

**PHARMACIA**

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

Re: Docket No. 00N-1463 - FDA Proposed Rule for Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use (*Federal Register*, Vol. 65, No. 182, September 19, 2000, page 56511)

Sir/Madam:

PHARMACIA Corporation submits the following comments on the Proposed Rule, "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use". Our response is provided in accordance with the request stated in the Federal Register referenced above to submit written comments by December 4, 2000.

PHARMACIA is in general agreement with the comments sent to FDA by the Pharmaceutical Research and Manufacturers of America (PhRMA). We are providing comments on the Proposed Rule to emphasize those issues of significant importance to the development and implementation of drug labeling. Our specific comments and recommendations on the various sections of the Proposed Rule are provided in the attached table, which is designed to follow the outline of the Proposed Rule. General comments are provided below.

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- PHARMACIA shares the concern expressed by FDA with regard to antimicrobial resistance among disease-causing bacteria. However, we do not share FDA's belief that product labeling can and should be used "to educate physicians and the public about the problem of antibiotic resistance and to encourage more judicious use of antimicrobial drugs." It is our opinion that Product labeling should not dictate medical practice, which requires individualized clinical assessment of the patient and the circumstances under which the patient is being treated. The purpose of product labeling is to provide health care professionals with sufficient information to permit the safe and effective use of a prescription product.
- With regard to educating physicians, the Agency itself has recognized that changes to product labeling do not change prescribing behavior. Dr. Peter Honig, Director of CDER's Office of Postmarketing Drug Risk Assessment, expressed this idea at the Regulatory Affairs Professionals Society Conference that took place on October 2, 2000. Dr. Honig indicated that "knowledge does not necessarily drive behavior" and that labeling changes and Dear Doctor letters do not alter the prescribing habits of physicians. Perhaps other avenues to educate doctors should be explored. We respectfully point out that the role of the Agency should not include the teaching of medicine.
- Likewise, we believe that the attempt to educate the public through product labeling is misguided. A recent study<sup>1</sup> evaluated the effectiveness of a Medication Guide for a prescription product that cannot safely be used by certain patients or in combination with many other drugs. The study found that less than 50% of the patients who received the guide read it, and of the patients who reported having read the guide, only 50% could recall at least one issue discussed in it. Only 20% of the patients who knew the contents of the guide said they had taken some action based on it.
- In our opinion, the wording proposed in the rule has significant shortcomings. First, it contains basic medical information that is well known to physicians. Including this type of information in product labeling may be offensive to the health care professional and will not impart new knowledge to them. In addition, the use of standard labeling statements regarding medical practice is likely to make physicians skip those paragraphs when reading a package insert.
- The proposed language is very categorical with regard to the treatment of bacterial infections, while the reality is that in many areas of the country physicians do not have access to susceptibility testing. In addition, many infections are not easily cultured. We strongly believe that the proposed new language would result in significant legal liability for physicians because in many cases they would not be able to abide by the standard of practice dictated in the labeling. The result would be increased litigation against physicians, with the consequential increase in the cost of medical treatment.

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<sup>1</sup> Chianese CP. An overview of an initial experience with a medication guide. *Drug Info J* 2000;34:855-9.

- We feel that the information provided in the five proposed paragraphs is repetitive, forcing the inclusion of the same type of information in several sections of the labeling, and that the Proposed Rule would clutter the labeling without adding value to it.
- We agree with FDA's proposed implementation plan for new and abbreviated drug applications. However, we disagree with the implementation plan for approved applications. We feel that currently approved labeling should be "grandfathered." Certainly, the Agency should not expect industry to modify product labeling prior to the effective date of the Final Rule.
- The proposed rule should be coordinated with other upcoming labeling initiatives to ensure that the entire labeling document can be clearly and consistently understood by the reader and to maximize the limited resources of both FDA and industry. So far, labeling initiatives from the Agency seem to have been prepared independent of each other. It is increasingly difficult to envision what product labeling will look like after all these separate initiatives are implemented, and what benefit, if any, will be obtained from them.

We appreciate the opportunity to provide comments on this Proposed Rule and would be pleased to discuss these comments with the Agency, at your request.

Sincerely,



Kathleen J. Day

**Attachment**

**PHARMACIA's Assessment of the FDA Proposed Rule  
Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use**

FDA PROPOSAL	RECOMMENDATION
<p><b>Proposed §201.24(a)</b></p> <p><b>At the beginning of the label, after product name, add:</b>            Inappropriate use may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of this product and related antimicrobial agents. This product should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms.</p>	<p>Delete the new paragraph in its entirety. The area of the labeling between the product name and DESCRIPTION has been reserved in the past for Black Box Warnings. Health care providers look at this area of the labeling for critical safety information about the product, not for standard statements describing routine medical practice. The proposed new paragraph does not warrant the placement suggested by the Agency.</p> <p>As explained in our general comments, product labeling should not dictate medical practice.</p> <p>In addition, the exact same wording is proposed in PRECAUTIONS, General, resulting in cluttering of the labeling without adding value.</p> <p>If the Agency considers §201.24(a) necessary, we suggest the paragraph be changed to read:</p> <p style="padding-left: 40px;">Appropriate use of antimicrobial agents may help decrease the prevalence of drug resistant microorganisms, resulting in the continued effectiveness of this product and related agents. This product should be used only to treat infections that are strongly suspected or proven to be caused by susceptible microorganisms.</p> <p>The Proposed Rule uses the term "label" in the first paragraph of Proposed §201.24(a). To avoid confusion with the product's immediate label, we recommend that the Final Rule specify "package insert" instead of "label."</p>

**PHARMACIA's Assessment of the FDA Proposed Rule,  
Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use**

FDA PROPOSAL	RECOMMENDATION
<p><b>Proposed §201.24(b)</b></p> <p><b>CLINICAL PHARMACOLOGY</b> Appropriate use of this product includes, where applicable, identification of the causative microorganism and the determination of its susceptibility profile.</p>	<p>Many infections are not easy to culture and, as explained in our general comments, susceptibility testing is not readily available in all areas of the country.</p> <p>We recommend that the Final Rule specify that the statement be added to the Microbiology subsection, to avoid potential confusion regarding its placement. This type of information does not belong in any other area of the Clinical Pharmacology section.</p> <p>We also recommend that the statement be amended to read:</p> <p style="padding-left: 40px;">Appropriate use of this product may include, where applicable and practical, identification of the causative microorganism and the determination of its susceptibility profile.</p>
<p><b>Proposed §201.24(c)</b></p> <p><b>INDICATIONS AND USAGE</b> Local epidemiology and susceptibility patterns of the listed microorganisms should direct initial selection of the drug product for the treatment of the listed indications. Because of changing susceptibility patterns, definitive therapy should be guided by the results of susceptibility testing of the isolated pathogens.</p>	<p>Local epidemiology and susceptibility patterns may not be available or appropriate for a particular infection. Susceptibility testing may not be available in the region in which the patient is being treated.</p> <p>The categorical language of the second sentence would have extensive legal ramifications and should be modified.</p> <p>We recommend the following alternative wording:</p> <p style="padding-left: 40px;">Appropriate specimens for bacteriological examination should be obtained, when indicated and feasible, in order to isolate and identify causative organisms and to determine their susceptibility to [name of product]. Therapy may be instituted while awaiting the results of these studies. Once these results become available, antimicrobial therapy should be adjusted accordingly.</p>

**PHARMACIA's Assessment of the FDA Proposed Rule,  
Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use**

FDA PROPOSAL	RECOMMENDATION
<p><b>Proposed §201.24(d)</b></p> <p><b>PRECAUTIONS</b>  <b>General:</b>            Inappropriate use may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of this product and related antimicrobial agents. This product should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms.</p>	<p>The proposed information is well known to physicians and does not add any value, while cluttering the labeling. We recommend deleting it in its entirety.</p> <p>If the Agency considers §201.24(a) necessary, we suggest the paragraph be changed to read:</p> <p style="padding-left: 40px;">Appropriate use of antimicrobial agents may help decrease the prevalence of drug resistant microorganisms, resulting in the continued effectiveness of this product and related agents. This product should be used only to treat infections that are strongly suspected or proven to be caused by susceptible microorganisms.</p> <p>In addition, we recommend that this information appear only once in the labeling, not twice as proposed in the Rule. The more appropriate location is in this section of the labeling (PRECAUTIONS), rather than between the product name and DESCRIPTION.</p>
<p><b>Proposed §201.24(e)</b></p> <p><b>PRECAUTIONS</b>  <b>Information for Patients:</b>            Patients should be counseled that this product should be used only to treat bacterial infections. This product does not treat viral infections. Patients should also be counseled to take this product exactly as directed.</p>	<p>The proposed statement should be deleted in its entirety because it adds no value. Patients do not know how to identify bacterial or viral infections, or how to distinguish one from the other. The advice to take a product as directed applies to all medicinal products, not just antimicrobial agents.</p> <p>If the Agency considers §201.24(3) necessary, we suggest the following alternative:</p> <p style="padding-left: 40px;">Patients should be counseled to take all medicinal products exactly as directed.</p>