Developing Drugs for Resistant Pathogens

Anti-Infective Drugs Advisory Committee

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FDA Briefing Document

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Introduction

Antimicrobial Resistance – The Challenge

Since the introduction of antimicrobial therapy antimicrobial resistance has been observed in a number of important microbial pathogens in both the community and health care setting. Historically, resistance to penicillin due to penicillinase- and beta-lactamase producing pathogens such *as Staphylococcus aureus, Haemophilus influenzae, Neisseria gonorrhoeae* was met by the development of drugs in the cephalosporin and other drug classes. The availability of vancomycin meant that methicillin-resistant *S. aureus* (MRSA) could be effectively treated. As pathogens develop resistance to available antimicrobials, new agents are needed. Recent trends in antimicrobial resistance rates among various pathogens isolated in nosocomial infections are shown in Figure 1. Temporal trends in drug resistance rates for *Streptococcus pneumoniae*, an important cause of community-acquired infections are shown in Figure 2.

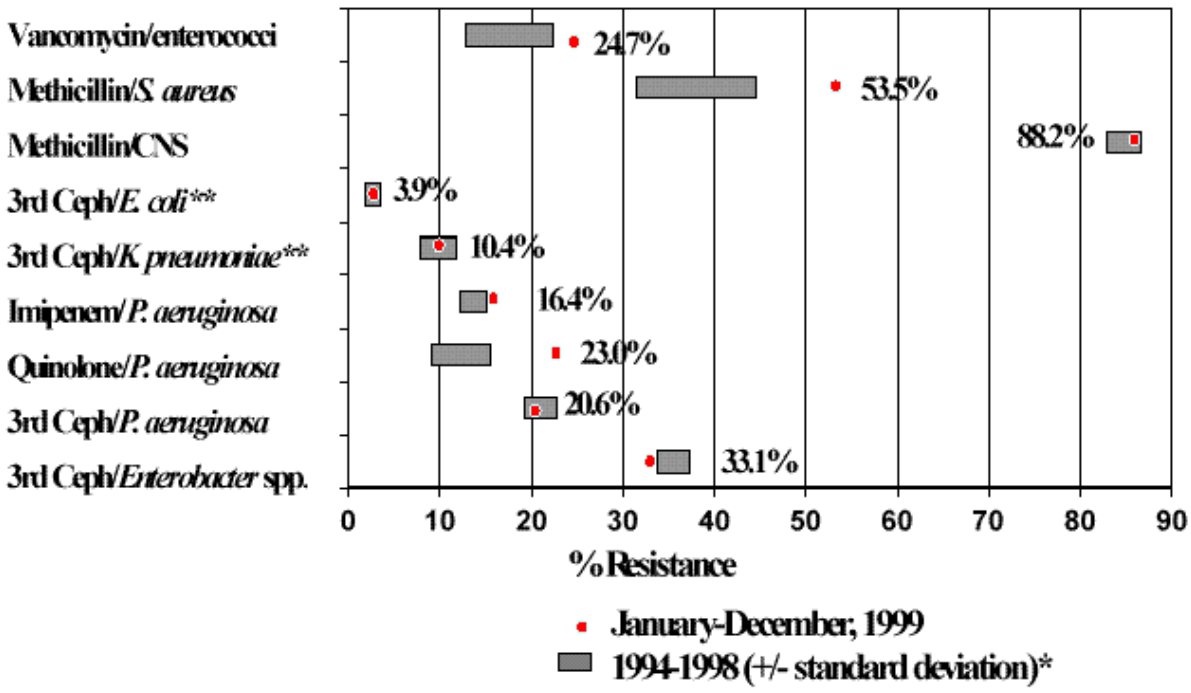

Figure 1. Selected antimicrobial resistant pathogens associated with nosocomial infections in ICU patients, comparison of resistance rates from January-December 1999 with 1994-1998. National Nosocomial Infections Surveillance System Semi-Annual Report, December 2000.

CNS=coagulase-negative staphylococci, 3rd Ceph = resistance to 3rd generation cephalosporins (either ceftriaxone, cefotaxime, or ceftazidime), Quinolone=resistance to either ciprofloxacin or ofloxacin.

Resistance for *E. coli* or *K. pneumoniae* is the rate of non-susceptibility of these organisms to either 3rd Ceph group or aztreonam.

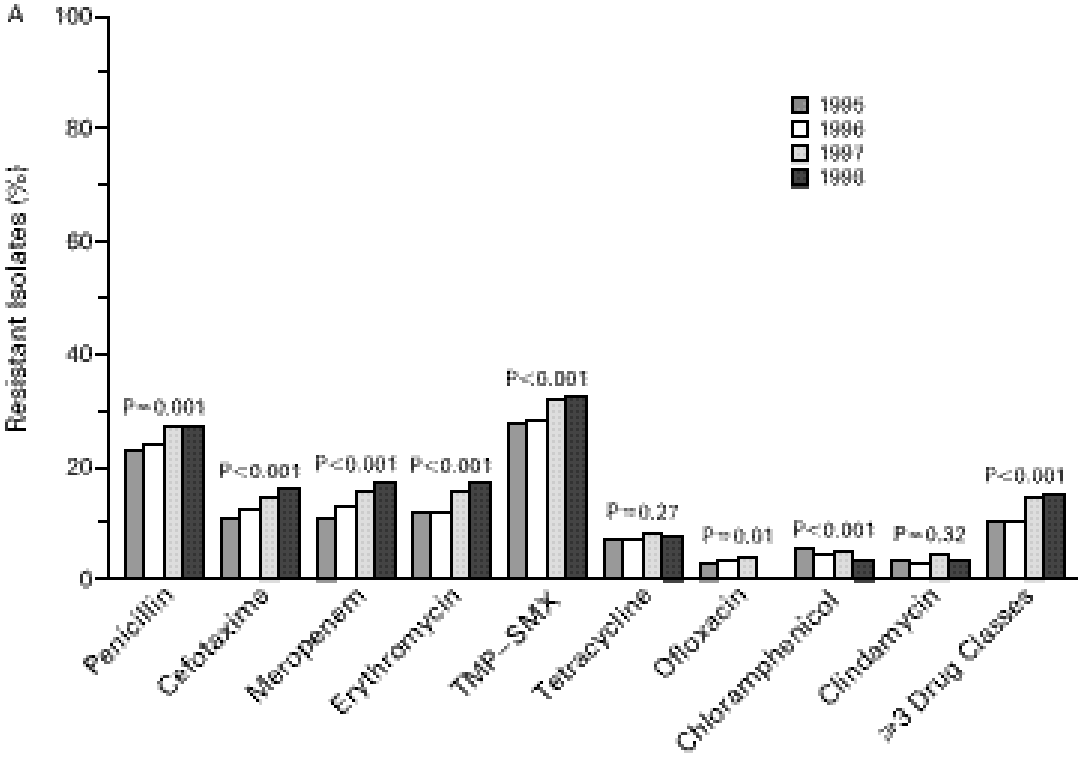

Figure 2. Frequency of resistance of invasive pneumococcal isolates to various agents according to year, 1995 through 1998, for selected counties in the United States. Whitney CG *et al.* New Engl J Med 2000; **343:**1917-1924. Total number of isolates is 12,045.

Some of the key resistant bacterial pathogens of public health concern are listed in Table 1; this list is not intended to be all-inclusive.

Table 1. Selected Resistant Pathogens of Public Health Concern	
Pathogen	**Antimicrobial Resistance Patterns**
Gram-Positive	
Streptococcus pneumoniae	Penicillin Macrolides Vancomycin tolerance
Staphylococcus aureus	Oxacillin (and all other â-lactams) Intermediate to vancomycin
Coagulase-negative *Staphylococcus* spp.	Intermediate to vancomycin
Enterococcus faecium	Vancomycin, aminoglycosides

Table 1 (cont.)	
Gram-Negative	
Enterobacteriaceae *Klebsiella pneumoniae* *Escherichia coli* *Proteus mirabilis* *Salmonella spp.*	Extended-spectrum â-lactamase (ESBL)-mediated
Pseudomonas aeruginosa	Multi-drug resistance (MDR)
Burkholderia cepacia	Trimethoprim/sulfamethoxazole Chloramphenicol
Salmonella (non-*typhi*)	*S. typhimurium* DT104 - MDR (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. Sometimes also quinolones and trimethoprim)

The increases in resistance rates in these pathogens may lead to increased mortality, morbidity, and health care costs in affected patients, and represent a major public health problem. While the current meeting focuses on resistance in bacterial organisms, resistance among fungal, mycobacterial, parasitic, and viral agents also represent evolving clinical problems in the arena of antimicrobial resistance.

In addition to the essential practice of prudent use of antimicrobial agents, efforts to foster the development of new antimicrobial agents represent an important part of the response to the problem of increasing antimicrobial resistance. However, as shown in Table 2, the numbers of reported deaths due to pathogens that have been associated with resistant phenotypes are lower than those due to some other medical conditions. Although these data may be affected by underreporting for a variety of reasons and do not take into account empiric use of antimicrobials, they suggest that the market for drugs aimed at resistant organisms may be significantly less attractive economically than that for other, more prevalent, serious conditions. In addition, the relative difficulty of identifying patients with infections due to resistant pathogens may greatly complicate accrual of subjects into Phase 3 trials. Thus, despite the serious public health problem of antimicrobial resistance, current market incentives may not be adequate to foster development of new antimicrobial compounds targeting resistant pathogens.

Table 2. Reported mortality for selected conditions, 1998		
Condition	**Deaths**	**Resistance rates**
Infectious		
Klebsiella pneumonia	134	10.7%
Pseudomonas pneumonia	388	17.1% - 23.3%
S. pneumoniae pneumonia	2411	24.1%
S. aureus pneumonia	933	46.7%
Staphylococcal septicemia	1269	46.7% - 85.7%
Non-infectious		
Congestive heart failure	46,980	N/A
Colon carcinoma	46,015	N/A
Alcoholic cirrhosis	8,222	N/A
Alzheimer's disease	22,725	N/A
Diabetes mellitus	47,448	N/A
Acute myocardial infarction	203,551	N/A

Sources: CDC WONDER database; 1998 NNIS report; Whitney *et al*. NEJM 343:1917.
Resistance rates refer to the following markers: Klebsiella - 3rd Ceph; Pseudomonas - 3rd Ceph, imipenem, and quinolones; *S. pneumoniae* – penicillin; *S. aureus* and other staphylococci - methicillin

Background – Prior History

There have been several prior DAIDP Advisory Committee meetings addressing the problem of increasing antimicrobial resistance. Meetings of the DAIDP Advisory Committee held in July 1996 and October 1998 addressed a number of issues in antimicrobial resistance, including recent trends among resistance rates in problem pathogens, the design of clinical studies to develop drugs for resistant pathogen indications, and regulatory approaches that could facilitate the development of antimicrobial agents for the treatment of resistant pathogens.

In addition, several recent product-specific Advisory Committee meetings have been held to discuss New Drug Applications that requested claims for the treatment of infections due to resistant pathogens. Table 3 lists these Advisory Committee meetings and some of the proposed claims.

Table 3. Resistant Pathogen Claims Discussed at Recent Product-Specific DAIDP Advisory Committee Meetings			
Meeting Date	**Agent**	**Formulations**	**Proposed claim discussed**
February 1998	Synercid (quinupristin/ dalfopristin)	IV	Vancomycin-resistant *Enterococcus faecium* infections; *methicillin-resistant *Staphylococcus aureus* in complicated skin and skin structure infections and nosocomial pneumonia

Table 3 (cont.)			
October 1999	Levaquin (levofloxacin)	IV/PO	Penicillin-resistant and *penicillin-intermediate *S. pneumoniae* in community-acquired pneumonia
October 1999	Avelox (moxifloxacin)	PO	*Penicillin-resistant and penicillin-intermediate *S. pneumoniae* in community-acquired pneumonia and acute bacterial sinusitis
April 2000	Zyvox (linezolid)	IV/PO	Vancomycin-resistant *Enterococcus faecium* infections; methicillin-resistant *S. aureus in* nosocomial pneumonia and complicated skin and skin structure; *penicillin-resistant *S. pneumoniae* in community-acquired pneumonia
January 2001	Augmentin 14:1 (amoxicillin/ clavulanate)	PO	*Penicillin-resistant and penicillin intermediate *S. pneumoniae* in otitis media
May 2001	Ketek (telithromycin)	PO	*Penicillin-resistant and macrolide-resistant *S. pneumoniae* in community-acquired pneumonia and acute bacterial sinusitis
*Not an approved claim in current labeling			

In addition to discussions of this issue by FDA Advisory Committees, a Federal Interagency Task Force on Antimicrobial Resistance has developed a response plan for addressing the problem of increasing antimicrobial resistance. This Task Force is co-chaired by the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health, and also includes the Agency for Healthcare Research and Quality, the Health Care Financing Administration (since renamed the Center for Medicare and Medicaid Services), the Health Resources and Services Administration, the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, and the Environmental Protection Agency. The Task Force also received valuable input from state and local health agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and other members of the public. With input from all of these stakeholders, the Task Force developed an action plan to combat antimicrobial resistance entitled, *A Public Health Action Plan to Combat Antimicrobial Resistance – Part 1: Domestic Issues*.[1] Part I of the *Action Plan* provides a blueprint for specific, coordinated federal actions to address the emerging threat of antimicrobial resistance domestically.

[1] *A Public Health Action Plan to Combat Antimicrobial Resistance – Part 1: Domestic Issues.* Interagency Task Force on Antimicrobial Resistance. Source: http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf

The *Action Plan* includes four focus areas: Surveillance, Prevention and Control, Research, and Product Development. Of the several Action Items from the Product Development Section that are particularly germane to the February 20, 2002 DAIDP Advisory Committee meeting, the most relevant is Action Item 82, which is provided in the excerpt below.

> *(82) Continue ongoing approaches that streamline the regulatory process, including clinical trials and enhanced pre-clinical studies (e.g., use of pharmacokinetics, and pharmacodynamics data) to help bring AR* [Antimicrobial Resistance] *products (including drugs, vaccines, diagnostics and devices) to market as efficiently and rapidly as possible, while still assuring their safety and efficacy.*
>
> - *This approach might involve use of an expedited process in which certain drugs are considered for approval, in accordance with Subpart E of the Investigational New Drug (IND) regulations. It might also involve defining new surrogate endpoints that indicate a meaningful response benefit over existing treatments for particular infections (e.g., HIV-1 RNA viral loads or CD4 counts as surrogate markers in the treatment of HIV/AIDS), in accordance with Subpart H of New Drug Application (NDA) regulations.*
> - *In the case of approvals for anti-infective medical devices, AR concerns will be addressed during the pre-and post-licensing review, to ensure that these products reduce infection without engendering significant resistance.*
> - *For products specifically targeted to serious or life-threatening AR infections, for which there are few therapeutic alternatives, develop approaches for more focused development programs that would streamline product availability. This should be done in consultation with all of the stakeholders in the process.*

Other Action Items in the *Action Plan* that are relevant to the February 20, 2002 Advisory Committee meeting include Action Items #80, #79, #30, and #27. (Note that the Action Plan is provided as one of the references within this briefing package.) Although incentives will not be formally discussed, Action Item # 80 is provided below because of its relevance to the issues that will be discussed.

> *(80) TOP PRIORITY ACTION ITEM - Identify ways (e.g. financial and/or other incentives or investments) to promote the development and/or appropriate use of priority AR products, such as novel compounds and approaches, for human and veterinary medicine for which market incentives are inadequate.*
>
> - *This process should include consultation with outside stakeholders, economic consultants, and the AR Product Development Working Group (Related Action Item: Product Development #79).*
> - *All such proposals will require careful economic modeling and analysis. New approaches should be used on a trial basis for*

appropriate time periods and the costs and benefits of incentives used in these pilot programs should be monitored to assess the return on the public investment.

- *Similar incentives should be explored for ensuring adequate availability of existing products that meet critical public health needs but for which market incentives are inadequate to assure supply. (Related Action Item: Product Development #79).*

While this committee meeting will focus on the issues described in Action Item # 82, other related comments from stakeholders regarding the development of antimicrobial drugs for the treatment of resistant pathogens are welcomed. It is also expected that a Docket will be available to receive written comments from interested parties following the February 20, 2002 Advisory Committee Meeting.

Purpose of this meeting

Background information has been provided on recent product-specific Advisory Committee meetings addressing resistant pathogen claims to describe agents that have pursued such claims. Given that antimicrobial resistance is an increasing problem, a trend likely to continue, the development of new agents for the treatment of resistant pathogens is an important issue both now and for the future. Therefore this briefing document explores a possible additional drug development pathway for agents that may have a specific role in the treatment of resistant pathogens. This approach is not meant to replace the one used to date, but rather represents an alternative strategy that may be appropriate for selected agents.

The primary goal of the February 20, 2002 meeting is to explore the development of antimicrobial drugs specifically for the treatment of resistant pathogens, as outlined in Action Item # 82. Implicit in this Action Item is the concept that in the setting of increasing antimicrobial resistance, there is a greater need for therapeutic agents for the treatment of serious or life-threatening infections caused by resistant pathogens, where no comparable or satisfactory alternative therapies exist. Because such therapies address an unmet need, appropriate risk management strategies may achieve a satisfactory risk-benefit profile when there is more actual or potential risk than would be acceptable for an agent treating a broad range of infections, including less serious infections, for which alternative therapies exist. For example, if an agent has the potential for notable toxicities, but preserved activity in the treatment of a resistant pathogen(s) when there are no alternative therapies available, then such an agent could potentially be appropriate for development within the type of program described below.

This issue is raised in large part because over the years there have been agents that have not been brought to market because of benefit-risk ratios that would not support the broad range of indications for which the product was developed. The approach described below is intended to offset some of these difficulties by providing a more expedited route for drug development that

involves smaller clinical efficacy databases. A drug with risks that make it inappropriate for use in a broad range of indications for which there are alternative therapies could be developed instead for use against a resistant pathogen in a serious indication for which there are few or no alternative therapies, potentially resulting in a satisfactory benefit-risk ratio.

What follows is a description of a potential pathway to foster the development of agents, particularly those that might otherwise not be developed, to address an unmet medical need in the treatment of serious infections due to resistant pathogens. Taking into consideration the limited use(s) for which a satisfactory risk-benefit profile is likely to be supported for such a focused, expedited drug development program, approval of these agents would likely involve at least one of the following:

- Product labeling noting that the indication is limited to the treatment of specific serious and life-threatening condition(s) when caused by the particular resistant pathogen(s) for which the drug has been developed, or when this particular pathogen is considered a likely causative organism.
- Products with particular safety issues that require restrictions in the distribution or use of the drug to assure safe use of the product would be considered for approval under Subpart H of 21 CFR Part 314. Approval under Subpart H-restricted distribution would provide a means of managing both the established and potential risks of the agent.
- For products for which approval is based upon adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint(s) reasonably likely to predict clinical benefit, approval under Subpart H could be applied.

Antimicrobial agents intended for a broader range of indications (including less serious conditions and conditions for which satisfactory alternative therapies already exist) would not typically be expected to be candidates for development as described within the conceptual drug development plan described in this briefing document.

To further define drugs that would be appropriate for this conceptual development plan, it may be helpful to describe four theoretical categories of antimicrobial agents. The categories are defined by whether the agent is intended for a broad range of indications or for a narrow range (i.e., specifically for a particular resistant pathogen in a serious indication) and then also examine which of these agents are new agents (i.e., unapproved agents) vs. drugs that are old agents (drugs that are approved). These categories of agents are delineated in the following chart. This meeting will focus on potential strategies for the development of agents that fall into Categories 3 and 4 (Fig. 3). (Note:

These theoretical "categories" are only intended for the purpose of discussion within the context of the information presented in this briefing document.)

Figure 3. Theoretical "Categories" for Antimicrobial Agents

	New	**Old (Approved)**
Broad Range of Indication(s)	**Category 1**	**Category 2**
Narrow Range of Indication(s)*	**Category 3**	**Category 4**

* Specifically for the treatment of one or more resistant pathogens in a serious indication or a limited range of serious indications

While the development of agents that would fall into Categories 1 and 2 remains an important area of drug development, this meeting will focus on the development of drugs for a narrower range of indications.

This meeting will explore:

- the development of antimicrobial agents specifically for the treatment of resistant pathogens.
- what approaches might be most helpful to the pharmaceutical industry with regards to fostering the development of agents that are intended specifically for the treatment of resistant pathogens.

One of the issues for discussion will be what are the obstacles to such a development plan and what measures could overcome such obstacles. In addition, this meeting will provide an opportunity for stakeholders to comment on what types of approaches or incentives would be most helpful in fostering the development of drugs for the treatment of resistant pathogens.

It is important to note that the purpose of the discussion at this meeting is not to set policy. Rather the meeting is intended to provide a forum for open discussion of approaches or ideas that may be further developed to promote the development of drugs for the treatment of resistant pathogens.

Regulatory Approaches

Existing regulatory mechanisms provide for an expedited approach to drug development for drugs that treat serious or life-threatening conditions for which there are few or no alternative therapies available. Subpart E of 21 CFR 312 and Subpart H of 21 CFR 314 are two regulations that address the development of such therapies. The initial section(s) of each of these regulations are excerpted below.

Subpart E of 21 CFR 312

§ 312.80 Purpose

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated in Sec. 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

Subpart H of 21 CFR 314

§ 314.500 Scope.

This subpart applies to certain new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on

epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

Description of the Concept Drug Development Program

Over the years some drugs have been studied that appeared to have potential utility in the treatment of resistant pathogens, but had particular safety issues that made it unlikely that they would be able to achieve a satisfactory risk-benefit profile for a more conventional antimicrobial drug development program (i.e., a broad range of indications, including less serious indications, for which there existed a number of alternative agents). However, if such a drug were developed in a more focused fashion, specifically to treat a problem resistant pathogen in a serious or life-threatening indication where few or no alternative therapies exist, such an agent might be able to attain a benefit-risk profile that was satisfactory (owing to the larger benefit afforded by providing an important therapeutic option for a serious condition where there was a significant unmet medical need).

The sections that follow provide a conceptual discussion of the type of antimicrobial agent that might be appropriate for such a development strategy, along with a rough description of what the drug development program might involve for such an approach.

Characteristics of a Candidate Antimicrobial Agent

An antimicrobial agent appropriate for development within the concept drug development approach described herein should have activity against a resistant pathogen or a group of resistant pathogens in a specific serious or life-

threatening indication(s) for which there exist no comparable or satisfactory alternative treatment options. The subject resistant pathogen or group of resistant pathogens should pose an important public health problem in the indication being studied. Ideally, the antimicrobial agent should retain clinically meaningful activity in the treatment of resistant pathogen(s) in the subject indication(s) in the setting of resistance to other approved antimicrobial therapies. The characteristics delineated in the list below attempt to take into consideration the type of information about an antimicrobial agent that would be available, depending upon the agent's stage within the course of drug development.

- The agent should have significant *in vitro* activity against a resistant pathogen(s). Ideally, its effectiveness should not be reduced by the development of resistance to other approved antimicrobial therapies (either to other drugs within its class or drugs outside its class). For example, the agent may derive from a new antimicrobial class and possess a unique mechanism of action or the mechanism of resistance to the agent may be unique. Its activity against drug-resistant pathogens may also be supported by results from validated animal models of experimental infection that are applicable to the human disease that is being evaluated. Similarly, the agent's utility in the treatment of a resistant pathogen(s) in the setting of resistance to other antimicrobials (in-class or out-of-class) may also be supported by results from validated animal models of infection and/or *in vitro* studies. For an antimicrobial agent that is being considered for development within the concept framework described herein that is at a later stage in development, the available human clinical efficacy data should support the utility of the drug in the treatment of the subject resistant pathogen(s) in the subject indication(s).
- There should be an absence of comparable or satisfactory alternative therapies available to treat the subject resistant pathogen(s) in the subject indication(s) in the intended patient population.
- The subject resistant pathogen-indication combination should be a serious or life-threatening condition representing an important public health problem. Development within this framework should be considered only for those resistant pathogens in indications where there is an important public health need. Because such agents are intended to treat serious or life-threatening infections, it is expected that most agents will be available in an intravenous formulation. [There may, under certain circumstances, be exceptions to the proviso that an intravenous formulation should be available. For instance, there are some serious infectious diseases due to resistant pathogens where the mainstay of therapy is treatment with an oral formulation (e.g., multidrug-resistant tuberculosis). Sponsors entertaining the development of antimicrobial agents for which an intravenous formulation will not be available, would be encouraged to discuss their plans with the Agency prior to initiating their drug development program.]

- The available safety information on the candidate drug (information appropriate for the agent's stage within its course of drug development) should support an acceptable risk-benefit profile for the agent in the treatment of the subject resistant pathogen(s) in the subject indication in the intended patient population(s).[2]

An antimicrobial agent with the above characteristics would typically be an appropriate candidate for development with a more focused drug development program targeting problem resistant pathogens in a serious indication(s). For agents that are further along in the drug development process, as noted in the criteria above, the development program should provide additional information that supports the clinical efficacy of the agent in the treatment of a resistant pathogen in an indication in which the resistant pathogen-indication combination represents an important public health problem. In addition, the available safety data should support an acceptable risk-benefit profile in the treatment of the subject resistant pathogen(s) in the subject indication(s).

Safety and efficacy must be demonstrated for the agent. However, since the agent is intended to address an unmet medical need in the treatment of a resistant pathogen(s) in a serious or life-threatening condition(s), a satisfactory risk-benefit ratio may be achieved, despite a degree of risk that would prevent "typical" antimicrobial agents (developed for a broader range of less serious indications against susceptible pathogens where alternative therapies exist) from achieving a satisfactory risk-benefit profile. This risk-benefit calculus is reflected by the following statement from the Subpart E regulation: *these procedures generally reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses*.[3]

Given the types of agents that may be developed using the approach described in this briefing document, it is likely that most agents will require specific risk management measures such as limiting distribution or use in order to support an acceptable risk-benefit profile for the agent. (See Subpart H (21 CFR 314).) It is also likely that an agent being developed as described herein will be an appropriate candidate for the procedures described under Subpart E (21 CFR 312).[3] For those agents for which the drug development program relies upon a surrogate endpoint as described in Subpart H (21 CFR 314), the procedures described in Subpart H would apply.[4]

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[2] The risk-benefit ratio calculus should take into consideration a risk-management program (e.g., approval with restrictions to assure safe use – see Subpart H (21 CFR 314)).

[3] 21 CFR parts 312 and 314, Investigational New Drug, Antibiotic and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses; Interim Rule (53 *Federal Register* 41516, October 21, 1988).

[4] 21 CFR 314 , New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval; Final Rule (57 Federal Register 58942, December 11, 1992).

What the Drug Development Plan Might Look Like

For an agent to be developed in an expedited and more focused approach as described herein, the Sponsor and the Agency should be in mutual agreement that such an approach to drug development is appropriate. As part of this process, when appropriate, the Agency may engage outside scientific experts or Advisory Committee members in determining the suitability of development in this fashion.

Given that the intended use for the agents described herein is to treat a resistant pathogen(s) in a serious or life-threatening indication(s) in a patient population where an unmet medical need exists, the risk-benefit ratio for such an agent will typically support a more focused drug development program than a general use antimicrobial agent developed for a broader range of indications. The risk-benefit ratio may also be supported by the provisions for restrictions to assure safe use in Subpart H, 21 CFR 314. The goal of drug development for such an agent should be the demonstration of safety and efficacy in the treatment of the subject resistant pathogen(s) in the subject indication(s).

Beginning with the early stages of drug development and throughout the drug development process, Sponsors would be encouraged to meet with the Agency to discuss the proposed drug development program for the agent.

A development program for a such an agent would typically include a phase 1 dose escalation study with measurements of blood concentrations (and other body fluids or tissues, as appropriate), and clearance. In addition the safety and the efficacy of the agent at the doses studied should be assessed. Traditional or sparse sampling techniques may be used to estimate the PK parameters and develop pharmacokinetic and pharmacodynamic relationships. Required phase 1 special population studies should also be conducted.

The phase 2 studies (or pilot studies) may include a dose-finding study designed to determine the optimal dose(s) for subsequent study based upon assessments of safety and efficacy in patients with the disease of interest. The studies should be designed to assess a clinical endpoint or an agreed upon disease-specific surrogate.

Two possible approaches to performing phase 2 or 3 studies that may be appropriate are described below. These two approaches differ depending on whether or not sufficient numbers of cases of the resistant pathogens causing the infection of interest are available to permit the timely clinical evaluation of the agent. In Approach 1 sufficient numbers of cases of the resistant pathogen in the indication of interest are anticipated to allow for clinical studies of the resistant pathogen-indication combination. Approach 2 relies on the use of surrogate endpoints in situations where the numbers of clinical cases of the resistant pathogen in the indication of interest are insufficient to permit the timely evaluation of the agent in clinical studies. Throughout the clinical studies, efforts should be undertaken to ensure the efficient and complete collection of safety data.

The following sections also describe some of the types of adjunctive non-clinical data that may provide additional supporting evidence of the drug's activity. While in concept such non-clinical data can be considered, their exact role in providing supportive evidence of the drug's activity will need to be discussed on a case-by-case basis. In general, there exist unresolved scientific issues as to the type and weight of evidence that such non-clinical data may provide. Sponsors considering submitting these or other non-clinical data should discuss their plans with the Agency early in their drug development program.

When the mechanism of resistance of the subject resistant pathogen affects the efficacy of the antimicrobial agent under study, the burden of evidence required to support the agent's efficacy is expected to be considerably larger than for agents where the mechanism of resistance has no relationship to the agent under study (e.g. in-class vs. out-of-class resistance). Sponsors considering development of such an agent should discuss their proposed drug development program with the Agency prior to its initiation.

1. Approach 1 – Developing the Agent Where Sufficient Data on Resistant Pathogens from Adequate and Well-Controlled Studies are Available

For the development of an agent where it is anticipated that clinical studies can be performed in sufficient numbers of patients with the resistant pathogen(s) in the subject indication(s), the data from these studies should provide clinical evidence of the drug's safety and efficacy in the treatment of the subject resistant pathogen(s) in the subject indication(s). (Note: Sponsors may wish to use enrichment strategies as a means of enrolling patients with the resistant pathogen(s) of interest.)

It may also be appropriate to complement the clinical data with data from animal models of infection with the subject resistant pathogen(s) and pharmacokinetic and pharmacodynamic (PK/PD) information. As previously noted, the exact role that such information may play in support of the drug's activity would need to be addressed on a case-by-case basis in an open forum such as an Advisory Committee meeting.

Because of the challenges of developing adequate and well-controlled clinical studies to evaluate the efficacy of an agent where few or no alternative therapeutic agents are available, Sponsors should discuss their plans for the development of a candidate agent with the Agency prior to embarking upon their drug development program. For those agents for which substantial evidence of safety and efficacy is demonstrated, the product labeling that will result from such a development program will reflect the data from the clinical studies in the treatment of the subject resistant pathogen, in the subject indication, in the intended population.

2. Approach 2 – Developing an Agent Where Sufficient Data on Resistant Pathogens from Adequate and Well-Controlled Studies are Not Available

For the development of an agent where insufficient numbers of patients are available with the subject resistant pathogen(s) in the subject indication(s) to permit the timely evaluation of the antimicrobial agent in clinical studies, alternative means of demonstrating efficacy may be considered. Such a drug development program might rely upon the use of surrogate endpoints as described in Subpart H. Data collected using such an approach should typically include data from clinical studies demonstrating activity against the subject pathogen(s) (some with and some without the specified resistance for which an indication is being sought) in the subject indication(s). The data examining the agent's clinical efficacy in the treatment of serious infections due to the pathogen of interest (in the absence of the specified resistance for which the drug is being developed) in the subject indication may potentially serve as a surrogate clinical endpoint for the treatment of the resistant pathogen of interest. Sponsor's considering such a development plan would be strongly encouraged to discuss their plans with the Agency prior to embarking on such a program.

Similar to Approach 1, it may also be appropriate to complement the clinical data with data from animal models of infection with the subject resistant pathogen(s) and pharmacokinetic and pharmacodynamic (PK/PD) information. As previously noted, the exact role that such information may play in support of the drug's activity would need to be addressed on a case-by-case basis and discussed in an open forum such as an Advisory Committee meeting.

Because this development program would rely on data from a surrogate endpoint(s) (e.g., clinical efficacy in the treatment of "susceptible" organisms, *in vitro* and pharmacokinetic data), it would most likely to lead to a submission under the provisions for the use of a surrogate endpoint of Subpart H (21 CFR 314).[5] If the Application receives approval under Subpart H, Sponsors would then be required to complete additional studies that establish and define the degree of clinical benefits to patients in accordance with Subpart H regulations.

General Comments Regarding Drug Development for Candidate Agents

Because of the unmet medical need that these agents are intended to address in the treatment of serious or life-threatening infections due to resistant pathogens and with the use of the provisions of Subpart H (21 CFR 314) restricting distribution or use, it is expected that the risk-benefit ratio (based upon the benefits of the drug and its known and potential risks) for such a product may be supported with a smaller clinical trials database. A smaller clinical efficacy

[5] As noted previously, taking into consideration the limited use(s) for which a satisfactory risk-benefit profile is likely to be supported for the agent, approval of these agents would likely require restricting the distribution or use of the drug to assure safe use of the product. (See subpart H (21 CFR Part 314).) Hence an approval that also involves a surrogate endpoint would involve both the provisions of Subpart H (21 CFR 314) addressing the use of surrogate endpoints and the provisions addressing limiting distribution or use to assure safe use of the product.

database (e.g., potentially as few as 300 to 500 patients) from the clinical studies along with the required special population phase 1 studies, may be submitted in support of a New Drug Application for the agent. In addition to providing general safety information, for agents with particularly notable toxicities, the available information should sufficiently characterize these noteworthy toxicities and the measures required to mitigate such risks, in order to allow for safe use of the agent.

Within the more focused drug development program for the agent, it will be essential to provide sufficient data characterizing the safety profile of the agent. Because of the potentially smaller size of the expected safety population, efforts should be undertaken to ensure the efficient and complete collection of safety data to maximize the value of the information obtained.

There may be situations where either the nature of the antimicrobial agent (and its associated toxicities), the resistant pathogen, or the disease under study pose unique challenges for the clinical development of a therapeutic agent. In such circumstances, Sponsor's are encouraged to discuss with the Agency their proposed plans for developing their drug.

While an agent is in development, surveillance data should continue to support that the agent has clinically meaningful activity against the subject resistant pathogen(s). For an agent that receives approval, it is likely that the approval will include a phase 4 commitment to provide continued surveillance data on an annual basis.

Summary

The conceptual drug development program described in this briefing document is intended to foster the development of antimicrobial agents specifically for the treatment of resistant pathogens in serious of life-threatening indications where few or no alternative agents exist. This approach to development allows a more focused drug development program based upon the likely larger benefit that such a drug will support while allowing for either greater risk or greater uncertainty regarding risk. This more expedited development program is intended to offset in part the limited scope of the marketing approval for which the agent would be developed. This limited range would be reflected in the labeling of the product which would be limited to the resistant pathogen(s) in the serious or life-threatening indications for which the drug was developed. The ultimate goal of this approach is to foster the development of antimicrobial agents where there exists an unmet medical need in the treatment of resistant pathogens where few or no alternative therapies exist. Ideally the availability of a concept drug development program such as described herein will foster the development of drugs that would otherwise not be brought to market. It is also important to note that this would be only one component in the overall response to antimicrobial resistance, but successful adoption of such a program could provide meaningful benefit to the public health.

Request for Feedback

This concept drug development program is provided to seek feedback from stakeholders as to the role that such a program might play in developing drugs for the treatment of resistant pathogens. Suggestions from interested parties as to how the program might be altered to better achieve its goals are welcomed, as are any alternative strategies. A docket will be made available to receive written comments subsequent to the February 20, 2002 meeting. Constructive criticism, alternative ideas, and any other thoughts from stakeholders as to what might be of value to stakeholders in fostering development of drugs for resistant pathogens are encouraged.

Appended References and Selected Readings

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