FDA Briefing Document

Anti-Infective Drugs Advisory Committee Meeting

October 17, 2013

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I. BACKGROUND

Susceptibility test interpretive criteria (breakpoints) are used by healthcare providers to select an appropriate antibacterial drug to treat a patient with a bacterial infection (typically choosing from among different antibacterial drugs to which the bacterial isolate is susceptible). Epidemiologic information about the susceptibility profile of bacterial pathogens can also inform empiric treatment of patients when a bacterial isolate has not been cultured in the laboratory. Susceptibility test interpretive criteria are set using clinical, pharmacokinetic and microbiologic data. Over time, new information may become available and/or new resistance mechanisms may develop such that the relationship between the current susceptibility test interpretive criteria and the likelihood of clinical response may change. Similarly, changes in testing methods may necessitate a change in susceptibility test interpretive criteria to more accurately categorize bacteria as susceptible or nonsusceptible.

Several scientific issues have come up during the ongoing efforts to update susceptibility test interpretive criteria. These issues include:

- Different types of evidence can be considered collectively in the evaluation of susceptibility test interpretive criteria, including clinical, microbiologic, and pharmacokinetic/pharmacodynamic data.
- Product labeling for certain antibacterial drugs has different approved dosing regimens for different indications. Different dosing regimens could potentially lead to different susceptibility test interpretive criteria for each of the different dosing regimens/indications.
- Scientific information could support increasing the recommended dose for one indication to make it consistent with other higher dosing regimens in the product labeling. Consistency in the dosing regimens could also lead to similar susceptibility test interpretive criteria for a specific bacterium across the approved indications.

In addition to these issues, increasing resistance in a number of different types of bacteria limits the available antibacterial drug choices to treat patients' infections. How the inter-related issues of susceptibility test interpretive criteria and dosing regimens are addressed can impact upon whether certain antibacterial drugs remain possible therapeutic options, or not.

At the time of initial approval, clinical efficacy data are generally available from randomized controlled clinical trials at the doses studied. Safety data at higher doses may be available if higher doses are approved for another indication. In the setting of increasing MICs for a drug, this raises the question whether the labeling should be revised to recommend a higher dose for all indications in the absence of any or limited clinical efficacy data for that particular indication at the higher

dose. In general, when considering a higher dose, one expects that efficacy will be preserved and the question is the safety of the higher dose and the benefit – risk of the proposed higher dose in the indication being considered. Safety data from the indication that uses the higher dose may be able to provide data to support increasing the dose for the indication with the lower labeled dose.

A second option would be to base the susceptibility test interpretive criteria on the lowest approved dose, which would result in lowering the susceptibility test interpretive criteria such that a greater proportion of pathogens may be categorized as resistant to the particular antibacterial drug. An undesired consequence of such a change would be the earlier loss of a therapeutic option and increased use of alternative antibacterial drugs.

A third possible approach to the situation is the possibility of having multiple susceptibility test interpretive criteria for an organism, each specific to an indication and supported by an approved dosing regimen in the product labeling. The practical implications of such a change will need further discussion.

Typically, the types of data that become available in the postmarketing setting have limitations. For example, while pharmacokinetic and pharmacodynamic simulations may support a higher dose to cover higher minimum inhibitory concentrations (MICs), clinical efficacy data may not be available evaluating the proposed higher dose in each of the indications. In addition, safety data would also be needed to evaluate the safety profile of the higher dose and higher exposures achieved. Typically, postmarketing clinical data are generally limited to case series or observational studies with wide variability in both quality and quantity. Microbiology data are usually limited to surveillance data or data from published studies.

This briefing package describes two hypothetical scenarios that highlight some of the issues discussed above. Despite our best attempts, creating perfect hypothetical scenarios is extremely challenging. Using the hypothetical scenarios, we have tried to highlight some key concepts on which we seek the committee's advice.

Scenario 1 describes Drug A, a beta-lactam antibacterial drug approved for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) at a dosing regimen of 1 g IV q8h and for the treatment of Hospital Acquired Bacterial Pneumonia (HABP) at a dosing regimen of 2 g IV q8h. *Pseudomonas aeruginosa* is listed as a pathogen in the ABSSSI and HABP indications. It is also approved for an indication of osteomyelitis at a dose of 4 g IV q8h. The osteomyelitis indication does not include *P. aeruginosa.* Currently, the susceptible breakpoint for *P. aeruginosa* is 8 mcg/ml. However, based on microbiology surveillance data, emergence of resistance and probability of target attainment analysis, the current susceptibility test interpretive criteria may need to be

modified. Probability of target attainment analysis can support a susceptibility breakpoint of 4 mcg/mL for the 2 g IV q8 h dosing regimen, while a breakpoint of 2 mcg/mL can be supported for the 1 g q 8h dosing regimen. Clinical safety data from randomized clinical trials are available at the 2 g IV q8 h dosing regimen for HABP and at the 4 g IV q 8h dosing regimen for the osteomyelitis indication. However, no safety or efficacy data are available for Drug A at the 2 g IV q8 h dosing regimen in patients with ABSSSI due to *P. aeruginosa*. This scenario is intended to facilitate discussions regarding:

- increasing the dose in the ABSSSI indication to match the dose in the HABP indication and using the same susceptibility test interpretive criteria for *P. aeruginosa* for ABSSSI and HABP
- not changing the dose for the ABSSSI indication and using different susceptibility test interpretive criteria for ABSSSI and HABP for *P. aeruginosa*
- using a single susceptibility test interpretive criteria based on the lowest exposure achieved with the ABSSSI indication
- the role of the different types of data that may inform modifying the susceptibility test interpretive criteria

Scenario 2 describes Drug B, a beta-lactam antibacterial drug approved for the treatment of ABSSSI, complicated intra-abdominal infections (cIAI) and HABP. The dosing regimens for the three indications are as follows: 0.5 g IV every (q) 12 h for ABSSSI, 1 gram IV q 8 h for cIAI, and 2 g IV q 8 h for HABP. *Escherichia coli* is listed as a pathogen for each of the three approved indications. Currently, the susceptible breakpoint for *E.coli* for Drug B is 8 mcg/ml. However, based on microbiology surveillance data, emergence of resistance and probability of target attainment analysis, the current susceptibility test interpretive criteria may need to be modified. Probability of target attainment analysis can support three potential susceptible breakpoints for *E.coli* based on the different dosing regimens. Alternatively, a susceptibility breakpoint of 4 mcg/ml can be supported by the 2 g IV q 8 h dosing regimen across all the approved indications. Safety data from randomized clinical trials are not available for Drug B at the 2 g IV q8h dosing regimen in patients with ABSSSI or cIAI, but are available for the at 2 g IV q8h dosing regimen for the HABP indication.

This scenario also raises similar topics for discussion similar to Scenario 1:

- increasing the dose in the ABSSSI and cIAI indications to match the dose in the HABP indication and using the same susceptibility test interpretive criteria for all three indications
- not changing the dose for the ABSSSI or cIAI indications and using different susceptibility test interpretive criteria for each of the three approved indications

- using a single susceptibility test interpretive criteria based on the lowest exposure achieved with the ABSSSI indication
- the role of the different types of data that may inform modifying the susceptibility test interpretive criteria

II. SCENARIO 1

A. CLINICAL

Drug A is an intravenously administered β-lactam antibacterial drug approved for the following indications:

- ABSSSI at a dose of 1 g IV q8h
- HABP at a dose of 2 g IV q8h
- Osteomyelitis at a dose of 4 g IV q8h

P. aeruginosa is listed as a pathogen in the ABSSSI and HABP indications and not in the osteomyelitis indication. Current susceptibility test interpretive criteria for *P. aeruginosa* for Drug A are shown in Table 1.

Table 1: **Current Susceptibility Test Interpretive Criteria for *P. aeruginosa***

	Susceptible	Intermediate	Resistant
MIC (mcg/mL)	≤ 8	16	≥ 32

Recent microbiologic surveillance data, prevalence of resistant organisms across the different MICs, and target attainment analysis suggest that the susceptibility test interpretive criteria may need to be revised. The probability of target attainment analysis based upon population pharmacokinetic model and simulations, suggest that effective treatment for infections caused by *P. aeruginosa*, including ABSSSI, would require the use of at least a 2 g IV q8h dose. (Although *P. aeruginosa* is not the predominant pathogen associated with ABSSSI, such infections are possible for this hypothetical scenario).

No clinical efficacy or safety data from randomized, controlled clinical trials or observational studies are available for the treatment of ABSSSI due to *P. aeruginosa* using the 2 g IV q8h dosing regimen. Additionally, no clinical data are available that show higher treatment failures in patients with ABSSSI treated with the 1 g q8h dose or higher efficacy at the 2 g q 8 h dosing regimen. However, it may be reasonable to assume that the 2 g IV q8h dosing regimen for ABSSSI will be at least as efficacious as the 1 g IV q8h dosing regimen for ABSSSI.

As the 2 g IV q8h dosing regimen is approved for the treatment of HABP due to *P. aeruginosa* and the 4 g IV q8h regimen is approved for the treatment of osteomyelitis, safety information for the 2 g IV q8h dosing regimen is available from randomized controlled trial(s) of HABP and at the 4 g IV q8h regimen from a randomized clinical trial in osteomyelitis. Overall, the most common serious adverse events associated with the use of Drug A include hypersensitivity reactions, seizures and *Clostridium difficile*-associated diarrhea (CDAD). Seizures were reported with higher frequency in patients with renal impairment.

In a randomized controlled clinical trial for ABSSSI with approximately 500 patients treated at the 1 g IV q8h dose, the most common AEs were nausea, headache, constipation, diarrhea, and anemia. Among a total of approximately 1000 patients treated with 2 g q8h for HABP and 500 patients treated with the 4 g q8h doses for osteomyelitis, the most common AEs were diarrhea, nausea/vomiting, headache, rash, and pruritus. At the 4 g q8h dose, seizures were reported more commonly than that seen with the 1 or 2 g q8 h dosing regimen.

B. MICROBIOLOGY

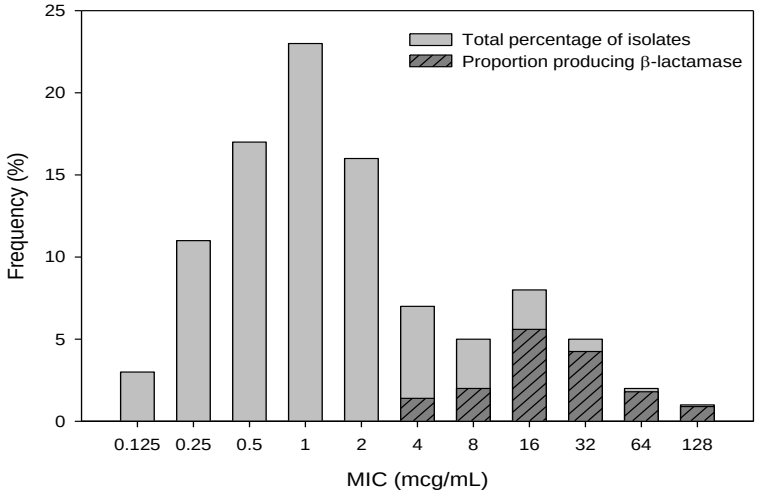
Mechanism of Action: The bactericidal activity of Drug A results from the inhibition of cell wall synthesis. Drug A readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Bactericidal concentrations (defined as a 3 $\log_{10}$ reduction in cell counts within 12 to 24 hours) are typically 1-2 times the bacteriostatic concentrations. Drug A has significant stability to hydrolysis by β-lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria.

Mechanisms of Resistance: Mechanisms of resistance to Drug A include the following:

- decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake,
- reduced affinity of the target PBPs,
- increased expression of efflux pump components, and
- production of β-lactamases

Surveillance Studies:
Recent MIC susceptibility data for *P. aeruginosa* isolates are shown in Figure 1.

Figure 1. US *Pseudomonas aeruginosa* Drug A MIC frequency distribution



Notice the increase in the proportion of beta lactamase producing isolates from a Drug A MIC of 4 mcg/ ml to 128 mcg/ml.

Recent data from a surveillance study (Antimicrobial Surveillance) show an increase in Drug A MIC90 values for *P. aeruginosa* isolates from the lower respiratory tract (Table 2). MIC90 values increased from 16 t0 32 mcg/ml in one year (2012-2013).

Table 2. MICs for *Pseudomonas aeruginosa* isolates from Lower Respiratory Tract

		MICs (mcg/ml)					
Year	**N**	**MIC range**	**Mode**	**MIC90**	**S n (%)**	**I n (%)**	**R n (%)**
2011	900	≤0.03->64	0.50	16	762 (84.7)	63 (7.0)	75 (8.3)
2012	1293	≤0.03->64	0.50	16	1068 (82.6)	102 (7.9)	123 (9.5)
2013	1008	≤0.03->64	0.50	32	831 (82.4)	75 (7.5)	102 (10.1)

C. CLINICAL PHARMACOLOGY

Summary of General Pharmacokinetic Properties of Drug A

The pharmacokinetics of Drug A are known to be linear and dose proportional from 0.5 g to 4 g. Drug A is only available in an intravenous formulation, so the absorption is complete. It penetrates into most tissues and is less than 5% protein bound. Drug A is not metabolized and is almost entirely excreted in the urine. The elimination half-life of Drug A is 1-2 hours. Drug A is not a substrate inhibitor or inducer for any CYP450

isoform or for P-glycoprotein. A dosage adjustment of Drug A is required in patients with moderate to severe renal impairment. In adult patients, no dose adjustment is required on the basis of hepatic impairment, gender, or age.

Population Pharmacokinetic Analysis
A population PK model was developed with PK data from patients being treated with Drug A at either a 1 g, 2 g, or 4 g dose, all given q8h. The population PK model was subsequently used to simulate the probability of target attainment (PTA). Approximately 100 patients were enrolled in the study. The age range of the patients included in this study was from 18 to 90 years of age. These patients were being treated for ABSSSI, HABP, or osteomyelitis.

The population PK analysis was performed using NONMEM. One and two compartment models with zero-order input and first-order elimination were assessed as the pharmacokinetic structural model. An assumption was made that the population pharmacokinetic parameters followed log-normal distributions. The inter-individual variability was characterized using a combination of additive and proportional error models. A two-compartment model provided the best fit for the data. The following possible covariates were evaluated: gender, disease, age, body weight, height, and creatinine clearance. Creatinine clearance and age were found to be significant covariates.

Pharmacokinetics/Pharmacodynamics of Drug A
Drug A is a β-lactam antibacterial drug, and the PK/PD parameter shown to most closely correlate with efficacy of Drug A in animal models is the %T>MIC. Mouse neutropenic thigh models with *P. aeruginosa* and other Gram-negative pathogens have shown that a bacteriostatic effect is observed when the free Drug A concentration remains above the MIC of the infection pathogen for 30% of the dosing interval; near maximal bacterial killing occurs when the free Drug A concentration remains above the MIC of the infecting pathogen for 50% of the dosing interval.

Probability of Target Attainment Analysis
Probability of target attainment analyses were conducted using Monte Carlo simulations for both the bacteriostatic (30% *f*T>MIC) and bactericidal (50% *f*T>MIC) targets. The simulations included Drug A dosing regimens of 1 g q8h and 2 g q8h and were conducted over an MIC range of 1 to 8 mcg/mL (See Table 3). For both dosing regimens, a total of 8,000 simulated patient concentration-time profiles were generated based on the population PK model. These target attainment results were used to support a breakpoint for the respective dosing regimens that would be supported by PK/PD.

Table 3: Probability of Target Attainment for Drug A Dosing Regimens

MIC (mcg/mL)	Dose: 1 g q8h		Dose: 2 g q8h	
	30% *f*T> MIC	50% *f*T> MIC	30% *f*T> MIC	50% *f*T> MIC
1	1.0	0.948	1.0	0.963
2	0.991	0.874	0.997	0.953
4	0.951	0.699	0.985	0.884
8	0.828	0.406	0.943	0.721

Summary of Issues with Drug A

Drug A is approved for the treatment of ABSSSI at a dosing regimen of 1 g IV q8h and for the treatment of HABP at a dosing regimen of 2 g IV q8h. It is also approved for an indication of osteomyelitis at a dose of 4 g IV q8h. *P. aeruginosa* is listed as a pathogen only in the ABSSSI and HABP indications. Currently, the susceptible breakpoint for *P. aeruginosa* is 8 mcg/ml. However, based on recent microbiology surveillance data, emergence of resistance and probability of target attainment analysis, the current susceptibility test interpretive criteria may need to be modified. Probability of target attainment analysis can support a susceptibility breakpoint of 4 mcg/mL with the 2 g IV q8h dosing regimen, while a breakpoint of 2 mcg/mL can be supported by the 1 g IV q8h dosing regimen. Clinical safety data from randomized clinical trials are available at the 2 g IV q8 h dosing regimen for HABP and at the 4 g IV q8h dosing regimen for the osteomyelitis indication. However, no safety or efficacy data are available for Drug A at the 2 g q8h dosing regimen in patients with ABSSSI due to *P. aeruginosa*.

It is reasonable to assume that there will be no loss of efficacy at the 2 g IV q8h regimen for ABSSSI. The frequency of certain adverse reactions were slightly different in the trials evaluating the 2 g IV q8h dosing regimen for HABP, compared to the ABSSSI trials that used a 1 g IV q8h regimen. This is more likely a reflection of the differences in the patient populations between the two indications rather than a dose dependent increase in adverse reactions. At the 4 g IV q8h dose, seizures were commonly reported than at the 1 or 2 g IV q8h dosing regimens. Considering the available safety data for the 2g IV q8h dose, the benefit/risk assessment for Drug A for the treatment of ABSSSI at the 2 g IV q8h dose is favorable.

Options for moving forward include:

- Changing the susceptible breakpoints for *P. aeruginosa* to 2 mcg/ml such that both the 1 g IV q8h and 2 g IV q8h regimens are likely to be effective. This would be applicable to both ABSSSI and HABP indications.

- Changing the susceptible breakpoints for *P. aeruginosa* to 4 mcg/ml and change the dosing regimen for ABSSSI to 2 g IV q8h.

- Have separate susceptible breakpoints for *P. aeruginosa;* 2 mcg/ml for ABSSSI and 4 mcg/ml for HABP and maintain the current dosing regimens of 1 g IV q8h for ABSSSI and 2 g IV q8h for HABP.

III. SCENARIO 2

A. CLINICAL

Drug B is an intravenously (IV) administered β-lactam antibacterial drug. It was originally approved in the U.S. in the 1990's for the treatment of the following infections:

- ABSSSI at a dose of 0.5 gram IV q 12 h
- cIAI at a dose of 1 gram IV q 8 h
- HABP at a dose of 2 grams IV q 8 h

For each of the above indications, safety and efficacy data were derived from two adequate and well-controlled noninferiority trials. *Escherichia coli* is listed as a pathogen for all three approved indications. Current susceptibility test interpretive criteria for *E. coli* are shown in Table 4.

Table 4: Current Susceptibility Test Interpretive Criteria for *E. coli*

	Susceptible	Intermediate	Resistant
MIC (mcg/mL)	≤ 8	16	≥ 32

Recent case series in the literature have noted clinical and microbiologic failures with Drug B in infections due to *E. coli* with an increased minimum inhibitory concentration (MIC). The prevalence of *E. coli* with high MICs has increased over the past several years since the approval of Drug B. No new clinical trials have been conducted since the original registrational trials. Clinical efficacy and safety data with the use of 2 grams IV q 8 h in the treatment of ABSSSI and cIAI caused by *E. coli* with high MICs has been limited to case reports and case series in the literature. No clinical efficacy or safety data are available from randomized controlled trials for ABSSSI or cIAI at the 2 g IV q 8 h dosing regimen. Safety data for the 2 g IV q 8 h dosing regimen are available from randomized controlled clinical trials in HABP.

The safety profile of Drug B is similar to that of other β-lactam antibacterial drugs. Common adverse reactions with Drug B include hypersensitivity reactions, seizures, and *Clostridium difficile*-associated diarrhea. Seizures were reported with higher frequency in patients with renal impairment. In randomized controlled trials, the frequency and severity of certain adverse reactions increased as the daily dose increased. The most

common clinical adverse reactions at the 2 g IV q 8 h dosing regimen included: rash, diarrhea, nausea, local injection site reactions, vomiting, pruritus, fever, and headache.

The most common adverse laboratory events at the 2 g IV q 8 h dosing regimen included: increased alanine aminotransferase (ALT) (5%), increased aspartate aminotransferase (AST), prolongation of the prothrombin time, and increased eosinophils. Less common laboratory adverse events (< 1%) included: increased blood urea nitrogen (BUN), increased creatinine, decreased hematocrit, decreased platelets, and leukopenia.

B. MICROBIOLOGY

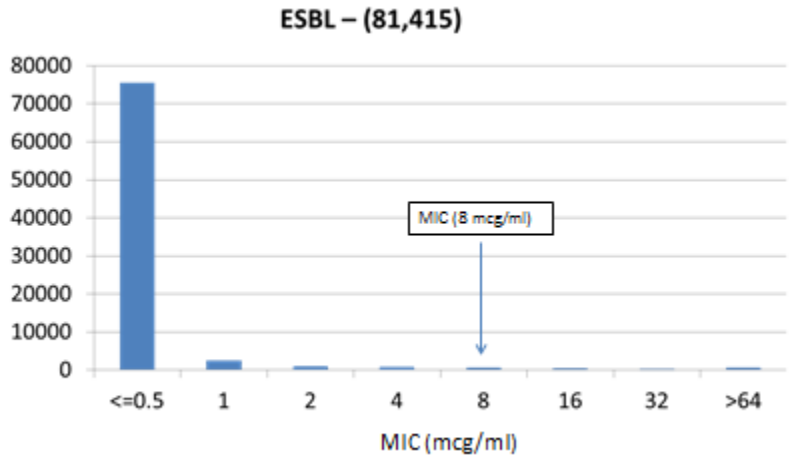
Mechanism of Action: Drug B is a bactericidal agent that inhibits cell wall biosynthesis through covalent binding of penicillin-binding proteins (PBPs), impeding the final transpeptidation step of peptidoglycan synthesis. Drug B demonstrates in vitro bactericidal activity against both Gram-positive and Gram-negative bacteria.

Mechanisms of Resistance: Resistance to Drug B in Enterobacteriaceae is most often associated with the production of β-lactamases (including Class A ESBLs and, less often, Class A and B carbapenemases) that hydrolyze the drug. Resistance to Drug B in *Pseudomonas aeruginosa* is generally associated with chromosomal Class C β-lactamases or the upregulation of efflux pumps. Resistance to Drug B in Gram-positive bacteria is typically mediated by alterations in PBPs.

Surveillance Studies:
Since approval of Drug B, the Antimicrobial Surveillance Study (established to monitor the occurrence of pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a network of hospitals distributed by geographic locations) evaluated the in vitro activity of Drug B against a large 6-year collection of clinical isolates in North America from 1998-2003. The results of the study found that all *E. coli isolates* evaluated were susceptible to Drug B, with susceptibility rates at 98%. Drug B demonstrated relatively good activity against Extended Spectrum β-lactamase (ESBL)-producing *E. coli* (93.8% susceptible)). Recent data indicate that the susceptibility profile of Drug B against ESBL producing *Enterobacteriaceae* has now decreased to approximately 20%.

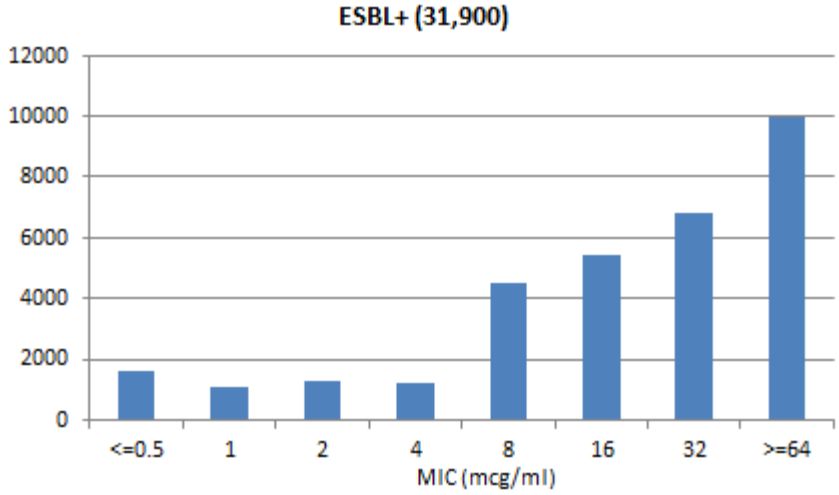
The results from the 1998-2003 Antimicrobial Surveillance analysis showed that Drug B demonstrated activity against *E. coli* isolated in North American medical centers. Drug B continues to demonstrate efficacy against non-ESBL producing *E. coli*, as presented in Figure 2.

Figure 2. Drug B MIC Distribution of ESBL (-) *Escherichia coli*



Recent data from other surveillance studies and clinical studies suggest that resistance to Drug B in *E. coli* resistance may be increasing (Figure 3). Resistance is associated with the identification of novel ESBLs and AmpC enzymes that are capable of hydrolyzing extended spectrum cephalosporins with increasing efficiency.

Figure 3. Drug B MIC Distribution of ESBL (+) *Escherichia coli*



Although ESBL-positive isolates cluster at higher MICs such as ≥ 64 mcg/ml, there are still a number of ESBL-positive isolates at the MICs to ≤1 mcg/ml. Therefore, a specific MIC will not effectively exclude all ESBL-positive isolates.

C. CLINICAL PHARMACOLOGY

Summary of General Pharmacokinetic Properties of Drug B
The pharmacokinetics of Drug B are known to be linear and dose proportional over the dose range from 0.5 to 4 g. Drug B is only available in an intravenous formulation, so the absorption is complete. It penetrates into most tissues and is approximately 20% protein bound. Drug B is metabolized to an N-methyl metabolite and is about 85% excreted in the urine as a parent. The elimination half-life of Drug B is around 2 hours. Drug B is not a substrate, inhibitor or inducer for any CYP450 isoform or for P-glycoprotein. A dosage adjustment of Drug B is required in patients with a creatinine clearance (CrCL) <60 mL/min. In adult patients, no dose adjustment is required on the basis of hepatic impairment, gender, or age.

Population PK Analysis
A population PK model was developed with PK data obtained from healthy adult subjects pooled across six Phase 1 studies. The population PK model was subsequently used to assess attainment of PK/PD targets via simulations. These target attainment results were interpreted in the context of selecting dose-dependent breakpoints. Data from six Phase 1 studies conducted in healthy adult volunteers were used to develop the structural population PK model for Drug B. The age range of these subjects was 17 to 47 years. In each of these studies, Drug B (0.5 to 2 g) was administered as an intravenous (IV) infusion over 30 minutes as either a single dose, or as multiple doses given every 8 or 12 hours for 10-14 days.

Both two- and three-compartment models with zero-order input and first-order elimination were initially evaluated to describe the Drug B concentration-time data in healthy subjects. A three-compartment model with zero-order input and first-order elimination best described the Drug B concentration-time data. In the final three-compartment model, inter-subject variability for total plasma clearance, central volume of distribution, distributional clearance between the central compartment and the first peripheral compartment, and volume of the first peripheral compartment were estimated using exponential error models and residual variability was described using a proportional error model.

Pharmacokinetics/Pharmacodynamics of Drug B
Nonclinical PK/PD models indicated that *f*T>MIC is the primary driver of the efficacy of Drug B. Further, it is generally agreed that target attainment of 50% for non-ESBL producing organisms and 70% for ESBL producing organisms are acceptable targets based on nonclinical and clinical models.

Probability of Target Attainment Analysis

Using the parameter estimates and variance-covariance matrix from the final population PK model, steady-state Drug B concentration-time data were simulated for 6,000 subjects using NONMEM® following IV administration of three different Drug B dosing regimens: 0.5 g infused every 12 hours, and 1 and 2 g infused every 8 hours. Given the 20% protein binding of the drug, free-drug concentrations were estimated by multiplying each of the simulated total-drug concentrations by 0.8.

The percentage of simulated subjects that attained free-drug %T>MIC targets during the dosing interval at steady-state, for MIC values ranging from 0.0625 to 16 mg/L, was then determined for each of the 3 Drug B dosing regimens evaluated. The free-drug %T>MIC was first determined for each subject by counting the total number of free-drug Drug B concentrations that were above the MIC and multiplying this number by the time interval between simulated concentrations, then dividing this product by the duration of the dosing interval (either 8 or 12 hours). The percentage of subjects achieving free-drug %T>MIC targets of 50 and 70% for each Drug B dosing regimen was then determined. The probability of target attainment for various Drug B dosing regimens over a range of MICs is given below in Table 4.

Table 5: Target Attainment Results for Drug B for Three Dosing Regimens Simulated Using the Final Population PK Model

Drug B Regimen/ MIC (mg/L)	Probability of Target Attainment (%)	
	*f*T>MIC ≥50%	*f*T>MIC ≥70%
0.5 g every 12 h		
0.0625	100	100
0.125	100	**99.98**
0.25	100	82.58
0.5	**99.45**	32.68
1	48.52	0.09
2	0.06	0.00
4	0.00	0.00
8	0.00	0.00
16	0.00	0.00
1 g every 8 h		
0.0625	100	100
0.125	100	100
0.25	100	100
0.5	100	100
1	100	**99.98**
2	**99.89**	76.52
4	65.62	1.78
8	0.06	0.00
16	0.00	0.00
2 g every 8 h		
0.0625	100	100
0.125	100	100
0.25	100	100
0.5	100	100
1	100	100
2	100	**99.98**
4	**99.89**	76.52
8	65.62	1.78
16	0.06	0.00

As expected, the percentage of simulated subjects achieving free-drug %T>MIC increased as Drug B dose increased and as Drug B dosing interval, MIC value, or the free-drug %T>MIC target decreased. Based upon a free-drug T>MIC target of 70%, the MIC susceptibility breakpoints for Drug B administered: 0.5 g every 12 hours, 1 g every 8 hours and 2 g every 8 hours were: 0.125, 1 and 2 mg/L, respectively. Similarly, based upon a free-drug T>MIC targets of 50%, the MIC susceptibility breakpoints for Drug B administered: 0.5 g every 12 hours, 1 g every 8 hours and 2 g every 8 hours were: 0.5, 2 and 4 mg/L, respectively.

Summary of Issues with Drug B

Drug B is approved for the treatment of ABSSSI at a dosing regimen of 0.5 gram IV q 12 h, for cIAI at a dosing regimen of 1 gram IV q 8 h, and for HABP at a dosing regimen of 2 grams IV q 8 h. *E.coli* is listed as a pathogen in all three indications. However, based on limited clinical data, recent microbiology surveillance data, emergence of resistance and probability of target attainment analysis, the current susceptibility test interpretive criteria may need to be modified.

It is reasonable to assume that there will be no loss of efficacy at the 2 g IV q8h regimen for ABSSSI or cIAI. Although the frequency of certain adverse reactions varied slightly across trials for different indications, the overall safety profile of Drug B was consistent across the various indications and dosing regimens. Considering the available safety data for the 2g IV q8h dosing regimen, the benefit/risk assessment for Drug B for the treatment of ABSSSI and cIAI at the 2 g IV q8h dosing regimen is favorable.

Options for moving forward include:

- Revise the susceptible breakpoints for *E. coli* to 0.5 mcg/ml, based on the lowest dosing regimen approved for ABSSSI.
- Revise the susceptible breakpoints for *E.coli* to 4 mcg/ml and change the dosing regimens for ABSSSI and cIAI to 2 g IV q 8 h.
- Have separate susceptible breakpoints for *E. coli*, for each of the approved indications and dosing regimens as shown in Table 6.

Table 6: Susceptible Breakpoints by Indication for *E.coli*

Indication	Regimen	Potential Susceptible Breakpoint (mcg/mL)
ABSSSI	0.5 gram IV q 12 hours	0.5
cIAI	1 gram IV q 8 hours	2
HAP	2 grams IV q 8 hours	4

IV. ISSUES FOR DISCUSSION

1. Drug A is approved for the following :
    - ABSSSI: 1 g IVq 8 h
    - HABP: 2 g IV q 8 h

The current breakpoint for *P. aeruginosa* is 8 mcg/ml. Microbiology data and probability of target attainment analyses suggest that the 2 g IV q8h dosing regimen can support a susceptible breakpoint of 4 mcg/ml for *P. aeruginosa*. No clinical efficacy data are available at the 2 g IV q 8h dosing regimen. Safety data from randomized clinical trials using the 2 IV g q 8h dose are available in patients treated for HABP.

a. Would it be acceptable to recommend the 2 g IV q 8h dosing regimen for both ABSSSI and HABP?

b. If it is not acceptable, then please discuss alternate proposals.

2. Drug B is indicated for the following:

- HABP: 2 g IV q 8 h
- cIAI: 1 g IV q 8 h
- ABSSSI: 500 mg IV q 12 h.

The current susceptible breakpoint for *E. coli* is 8 mcg/mL. Clinical and microbiology data and probability of target attainment analysis support different susceptible breakpoints for each of the approved dosing regimens. Efficacy and safety data from randomized controlled trials are only available at the approved dosing regimens (as listed above) for each of the indications.

a. Would it be acceptable to have separate susceptible breakpoints for *E. coli* for each of the approved indications based on different dosing regimens, i.e. a breakpoint of 0.5 mcg/mL for ABSSSI (500 mg q 12 h), 2 mcg/ml for cIAI (1 g q 8 h), and 4 mcg/ml for HAP (2 g q 8h)?

b. If it is not acceptable, should a dosing regimen of 2 g IV q 8 h and a susceptible breakpoint of 4 mcg/ml be used across all approved indications?

c. What are the practical implications of having different susceptible breakpoints for an organism for each of the different indications? What are the practical issues regarding conveying this information to a clinician reviewing a patient's susceptibility data.