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IDSA

Infectious Diseases Society of America

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March 21, 2001

Food and Drug Administration
Dockets Management Branch
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

Re: Comments on Proposed Rule [Docket No. 00N-1269]: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels

To whom it may concern:

The Infectious Diseases Society of America (IDSA) appreciates the opportunity to comment on the above-captioned Food and Drug Administration (FDA) proposed rule on prescription drug product labels.

IDSA represents more than 6,000 physicians and scientists devoted to patient care, education, research, and community health planning in infectious diseases (ID). The discipline of infectious diseases is a subspecialty of both internal medicine and pediatrics, typically involving a two-to-three year fellowship and then board certification. Infectious diseases physicians care for patients with serious infections, including persons with HIV/AIDS, meningitis, heart valve infections, severe bone, joint or wound infections, and those with cancer or transplants who have life-threatening infections caused by unusual organisms. IDSA is the principal organization representing infectious diseases physicians.

Under FDA's proposed rule, in vitro data related to the activity or efficacy for anti-infective drugs would be removed from the prescription drug package inserts (PIs) and only would be included if FDA grants a waiver to the drug manufacturer [p.81095, subsection k]. Many of our members have expressed grave concerns about FDA's proposal to remove in vitro information from all PIs. Clinicians, of course, do not only rely on in vitro data when making decisions off-label. They also rely on their clinical experience with the drug and the principles of infectious disease therapy in general. However, as physicians weigh decisions and make judgments in their practice of medicine, it is important that all relevant data be available to them. Removing in vitro data from PIs poses problems that our member physicians believe, ultimately, will impact negatively on physician decision-making and patient care. Of particular concern, our members believe that FDA's action will impede physicians' ability to determine appropriate anti-infective therapy for patients with drug resistant or unusual infections.

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FDA articulates its reasoning for proposing to remove the in vitro data from PIs by stating that,

> *"despite the disclaimer concerning their lack of clinical relevance, inclusion of these data in approved product labeling creates the misleading impression that a product's in vitro action represents sufficient information to treat infections with the listed pathogens in humans. In vitro data alone do not provide information about factors critical to effective therapy, including tissue levels of the product necessary to cure the treated infection, and appropriate length of treatment. Such information is often essential to help ensure safe and effective use and avoid the development of antibiotic resistance."*

Our members disagree with FDA's logic for the following important reasons:

1) In vitro data related to a drug's activity or effectiveness are often helpful in situations where off-label use of a drug may be appropriate and may be particularly useful in the case of life-threatening infections with resistant pathogens. Often clinical studies do not include all of the relevant information necessary to make an informed decision. Thus, in vitro data provide clinicians trained in infectious diseases with some level of additional practical guidance based on tested information.

   Some practical examples may help to illustrate this point. One of our constituent ID physicians recently considered using caspofungin for a patient with azole-resistant *C. glabrata* endocarditis. This patient was not a surgical candidate and his infection was refractory to treatment with amphotericin B. The only data for the potential effectiveness of caspofungin for *C. glabrata* infection is in vitro data. Removing in vitro information would hamper efforts to care for patients with such refractory or unusual infections. As a result, our members feel strongly that FDA should not move in the direction outlined in the proposal (i.e., to remove the in vitro data), especially in the case of anti-infective drugs.

2) Many clinical situations often are not "typical" presentations and judgement becomes an important measuring stick. In those instances, it may be helpful to know that the drug either is not active in vitro or that the drug does not perform well in clinical situations. By being denied available information demonstrating that an antibiotic is inactive against a certain infectious agent in vitro (i.e., the infectious agent is resistant to the drug) there is potential for choosing the wrong anti-infective agent in a clinical situation (often called "major error"). This major error could lead to poor clinical outcomes with increased morbidity, the development of resistance, or even death. Withholding "negative data," may then impede a physician's decision-making ability with negative implications for patient care. Moreover, FDA's intended goal (as stated in its proposal) to avoid the development of resistance by withholding the in vitro information is undermined if, in so doing, they are creating other opportunities for resistance to develop.

3) As FDA notes in its proposed rule, in vitro data related to the activity or efficacy on drug labeling currently carries a disclaimer concerning their lack of clinical relevance. Our members believe that this disclaimer is sufficient to adequately notify clinicians about the level of reliance that should be afforded these data when making clinical decisions.

4) There is an important issue beyond clinical prescribing that may be affected by the changes outlined in the proposed rule. Clinicians, such as microbiologists, rely on PIs to tell them what organisms are appropriate for testing and what preliminary breakpoints should be used for new antimicrobial agents in that interval of time from FDA approval of the agent and to publication of in vitro breakpoints by the NCCLS. In some cases, as with the 2-year gap with trovafloxacin, microbiology laboratories have no guidance as to testing of the drug except for the information provided in the PIs. Information regarding activity against staphylococci, anaerobes and other organisms currently are present in PIs. In other instances, only limited information on certain organism groups is available, but this is an important indication of whether a drug should even be tested against that group of bacteria. An example is quinupristin/dalfopristin (Synercid), which was shown not to be effective against *E. faecalis*. This was important information and it was clearly indicated in the PI. If this information is expunged, it will have an adverse affect on the practice of antimicrobial susceptibility testing in clinical microbiology laboratories.

As the physicians who care for patients with serious and often life-threatening infections and as researchers who study drug resistance and are involved in development of new and better antimicrobial agents, our goal is to ensure that our patients have access to state-of-the-art care and that the care provided is the most clinically appropriate for each patient. Thus, we do not believe that in vitro data should be removed from the PI, and it is especially important that this should be maintained for anti-infective agent labeling.

Finally, as the PI format is being revised to make it more readable and to provide information more easily and rapidly, IDSA suggests that the in vitro activity of the agent along with clear cautions about its relevance be moved away from the clinical indications to a different location within the PI. In our view, this in vitro information is too valuable to be excluded from the PI, but we agree that every effort should be made to clarify the limitations of this information while continuing to make it available to the clinician.

We appreciate the opportunity to comment on the important issues raised in this proposed rule. We hope that FDA will make changes in response to the issues we have raised.

If you have any questions, or if we can provide you with additional information, please contact Robert Guidos, director of public policy at 703-299-0202.

Sincerely,

Carol J. Baker, MD
President

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