

Background

Introduction:

The March 5, 2003 meeting of the Anti-Infective Drugs Advisory Committee is a continuation of previous discussions by the U.S. Food and Drug Administration (FDA) with various stakeholders regarding drug development for pathogens resistant to antimicrobial agents.

There is general agreement that the rate of *in vitro* resistance of many pathogens to current antimicrobial agents is increasing. The increasing concentrations of antimicrobials necessary to inhibit or kill microorganisms in the test tube in some cases are already translating into clinical failures of antimicrobial therapy. In other cases, *in vitro* resistance may not yet translate into clinical failures but may be a warning signal that the useful life of a drug or drug class as a therapeutic agent is in danger. In addition to antimicrobial resistance, the reemergence of infections such as tuberculosis, the emergence of new infectious diseases in the United States such as West Nile virus, the increasing prevalence of hospital acquired and opportunistic infections, and the imminent threat of bioterrorism all make drug development of new antimicrobial agents a matter of public health importance.

At previous advisory committee meetings, workshops and in publications, the pharmaceutical industry has reported shifting more resources toward research and development of agents to treat more common and chronic illnesses¹. This shift has resulted in a reduction in research and development of new antimicrobials. While clinicians use many therapeutic agents to treat serious infectious diseases and thereby prevent mortality and decrease morbidity, they most often prescribe these drugs for relatively short periods of time. However, drugs that are used by large numbers of individuals for prolonged time periods are more profitable for development than those used for short-term illness.¹ Fortunately in the United States many of these serious diseases are still relatively infrequent relative to more common chronic diseases, but in turn this makes these diseases more difficult to study in the context of a clinical trial.

The FDA began discussions on drug development for resistant pathogens at advisory committee meetings in the late 1990's and continued these discussions in February of 2002. At the February 2002 advisory committee meeting, representatives from the pharmaceutical industry presented several suggestions for streamlining the development process for resistant pathogens². The FDA will ask the committee to focus on two of these suggestions: 1) creating a list of pathogens considered of public health importance for the purposes of targeting drug development and 2) considering the degree to which a study performed in one indication could support safety and efficacy in another indication

¹ IDSA/PhRMA/FDA Workshop on Antimicrobial Drug Development, November 19-20, 2002, <http://www.fda.gov/cder/present/idsaphrma/>

² Anti-Infective Drugs Advisory Committee Meeting, February 20, 2002, <http://www.fda.gov/ohrms/dockets/ac/02/slides/3837s2.htm>

so that multiple studies would not be required in each indication in a multi-indication new drug application (NDA).

Listing Pathogens of Public Health Importance:

At a workshop in November 2002 co-sponsored by FDA, the Infectious Diseases Society of America (IDSA) and the Pharmaceutical Research and Manufacturers of America (PhRMA), the participants further explored the concept of a list of pathogens of public health importance for drug development. At that meeting, representatives of the FDA proposed an outline for the criteria for designating a pathogen of public health importance within a given disease for the purposes of drug development. Since the importance of various pathogens may change over time with the changing epidemiology of infectious diseases and the availability of alternative therapies, the criteria would be a way of ensuring consistency in the list over time. A resistant pathogen would not have to meet all these criteria to merit consideration for inclusion on the list. The criteria presented at the workshop are as follows:

Table 1. Criteria for pathogens of public health importance:

1. The pathogen is sufficiently common in the population and in the disease under study
2. The pathogen is capable of causing serious disease with significant morbidity and mortality in the disease under study
3. The drug(s) to which the pathogen is resistant are commonly used to treat the disease under study
4. There are few alternatives to treat the pathogen in the disease under study (i.e. the pathogen is resistant to multiple drug classes)
5. The drug(s) to which the organism is resistant is important in controlling the spread of the pathogen in the population (e.g. there is no vaccine for that pathogen)
6. Clinical data show *in vitro* resistance correlates with clinical outcomes

These criteria also raise several other considerations that merit discussion. The first is that this list would be to designate the pathogen as a threat to the health of a population. This is a different consideration than making treatment decisions for individual patients. Whether a drug gains regulatory approval and whether it garners a claim for resistant organisms are issues that may be considered separately.

The second consideration is the idea that a pathogen would be designated as important for diseases in which that pathogen is common. For instance, drug resistant *Neisseria gonorrhoeae* is a common cause of urethritis but it is not a common cause of community-acquired pneumonia. On the other hand, some pathogens may be a common cause of a wide spectrum of diseases. For instance *Escherichia coli* is a common pathogen in a number of infections from complicated urinary tract and intra-abdominal infections to hospital-acquired pneumonias.

The second consideration is the natural history of the disease in question. If an organism is important in a disease with a high morbidity and mortality, such as acute bacterial meningitis, is it equally important in a disease with less mortality where the magnitude of the contribution of antimicrobials to decreasing morbidity is uncertain, such as acute exacerbations of chronic bronchitis.

The last consideration is the idea that some pathogens have acquired resistance determinants that confer antimicrobial resistance to a wide spectrum of antimicrobial agents. If cross-resistance is high enough, should one consider a pathogen as “multi-drug resistant”? In this case, the pathogen would be given one designation on the list. For instance, methicillin-resistant *Staphylococcus aureus* are often resistant to quinolones as well. Should the designation of MRSA then by definition include quinolone resistant organisms or do methicillin-resistant and quinolone resistant *S. aureus* merit separate consideration?

On March 5, the committee will hear presentations discussing the nature of multi-drug resistant organisms, the perspective on the need for such a list from the pharmaceutical companies, and the FDA’s ongoing efforts to obtain data on the resistance patterns of such organisms that would potentially populate such a list.

Data from Studies in One Disease Supporting Studies in a Different Disease:

The second point the FDA is asking the committee to discuss is the request made in February 2002 by pharmaceutical industry representatives to allow one trial per disease instead of the requisite two studies per disease indication. The need for at least two trials is in part based on the inherent variability in clinical trials and the desire to ensure that drug efficacy and safety as demonstrated in a single trial is reproducible.

There is precedent, however, for accepting less than two trials for approval in a given disease indication. For instance, itraconazole was approved for empiric antifungal therapy in febrile neutropenic based on one trial in this indication but with supportive data from other treatment trials in fungal disease. Other examples include the treatment and prevention indications for *Pneumocystis carinii* pneumonia and *Mycobacterium avium*.

One way of approaching the idea of supportive studies is to consider information from other clinical studies within the development program of that drug. Several questions arise in discussing the issue of supportive studies. The first is the quality of the data from each study. If one is going to only perform one study in a given disease, should that study provide the strongest possible information e.g. a comparative trial with both microbiologic and clinical endpoints as appropriate rather than an open label trial with only microbiologic or only clinical endpoints. For example, if one were to do only one trial in acute bacterial sinusitis, would the most appropriate design be a randomized, controlled trial with microbiologic data obtained by sinus puncture (or some other validated method) as opposed to an open-label, non-comparative study with only clinical endpoints?

To address the question of which studies might be used to support studies in other indications, some of the factors which merit discussion and which the FDA will ask the committee to consider include:

Table 2. Factors to consider in data from one indication supporting another

1. Natural history of the disease under study - what is the spontaneous resolution rate and what is morbidity/mortality without treatment
Example: A quinolone is indicated for *Enterococcus faecalis* in complicated skin infections but does that data give one confidence that it would be effective in enterococcal bacteremia?
2. Factors other than the antimicrobial which may affect outcome in a given indication -
Examples: Surgery in intra-abdominal, debridement in complicated skin infections, numerous factors (smoking cessation, beta-agonists, anticholinergics, and steroids) in AECB
3. Characteristics of the study drug e.g. pharmacokinetics of the drug - does it reach site of infection?
Example: norfloxacin is indicated for UTI but not other infections.
pH effects - are aminoglycosides effective in intra-abdominal infections in a low pH environment?
4. monomicrobial vs. polymicrobial nature of infection –
Examples: complicated skin and intra-abdominal; debate on significance of enterococci when isolated in polymicrobial intra-abdominal infection
5. similar site of infection
Example: hospital-acquired pneumonia (HAP) and community acquired pneumonia (CAP)
6. host effects-
Example: are different cure rates in HAP vs. CAP due to effects of organism or host?
7. similarity in spectrum of organisms causing disease -
Example: differences in organisms most commonly causing HAP vs. CAP

Based in part on these and other factors, the FDA will ask the committee to discuss which clinical trial data from which indications may be supportive of efficacy and safety in other indications. The committee will also be asked to discuss whether data from more serious diseases can support safety and efficacy in less serious disease and whether the converse is true as well. The strongest supportive evidence would consist of studies in which the drug is used for the same duration and at the same dose, but the FDA will also ask the committee to discuss situations where data using other durations or dosing may be supportive as well.

The presentations planned for March 5 will include an expert clinician discussing how practitioners make decisions about safety and efficacy in drugs and how they extrapolate efficacy and safety on one disease from one disease to another. A presentation by a FDA representative will outline the above factors in more detail for further discussion by the committee.