Reference Docket No. 00N-1269 (Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels

244 East Main Street
New Freedom, PA 17349

January 19, 2001

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

Dear Sirs:

The following comments are made in reference to the above document.

1. The in vitro (i.e. second list) information relating to the activity of an anti-infective provided in the current label **should remain** without the need for a waiver by the applicant. The reasons for this are based on and supportable by sound scientific evidence:

a. The Food and Drug Administration issued a document (NDA Holder's Letter – 1993) that provides to drug companies the algorithm for inclusion of organisms in the in vitro list of the product label. The algorithm is as follows:
   1. The organisms must be clinically relevant to the indications being sought. Organisms that are susceptible but are not pathogens for the indications approved may not be included in the product label.
   2. A certain number of isolates must be tested against the anti-infective before inclusion in the list.
   3. The in vitro susceptibility data for the organisms must have been obtained by using standardized methods of susceptibility testing. When standardized methods of susceptibility are not available the method must be thoroughly validated.
   4. The mean MIC_{90} for the isolates should be equal to or less than the final clinical "susceptible" breakpoint for the investigational drug.
   5. If there is any indication that the anti-infective would not be clinically efficacious, even if in vitro testing showed otherwise, it will not be included in the list.

b. All of the pharmacokinetic/pharmacodynamic parameters of the anti-infective and the in vitro susceptibility data that are considered for organisms in the "Indications and Usage" section of the label are taken into account for those organisms being considered for inclusion in the in vitro list. The pharmacokinetic information used to make the decision includes the absorption, distribution, metabolism, and elimination of the drug as described in the pharmacology section of the label. Critical to the approval of a pathogen for inclusion in the in vitro section is assessment of drug concentrations at the site of the approved indications.

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c. The in vitro list provides a valuable guideline for those in the practice of medicine. Some organisms cause diseases but not in high enough frequency to obtain sufficient numbers of organisms during clinical trials to provide proof of clinical efficacy. Physicians need guidelines on how to treat such organisms. Guidelines are also needed when the recommended antibiotics for a given infection do not work. Physicians have large demands on their time and are not able to obtain such information by consulting the scientific literature but must rely on information contained in the package insert. Therefore this valuable information should remain in the package insert.
d. The in vitro list provides an objective list of organisms that the anti-infective is active against thus decreasing the improper use of the anti-infective that may lead to development of resistance to the anti-infective.
e. The organisms in the in vitro section are reviewed when the drug company's annual report is submitted to the Agency. At that time organisms may be removed if the efficacy of the drug against the organism is questionable.
f. Organisms in the in vitro list are reviewed at the time that efficacy or other labeling supplements is submitted. At that time organisms may be removed if the efficacy of the drug against the organism is questionable.
g. The second list is used by the Center for Devices and Radiological Health (CDRH) to allow the labeling of a susceptibility test device to include particular organisms.

2. The current sentence ("The following in vitro data are available but their clinical significance is unknown.") preceding the in vitro list should be changed to:
   "The available pharmacological parameters and in vitro susceptibility data for the drug suggest in vivo activity against the following organisms for infection occurring at those sites indicated under "Indications and Usage". **This has not been proven clinically."**

3. Add to the label a "Clinical Microbiology" section following the "Clinical Pharmacology" section when the label is for an anti-infective. Clinical microbiology is a separate science from pharmacology.

   Clinical Microbiology deals with the interaction of the anti-infective and the microorganism responsible for the infection:
   a. Mechanism of action of action of the anti-infective on the microorganism
   b. Microorganisms the antibiotic is active against
   c. Infectious diseases the anti-infective is active against
   d. Pharmacokinetic/pharmacodynamic parameters of the anti-infective
   e. Susceptibility testing interpretive breakpoints and susceptibility test methods
   f. Mechanisms by which microorganisms become resistant to an anti-infective and the frequency with which this occurs
   g. The epidemiology of infectious diseases.

   Clinical Pharmacology deals with the interaction of the drug and the physiology of the patient:
   a. Absorption of the anti-infective

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b. Metabolism of the anti-infective
c. Excretion of the anti-infective
d. Side effects and toxicity's of the anti-infective

In addition a "Clinical Microbiology" section would more clearly identify to the user important information about the drug as it relates to its use to treat infection. Physicians and nurses are more familiar to seeing information that pertains to the effectiveness of an anti-infective against microorganisms under the heading "Clinical Microbiology" than under "Clinical Pharmacology".

4. This labeling proposal needs to take into consideration the proposals presented in FR proposed rule "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use" docket No. 00N-1463. This proposal would require that all systemic antibacterial drug products (i.e., antibiotics and their synthetic counterparts) intended for human use contain additional labeling information about the emergence of drug-resistant bacterial strains.

Allowing the in vitro list to remain under the current guidelines used for inclusion of the organisms in the second list will provide a valuable service to those using anti-infectives. What is required is that the Agency properly educate the user of anti-infectives as to the criteria that are used for allowing organisms into the list and how the list can be used to assure the that the anti-infective is used safely and efficaciously.

Sincerely,

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