

WORLDWIDE REGULATORY AFFAIRS

December 4, 2000

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

**Re: Docket No. 00N-1463**

Dear Sir or Madam:

Wyeth-Ayerst Laboratories, a Division of American Home Products Corporation, respectfully submits comments to Docket No. 00N-1463, the proposed rule on Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use.

Wyeth-Ayerst Laboratories is a major research-oriented pharmaceutical company with leading products in the areas of women's health care, cardiovascular disease therapies, central nervous system drugs, anti-inflammatory agents, anti-infective agents, vaccines and generic pharmaceuticals. American Home Products Corporation is one of the world's largest research-based pharmaceutical and health care products companies, and is a leading developer, manufacturer and marketer of prescription drugs and over-the-counter medications.

We acknowledge the Agency's concern that inappropriate use of antibacterial products is a contributing factor to an increase in antimicrobial resistance, and we agree that physicians should be educated on proper prescribing for anti-infective agents. However, we believe that product labeling is not an effective, nor is it an appropriate, means to educate physicians on the proper prescribing practices for anti-infective agents. We therefore disagree with the Agency's proposal to include such educational language in product labeling. We do agree with the Agency that patients should be counseled on the appropriate use of antimicrobial products, and we agree with the proposed language for the Information for Patients subsection of labeling. Further, we are in support of comments submitted to this Docket by the Pharmaceutical Research and Manufacturers of America (PhRMA).

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— We offer the following additional comments on the proposed rule:

Labeling is not an effective means to educate physicians on the proper prescribing practices for anti-infective products.

It is well-known that the pharmaceutical industry contributes significantly towards physician education, advancing physician knowledge about current research, including information on the mechanism of action and mechanism of resistance of antibacterial agents, as well as product profiles. This usually occurs at seminars and at scientific symposia, and physicians are receptive to participating in the scientific exchange of information afforded by such venues. Efforts to educate physicians on the proper prescribing practices regarding antimicrobial products will be most effective, therefore, if information is provided by seminars, symposia and distribution of print proceedings from such activities rather than in a product label. Dissemination of information by these means could be provided by the pharmaceutical industry or by other associations, such as the AMA, IDSA, NFID, SHEA, ASM, ATS, ASH or even the CDC and FDA.<sup>1</sup>

Physicians consult the labeling of anti-infective products to obtain product characteristics and determine the proper dosing regimen to use. Appropriate antibiotic use should involve a complex decision-making process. This process needs to include consideration of patient diagnoses, likely or proven etiologies, local epidemiology, and many other factors. Professional societies such as the IDSA, AAP (and others) have made great efforts to develop clinical guidelines to address judicious antibiotic use. Education regarding a process this complex is unlikely to be accomplished by adding a few words to a product label. In fact, inclusion of information in labeling intended to educate the prescribing physician about the problem of antimicrobial resistance may not be read. If labeling is read by the physician, its impact for antimicrobial resistance education is likely to be minimal if it appears in all labels in numerous places in the label (i.e., all systemic antibiotic product labels); it will be seen as "boilerplate" noise, and not intended for significant impact.

The proposed language is not appropriate for inclusion in product labeling.

There is no statutory basis for the FDA to regulate physician conduct nor is there statutory obligation for the FDA or industry to train physicians; this is reflected in the information provided in product labeling, as supported by regulation [21CFR 201.57]. In general, product labeling does not address the practice of medicine. The clinical knowledge gained from years of medical training and experience can not, in a practical sense, be completely provided for in labeling, due to space constraints and the continuous evolution of medical knowledge (even several pages of information could not provide complete information on the application of medicine to a particular product). For example, the labeling for anti-

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<sup>1</sup> American Medical Association (AMA), Infectious Disease Society of America (IDSA), National Foundation for Infectious Diseases (NFID), Society for Healthcare Epidemiology of America (SHEA), American Society of Microbiology (ASM), American Thoracic Society (ATS), American Society of Hematology (ASH), Centers for Disease Control (CDC), Food and Drug Administration (FDA).

– infective products does not provide complete information to instruct the practicing physician on how to diagnose an infection, on how to handle all aspects of hypersensitivity reactions or on decision trees for further clinical intervention. Nor is there instruction or direction on how to correctly obtain a culture for susceptibility testing. There are medical/legal perspectives to be considered if incomplete medical practice is recommended in product labeling.

The proposed language is contrary to labeling recommendations for products that have prophylaxis indications, such as the prophylactic use of an anti-infective agent prior to open heart surgery. The proposed language also ignores the practicalities of medical practice which frequently demand empiric initiation of antibiotics, e.g., the febrile neutropenic patient,<sup>2</sup> or the ICU patient with pneumonia.<sup>3</sup>

The proposed language positions the potential to generate resistance as the same for all systemic antibacterials. In fact, several studies indicate that certain antibiotics, for example, cephalosporins, are more likely to be associated with the development of resistance than others.<sup>4,5</sup> Therefore, the general nature of the proposed language is misleading.

It is not appropriate, in the current health care system in the United States, to propose that a particular anti-infective product be used to treat infections only after culture and susceptibility testing information have been obtained. While there is no substitute for a correct diagnosis, susceptibility testing is not routinely performed for a great many of the infections treated in the United States. Indeed, current clinical laboratories could not handle the volume of work if susceptibility testing was performed for each antibiotic prescription written. Healthcare institutions, and individual physicians, could incur significant vulnerability if susceptibility testing was essentially mandated in product labeling but not performed, or if therapy was delayed until outcome of susceptibility testing was known. The labeling recommendation to require susceptibility testing would therefore impose a significant cost burden, and delay of treatment initiation could result in disastrous public health consequences.

#### Educational efforts regarding antimicrobial resistance are broader than systemic human antibacterial products.

The problem of antimicrobial resistance is an aggregate one. Significant resistance patterns can result from topical anti-infective use, as well as veterinary use of anti-infective products. Seemingly disparate microorganisms have been shown to transfer genetic

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<sup>2</sup> Hughes, W. et al. 1997 Guideline for the Use of Antimicrobial Agents in Neutropenic Patients. Clin Infect Dis 1997 25:551.

<sup>3</sup> Bartlett, JG et al. Practice Guidelines for the Management of Community-Acquired Pneumonia. Clin Infect Dis 2000 31:347.

<sup>4</sup> Lucet, JC et al. Outbreak of Multiply-Resistant Enterbacteriaceae in an Intensive Care Unit: Epidemiology and Risk Factors for Acquisition. Clin Infect Dis 1996 22:430.

<sup>5</sup> Hibbet-Rogers LCF, et al. Molecular Epidemiology of Ceftazidime-Resistant Enterobacteriaceae from Patients on a Pediatric Oncology Ward. J Antimicrob Chemother 1995 36:65.

material coding for drug resistance. In addition, resistant mycobacterium have contributed to the rise in tuberculosis seen worldwide, and resistance to anti-protozoal, anti-fungal and anti-viral compounds is also increasing. Educational efforts on all aspects of resistance should be pursued, as recommended above.

Alternate proposal for labeling language.

If the Agency goes forward with the concept of the proposed rule, it may be more appropriate to include language regarding antimicrobial resistance in a new section of labeling. This section could be a "General" section, and could be placed before one of the following existing sections of labeling that physicians are more inclined to read: Microbiology, Indications and Usage or Dosage and Administration. The following may be an appropriate phrase for this new section of labeling:

"Inappropriate use of antibiotic products may increase the prevalence of drug resistant microorganisms, leading to a potential decrease in the general overall effectiveness of antimicrobial agents."

Concluding Remarks

Wyeth-Ayerst appreciates the opportunity to comment on the proposed rule on Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use. We look forward to further Agency comments.

Sincerely,

WYETH-AYERST LABORATORIES

A handwritten signature in black ink that reads "Diane Mitrione". The signature is written in a cursive style with a large initial 'D'.

Diane Mitrione  
Assistant Vice-President  
Worldwide Regulatory Affairs