SUSCEPTIBILITY TESTING MANUFACTURERS ASSOCIATION

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May 8, 2001

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

Dear Sirs:

The Susceptibility Testing Manufacturers Association (STMA) is an organization recently formed to stimulate and enable cooperative and effective interaction between manufacturers of antimicrobic susceptibility test devices and pharmaceutical companies, regulatory agencies, standards organizations, and others regarding issues related to the field of susceptibility testing. We have reviewed "Reference Docket No. 00N-1269 (Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics: Requirements for Prescription Drug Product Labels)", and offer the following comments on the proposal to remove *in vitro* information related to the activity of an anti-infective from the drug's package insert.

Comment 1

We understand and support FDA's desire to help combat the spread of bacterial resistance to anti-infective agents, but we believe the proposed labeling changes will not help accomplish that goal, and may in fact hinder the efforts of physicians to effectively treat infections.

Our members strongly believe that *in vitro* information should be retained in drug labeling.

Comment 2

Presently, species of microorganisms are only included in the "*in vitro*" section of an anti-infective's package insert (PI) if (1) they are associated with an infection that appears in the "approved indications" section of the PI; and (2) at least 90% of the strains tested were susceptible *in vitro*, using the approved interpretive breakpoints. Since those breakpoints were developed using pharmacokinetic/pharmacodynamic properties (along with other information), and since the nature of the causative organism has no impact on tissue levels achieved by a given drug, it is not unreasonable to believe that a species on the "*in vitro*" list may respond to treatment with the drug. The current wording in drug PI's (i.e., "The following *in vitro* data are available, but their clinical significance is unknown... However, the safety and efficacy of [drug] have not been established in

00N-1269 C42

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adequate and well-controlled clinical trials.") seems to clearly convey to the reader the limitations of the data. In fact, we consider the change proposed by Dr. F. Marsik and H. Silver in their January 19, 2001 comments to the docket to be even more useful in educating physicians about how to interpret the "*in vitro*" section:

> "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."

The STMA supports this proposed wording.

Comment 3

Practically speaking, the vast majority of courses of antimicrobial therapy are initiated knowing only the possible site of infection (and, therefore, the probable causative agents based on historical data). The precise species is almost never known when empiric therapy is started, so knowing which drugs are most active against the majority of the species known to cause specific types of infections is essential to selection of the most appropriate drug. Removal of the "*in vitro*" section of an anti-infective's PI will effectively remove a large amount of information needed by physicians to determine which drug will give the broadest coverage of the probable pathogens.

Comment 4

There are a number of causative agents of infectious disease that do not occur frequently enough in a given clinical trial to be included in the "indicated uses" section, yet are known to cause the infections for which the drug is approved. Excluding these organisms from the "*in vitro*" section of drug PIs will make it more difficult to physicians to know how to treat infections caused by those particular species.

Comment 5

Antimicrobial susceptibility testing (AST) device submissions to FDA may only include data for evaluation of species listed in a drug's PI. As more species appear in the "*in vitro*" section than in the "indicated uses" section, removal of the former will severely limit the data used to demonstrate essential equivalence between AST test devices and reference methods. This deletion would potentially lead to a need for more and more 510(k) and PMA submissions, as each time a pharmaceutical company seeks and receives FDA approval for additional indications, the device manufacturers would have to seek additional clearances to add the new species to the device labeling. Unnecessary delays could be avoided if all of the possibly relevant species could be included in the initial device submissions.

To summarize, the STMA agrees with the conclusions provided by others in their comments that the *in vitro* list provides valuable information to clinicians and that the

user of anti-infectives should be appropriately informed as to how this *in vitro* information can be used.

Sincerely,

Willem Folkerts
President

Robert Badal
Vice President

Joanna Gerst
Secretary

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