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

January 19, 2001

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

Dear Sirs:

The following comments are made to Reference Docket No. 00N-1269:

1. 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. Microbiology deals with the action of an anti-infective against microorganisms (mechanism of action), the spectrum of activity of anti-infectives, the pharmacokinetic/pharmacodynamic parameters of anti-infectives, the establishment of susceptibility interpretive breakpoints, mechanisms by which microorganisms become resistant to an anti-infective, and the epidemiology of infectious diseases. Pharmacology deals with the interaction of drugs with the physiology of humans. The addition of 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". They refer to the "Clinical Pharmacology" section to obtain information about the behavior of the drug in the patient (ex. absorption, metabolism, excretion).
2. The *in vitro* (i.e. the 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:
   a. There is a current FDA document (NDA Holder's Letter – January 26, 1993) which has been provided to drug companies that provides the algorithm for inclusion of organisms in the *in vitro* list of the drug product label. The algorithm is as follows.
      A certain number of isolates must be tested against the anti-infective before inclusion in the list.
      The organisms must be clinically relevant to the indications being sought.
      The *in vitro* susceptibility data for the organisms must have been obtained by using standardized methods of susceptibility testing. Where standardized methods of susceptibility do not exist the method must be thoroughly validated.
      The mean MIC_{90} for the isolates should be equal to or less than the final clinical "susceptible" breakpoint for the investigational drug.
      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.

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b. All of the pharmacokinetic/pharmacodynamic parameters of the anti-infective 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.

c. The organisms in the *in vitro* section are reviewed when the drug company's annual report is submitted to the Agency. At that time, if it is appropriate, organisms may be removed if the efficacy of the drug against the organism is questionable.

d. Organisms in the *in vitro* list are reviewed at the time that efficacy or other labeling supplements are submitted. When appropriate organisms are removed if the efficacy of the drug against the organism is questionable.

e. The *in vitro* list provides a place for inclusion of organisms that are rarely encountered or may be difficult to treat. Thus, it provides an objective source of information to the physician that may not be readily available by other means.

f. 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.

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.

3. 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 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."

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 enhance the efficacy of the drug product.

Sincerely,

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