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May 15, 2001

Dockets Management Branch
HFA-305
Food and Drug Administration
563 0 Fishers Lane
Room 1061
Rockville, MD 20852

Reference Docket No. OON-1269: Requirements on Content and format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels

Dear Sirs:

I am the Director of Medical Affairs for BD Diagnostic Systems, a division of Becton Dickinson. I am also Board-certified in both Infectious Diseases and Medical Microbiology and have been in clinical practice in both of these disciplines, I would like to make the following comments surrounding the proposal for removing the in *vitro* microbiologic data from the anti-infective drug labeling:

1. The Proposed Rule states "inclusion of these data in approved product labeling creates the misleading impression that a product's in vitro action represents sufficient information to treat infection with the listed pathogens in humans"

   - As a clinician I feel that the labeling is clear and does not mislead the prescriber, "The following *in vitro* data are available, **but the clinical significance is unknown."**

   - In addition, *in* vitro data alone, whether it pertains to organisms listed in the "Indications for Use" section, or in the *in vitro* section, never constitutes sufficient information to guide therapy--even regardless of the antimicrobial susceptibility result.

Examples:

- Erythromycin and *Staphylococcus aureus* (which is listed under the "Indications for Use" section for that drug): Even if this organism were susceptible to this drug, it should never be used to treat a serious staphylococcal infection. I would contend that it's inclusion in



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the "Indications for Use" section does not provide sufficient information to guide all therapeutic situations and therefore is actually misleading.

- Amoxicillin and *Escherichia coli*: Even if the organism were resistant to this drug, it still could be used successfully in a non-allergic patient who simply had cystitis, due to the increased drug levels available in the urine.

The point with these examples is that *in vitro* data alone, whether for organisms listed in the "Indications for Use" section or the *"in vitro" section,* never alone is sufficient information to help make therapeutic judgements.

More importantly, however, is the fact the many drugs are the antimicrobial agent of choice for organisms listed in the *"in vitro"* section, according to standard antimicrobial therapy guidelines (The Medical Letter 2000, Sanford Guide 2000).

A few examples:

- Rocephin® (Ceftriaxone) is listed as one of the drugs of choice for treatment of infections due to both *Salmonella typhi* and *Salmonella spp.,* yet both of these organisms are only included in the "*in* vitro" section of the labeling for this drug.

- Ciprofloxacin (as a fluoroquinolone) is listed as the drug of choice for treatment of the following organisms, all of which are only included in the "*in* vitro" section of the drug labeling:
  *Aeromonas hydrophila, Klebsiella oxytoca, Legionella pneumophila, Vibrio cholerae, Yersinia entercolitica, and Salmonella spp.*

- Imipenem is the drug of choice for treatment of infections due to *Alcaligenes faecalis* and *Campylobacter fetus,* yet neither of these organisms are included in the "Indications for Use" section, however, *A. faecalis* is included in the *"in vitro"* section.

Finally, there are organisms that are not even listed in the PDR in which a particular drug is the drug of choice:

Bactrim® (Trimethoprim/Sulfamethaxozole) is the drug of choice for treatment of infections due to both *Stenotrophomonas maltophila* and *Nocardia asterioides.*

2. The proposed ruling states, "in vitro data alone do not provide information about factors critical to effective therapy, including tissue levels of the product necessary to cure the infection and appropriate length of therapy" and that "such information is often essential to help ensure safe and effective use and avoid the development of antimicrobial resistance" and "more specifically, using anti-infectives at subtherapeutic levels.. . facilitates antimicrobial resistance".

   - Neither do the "Indications for Use" data provide this information or guarantee that sufficiently high enough tissue levels are going to be achieved in treating infections with the organisms listed. The breakpoints apply equally to both groups and simply

state that the pathogen is likely to be inhibited if the antibiotic in the blood reaches the concentrations usually achievable with the recommended doses.

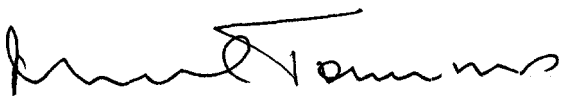
- Using anti-infectives at subtherapeutic levels does facilitate antimicrobial resistance, but this applies to the treatment of all organisms, regardless of whether they are in the "Indications for Use" section or the "in vitro" section. Is the FDA suggesting that for the treatment of only those organisms in the "in vitro" section that subtherapeutic doses could be used?

3. "FDA believes that "in vitro" labeling information contributes to the inappropriate prescribing of anti-infectives" and "may also be contributing to the further development of antimicrobial resistance for many drugs":

   - Does the FDA have data from peer-reviewed studies to support these statements?
   - Additionally, remember that many drugs are the first line/preferred choices for organisms listed in the "in vitro" section.. . so how can this be "inappropriate prescribing"?
   - Physician surveys, cited by the FDA in support of the proposed ruling, failed to mention any of these concerns or even made a statement that they concur that the *in vitro* information should be excluded in the labeling.

4. Finally, since drugs in antimicrobial susceptibility testing systems are approved only for organisms included in the approved drug labeling, no antimicrobial susceptibility test results could presumably be reported for those organisms currently in the "*in* vitro" section, when clearly, as indicated above, it would be appropriate to do so. Not providing these results might jeopardize the clinical care of patients. Moreover, this exclusion might actually increase antimicrobial resistance since physicians would not have *in vitro* antimicrobial susceptibility data to guide therapy in those instances of using a drug-of-choice against a pathogen in the *in vitro* section.

Respectfully submitted,



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