

December 1, 2000

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**Pharmaceutical
Division**

Carl E. Calcagni, R.Ph.
Vice President
Regulatory Affairs

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

Re: Docket No. 00N-1463
Labeling Requirements for Systemic Antibacterial Drug Products
Intended for Human Use: Proposed Rule

Dear Sir or Madam:

Bayer Corporation, Pharmaceutical Division, would like to provide comments on Docket No. 00N-1463 referenced above.

Bayer Corporation, (Bayer) supports the Food and Drug Administrations efforts to reduce antibiotic resistance and to improve the appropriate use of antibiotics, but would like to offer comments and recommendations to the approach offered in Docket No. 00N-1463.

In addition, Bayer would like to suggest that the FDA use educational and scientific forums as an alternative to the proposed label requirements. Bayer bases its suggestion on having long taken a responsible public position and an active role in fostering the appropriate use of antimicrobials in an effort to curb antibiotic resistance, to protect the public health, and to preserve the usefulness of antimicrobial agents in fighting disease. Bayer views communication, education and scientific debate as among the best means to curb antimicrobial resistance. Bayer is deeply concerned with the issue and recognizes the harmful implications that a continued rise in antibiotic resistance would have to public health and to our ability to continue to provide innovative therapeutic options in the treatment of infectious disease.

The following commentary addresses Bayer's specific concerns with Docket No. 00N-1463. A patient information section could be used to convey necessary product information to insure proper use of the product consistent with the approved labeling. Bayer understands the intent of the proposed FDA labeling rule, but believes the label is not the best place to communicate the message. Further, we believe that any additional labeling requirement *must not*:

- (1) Corrupt the intended purpose of the package insert.
- (2) Result in inconsistent communication within a given section of the package insert.
- (3) Compromise the physician's role as the primary and best-informed decision-maker.

00N-1463

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Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2065
Fax: 203 812-5364

The primary purpose of the package insert is to convey information to a learned intermediary, the physician. It is not intended as a promotional vehicle or as a means to tell a physician how to conduct his/her practice of medicine. Specifically, the package insert is included to convey how a product has been studied, how it is to be dosed, and to inform the health care practitioner of adverse reactions, warnings, etc

§ 201.24(a)

A statement that inappropriate use of antimicrobial drugs may increase the prevalence of drug resistant microorganisms and may decrease the effectiveness of antibacterial drug products.

- The beginning of the label should be reserved for critical safety information, or for a boxed WARNING, when warranted. Labeling regulation [21CFR 201.57(e)] requires a boxed warning for special problems, particularly those that may lead to death or serious injury and is specifically intended to provide prominence. Unless the Food and Drug Administration has elevated antibiotic drug resistance to such status, placing a statement concerning drug resistance right at the front of the package insert underneath the product name would set a precedent and further dilute the effectiveness of the “boxed WARNING”.
- Equally important, the definition of “inappropriate use” is subject to a broad range of interpretation. Until a more widely accepted definition is established, any such arbitrary use of the phrase should not be incorporated.

Antibacterial drug products should be used only to treat infections that are proven, or strongly suspected to be caused by, susceptible microorganisms.

- Specimen for culture and susceptibility testing are not routinely obtained from patients with community acquired infections.
- Diagnostic tests that immediately distinguish between viral and bacterial infections currently are not available.

§ 201.24(b), (c)

Susceptibility testing of isolated pathogens should be done when possible to guide the choice of an antibacterial drug product.

Initial selection of an antibacterial drug product should be based on local epidemiology and susceptibility patterns of suspected or identified microorganisms.

Definitive therapy should be guided by the results of susceptibility testing of isolated pathogens

It is our view, for the reasons stated below, that the agency's class labeling proposals for the "CLINICAL PHARMACOLOGY" and "INDICATIONS AND USAGE" sections are impracticable and will have little impact on current practice. Bayer currently employs the following language in its anti-infective labeling:

"Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to (name of drug). Therapy with (name of drug) may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued."

- While labeling can sometimes influence physicians, it is prudent to resist promulgating language that would seem to impose a specific standard of care or practice that must be followed.
- The approach of culturing microorganisms as part of the treatment of infections is usually not feasible in a clinical setting such as a physician's office.
- Managed care and third party payors have not funded the infrastructure that is required to support diagnostic testing in primary care settings. The cost effectiveness of having susceptibility data to guide antimicrobial therapy vs. prescription of a broad-spectrum antimicrobial agent has not been established.
- There is no scientific consensus on the need to use narrow spectrum antibiotics targeted towards organisms that have been identified through cultures in ambulatory patients.

§ 201.24(d)

Inappropriate use of antibacterial drug products may increase the prevalence of drug resistant microorganisms and may decrease the future effectiveness of antimicrobial agents.

- As in § 201.24(a) above, Bayer feels the definition of "use" is subject to a broad range of interpretation. Therefore, this statement should not be included.

§ 201.24(e)

There is a need to educate patients about when and how to take antibiotics, including the following:

- In Section 201.24(e), Bayer wholly supports inclusion of the following statement since it is an entirely appropriate communication because more and more patients do reference package inserts:
"Patients should be counseled that the antibiotic should be taken exactly as prescribed. Patients should be told that skipping doses or not finishing the full course of antibiotic may (1) decrease the effectiveness of their treatment and (2) increase the likelihood that bacteria will develop that will not be treatable by this antibiotic in the future."

Recommendation:

Bayer views communication, scientific debate, and physician/patient education as the best means to curb antimicrobial resistance. For the last thirteen years the Bayer Institute for Health Care Communication has sought to enhance the quality of health care by improving the communication between health care professionals and patients through education, research and advocacy. The Institute is a non-profit organization with an independent board of directors.

Bayer would like to recommend that the Food and Drug Administration meet with the Bayer Institute for Health Care Communication to consider their services to support an educational program for health care professionals on the issue and control of increased antibiotic resistance.

Bayer Corporation has taken an active and responsible role in fostering debate and education on the subject of antimicrobial resistance, as outlined below.

1. At the Inter-science Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Toronto in September 2000, Bayer presented three areas where the pharmaceutical industry can make a difference in curbing antimicrobial resistance:
 - Continued research and development to find efficacious innovative antibiotics.
 - Researching the mechanisms, the driving factors and epidemiology of resistance.
 - Public education projects—two of Bayer's most recent being:
 - *Operation Clean Hands* developed in collaboration with the American Society of Microbiology to promote hand washing as a means to stop the spread of bacteria.
 - A Canadian community pilot project, designed to decrease antibiotic use through specific and directed communication between physicians and patients, was launched in 1997.
2. A similar presentation on antimicrobial resistance was provided in May 2000 at the Royal Society of Medicine symposium in Washington, D.C.

While Bayer fully understands the intent of the proposed labeling rule, we urge the Food and Drug Administration to:

- Consult with organizations such as the Bayer Institute for Health Care Communication to educate through specifically designed programs for health care professionals about antibiotic resistance.
- Sponsor and encourage, along with the Center for Disease Control (CDC) and other regulatory agencies, scientific forums where antimicrobial resistance is addressed.
- Require patient directed information in package inserts as class labeling for antimicrobials.

Bayer appreciates the opportunity to comment and looks forward to an ongoing dialogue on this important public health issue.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Carl E. Calcagni', with a long, sweeping horizontal stroke extending to the right.

Carl E. Calcagni, R.Ph.
Vice President Regulatory Affairs