disease states do not have the benefit of universal agreement on the definitions of their patient populations. Such diseases make it difficult for a physician to delineate whether a particular patient has a certain disease. Moreover, many patients present with concomitant diseases. When treating such patients, the physician finds it valuable to have access to additional clinical data in the labeling when determining the appropriate course of therapy, and would benefit from having this information within Agency–approved labeling. Such studies would, of course, need to be robust, adequate, and well-controlled to be useful. In addition, it is incumbent upon sponsors to assure that the indications are clear, and that any promotion of such clinical data be presented in a way that does not suggest an approved indication.

(1.15) FDA Proposal – How Supplied/Storage and Handling

In proposed Section 201.57(c)(4)(3)(v), FDA is requiring a statement directed to the pharmacist specifying the type of container to be used in dispensing the drug product.

Recommendation: Merck recommends the Proposed Rule be amended to only include this information if the product cannot be dispensed in standard amber pharmacy vials. This will serve to highlight the need for special considerations when dispensing a product which has special storage conditions.

(2) Specific FDA Questions

Merck appreciates the opportunity to respond to the following questions posed in the Proposed Rule.

1. Whether and under what circumstances, it may be inappropriate to include the proposed "Highlights of Prescribing Information" section in the labeling of a particular drug or drug class.

Merck Response: The Highlights section should not be included in the New Format. It would duplicate the majority of the dosing and safety information available in the reformatted Comprehensive Prescribing Information. It would be extremely difficult to eliminate from the Highlights section any of the safety or dosage information already described in the Comprehensive Prescribing Information and could result in somewhat arbitrary decisions being made as to what should be included in the section. The reformatted Comprehensive Prescribing Information, which moves the prescribing information identified by physicians as being most necessary and critical to the beginning of the PI, addresses physician concerns without resulting in redundancy in the text, arbitrary decision making regarding information to be included, increased costs to industry and increased environmental impact.

However, if the Highlights is retained, it should apply to all prescription drugs and biological products, rather than selectively eliminating the requirement for certain products.

2. Does the inclusion of a Highlights section have a significant effect on manufacturers' product liability concerns and, if so, is this concern adequately addressed by: (a)Titling this section "highlights" rather than "summary"; and (b) including the following statement, in bold, at the end of the highlights section: "These highlights do not include all the information needed to prescribe [name of drug] safely and effectively. See [name of drug]'s comprehensive prescribing information provided below." If these are not sufficient, could the Agency take different or additional measures to alleviate product liability concerns without eliminating the highlights section altogether or lengthening it to an extent that it would no longer serve its intended purpose?

Merck Response: Merck's experience with product liability litigation leads us to conclude that the inclusion of the Highlights section would have a significant effect on manufacturers' product liability exposure. For pharmaceutical products, the majority of states have adopted the liability standards established in Section 6(d) of the Restatement (Third) of Torts. Because of the vital importance of pharmaceuticals to the general public welfare and the risks that are unavoidable with prescription pharmaceuticals, the drafters of the Restatement stated that a pharmaceutical manufacturer complies with its duty of care if it provides "reasonable instructions or warnings regarding foreseeable risks of harm" to "prescribing and other health care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings...."

As noted in the comments to Section 6(d), "[f]ailure to instruct or warn is the major basis of liability for manufacturers of prescription drugs." Generally, therefore, when a patient sues a pharmaceutical manufacturer alleging that he or she was injured as a result of a pharmaceutical product, the court's focus is on the adequacy of the warning provided to the physician. A warning is usually considered adequate, and a manufacturer will not be found liable for a patient's injury, if the package circular for the pharmaceutical product states that the injury suffered by the patient may occur or has been reported to have occurred with the use of the pharmaceutical product.

The Agency's proposal to include a Highlights section at the beginning of the PI forces manufacturers to pick and choose for inclusion in the Highlights section only

certain of the safety information that is listed in the Comprehensive Prescribing Information. This would allow an expert witness testifying on behalf of a patient who suffered an adverse reaction listed in the Comprehensive Prescribing Information to argue that a manufacturer's warning was inadequate or "buried" because that specific adverse reaction was not also set forth in the Highlights section. However unjustified this position may be, it will increase the manufacturer's liability exposure with no offsetting benefit that could not be achieved with the reformatting of the PI and/or the inclusion of an Index section.

In the preamble to the Proposed Rule, the Agency stated that it "believes that it is highly speculative to assert that, because certain risk information has been summarized in or omitted from the Highlights section of prescription drug labeling (but included in its entirety in the Comprehensive Prescribing Information), a manufacturer may be found liable in a product liability action based on a theory that the warning is 'buried'." Based upon Merck's experience in prescription drug product liability litigation, however, we must respectfully disagree with the Agency's assessment that this argument is "speculative." Given that the focus of most prescription drug product liability litigation is on the adequacy of the warning provided to the physician, it has been Merck's experience that plaintiffs' experts do, in fact, focus on issues such as placement and prominence in alleging that a warning is not adequate.

For the above reasons, all of the information contained in the prescribing information is important and cannot (and should not) be condensed into a Highlights section. The Index section and the reformatting of the PI as proposed better serves the Agency's purposes by allowing the provider to quickly and easily locate relevant portions of the PI.

If the Highlights section is retained, Merck recommends that the section be titled, "Selected Highlights," to further communicate to physicians the idea that the information contained therein is only a selected portion of the information contained in the Comprehensive Prescribing Information.

In addition, if the Highlights section is retained, Merck recommends that the statement proposed by FDA be revised to read as follows:

> You should not rely exclusively on this Selected Highlights section, which cannot contain all of the important prescribing information about [drug]. One important source of more complete information that you should read is the Comprehensive Prescribing Information provided below.

This statement more accurately describes the Highlights section, clearly instructs providers not to rely solely on the Highlights section, and refers providers to the Comprehensive Prescribing Information as an additional, more complete source of information. In addition, in order to increase the prominence of this important statement, Merck recommends that it be placed immediately below the current header "Highlights of Prescribing Information."

3. Whether the full text of any boxed warning should be included in the "Highlights of Prescribing Information" section, regardless of length.

Merck Response: Merck disagrees with the inclusion of a Highlights section. However, if the Highlights section is retained, the entire text of any boxed warning should appear to avoid any confusion or misinterpretation of the warning information.

In addition, per the Proposed Rule [21CFR 201.57(a)(4)], "...both the text of the boxed warning or summary statement of the boxed warning and heading must be contained within a box and bolded." In the example provided,[6] it appears that only the first sentence of the text is bolded. Requiring bolding of the entire text of the boxed warning may be inconsistent with the "actual" boxed warning contained in the Comprehensive Prescribing Information. Therefore, Merck recommends that the typeface of the boxed warning be consistent with that in the Comprehensive Prescribing Information.

4. What different types of icons could be used to signal a boxed warning and what are their costs and benefits:

Merck Response: Although there should be no added costs to include a specific icon or symbol to designate a boxed warning, there also would be no added benefit as the interpretation of the symbol or icon could lead to confusion as to its meaning. Always providing the boxed warning information at the beginning of the Highlights section (if included) and the beginning of the Comprehensive Prescribing Information, rather than at different locations throughout the PI, and enclosing the text in a box should be adequate to draw the provider's attention to the information. This would not need to be referenced in the Index or could be referenced without interrupting the numbering sequence already planned.

Furthermore, the use of symbols can create problems with different computer software used to generate text, print labeling or prepare portable document formats (pdf) as symbols sometimes change between or among different software programs. Merck recommends, therefore, that no icons or symbols other than boxed text be used, that the boxed warning not be referenced in the Index, and that the boxed text always be placed at the beginning of the prescribing information.

5. Whether there should be a time limit by which the "Recent Labeling Changes" section must be removed:

Merck Response: Placing a time limit by which the "Recent Labeling Changes" section must be removed could lead, in some cases, to unnecessary expense and discard of printed material for no useful purpose if no other sections of the PI required revision in that time frame. If the Highlights section is retained, the "Recent Labeling Changes" subsection title should be changed to "Sections Revised." No time limit should be placed on the removal of this information. This would indicate to the reader what sections had actually changed from the previous version without

[6] Federal Register, December 22, 2000, Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels; Proposed Rule, p. 81125.

specifying the timing for the changes. Using the term "Recent Labeling Changes" could be interpreted to include revisions that occurred in more than one previous edition of the PI if multiple revisions had occurred within a short time frame.

6. Whether the information required under the "Indications and Usage" subsection in the proposed Highlights section should be presented verbatim from the comprehensive labeling section or summarized in a bulleted format.

   Merck Response: If the Highlights section is retained, manufacturers should be allowed to present indications either in a bulleted format or verbatim per the Comprehensive Prescribing Information. Some products with minimal information in the "Indications and Usage" section could provide a verbatim version in the Highlights section while other products with more extensive verbiage in "Indications and Usage" could use a shorter bulleted list of indications.

7. Whether it is necessary to include the proposed requirement for an index section given the proposed requirement for a highlights section (i.e., do the additional purposes served by the index justify its inclusion?)

   Merck Response: Merck strongly disagrees with the inclusion of a Highlights section. The Index is more useful. However, if the Highlights section is retained, the Index section should be deleted.

8. Whether not including standardized headings in the "Warnings/Precautions" section is appropriate. If it is believed that specific standardized headings should be included, FDA requests comments about what they should be.

   Merck Response: Standardized subheadings should not be required for this section and industry should be allowed flexibility within this section when deciding on appropriate subheadings. It would be extremely difficult to develop standard subheadings to address all areas of concern across all therapeutic groups.

9. Whether it is necessary to include a contact number for reporting suspected serious adverse drug reactions in the proposed "Comprehensive Prescribing Information" section as well as the proposed "Highlights of Prescribing Information" section.

   Merck Response: It is not necessary to include the same contact number for reporting suspected serious adverse drug reactions in two locations within the PI. If the Highlights section is retained, it would be more appropriate to include the telephone number in that location as it would be the first discussion of adverse experiences. If, the Highlights section is deleted, the contact telephone numbers could be added as a separate, pre-defined section with a standard location in the Comprehensive Prescribing Information.

10. Whether the potential impact of the proposed rule on small entities has been accurately estimated by the Agency, and whether small business concerns have been addressed.

    Merck Response: The Proposed Rule, combined with other FDA labeling initiatives now proposed or in development, has the potential to double the length of paper-based PIs. This format may require extensive re-engineering and re-design of

packaging lines and ancillary equipment for many products. This has the potential to have a tremendous impact on the larger companies, which arguably are more capable of making these conversions than smaller businesses.

Using an electronic medium to provide information to the prescriber rather than add to the current paper PI provided with the product would enable both small and large entities, to provide clearer, more "user-friendly" information more economically, without extensive re-engineering costs and with minimal environmental impact.

11. Whether the proposed requirement to bold certain information in proposed §201.57 (d)(5) will serve its intended purpose of ensuring the visual prominence of the bolded information or whether different highlighting methods may be more effective.

Merck Response: The use of bolding will serve its intended purpose of highlighting information. Requiring different highlighting methods, e.g., different colors, would result in additional expense in preparation of printed materials, add additional concerns about printing in different software programs and would not be relevant to the text provided in other publications printed in black and white such as the PDR.

12. Whether the proposed one-half page limit on the "Highlights of Prescribing Information" section [not including boxed warning(s) or contraindications(s)] is adequate or whether there are alternatives that would be more appropriate and under what circumstances such alternatives should be considered.

Merck Response: If the Highlights section is retained, the half-page limit of the Highlights section is adequate and should be required for all products. However, the format suggested is inconsistent with that outlined in the FDA Guidance for Electronic Labeling Submissions[7] and would require this guidance also be amended to reflect these changes.

13. What means [other than the vertical line proposed in §201.57(d)(9)] could be used to facilitate access to, and identification of, new labeling information in the comprehensive prescribing information section.

Merck Response: Revision marks should not be included in the PI. The meaning of revision marks within a paper-based PI would likely not be clear to providers without explanatory text. It cannot be assured that providers are familiar with the use of such revision marks. In addition, revision marks would add an unnecessary measure of complexity to the printing process and printed columnar text. Moreover, revision marks could stress the new changes to such a degree as to encourage the reader to focus only on the revised portions and potentially disregard unmarked text. Also, in the case of extensive revisions to the PI, it would be difficult to clearly point out all the changes.

If the Highlights section is retained, including a listing of revised sections should be sufficient to point out areas of change. This type of information would be better served by including it in an electronic format or providing hypertext links in an electronic medium to the revised statements.

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[7] Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDAs, January 1999.

14. Whether the proposed 8-point font size for labeling is sufficient or whether a minimum 10-point font size would be more appropriate.

Merck Response: Merck proposes to use the 8-point font for physician labeling provided in trade packages and using a larger font (9 to 10 point), whenever possible, for approved patient information. The prescribing physician routinely reviews labeling in the PDR, available electronically or as provided by industry representatives in promotion, and rarely accesses the PI provided with trade packaging. Preparing the paper-based PI using 10-point font in trade packages would again require a substantial increase in use of paper with no substantial advantage for the prescriber. The PPI, however, is provided to the patient at the time the product is dispensed and is prepared using a larger font.

15. Whether the revised format and content requirements should be applied to drug products with an NDA, BLA, or efficacy supplement that is pending at the effective date of the final rule, or that has been approved from 0 up to and including 5 years prior to the effective date of the final rule, or whether alternative application criteria should apply.

Merck Response: The implementation schedule outlined in the Proposed Rule for new format revisions is appropriate. Revising the final rule to require new format as a condition for product approval or efficacy supplement approval for products with applications pending at the time of the new rule would place an unnecessary burden on industry and the Agency as labeling already under review at the Agency would have to be reformatted prior to final approval.

(3) Overall Conclusions

In conclusion, Merck supports the FDA proposal regarding the reformatting of the PI to provide the information identified by physicians as most important in the beginning of the PI while continuing to retain all of the elements of the present PI as described in the current labeling regulations.

The use of revision marks and features such as hypertext linking should be reserved for electronic media presentations and should not burden the paper version with additional duplicative text which would lead to potential environmental impact, liability issues, and additional unnecessary costs to industry. The inclusion of a Highlights section would place additional and unnecessary financial and liability burdens on industry. This Proposed Rule should focus entirely on responding to physician concerns regarding the ease of utilizing the PI and be based solely on the results of the physician surveys. It should not be used as a means to incorporate additional labeling proposals not discussed in the focus groups or via provider surveys.

Finally, we believe the Agency has underestimated the resources, such as the types of submissions, volume of submissions, time, money, and equipment needed to implement the Proposed Rule. We recommend that the Final Rule have a limited scope and that a Guidance for Industry be simultaneously issued to describe implementation, submissions, and review expectations.

We recommend, therefore, that the proposal be revised in light of our comments and welcome the opportunity to discuss our comments before the Final Rule is issued.

Sincerely,

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