

acquired infections, including many respiratory tract infections and *otitis media*. FDA also agrees that there are no diagnostic tests that can immediately determine whether an infection is bacterial or viral. The revised statement for the "Indications and Usage" section recognizes these realities by advising that culture and susceptibility information should be considered in selecting or modifying antibacterial therapy when it is available.

(Comment 29) Many comments stated that the majority of infections, especially those acquired in the community rather than in the hospital, are and should be treated empirically without waiting for identification of the causative microorganism. One comment asserted that antibiotics must be initiated empirically for a febrile neutropenic patient or a patient with pneumonia in an intensive care unit (ICU). Another comment stated that the American Thoracic Society Guideline for Pneumonia recommends empirical treatment of pneumonia and concludes that Gram stains of sputum, cultures, and susceptibility testing are not cost-effective, particularly for outpatient infection. One comment stated that to delay the start of treatment waiting for culture results would be unethical as well as impractical. Another comment maintained that when patients are at risk of serious complications from infection, they must be treated empirically, and broad-spectrum therapy may be used to avoid treatment failure. Another comment stated that the agency has not considered outcome data concerning the benefits of empiric treatment on mortality and morbidity. One comment stated that doctors should decide whether to change antibiotic therapy based on the clinical situation, not only on in vitro susceptibility data. Another comment stated that there are not many efforts to gather information on treatment outcomes in ambulatory settings. One comment asked what the agency meant by the phrase "where applicable" in the statement: "Appropriate use of (*insert name of antibacterial drug product*) includes, where applicable, identification of the causative microorganism and determination of its susceptibility profile."

(Response) FDA agrees that antibiotic therapy must often be initiated empirically, including for patients with febrile neutropenia or ICU patients with pneumonia, and that it may be unethical to delay the initiation of therapy. FDA recognizes that in many situations physicians must make difficult choices about the need for empiric therapy and broad-spectrum agent use. Most clinical

guidelines concerning the management of such situations also recommend taking measures to alter treatment to more targeted antimicrobial coverage, such as through the use of bacterial cultures, whenever possible.

The agency did not intend to call for physicians to always refrain from initiating antibiotic therapy until the causative microorganism has been identified. The statement proposed for the "Indications and Usage" section recommended that initial selection of an antibiotic be guided by local epidemiology and susceptibility patterns, thus clearly contemplating that antibiotic therapy would be initiated before the results of culturing had been obtained. In addition, the modifier "where applicable" was intended to indicate that it is not always possible to do culture and susceptibility testing.

In response to comments, the agency has revised the statements about the role of culture and susceptibility tests and the use of local epidemiology and susceptibility patterns to make clear that FDA is not advising physicians that they should never prescribe antibiotics without first obtaining culture and susceptibility results or without referring to local epidemiology and susceptibility patterns. The agency has decided that the statement about culture and susceptibility information is more appropriate for the "Indications and Usage" section than for the "Clinical Pharmacology" section. The statement suggests that after initiating antibiotic therapy empirically, physicians should consider modifying therapy if susceptibility information becomes available and indicates that the microorganisms causing the infection are different from those initially suspected. FDA recognizes, however, that the physician must also weigh the clinical situation.

(Comment 30) One comment asserted that there is no scientific consensus on the need to use narrow-spectrum antibiotics targeted at organisms that have been identified through cultures.

(Response) FDA believes that using narrower spectrum, more targeted therapy, to treat a known organism can reduce the development of resistance. Narrower spectrum antimicrobials may have less impact on the normal organisms that colonize the body. Normal flora may protect the body from becoming colonized with other, more pathogenic bacteria. Also, normal flora exposed to an antimicrobial may become resistant to that antimicrobial and pass resistance genes on to more pathogenic bacteria. Therefore, prescribing narrower spectrum drugs may limit the spread of resistance while

still treating the pathogenic organisms causing the disease. This subject was discussed by presenters and panel members at the January 8, 2003, Anti-Infective Drugs Advisory Committee meeting. However, the labeling statements in the final rule do not dictate the use of narrow-spectrum antibiotics.

(Comment 31) Comments maintained that there are not enough laboratories to perform susceptibility testing for all of the antibiotics prescribed and that, in many parts of the country, physicians do not have access to susceptibility testing. One comment stated that few clinics have access to local microbiology labs; that the majority of microbiological diagnostic testing is done in central locations by a few laboratories, and that many hospitals do not have microbiology laboratories. This comment noted that the Infectious Disease Society of America has recently issued a position paper on the lack of access to microbiology laboratories and the threat that this lack of facilities poses to the public health. Two comments stated that the regulations of the Clinical Laboratory Improvement Act provide that Gram stains should be performed and interpreted by qualified lab technicians, not doctors.

One comment stated that the infrastructure required to support diagnostic testing in primary care settings is not in place and that diagnostic testing is not likely to be funded unless there are data to support the cost-effectiveness of doing culture and susceptibility testing rather than using broad-spectrum antibiotics. This comment also stated that the pharmaceutical industry should not have to fund such testing. Another comment stated that managed care and third-party payers have not funded the infrastructure required for diagnostic testing in primary care settings.

(Response) FDA agrees that some physicians lack access to facilities that perform susceptibility testing. The agency also agrees that it is not the responsibility of the pharmaceutical industry to make such testing available. The final rule's statement in the "Indications and Usage" section takes into account that culture and susceptibility information may not always be available.

1. Local Epidemiology and Susceptibility Patterns

Proposed § 201.24(c) would have required the following statement in the "Indications and Usage" section:

Local epidemiology and susceptibility patterns of the listed microorganisms should direct initial selection of (*insert name of*