CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-755

MICROBIOLOGY REVIEW

Division of Anti-Infective Drug Products
Clinical Microbiological Review

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DRUG PRODUCT NAME:

Proprietary:	Augmentin® ES
Nonproprietary/USAN:	amoxicillin /clavulanate potassium, 14:1 ratio
Code Names/#'s:	
Therapeutic Class:	Antimicrobial

PHARMACOLOGICAL CATEGORY: β-lactam/β-lactamase inhibitor combination,
DOSAGE FORM: Powder for oral suspension
STRENGTHS: 600/42.9 mg per 5 mL
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ **Rx** __ **OTC**

RELATED DOCUMENTS (if applicable): None

A. BACKGROUND

Augmentin® (amoxicillin/clavulanate potassium) is an approved drug product and has been marketed in the U.S.A. with different formulations for several years. It's safety and efficacy profiles are well characterized. This application is a resubmission of the original NDA 50-755 and it contains a complete response to the non approvable Action Letter that the sponsor received on October 26, 1998. This application provides for the registration of Augmentin ES™ a 14:1, 600/42.9 mg per 5mL suspension of Augmentin® (amoxicillin/clavulanate potassium) administered at 90/6.4 mg/kg/day in divided doses q12h for 10 days for the treatment of acute

otitis media due to β-lactamase-producing strains of *H. influenzae* or *M. catarrhalis*, and *S. pneumoniae* (including penicillin-resistant strains.)

In the original application (NDA 50-755), the need for the 14:1 formulation of amoxicillin/clavulanate in the treatment of otitis media was described. Data were presented which demonstrated the increasing incidence of antimicrobial resistance in respiratory tract pathogens, with a particular focus on *S. pneumoniae*. It was recognized that resistance to all classes of antimicrobials was increasing in this pathogen. The increasing incidence of β-lactamase production in *H. influenzae* and *M. catarrhalis* emphasized the need for empiric therapy with an agent that is stable to these enzymes. Also, pharmacodynamic arguments suggested that a dose of 90/6.4mg/kg/day (14:1 ratio) of amoxicillin/clavulanate administered in two divided doses bid would be effective against infections due to *S. pneumoniae* with amoxicillin MICs of ≤ 4 μg/mL. This was supported by the results of an animal experimental respiratory tract infection model.

In this amendment, additional in vitro data are provided in an attempt to support the need for an increased dose of amoxicillin for treatment of acute otitis media caused by *S. pneumoniae* and the empiric use of amoxicillin/clavulanate for treatment of acute otitis media in which β-lactamase producing pathogens have not been ruled out. Additional support is derived from the baseline bacteriology in the Phase III study (BRL-025000/536) supporting this application. In this study, 359 baseline specimens were culture positive. Of these, *S. pneumoniae* was recovered in 157 (44%), *H. influenzae* was recovered in 197 (55%), and 50 (14%) of the cultures had mixed growth. Pharmacodynamic arguments are reiterated and clinical efficacy data from study BRL-025000/536 are presented to support the proposed susceptibility breakpoint of ≤ 4 μg /mL for this formulation against *S. pneumoniae*. As in the original application the sponsor is not proposing any changes to the current approved amoxicillin/clavulanic acid susceptibility breakpoints for *H. influenzae* and *S. aureus* (≤ 4 μg /mL).

B. REMARKS/COMMENTS

In vitro susceptibility testing is performed to assess the potential utility of an antimicrobial in the treatment of a pathogen isolated from a specified site of infection. Association of established susceptibility breakpoints with clinical outcome is critical in that the value selected must predict a successful clinical outcome.

In order to establish appropriate breakpoints, the sponsor have submitted the following data:

- In vitro antimicrobial spectrum of activity and MIC frequency distribution of Augmentin® as it relates to the pathogens indicated in acute otitis media namely *S. pneumoniae, H. influenzae, M. catarrhalis, S. pyogenes*, and methicillin-susceptible *S. aureus*. These data should help describe the association of the susceptibility profile of the clinical isolates and that of the general population.

- Pharmacokinetic and pharmacodynamic studies that describes serum concentration of Augmentin® ES during the dosing interval as it relates to the susceptibility patterns of the pathogen(s) under consideration.

- In vivo animal study to determine the efficacy of Augmentin® ES in experimental respiratory tract infections caused by *S. pneumoniae*.

- Clinical efficacy data using Augmentin® ES in an open-label study that describe the association of the susceptibility of the pathogen isolated during the clinical investigation to clinical outcome of the patient. These data should help further describe the predictive value of the proposed breakpoints.

1. In Vitro Antimicrobial Spectrum Of Activity

The in vitro susceptibility data in this section is generated from the Alexander Project 1997 – 1998 [1], the International Surveillance Study (ISS) [3]; the Clinical Microbiology Institute (CMI) [4], and the Consultants in Anti-Infectives Surveillance and Testing (CAST) [5]. Data is presented on *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes* and methicillin-susceptible *S. aureus*.

1.1.1 In vitro activity against *S. pneumoniae*

The current marketed Augmentin contains 7:1 amoxicillin/clavulanate ratio. Based on pharmacokinetic/pharmacodynamic, in vitro, in vivo and clinical data, a request by the sponsor for susceptibility breakpoint of ≤ 2 µg/mL is currently pending with the agency. The in vitro data in this review section are presented using both the ≤ 2 µg/mL (for the 7:1 ratio), and the ≤ 4 µg/mL breakpoints (for the 14:1 ratio).

Table 1 demonstrates decrease in penicillin susceptibility in *S. pneumoniae,* with a rate as low as 53.6% reported in one study [3].

Table 2 is generated from the Alexander Project [1] and demonstrates the change in susceptibility patterns of *S. pneumoniae* globally and in the US. It is clearly demonstrated that the percentage of *S. pneumoniae* isolates susceptible to penicillin decreased from 66.1% in 1997 to 54.1% for US isolates in 1998. Globally the same trend can be seen, a decrease in *S. pneumoniae* penicillin susceptibility from 75.7% in 1997 to 64.9% in 1998. A reduction was also seen in susceptibility to the cephalosporins and macrolides, particularly in the US. For example, 82.3% of *S. pneumoniae* were susceptible to ceftriaxone in 1997, compared with 69.7% in 1998; and 83.1% of *S. pneumoniae* were susceptible to azithromycin in 1997, compared with 65.9% in 1998. The same kind of trends can be seen for both cephalosporins and macrolides globally.

Table 1: Percent penicillin susceptible (MIC ≤ 0.06 μg/mL) *S. pneumoniae* isolates in the US

Study	Year	No. of isolates	% Susceptible	Reference
Alexander Project	1997	124	66.1	[1]
MRL surveillance	1997 - 1998	4148	65.1	[2]
Alexander Project	1998	1456	54.1	[1]
ISS	1997 – 1999	347	53.6	[3]
CMI	1999	576	64.8	[4]
CAST	1999	552	64.1	[5]

The data from the Alexander project (Table 2) seem to indicate that amoxicillin and amoxicillin/clavulanic acid remain most active in vitro as compared to cephalosporins and macrolides. In the US the percent susceptibility to amoxicillin and amoxicillin/clavulanic acid (at a breakpoint of ≤ 2 μg/mL) decreased to 88.6% and 89.0%, respectively, and remained at just over 94% susceptible for the global population.

Table 2: Susceptibility of *S. pneumoniae* Alexander Project 1997 - 1998

Agent	1997				1998			
	US (N=124)		Global (N=2036)		US (N=1456)		Global (N=4012)	
	MIC_{90}	% Sus.	MIC_{90}	% Sus.	MIC_{90}	% Sus.	MIC_{90}	% Sus.
Penicillin	4	66.1	2	75.7	4	54.1	2	64.9
Amoxicillin[a]	2	96.0	2	97.5	4	88.6	2	94.3
Amox./Clav.[a]	2	93.5	2	97.2	4	89.0	2	94.4
Amox./Clav.[b]	2	99.2	2	99.1	4	93.8	2	97.4
Cefaclor	64	66.1	64	78.1	128	42.8	128	58.5
Ceftriaxone	1	82.3	1	85.0	1	69.7	1	77.8
Cefuroxime	8	77.4	4	82.7	8	62.8	8	74.1
Azithromycin	4	83.1	32	78.0	64	65.9	64	71.8
Clarithromycin	4	83.1	32	78.1	32	65.9	64	71.9
Erythromycin	4	83.1	32	78.1	64	65.7	64	71.7

[a] Susceptible ≤ 2 μg/mL for amoxicillin, and ≤ 2/1 μg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio; MICs are expressed in terms of amoxicillin component.

[b] Susceptible ≤ 4/2 μg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio; MICs are expressed in terms of amoxicillin component.

In two other surveillance studies, CAST [5] and MRL [2], *S. pneumoniae* isolates in the US were 96.0% susceptible to amoxicillin/clavulanic acid at breakpoint of ≤ 2/1 μg/mL (Table 3).

Using the proposed breakpoint of ≤ 4/2 μ g/mL for the 14:1 amoxicillin/clavulanate suspension, 93.8% of the US isolates, and 97.4% of the global isolates in the Alexander Project (Table 2), and over 98% of US isolates in the CAST [5] and MRL [2] studies were susceptible (Table 3).

Data from other studies listed in Table 3 further support the activity demonstrated by amoxicillin/clavulanic acid against *S. pneumoniae*. Table 3 lists the MIC_{90}, percent susceptible at the breakpoint of ≤ 2/1 μg/mL (pending approval, NDA 50754-SLR-016, and NDA 50542), and percent susceptible at the proposed breakpoint for the 14:1 formulation of ≤ 4/2 μg/mL from a number of studies. The isolates were collected in the US and included penicillin-susceptible, intermediate and resistant strains. The MIC_{90}s ranged from [redacted] the percent susceptible at ≤ 2/1 μg/mL ranged from [redacted] and the percent susceptible at ≤ 4/2 μg/mL ranged from [redacted]

Table 3: Activity of amoxicillin/clavulanic acid against US isolates of *S. pneumoniae*.

	MIC_{90} μg/mL	**%Susc. @ ≤2 μg/mL[a]**	**%Susc. @ ≤4 μg/mL[b]**
Alexander Project 1997 (N=124) [1]	2	93.5	99.2
MRL surveillance 1997-1998 (N=4148) [2]	1	96.0	98.6
Alexander Project 1998 (N=1456) [1]	4	89.0	93.8
International surveillance study 1997-1999 (N=347) [3]	2	94.2	96.3
CMI 1999 (N=576) [4]	1	93.4	96.5
CAST 1999 (N=552) [5]	1	96.0	98.2

[a] Susceptible at ≤ 2/1 μg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio.
[b] Susceptible at ≤ 4/2 μg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio

Table 4 demonstrates the activity of amoxicillin/clavulanic acid against penicillin-susceptible, intermediate and resistant isolates of *S. pneumoniae*. Using the ≤ 2/1 μg/mL breakpoint, the percentage of penicillin-resistant isolates that were susceptible to amoxicillin/clavulanic acid ranged from [redacted] Using the proposed breakpoint for the 14:1 formulation (≤ 4/2 μg/mL), the percentage of penicillin-resistant isolates that were susceptible to amoxicillin/clavulanic acid ranged from [redacted]

Table 4: Activity of amoxicillin/clavulanic acid[a] against *S. pneumoniae* isolated in the US categorized by penicillin susceptibility.

	Penicillin-Susceptible				Penicillin-Intermediate				Penicillin-Resistant			
	N	Amx/Cla MIC_{90}	%Susc. @ ≤ 2 µg/mL[a]	%Susc. @ ≤ 4 µg/mL[b]	N	Amx/Cla MIC_{90}	%Susc. @ ≤2 µg/mL[a]	%Susc. @ ≤4 µg/mL[b]	N	Amx/Cla MIC_{90}	%Susc. @ ≤2 µg/mL[a]	%Susc. @ ≤4 µg/mL[b]
Alexander 1997	82	0.03	100	100	19	1	100	100	23	4	65.2	95.7
Alexander 1998	787	0.03	100	100	217	1	100	100	452	8	64.6	79.9
International surveillance study	186	0.03	100	100	65	1	100	100	96	8	79.2	86.5
CAST	354	≤0.25	100	100	87	1	100	100	111	4	80.2	92.8

[a] Susceptible at ≤ 2/1 µg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio
[b] Susceptible at ≤ 4/2 µg/mL for amoxicillin/clavulanic acid, tested as a 2:1 ratio

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1.1.2. Frequency distribution of *S. pneumoniae*

Frequency distribution histograms (Figures 1-4) showing the percentage and number of isolates by MIC are generated from the Alexander Project 1997-1998 [1] and the International Surveillance Study [3]. The amoxicillin/clavulanic acid MICs are expressed in terms of the amoxicillin component. A vertical line in each histogram indicates the proposed susceptibility breakpoint. From Figures 1-4 one is able to see that the MIC distributions are very similar in both studies for the US and the global isolates.

Figure 1. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from the Alexander Project 1997-1998 - US (N=1,580)

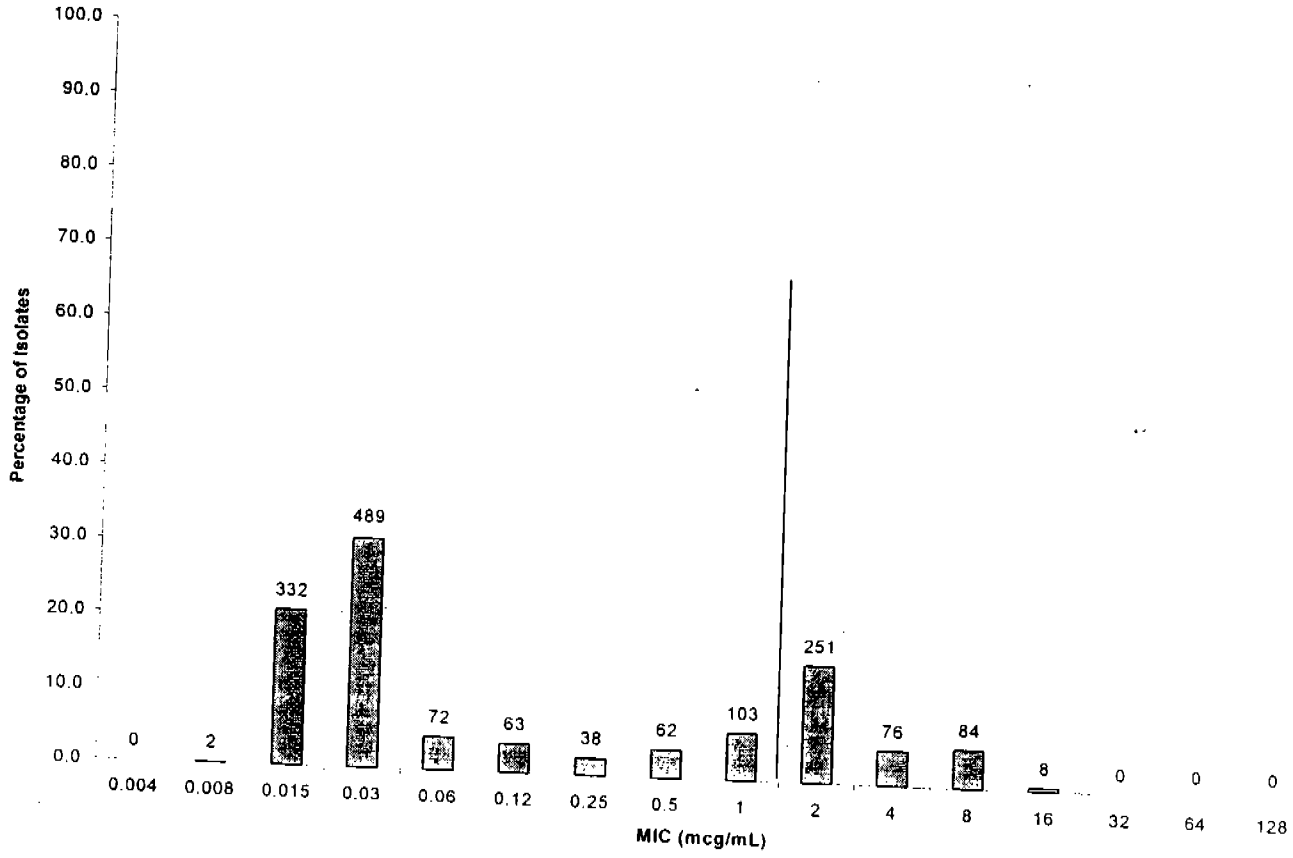

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Figure 2. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from the Alexander Project 1997-1998 - all geographic regions (N=6,048)

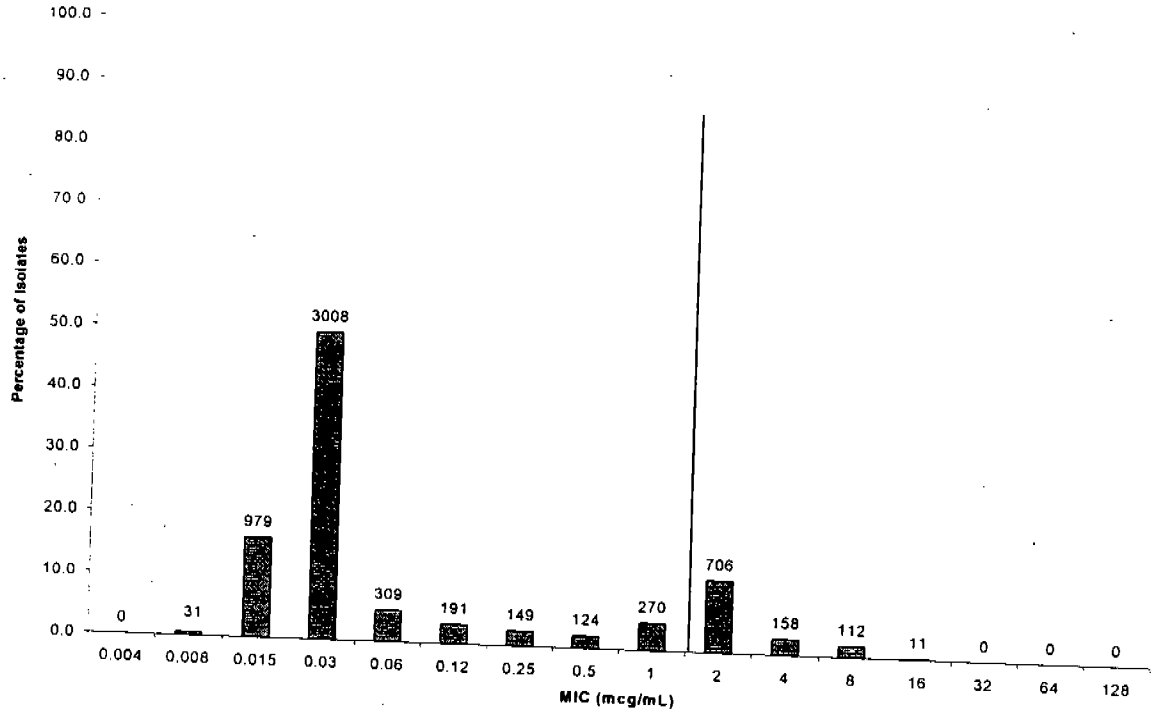


Figure 3. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from the International Surveillance Study - US (N=347)

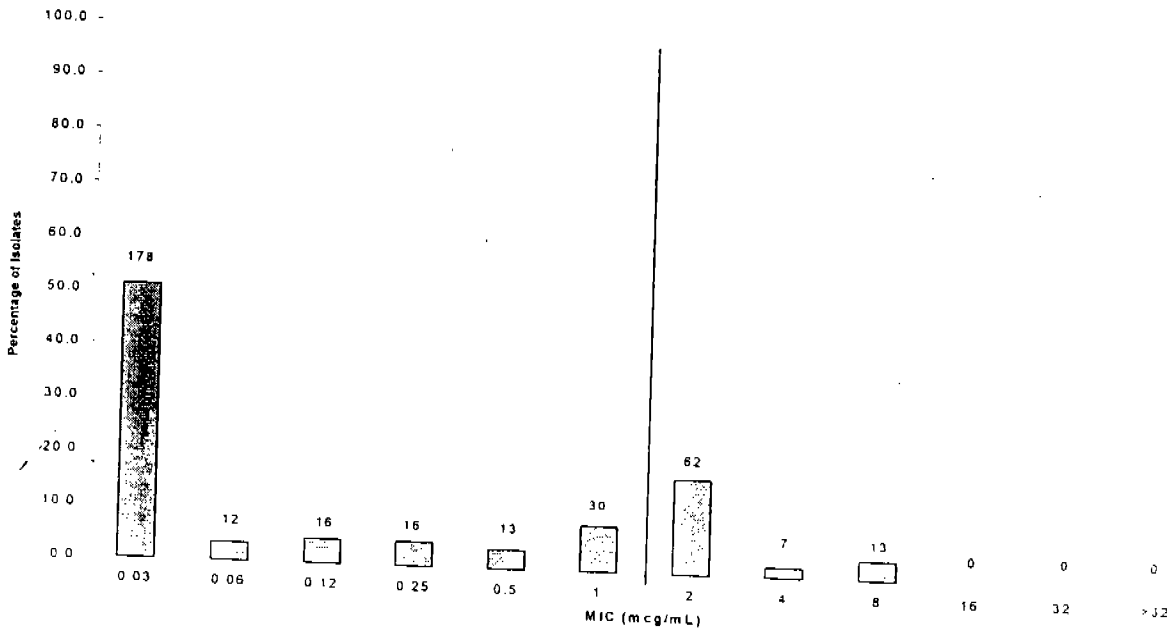
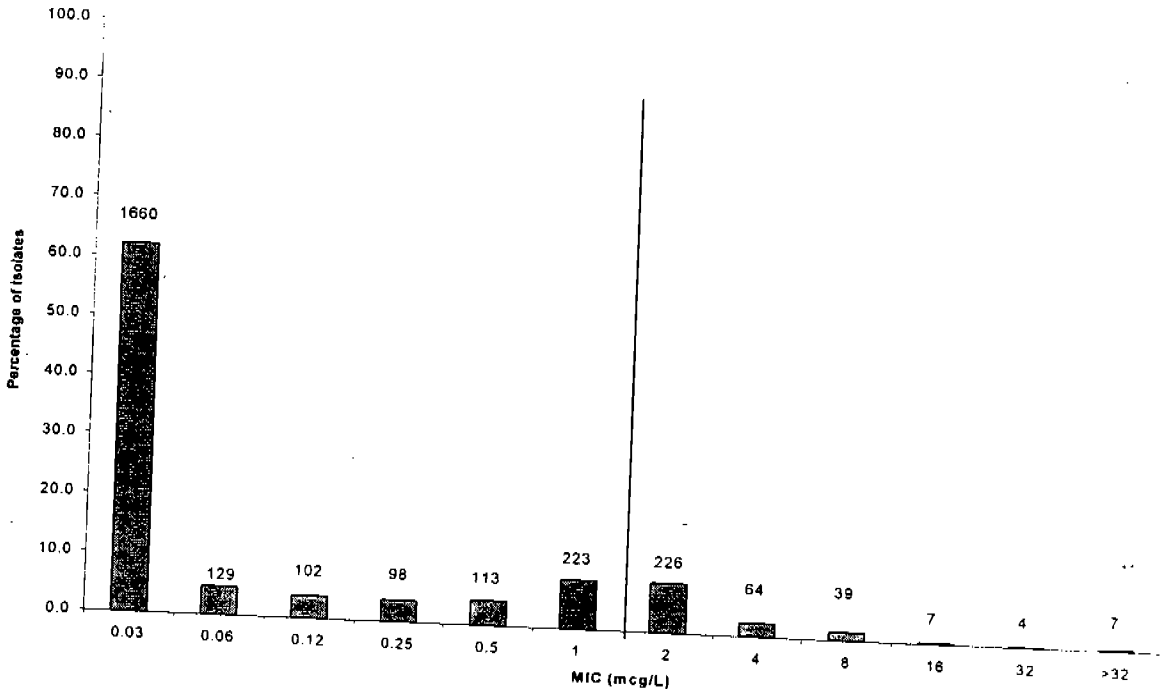


Figure 4. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from the International Surveillance Study - all geographic regions (N=2,672)



1.2.1 In vitro activity against *H. influenzae*

Rates of β-lactamase producing *H. influenzae* are increasing. Recent data from the 1998 Alexander Project [1] show a global incidence of β-lactamase positive *H. influenzae* of 20.3% and an incidence in the US of 35.7%. These data are supported by the MRL surveillance data in the US from 1998, which reported 33% β-lactamase positive *H. influenzae* [2].

Amoxicillin/clavulanic acid continues to demonstrate in vitro activity against *H. influenzae* (Table 5). At the currently approved breakpoint of ≤ 4/2 μg/mL, 99.7% of US and global isolates, were susceptible to amoxicillin/clavulanic acid in 1998 [1]. Ceftriaxone and cefixime remain more active in vitro than amoxicillin/clavulanic acid.

Table 5: Susceptibility of *H. influenzae* isolates from the Alexander Project 1997 - 1998

Agent	1997				1998			
	US (N=215)		Global (N=2721)		US (N=1370)		Global (N=4187)	
	MIC_{90}	% Sus.	MIC_{90}	% Sus.	MIC_{90}	% Sus.	MIC_{90}	% Sus.
Ampicillin	8	74.4	8	85.0	> 16	63.1	>16	73.2
Amox./Clav.[a]	2	100	1	99.8	2	99.7	1	99.7
Cefaclor	16	85.1	8	90.7	16	82.9	16	88.9
Cefixime	0.06	100	0.06	99.9	0.06	99.9	0.06	99.8
Ceftriaxone	0.015	100	0.008	100	0.008	99.9	0.008	99.9
Cefuroxime	4	94.4	2	96.7	2	98.1	2	98.2
Azithromycin	2	99.5	1	99.9	2	97.0	2	98.7
Clarithromycin	16	89.8	8	95.1	8	73.0	16	66.9

[a] Using the currently approved breakpoint of ≤ 4/2 µg/mL; MICs are expressed in terms of amoxicillin component

1.2.2 Frequency distribution of *H. influenzae*

Frequency distribution histograms (Figures 5-8) showing the percentage and number of isolates by MIC are generated from the Alexander Project 1997-1998 [1] and the International Surveillance Study [3]. The amoxicillin/clavulanic acid MICs are expressed in terms of the amoxicillin component. A vertical line in each histogram indicates the currently approved susceptibility breakpoint. From these figures it is evident that the population distribution is very similar between the US and the global isolates in both studies.

Figure 5. Frequency distribution of amoxicillin/clavulanic acid MICs for *H. influenzae* from the Alexander Project 1997-1998 - US (N=1,580)

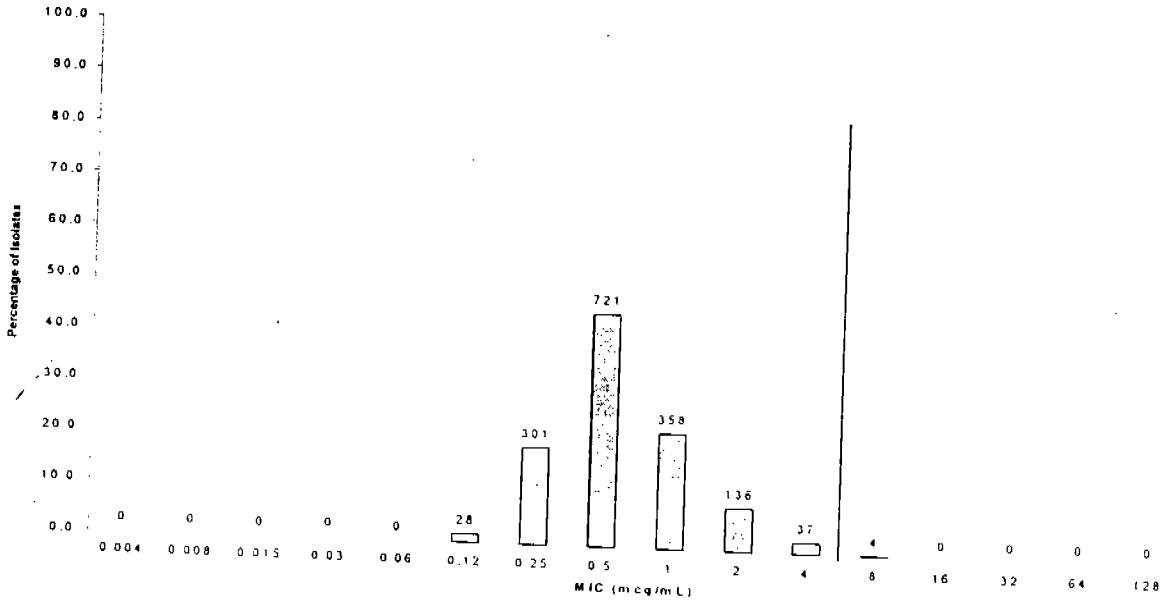


Figure 6. Frequency distribution of amoxicillin/clavulanic acid MICs for *H. influenzae* from the Alexander Project 1997-1998 - all geographic regions (N=6,908)

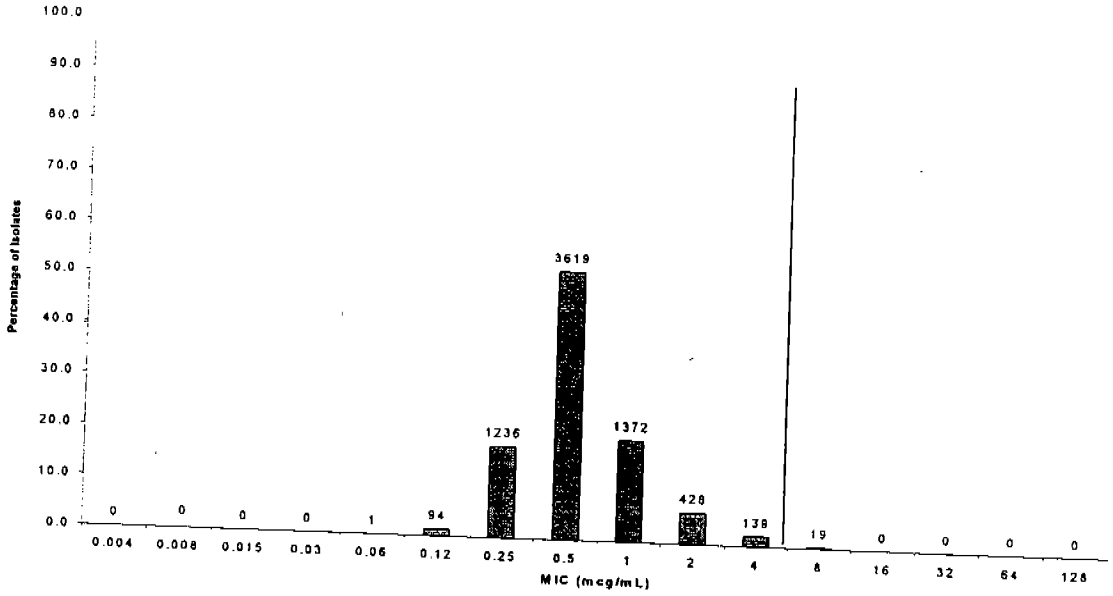


Figure 7. Frequency distribution of amoxicillin/clavulanic acid MICs for *H. influenzae* from the International Surveillance Study - US (N=45)

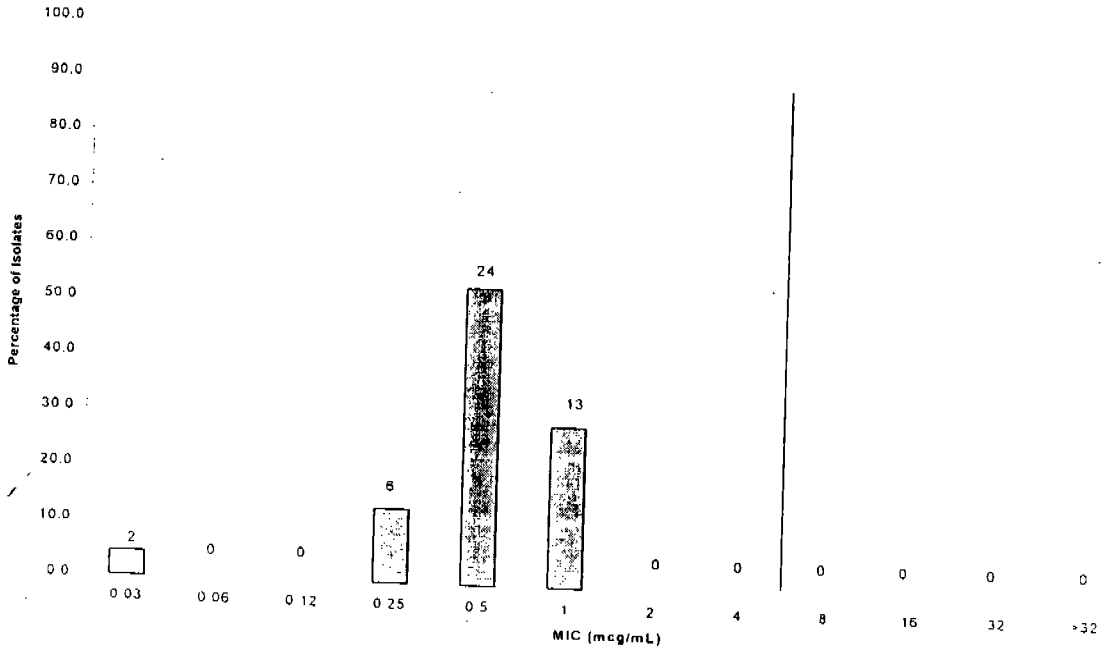
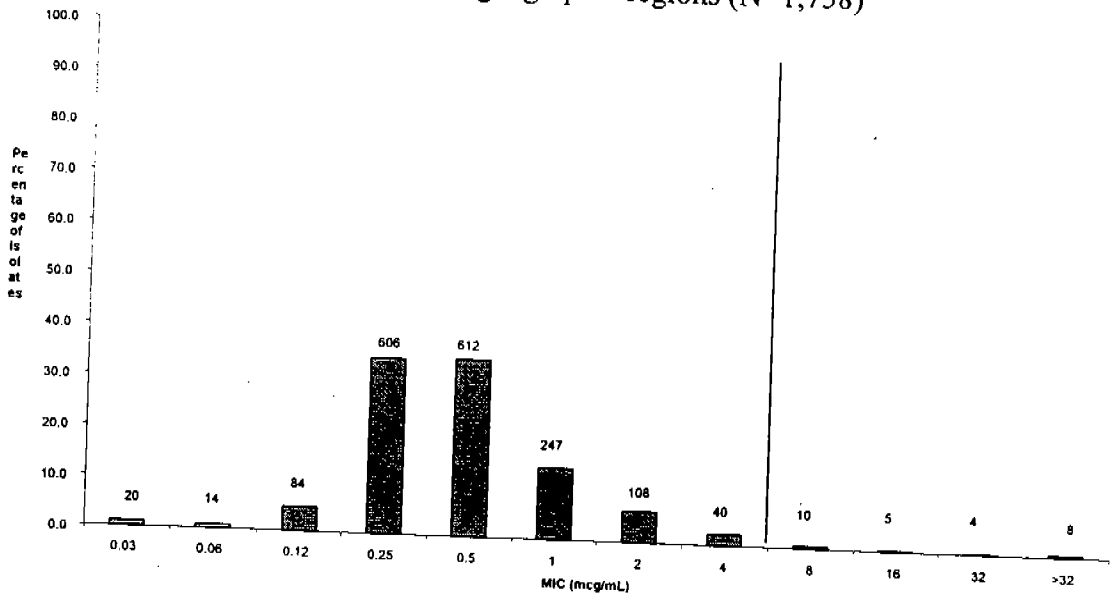


Figure 8. Frequency distribution of amoxicillin/clavulanic acid MICs for *H. influenzae* from the International Surveillance Study - all geographic regions (N=1,758)



1.3.1 In vitro activity against *M. catarrhalis*

Over 90% of *M. catarrhalis* isolates both globally, and in the US, produce β-lactamase [5][2], Table 6 show the in vitro activity demonstrated by amoxicillin/clavulanic acid against this organism. The MIC_{90} for isolates collected in 1997 and 1998, for both US and all geographic regions were 0.25 μg/mL [1].

Table 6: MIC_{90} of *M. catarrhalis* isolates from the Alexander Project 1997 - 1998

Agent	MIC_{90} μg/mL			
	1997		1998	
	US (N=111)	Global (N=685)	US (N=192)	Global (N=633)
Penicillin	8	8	NT[a]	NT[a]
Ampicillin	8	8	>16	16
Amoxicillin	8	8	32	16
Amox./Clav.[b]	0.25	0.25	0.25	0.25
Cefaclor	2	2	8	4
Cefixime	0.5	0.25	0.5	0.5
Ceftriaxone	1	1	1	1
Cefuroxime	2	2	4	2
Azithromycin	0.03	0.03	0.06	0.06
Clarithromycin	0.125	0.125	0.5	0.5
Erythromycin	0.25	0.25	0.5	0.5

[a] Not tested

[b] MICs are expressed in terms of amoxicillin component

1.3.2 Frequency distribution of *M. catarrhalis*

Frequency distribution histograms (Figures 9-12) showing the percentage and number of isolates by MIC are generated from the Alexander Project 1997-1998 [1] and the International Surveillance Study [3]. The amoxicillin/clavulanic acid MICs are expressed in terms of the amoxicillin component. From these figures it is evident that the population distribution is very similar between the US and the global isolates in both studies.

Figure 9. Frequency distribution of amoxicillin/clavulanic acid MICs for *M. catarrhalis* from the Alexander Project 1997-1998 - US (N=303)

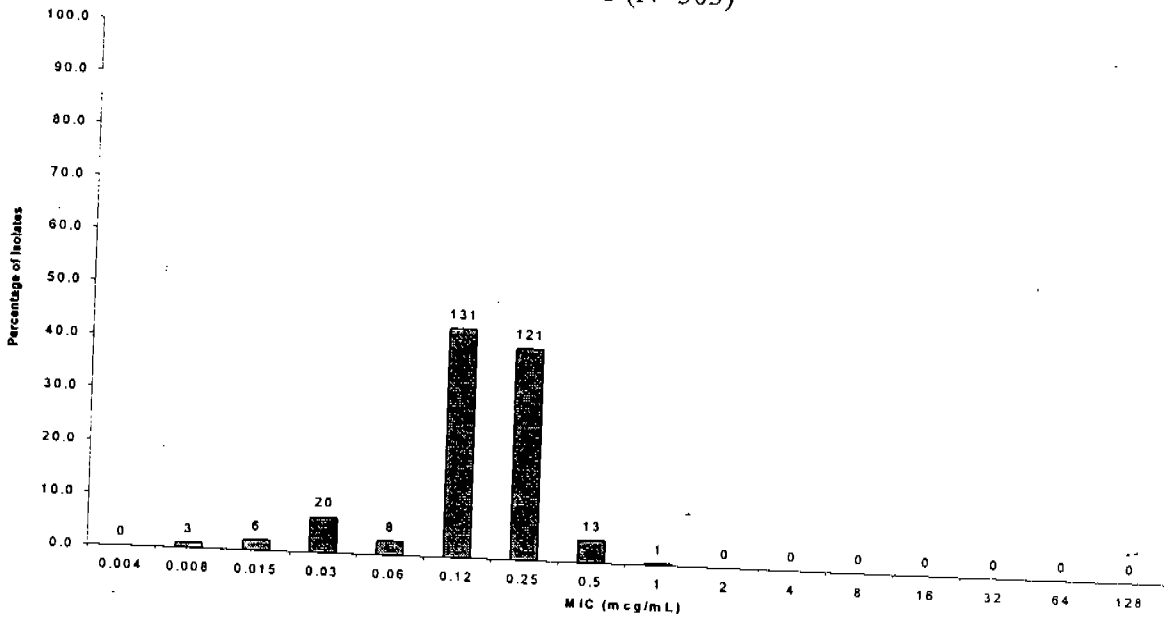


Figure 10. Frequency distribution of amoxicillin/clavulanic acid MICs for *M. catarrhalis* from the Alexander Project 1997-1998 - all geographic regions (N=1,318)

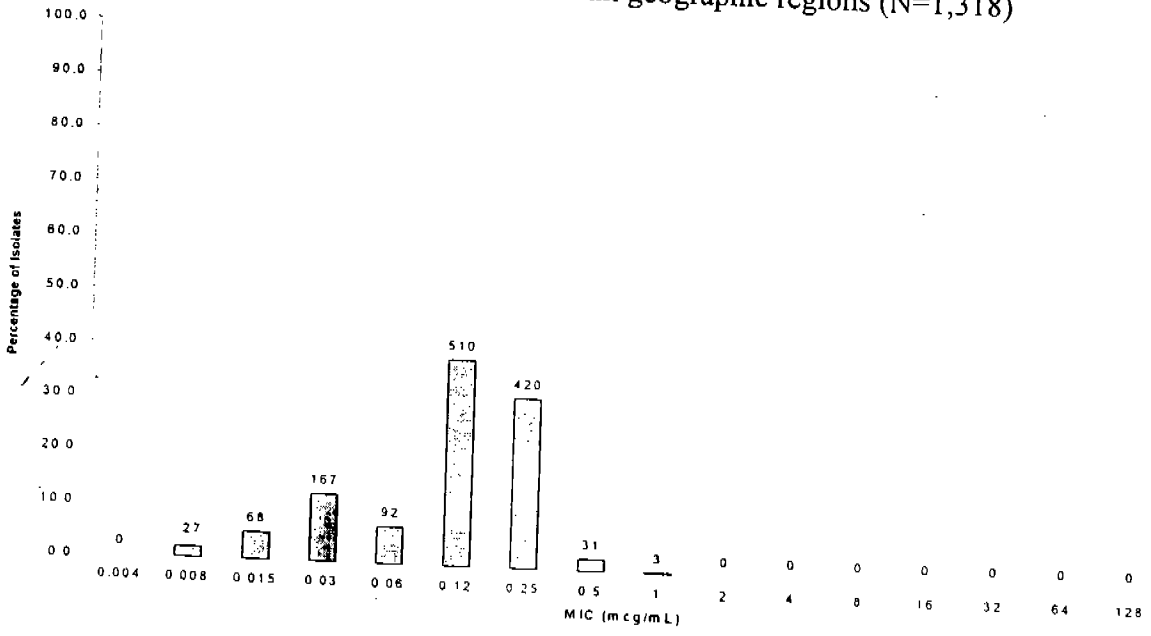


Figure 11. Frequency distribution of amoxicillin/clavulanic acid MICs for *M. catarrhalis* from the International Surveillance Study - US (N=184)

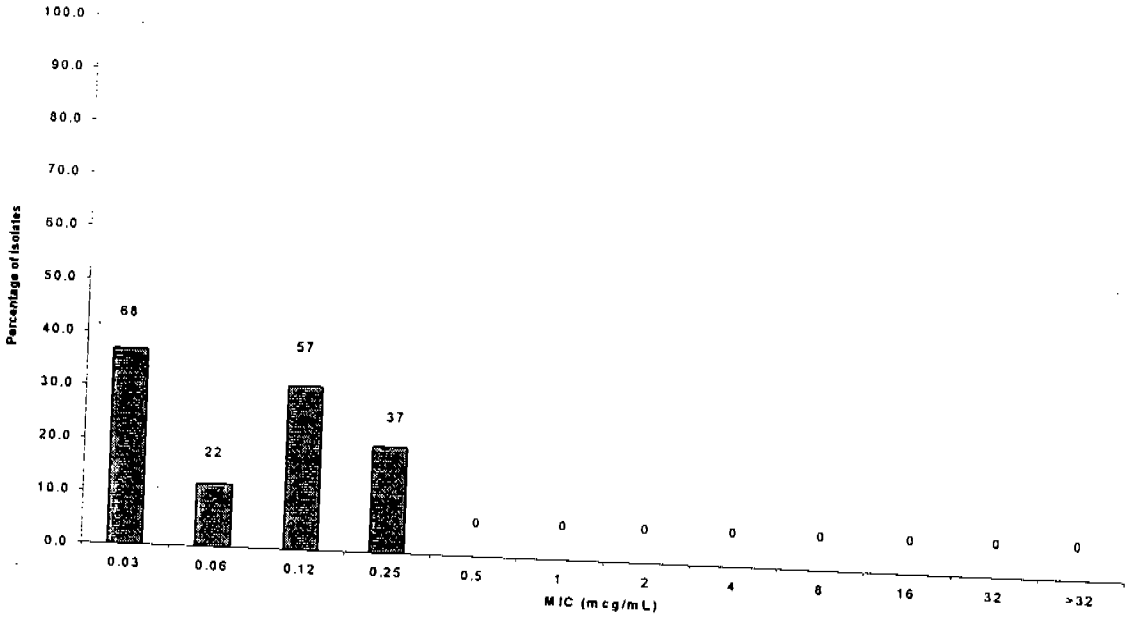
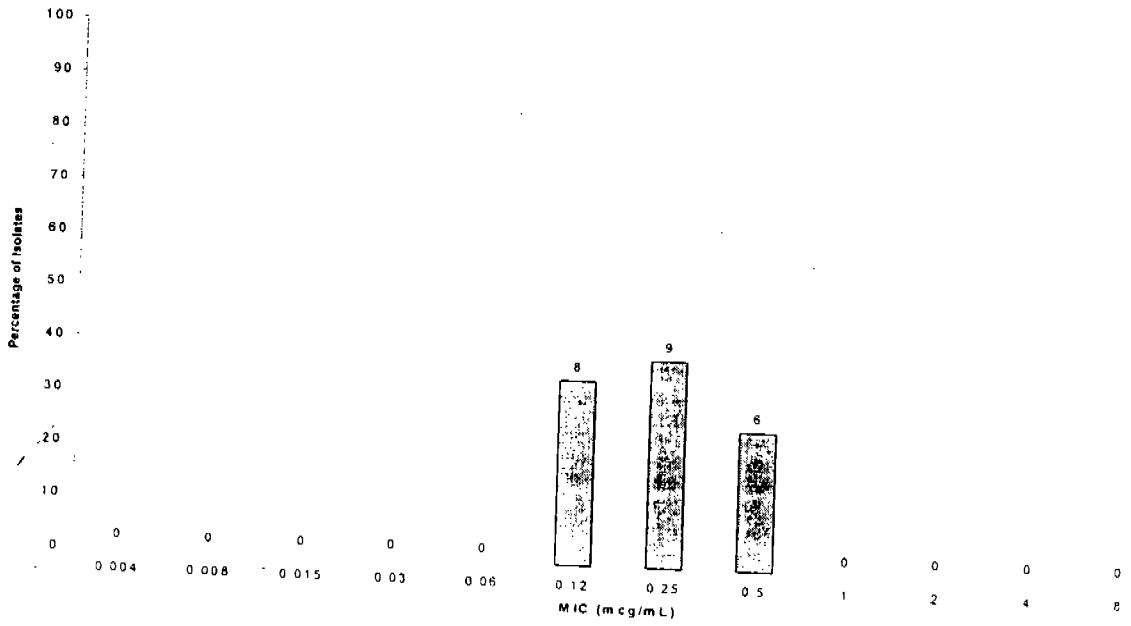


Figure 12. Frequency distribution of amoxicillin/clavulanic acid MICs for *M. catarrhalis* from the International Surveillance Study - all geographic regions (N=820)



1.4.1 In vitro activity against *S. aureus*

Methicillin-resistant *S. aureus* (MRSA) isolates are considered resistant to all β-lactam agents, including amoxicillin/clavulanic acid. However, amoxicillin/clavulanic acid demonstrates in vitro activity against methicillin-susceptible strains (MSSA), including β-lactamase producing isolates. Data from the International Surveillance Study [3] show that 98.6% of US isolates (N=69) and 95.8% of the global isolates (N=1130) were susceptible to amoxicillin/clavulanic acid at the currently approved breakpoint of ≤ 4 μg/mL. For the global isolates the MIC ranged from [redacted] with the MIC_{90} = 2 μg/mL. For the US isolates the MIC ranged from [redacted] with the MIC_{90} = 1 μg/mL.

1.4.2 Frequency distribution of methicillin-susceptible *S. aureus* (MSSA)

Frequency distribution histograms (Figures 13-14) showing the percentage and number of isolates by MIC are generated from the International Surveillance Study [3]. The amoxicillin/clavulanic acid MICs are expressed in terms of the amoxicillin component. A vertical line in each histogram indicates the currently approved susceptibility breakpoint. From these figures it is evident that the population distribution is very similar between the US and the global isolates.

Figure 13. Frequency distribution of amoxicillin/clavulanic acid MICs for MSSA from the International Surveillance Study - US (N=196)

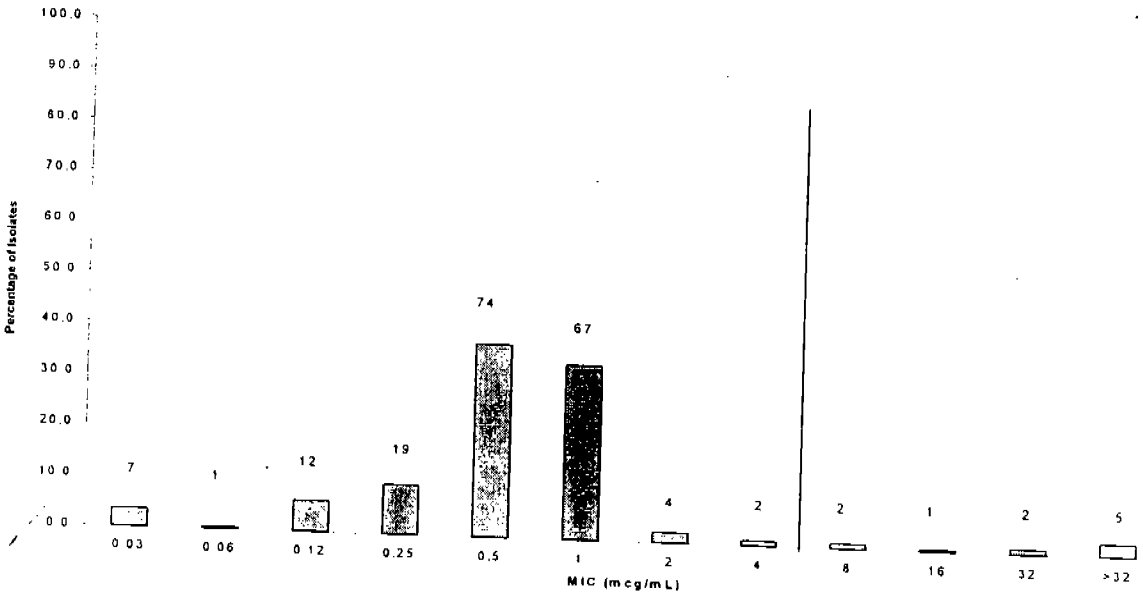
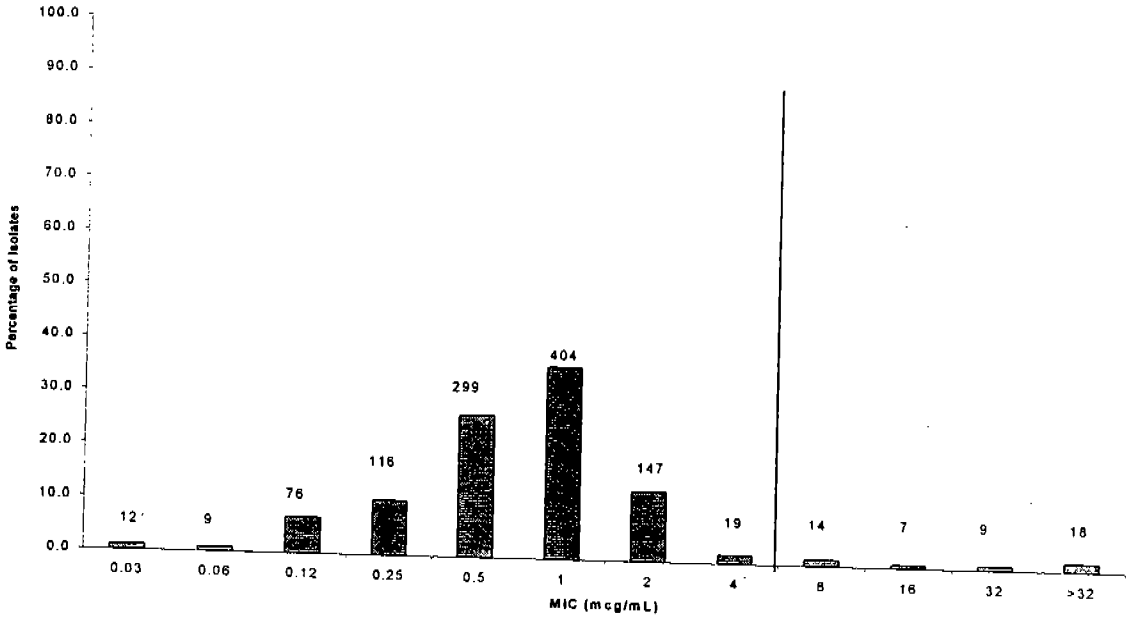


Figure 14. Frequency distribution of amoxicillin/clavulanic acid MICs for MSSA from the International Surveillance Study - all geographic regions (N=1,130)



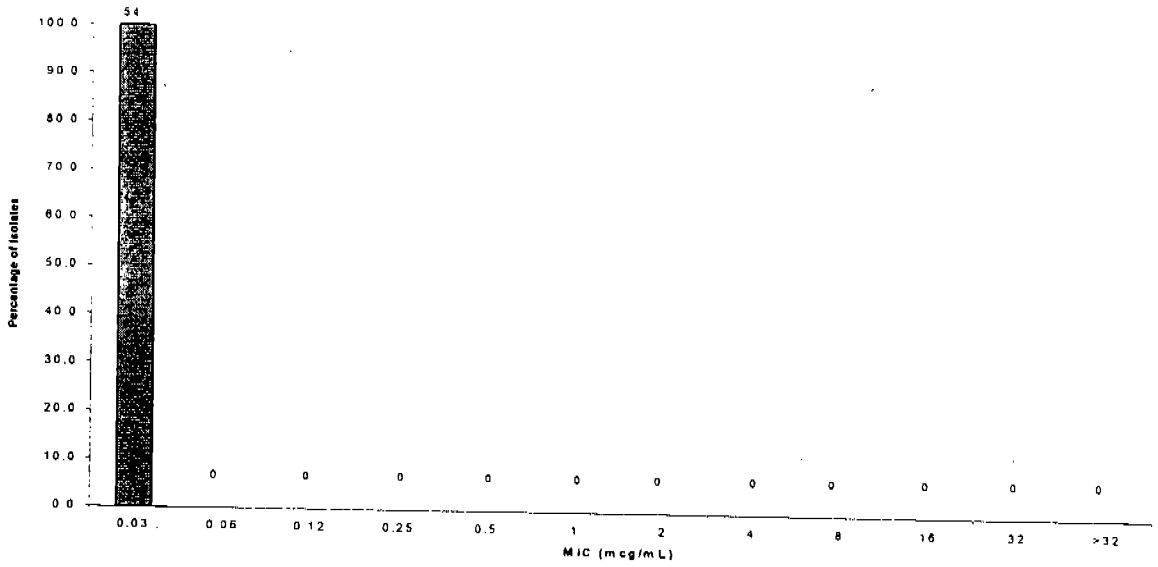
1.5.1 In vitro activity against *S. pyogenes*

S. pyogenes has also been implicated in acute otitis media and remains highly susceptible to penicillin. Data from International Surveillance Study [3] demonstrate that 100% of *S. pyogenes* in the US (N=54) were susceptible to penicillin. The same data indicates that the MIC range and MIC_{90} for *S. pyogenes* against amoxicillin/clavulanic acid is [redacted] respectively.

1.5.2 Frequency distribution of *S. pyogenes*

Frequency distribution histogram (Figures 15) showing the percentage and number of isolates by MIC are generated from the International Surveillance Study [3]. The amoxicillin/clavulanic acid MICs are expressed in terms of the amoxicillin component.

Figure 15. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pyogenes* from the International Surveillance Study - US (N=54)



2. Pharmacokinetic and Pharmacodynamic Studies

2.1 Animal Studies

The efficacy of amoxicillin and amoxicillin/clavulanic acid was compared in a neutropenic Murine thigh infection model caused by strains of *S. pneumoniae* of differing susceptibility [11]. There was correlation between therapeutic efficacy and the duration that serum levels of amoxicillin exceeded the MIC and good efficacy was observed if levels exceeded the MIC for at least 30% of the dosing interval.

A neutropenic mouse pneumoniae model was also used to assess the activity of amoxicillin against six strains of *S. pneumoniae* with MICs ranging from [redacted]. In this study, when T>MIC exceeded 40% the decrease in bacterial numbers was maximal (≥4 $\log_{10}$ cfu) and efficacy correlated directly with T>MIC irrespective of the dosing interval. However, there was no significant decrease in numbers at T>MIC of 25% or less of the dosing period.

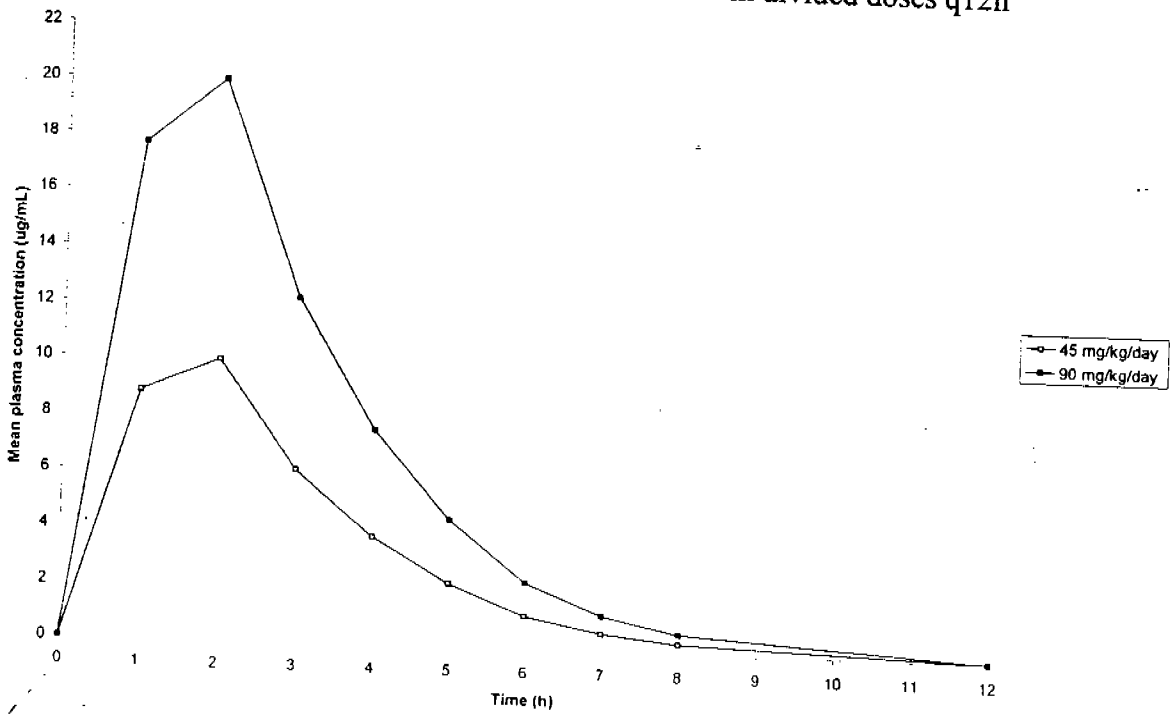
2.2 Human Studies

In the previous submission of this NDA two studies were described in which pharmacokinetic data were obtained in pediatric subjects. No additional pharmacokinetic data in pediatric subjects have been obtained since that submission and so relevant aspects of those two studies are briefly re-described. Of importance to note is that the mean T>MIC value described below for study 25000/382 is based upon extrapolated plasma concentrations due to the fact that pharmacokinetics of amoxicillin is linear.

Study 25000/382 [6] was designed to evaluate the steady state pharmacokinetic profiles of amoxicillin and clavulanate in children aged one month to 12 years after receiving *Augmentin*

45/6.4 mg/kg/day (7:1 ratio) in divided doses q12h, or 40/10 mg/kg/day (4:1 ratio) in divided doses q8h for a total of 10 days. In the study, **five subjects** were administered *Augmentin* at **45/6.4 mg/kg/day in divided doses q12h**. On the pharmacokinetic assessment day (no earlier than 48 hours after therapy was begun, and no later than nine days after start of therapy), blood samples were drawn at pre-dose, hourly up to eight hours, and at 12 h after the designated dose. In order to estimate the pharmacokinetics and T>MIC of amoxicillin that would have been achieved had the subjects given 45/6.4 mg/kg/day q12h actually received double the amoxicillin dose, i.e. 90/6.4 mg/kg/day in divided doses q 12h, their individual plasma concentration-time data were doubled on the basis of the known pharmacokinetic linearity of amoxicillin [7]. This principle has been depicted on mean data in Figure 16. The corresponding T>MIC values were then calculated from the new individual plasma concentration vs. time profiles. Using this approach, it is estimated that a dose of 90 mg/kg/day q12h will result in a **T>MIC of approximately 41% (4.9 h/ 12 h) of a dosing interval, for an amoxicillin MIC of 4 µg/mL.** This is within the T>MIC range of 30% or more that was reported for observed killing of penicillin-intermediate and penicillin-resistant *S. pneumoniae* [8].

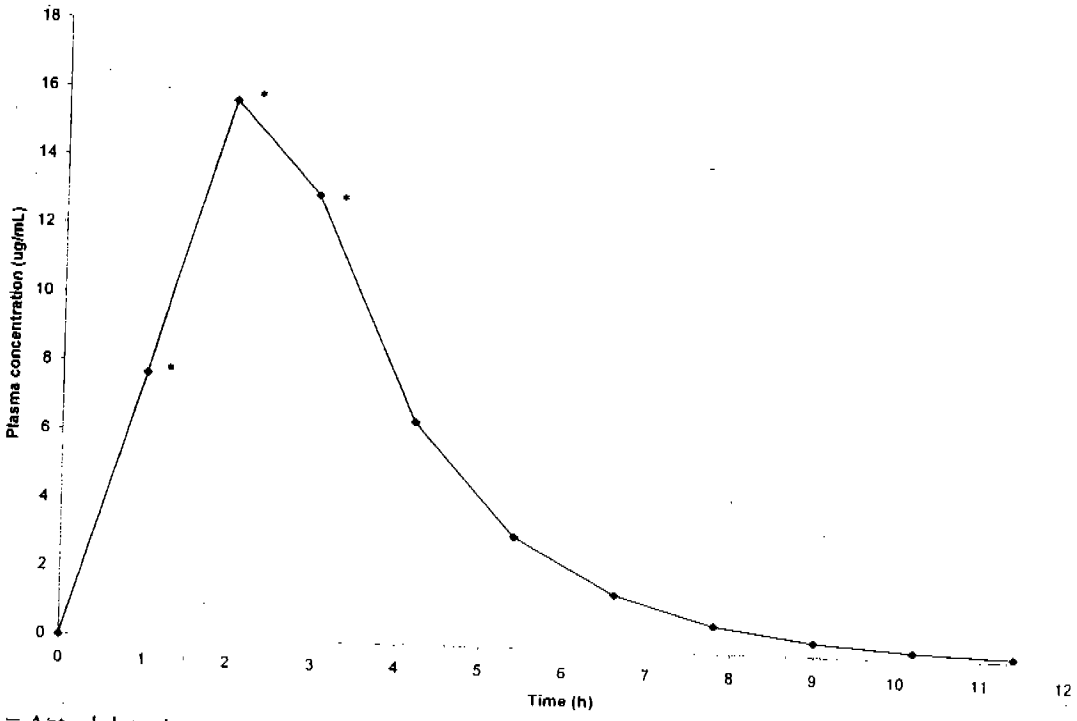
Figure 16. Mean plasma concentration vs. time profile of amoxicillin in children receiving 90/6.4 mg/kg/day of amoxicillin/clavulanate in divided doses q12h, derived from the mean plasma concentration profile of amoxicillin obtained in 5 children receiving 45/6.4 mg/kg/day of amoxicillin/clavulanate in divided doses q12h



Mean plasma concentrations of amoxicillin shown for 90 mg/kg/day have been derived by doubling those obtained with a dose of 45 mg/kg/day, calculations were based on individual data.

In the other pediatric study, **25000/446** [9], **19 subjects** 3 months to 12 years of age, diagnosed with acute otitis media, were administered Augmentin **90/6.4 mg/kg/day in divided doses q12h for 10 days.** Included during that study, was the collection of a single blood specimen (for plasma) from each child for determination of amoxicillin concentration at one, two or three hours after dosing (approximately N= 6 at each time point). The sponsor states that in the view of the investigator, it was felt not practical to keep the children in the clinic for more than 3 hours post dosing, and so the plasma concentration versus time profiles did not extend beyond 3 hours. Plasma concentrations of amoxicillin appeared to peak at 2 hours. From these data, it is possible to predict the rest of the profile by assuming an amoxicillin elimination half-life of 1.2 h (the mean value obtained in study 25000/382). This is illustrated with mean data in Figure 17. Using this approach, the **T>MIC for an amoxicillin MIC of 4 μg/mL is approximately 38% (4.7 h/12 h)**, and this estimate has been published [10].

Figure 17. Mean plasma concentration vs. time profile of amoxicillin in 19 children receiving 90/6.4 mg/kg/day of amoxicillin/clavulanate in divided doses q12h



* = Actual data; later points are derived assuming a T1/2 of 1.2 h

It is interesting, that with these two different approaches, in two different groups of children, the estimated T>MIC values from derived data are very similar to each other.

3. In Vivo Efficacy Studies

3.1 Animal Studies

Efficacy of the proposed 14:1 dose of amoxicillin/clavulanic acid (90 /6.4 mg/kg/day, in two divided doses q12h) against experimental respiratory tract infections caused by *S. pneumoniae* exhibiting decreased susceptibility to amoxicillin was investigated [13]. Amoxicillin/clavulanic acid was administered to simulate concentrations obtained in pediatric patients following administration of either 22.5/3.2 mg/kg amoxicillin/clavulanic acid bid or 45/3.2 mg/kg amoxicillin/clavulanic acid bid. Amoxicillin/clavulanic acid at both dose levels reduced the number of viable bacteria in the lungs of animals infected with strains N1387 (amoxicillin MIC = 2 μg/mL) significantly ($p<0.01$) compared with control animals (Table 7). However, amoxicillin/clavulanic acid at the higher dose of 45/3.2 mg/kg was significantly more effective than at the lower dose (22.5/3.2 mg/kg) against *S. pneumoniae* strains with an amoxicillin MIC = 4 μg/mL ($p<0.01$). Neither dose was effective against *S. pneumoniae* RS1 (amoxicillin MIC = 8 μg/mL; $p>0.05$).

Table 7. Activity of amoxicillin/clavulanic acid (14:1 dose) against penicillin-resistant *S. pneumoniae* in the rat RTI model

Strain	Amoxicillin MIC (μg/mL)	log_{10} cfu/lungs		
		Non-treated control (NTC)	Amox./Clav. (22.5/3.2 mg/kg) (bid)	Amox./Clav. (45/3.2 mg/kg) (bid)
N1387	2	6.97±0.30	4.37±0.93*	2.62±0.85**
14319	4	6.80±0.62	6.26±0.47	4.28±0.82**
410101	4	7.11±0.45	6.14±0.6*	3.91±0.81**
RS1	8	6.03±0.61	6.11±0.73	5.94±0.72

*Significantly different from NTC ($p<0.01$)
**Significantly different from NTC and amoxicillin (22.5 mg/kg; $p<0.01$)

3.2 Human Studies

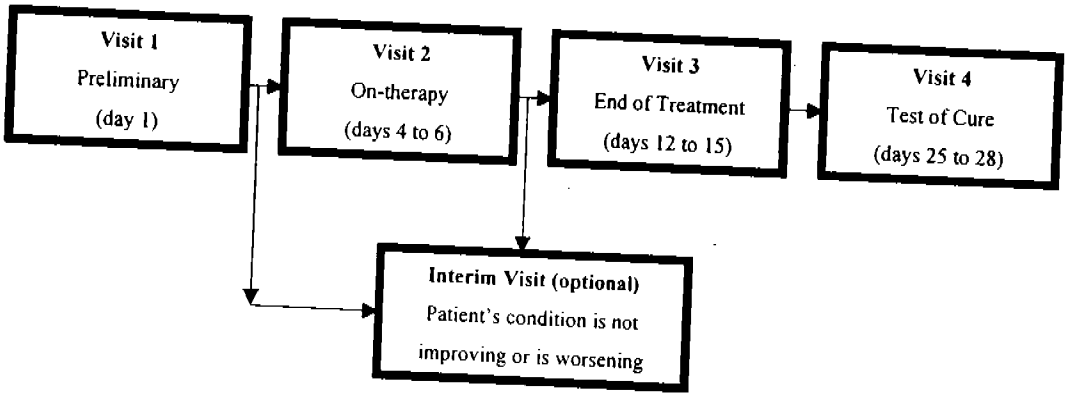
The efficacy of Augmentin ES (amoxicillin/clavulanate 14:1) in the treatment of resistant pathogens in AOM centers on a pediatric (ages 3 to 48 months) study 25000/536, titled: "An open-label study to demonstrate bacteriologic efficacy of Augmentin ES in the treatment of AOM due to *S. pneumoniae*." The purpose of this study was to identify children with isolates of *S. pneumoniae* with amoxicillin ± clavulanic acid MIC of 4.0 μg/mL and isolates of *S. pneumoniae* with penicillin MICs of ≥ 2.0 μg/mL, and to demonstrate bacteriological and clinical efficacy of treatment with amoxicillin/clavulanate at doses of 90/6.4 mg/kg/day in divided doses (q12h) for 10 days.

Tympanocentesis was performed at baseline and repeated at the on-therapy visit (day 4-6) in patients from whom *S. pneumoniae* had been isolated, and also in all clinical failures, regardless

of the initial pathogen isolated. Additionally, a few investigators repeated tympanocentesis in all enrollees (who grew a pathogen on initial tympanocentesis) at the on-therapy visit, day 4-6. Patients were monitored clinically with an on-therapy visit (day 4-6), returned for an end-of-treatment visit (day 12-15), and a test-of-cure visit (day 25-28). An interim visit was mandated within 24 hours for all patients who contacted the study site to report lack of clinical improvement or clinical worsening.

Bacteriological eradication in the treatment of AOM caused by *S. pneumoniae* was the primary efficacy variable of the study. Additionally, the study assessed the bacteriological and clinical efficacy of Augmentin ES in patients with AOM due to any pathogen. Approximately one half of the patients with "other pathogens" had a repeat tympanocentesis on day 4 to 6. Hence, a subset of the bacteriological efficacy results in "other pathogens" is an actual, not presumed, response. The remaining "other pathogens" group had bacteriologic efficacy assessed as a presumed eradication (success) or presumed non-eradication (failure) based on clinical evaluation at EOT and TOC.

Figure 18. Study Design



The *S. pneumoniae* bacteriological response (the primary efficacy variable) was characterized by the following bacteriological outcomes, as determined by repeat tympanocentesis on day 4-6 of therapy:

- **Bacteriological Eradication:** Eradication of *Streptococcus pneumoniae* or no fluid present.
- **Bacteriological Persistence:** Non-elimination of *Streptococcus pneumoniae.*
- **Bacteriological Superinfection:** Elimination of *Streptococcus pneumoniae* with the emergence of a new pathogen(s) with signs and symptoms of infection.
- **Unable to Determine:** Bacteriological evaluation cannot be made (e.g., sample lost, MIC values not recorded or not measured, etc.)

In the Per Protocol (PP) population, a patient's bacteriological response was defined as "success" if the bacteriological outcome was "bacteriological eradication" or "bacteriological superinfection"; "failure" was defined as a bacteriological outcome of "bacteriological

persistence". Additionally, for the ITT population, all outcomes of "unable to determine" were defined as "failure" when assigning response.

A total of 521 patients were randomized and received at least one dose of open label Augmentin ES. Of the 521 patients, 359 (68.9%) had a bacterial pathogen identified on initial tympanocentesis. Of 157 *S. pneumoniae* isolated at initial tympanocentesis, 41 (26.1%) were resistant to penicillin, with MIC of ≥ 2.0 μg/mL, while a total of 9 isolates had an amoxicillin/clavulanic acid MIC of ≥ 4.0 μg/mL (Table 8).

Table 8. Baseline Bacteriology – ITT Population

	Augmentin ES	
	n/N	**(%)**
No growth or missing sample	162/521	(31.1)
Baseline Pathogens		
S. pneumoniae alone or with other pathogens	157/521	(30.1)
S. pneumoniae alone or with other pathogens (Penicillin MICs ≥ 2.0 μg/mL)	41/521	(7.9)
S. pneumoniae alone or with other pathogens (Penicillin MICs < 2.0 μg/mL)	109/521	(20.9)
S. pneumoniae alone or with other pathogens (Amox/Clav MICs = 4.0 μg/mL)	3/521	(0.6)
S. pneumoniae alone or with other pathogens (Amox/Clav MICs > 4.0 μg/mL)	6/521	(1.2)
S. pneumoniae alone or with other pathogens (Amox/Clav MICs < 4.0 μg/mL)	146/521	(28.0)
Other/Multiple pathogens	246/521	(47.2)
H. influenzae	197/521	(37.8)
M. catarrhalis	29/521	(5.6)
S. pyogenes	16/521	(3.1)
S. aureus	12/521	(2.3)

Note: 7 patients have missing penicillin and/or amox/clav MICs. They are counted as missing when displayed by MIC and are not part of the pen ≥ 2 or < 2 populations nor the amox/clav < 4, = 4, > 4 populations.

The *S. pneumoniae* bacteriological outcomes (Table 9 and 9a) and bacteriological response (Table 10 and 11) listed by MIC to amoxicillin/clavulanic acid and penicillin respectively, follow:

Table 9. Bacteriological Outcome of *S. pneumoniae* at the **On-Therapy** Visit (**ITT** Bacteriological *S. pneumoniae* Alone/With Other Pathogens Population)

	Augmentin ES	
	ITT Bacteriological Population	
Bacteriological Outcome	**n/N**	**(%)**
S. pneumoniae alone/with other pathogens, penicillin MICs ≥ 2.0 µg/mL		
Eradication	38/41	(92.7)
Superinfection	0	
Persistence	2/41	(4.9)
Unable to Determine	1/41	(2.4)
S. pneumoniae alone/with other pathogens, penicillin MICs < 2.0 µg/mL		
Eradication	102/109	(93.6)
Superinfection	1/109	(0.9)
Persistence	0	
Unable to Determine	6/109	(5.5)
S. pneumoniae alone/with other pathogens, amox/clav MICs = 4.0 µg/mL		
Eradication	3/3	(100.0)
Superinfection	0	
Persistence	0	
Unable to Determine	0	
S. pneumoniae alone with/other pathogens, amox/clav MICs < 4.0 µg/mL		
Eradication	137/146	(93.8)
Superinfection	1/146	(0.7)
Persistence	1/146	(0.7)
Unable to Determine	7/146	(4.8)
S. pneumoniae alone/with other pathogens, amox/clav MICs >4.0 µg/mL		
Eradication	5/6	(83.3)
Superinfection	0	
Persistence	1/6	(16.7)
Unable to Determine	0	
S. pneumoniae Alone/With Other Pathogens		
Eradication	147/157	(93.6)
Superinfection	1/157	(0.64)
Persistence	2/157	(1.3)
Unable to Determine	7/157	(4.5)

Note: 7 patients have missing penicillin and/or amox/clav MICs. They are counted as missing when displayed by MIC and are not part of the pen ≥ 2 or < 2 populations nor the amox/clav < 4, = 4, > 4 populations.

Table 9a. Bacteriological Outcome of *S. pneumoniae* at the **On-Therapy** Visit (**PP** Bacteriological *S. pneumoniae* Alone/With Other Pathogens Population)

	Augmentin **ES** **PP Bacteriological Population**	
Bacteriological Outcome	**n/N**	**(%)**
S. pneumoniae alone/with other pathogens, penicillin MICs ≥ 2.0 mcg/mL		
Eradication	31/33	(93.9)
Superinfection	0	
Persistence	2/33	(6.1)
S. pneumoniae alone/with other pathogens, penicillin MICs < 2.0 mcg/mL		
Eradication	83/84	(98.8)
Superinfection	1/84	(1.2)
Persistence	0	
S. pneumoniae alone/with other pathogens, amox/clav MICs = 4.0 mcg/mL		
Eradication	3/3	(100.0)
Superinfection	0	
Persistence	0	
S. pneumoniae alone with/other pathogens, amox/clav MICs < 4.0 mcg/mL		
Eradication	112/114	(98.2)
Superinfection	1/114	(0.9)
Persistence	1/114	(0.9)
S. pneumoniae alone/with other pathogens, amox/clav MICs >4.0 mcg/mL		
Eradication	3/4	(75.0)
Superinfection	0	
Persistence	1/4	(25.0)
S. pneumoniae Alone/With Other Pathogens		
Eradication	120/123	(97.6)
Superinfection	1/123	(0.8)
Persistence	2/123	(1.6)

Note: 7 patients are missing penicillin MICs, 6 of who are in the bacteriological PP population. 2 patients are missing amox/clav MICs, both of whom are in the bacteriological PP population. They are counted as missing when displayed by MIC and are thus not included in tabulations by MIC.

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Table 10. Bacteriological Response by Baseline *S. pneumoniae* Susceptibility to Amoxicillin/Clavulanic Acid (PP and ITT Bacteriology *S. pneumoniae* Alone or With Other Pathogens Population) - **On-Therapy**

	Augmentin ES PP Bacteriological Population			
	Success		Failure	
Bacteriological Response	**n/N**	**(%)**	**n/N**	**(%)**
S. pneumoniae alone or with other pathogens				
Amoxicillin/clavulanic acid MIC (µg/mL)				
0.016*	2/2	(100.0)	0	
0.03 **	62/62	(100.0)	0	
0.06	8/8	(100.0)	0	
0.12	4/4	(100.0)	0	
0.25	10/10	(100.0)	0	
0.5	2/2	(100.0)	0	
1	3/3	(100.0)	0	
2	22/23	(95.7)	1/23	(4.3)
4	3/3	(100.0)	0	
8	3/4	(75.0)	1/4	(25.0)

	ITT Bacteriological Population			
	Success		Failure	
Bacteriological Response	**n/N**	**(%)**	**n/N**	**(%)**
S. pneumoniae alone or with other pathogens				
Amoxicillin/clavulanic acid MIC (µg/mL)				
0.016*	2/2	(100.0)	0	
0.03**	76/80	(95.0)	4/80	(5.0)
0.06	11/12	(91.7)	1/12	(8.3)
0.12	5/5	(100.0)	0	
0.25	12/13	(92.3)	1/13	(7.7)
0.5	2/2	(100.0)	0	
1	3/3	(100.0)	0	
2	27/29	(93.1)	2/29	(6.9)
4	3/3	(100.0)	0	
8	5/6	(83.3)	1/6	(16.7)

*Includes MICs reported as 0.016 and 0.023
**Includes MICs reported as 0.03 and 0.032
Note: 7 patients have missing penicillin and/or amox/clav MICs. They are counted as missing when displayed by MIC and are not part of the pen ≥ 2 or < 2 populations nor the amox/clav < 4, $= 4$, > 4 populations.

Table 11. Bacteriological Response by Baseline *S. pneumoniae* Susceptibility to Penicillin (PP and ITT Bacteriology *S. pneumoniae* Alone or With Other Pathogens Population) - **On-Therapy**

		Augmentin ES PP Bacteriological Population			
Bacteriological Response		**Success**		**Failure**	
S. pneumoniae alone or with other pathogens		**n/N**	**(%)**	**n/N**	**(%)**
	Penicillin MIC, µg/mL				
Susceptible	≤ 0.06	62/62	(100.0)	0	
Intermediate	≥ 0.12 to ≤ 1.0	22/22	(100.0)	0	
Resistant	≥ 2.0	31/33	(93.9)	2/33	(6.1)
		ITT Bacteriological Population			
Bacteriological Response		**Success**		**Failure**	
S. pneumoniae alone or with other pathogens		**n/N**	**(%)**	**n/N**	**(%)**
	Penicillin MIC, µg/mL				
Susceptible	≤ 0.06	76/81	(93.8)	5/81	(6.2)
Intermediate	≥ 0.12 to ≤ 1.0	27/28	(96.4)	1/28	(3.6)
Resistant	≥ 2.0	38/41	(92.7)	3/41	(7.3)

Note: 7 patients have missing penicillin and/or amox/clav MICs. They are counted as missing when displayed by MIC and are not part of the pen ≥ 2 or < 2 populations nor the amox/clav < 4, = 4, > 4 populations.

The **on therapy** data in Tables 9-11 show that Augmentin ES had acceptable bacteriologic efficacy against *S. pneumoniae* with MICs ≥ 2.0 µg/mL (i.e. penicillin-resistant *S. pneumoniae*, PRSP). The eradication rate of PRSP with MICs ≥ 2.0 µg/mL, (93.9% PP, 92.7% ITT) was comparable to that of the *S. pneumoniae* with MICs < 2.0 µg/mL (98.8% PP, 93.6% ITT) (Table 9 and 9a). The eradication rates of *S. pneumoniae* with amoxicillin/clavulanic acid MICs ≥ 4.0 µg/mL were somewhat lower than for PRSP eradication rates, 6/7 (85.7%) in the PP and 8/9 (88.9%) in the ITT populations, respectively (Table 9 and 9a).

Bacteriological success rates for Augmentin ES against PRSP were essentially the same for both the PP and ITT populations, 93.9% and 92.7% respectively (Table 11). Bacteriological response rates for Augmentin ES against *S. pneumoniae* with amoxicillin/clavulanic acid MICs from 0.02-4 µg/mL were essentially uniform (95.7%- 100%) in the PP population (Table 10). However, the bacteriological response rate dropped to 75% when the MIC was at 8 µg/mL in the PP population (Table 10). The bacteriological response rates followed the same trend in the ITT population. (Table 10)

The **secondary efficacy** parameters evaluated in the clinical trial (protocol 25000/536) were:

- bacteriologic response of other pathogens to study medication at the on-therapy visit (day 4-6) (for those with repeat tympanocentesis), and presumed bacteriological response of other pathogens to study medication at the end-of-treatment visit (day 12-15), and

- clinical response (clinical cure or clinical failure) at the end-of-treatment visit (day 12-15). It was from the clinical response at the end-of-treatment visit that the presumed bacteriology response was obtained in those patients who did not have a repeat tympanocentesis and culture.

For bacteriological response of other/multiple (other than or in combination with *S. pneumoniae*) pathogens to study medication, the bacteriological response was characterized by the following bacteriological outcomes:

- **Bacteriological Eradication:** Eradication of baseline pathogen(s) or no fluid present. (repeat tympanocentesis, performed at on-therapy visit or at time of failure)
- **Presumed Eradication:** Presumed eradication of pathogen due to clinical success at end of therapy. (no repeat tympanocentesis)
- **Bacteriological Persistence:** Non-elimination of baseline pathogen(s) (repeat tympanocentesis)
- **Presumed Persistence:** Presumed persistence of pathogen(s) due to clinical failure at end of therapy. (no repeat tympanocentesis)
- **Bacteriological Superinfection:** Elimination of baseline pathogen(s) with the emergence of a new pathogen(s) with signs and symptoms of infection (repeat tympanocentesis)
- **Unable to Determine:** Bacteriological evaluation cannot be made (*e.g.*, sample lost, etc.)

For the clinical efficacy evaluation, a patient's clinical response at the end of therapy was defined as "success" if the clinical outcome was "clinical cure" or "improvement"; or "failure" if the clinical outcome was "clinical failure" (or "unable to determine" for the ITT analysis).

It is the divisions' policy to evaluate bacteriological and clinical efficacy at the **Test of Cure** visit. Therefore, in addition to the secondary efficacy parameters listed above this reviewer had asked the sponsor to submit bacteriological and clinical response analysis at the **Test of Cure** visit. These tabulations will be presented for each secondary efficacy analysis.

The following tables (Tables 12 and 13) present the data for the bacteriological response of the other/multiple pathogens. The results for the "known response" (i.e. these patients had a repeat tympanocentesis) are presented for the ITT population (Table 13). The results for the "presumed" bacteriological efficacy (i.e. those patients without a repeat tympanocentesis) are based on clinical outcomes/response hence they are presented for the PP population (Table 12).

Table 12. Bacteriological Response by Baseline Pathogen (PP Bacteriological Other/Multiple Pathogens Population)

	Augmentin ES			
	Bacteriological Response			
Baseline Pathogens	**Success**		**Failure**	
*Known Response**	**n/N**	**(%)**	**n/N**	**(%)**
H. influenzae	76/81	(93.8)	5/81	(6.2)
S. pneumoniae	36/37	(97.3)	1/37	(2.7)
M. catarrhalis	12/12	(100.0)	0	
S. aureus	1/2	(50.0)	1/2	(50.0)
Baseline Pathogens	**Success**		**Failure**	
*Presumed Response***	**n/N**	**(%)**	**n/N**	**%**
H. influenzae	55/65	(84.6)	10/65	(15.4)
M. catarrhalis	8/9	(88.9)	1/9	(11.1)
S. aureus	7/8	(87.5)	1/8	(12.5)
S. pyogenes	11/12	(91.7)	1/12	(8.3)

*Patients with a 2nd tympanocentesis day 4-6 must have occurred within one day of the on-therapy visit
** Patients without a 2nd tympanocentesis on day 4-6, response based on clinical outcome at End of Therapy Visit

Table 13. Bacteriological Response at the Day 4-6 Visit by Baseline Pathogen Susceptibility to Amoxicillin/Clavulanic Acid: Patients with an **On-Therapy** Second Tympanocentesis (ITT Bacteriological Population)

		Bacteriological Response				
	MICs (µg/mL)	Success		Failure		Total
Pathogen	Amox/Clav	n	%	n	%	
H. influenzae	0.25	6	(100.0)	0		6
	0.5	57	(96.6)	2	(3.4)	59
	1	19	(82.6)	4	(17.4)	23
	2	3	(75.0)	1	(25.0)	4
	4	1	(100.0)	0		1
Moraxella catarrhalis	Missing	1	(100.0)	0		1
	0.06	1	(100.0)	0		1
	0.12	6	(100.0)	0		6
	0.25	4	(100.0)	0		4
	0.5	1	(100.0)	0		1
S. aureus	0.5	0		1	(100.0)	1
	2	1	(100.0)			1

The results in Tables 12 and 13 demonstrate that the rates of bacteriological success for Augmentin ES for the other pathogens that are involved in AOM are reasonably acceptable.

In order to demonstrate correlation of bacteriological eradication with clinical response at the Test of Cure visit for *S. pneumoniae*, by baseline susceptibility to penicillin and amoxicillin/clavulanic acid, Tables 14-16 are presented below.

Table 14. **Clinical Response** and Outcome at **Test of Cure** for *S. pneumoniae* and by Penicillin MICs (PP Clinical Population)

	Augmentin ES					
Clinical Response at Test of Cure	*S. pneumoniae* (alone/with other pathogens)		*S. pneumoniae* with penicillin MICs ≥ 2 µg/mL		*S. pneumoniae* with penicillin MICs < 2µg/mL	
	n/N	**%**	**n/N**	**%**	**n/N**	**%**
Success, n (%)	99/131	(75.6)	18/30	(60.0)	76/94	(80.9)
Failure, n (%)	32/131	(24.4)	12/30	(40.0)	18/94	(19.1)
Clinical Outcome at Test of Cure	*S. pneumoniae* alone/with other pathogens		*S. pneumoniae* with penicillin MICs ≥ 2 µg/mL		*S. pneumoniae* with penicillin MICs < 2µg/mL	
Clinical Cure, n (%)	99/131	(75.6)	18/30	(60.0)	76/94	(80.9)
Recurrence, n (%)	20/131	(15.3)	9/30	(30.0)	10/94	(10.6)
Failure, n (%)	12/131	(9.2)	3/30	(10.0)	8/94	(8.5)

Note: According to the sponsor 5 patients in this population were missing penicillin MICs. But numbers on this table indicate that 6 are missing.

Table 15. Clinical Response by Baseline *S. pneumoniae* Susceptibility to Amoxicillin/Clavulanic Acid (PP Clinical Population at Test of Cure)

	Augmentin ES PP Clinical Response TOC			
	Success		**Failure**	
	n/N	**(%)**	**n/N**	**(%)**
S. pneumoniae alone or with other pathogens				
Amoxicillin + clavulanic acid MIC (µg/mL)				
0.016	1/1	(100.0)	0/1	
0.03*	58/73	(79.5)	15/73	(20.5)
0.06	7/9	(77.8)	2/9	(22.2)
0.12	4/5	(80.0)	1/5	(20.0)
0.25	7/9	(77.8)	2/9	(22.2)
0.5	2/2	(100.0)	0/2	
1	1/2	(50.0)	1/2	(50.0)
2	14/23	(60.9)	9/23	(39.1)
4	2/3	(66.7)	1/3	(33.3)
8	1/2	(50.0)	1/2	(50.0)

Note: 2 patients in this population were missing amox+clav MICs.
*Includes MICs reported as 0.03 and 0.032

Table 16. Clinical Outcome at Test of Cure for *S. pneumoniae* by Amoxicillin/Clavulanic Acid MICs (PP Clinical Population at Test of Cure)

Clinical Response at Test of Cure	**Augmentin ES**					
	S. pneumoniae (alone/with other pathogens)		*S. pneumoniae* with amox ± clav MICs ≥ 4 µg/mL		*S. pneumoniae* with amox ± clav MICs < 4 µg/mL	
	n/N	**%**	**n/N**	**%**	**n/N**	**%**
Success, n (%)	99/131	(75.6)	3/5	(60.0)	94/124	(75.8)
Failure, n (%)	32/131	(24.4)	2/5	(40.0)	30/124	(24.2)
Clinical Outcome at Test of Cure	*S. pneumoniae* alone/with other pathogens		*S. pneumoniae* with amox ± clav MICs ≥ 4 µg/mL		*S. pneumoniae* with amox ± clav MICs < 4 µg/mL	
Clinical Cure, n (%)	99/131	(75.6)	2/5	(40.0)	95/124	(76.6)
Recurrence, n (%)	20/131	(15.3)	1/5	(20.0)	19/124	(15.3)
Failure, n (%)	12/131	(9.2)	2/5	(50.0)	10/124	(8.1)

Note: 2 patients in this population were missing amox+clav MICs.

These data indicate that for *S. pneumoniae* the clinical response at the TOC parallels bacteriological response. Clinical failures due to clinical recurrences seem to be associated with penicillin MICs of ≥ 2 µg/mL (Table 14). The number of isolates for *S. pneumoniae* with Amox /Clav. MICs of ≥ 4 µg/mL are only 5 in the PP population but one can see the trend where clinical failure is associated with MICs of ≥ 4 µg/mL (failure rate is at 40 %) (Table 16). Even at MIC of 2 µg/mL one can see a failure rate of 39.1% which is still too high (Table 15).

Further more, there is a discrepancy between the PP population determined by the FDA's medical officer Dr. Makhene /statistician Dr. Brittain reviewers and the sponsor's PP population. In the analysis performed by Dr. Brittain the patient failure rates who had isolates with MICs of 2, 4, and 8 were 56.5%, 25%, and 100% respectively.

In order to demonstrate correlation of bacteriological eradication with clinical response at the **Test of Cure** visit for the other pathogens, by baseline susceptibility to amoxicillin/clavulanic acid, Tables 17-18 are presented below.

Table 17. Clinical Response/Outcome at **Test of Cure** Visit by Baseline Pathogen (**PP** Clinical Population)

	Augmentin ES			
	Clinical Response			
	Success		Failure	
Pathogen	n/N	(%)	n/N	(%)
S. pneumoniae	99/131	(75.6)	32/131	(24.4)
H. influenzae	106/154	(68.8)	48/154	(31.2)
M. catarrhalis	14/25	(56.0)	11/25	(44.0)
S. aureus	8/11	(72.7)	3/11	(27.3)
S. pyogenes	12/14	(85.7)	2/14	(14.3)

	Clinical Outcome					
	Clinical Cure		Recurrence		Clinical Failure	
Pathogen	n/N	(%)	n/N	(%)	n/N	(%)
S. pneumoniae	99/131	(75.6)	20/131	(15.3)	12/131	(9.2)
H. influenzae	106/154	(68.8)	31/154	(20.1)	17/154	(11.0)
M. catarrhalis	14/25	(56.0)	7/25	(28.0)	4/25	(16.0)
S. aureus	8/11	(72.7)	2/11	(18.2)	1/11	(9.1)
S. pyogenes	12/14	(85.7)	1/14	(7.1)	1/14	(7.1)

Table 18. Clinical Response by Baseline Pathogen Susceptibility to Amoxicillin/Clavulanic Acid (PP Clinical Population at **Test of Cure**)

		Augmentin ES Clinical Response			
		Success		Failure	
Amoxicillin /clavulanic acid MIC (µg/mL)		n/N	(%)	n/N	(%)
H. Influenzae					
	0.25	6/9	(66.7)	3/9	(33.3)
	0.5	63/90	(70.0)	27/90	(30.0)
	1	27/39	(69.2)	12/39	(30.8)
	2	8/10	(80.0)	2/10	(20.0)
	4	1 / 3	(33.3)	2/3	(66.7)
M. catarrhalis					
	0.12	6/9	(66.7)	3/9	(33.3)
	0.25	4/7	(57.1)	3/7	(42.9)
	0.5	2/6	(33.3)	4/6	(66.7)
S. aureus					
	0.5	2/2	(100.0)	0	
	1	4/6	(66.7)	2/6	(33.3)
	2	1/1	(100.0)	0	
S. pyogenes					
	0.15	9/11	(81.8)	2/11	(18.2)
	0.03	1/1	(100.0)	0	

These data indicate that for *H. influenzae* the 8 clinical recurrences are all associated with isolates at MICs = 0.5 µg/mL. This probably indicates that the currently approved susceptible breakpoint of 4 µg/mL is too high for *H. influenzae*. The numbers for the remaining pathogens are too low for reasonable evaluation and comment.

Finally, bacteriologic and clinical response rates for *S. pneumoniae* are combined and compared to evaluate whether Augmentin ES is adequately efficacious in treatment of AOM caused by PRSP, the primary objective of the Study 25000/536. Tables 19 and 20 correlate bacteriologic response with clinical response in the treatment of AOM due to PRSP and *S. pneumoniae* isolates with Amox/Clav MICs of ≥ 4 µg/mL in this study.

Table 19. Bacteriological Response **On-Therapy** vs. Clinical Response at **End of Therapy** for *S. pneumoniae* (PP Bacteriological *S. pneumoniae* Alone or With Other Pathogens Population)

	Clinical Response			
	Success		Failure	
Bacteriological Response	**n**	**(%)**	**n**	**(%)**
S. pneumoniae alone/with other pathogens, penicillin MICs ≥ 2.0 mcg/mL				
Success	24/29	(82.8)	4/29	(13.8)
Failure	1/29	(3.4)	0	
S. pneumoniae alone/with other pathogens, penicillin MICs < 2.0 mcg/mL				
Success	78/84	(92.9)	6/84	(7.1)
Failure	0		0	
S. pneumoniae alone/with other pathogens, amox/clav MICs = 4.0 mcg/mL				
Success	3/3	(100.0)	0	
Failure	0		0	
S. pneumoniae alone with/other pathogens, amox/clav MICs < 4.0 mcg/mL				
Success	101/112	(90.2)	10/112	(8.9)
Failure	1/112	(0.9)	0	
S. pneumoniae alone/with other pathogens, amox/clav MICs >4.0 mcg/mL				
Success	2/2	(100.0)	0	
Failure	0		0	

Table 20. Bacteriological Response **On-Therapy** vs. Clinical Response at **Test of Cure** for *S. pneumoniae* (PP Bacteriological *S. pneumoniae* Alone or With Other Pathogens Population)

	Clinical Response			
	Success		Failure	
Bacteriological Response	**n**	**(%)**	**n**	**(%)**
S. pneumoniae alone/with other pathogens, penicillin MICs ≥ 2.0 µg/mL				
Success	16/27	(59.3)	10/27	(37.0)
Failure	1/27	(3.7)	0	
S. pneumoniae alone/with other pathogens, penicillin MICs < 2.0 µg/mL				
Success	67/82	(81.7)	15/82	(18.3)
Failure	0		0	
S. pneumoniae alone/with other pathogens, amox/clav MICs = 4.0 µg/mL				
Success	2/3	(66.7)	1/3	(33.3)
Failure	0		0	
S. pneumoniae alone with/other pathogens, amox/clav MICs < 4.0 µg/mL				
Success	83/109	(76.1)	25/109	(22.9)
Failure	1/109	(0.9)	0	
S. pneumoniae alone/with other pathogens, amox/clav MICs >4.0 µg/mL				
Success	1/1	(100.0)	0	
Failure	0		0	

The data presented in Tables 19 and 20 indicate that the efficacy rates for treatment of AOM due to PRSP as determined by clinical and bacteriological success, decrease from an acceptable rate of 82.8% at the EOT to an unacceptable rate of 59.3% at the TOC visit. The corresponding rates for PSSP however, are acceptable at EOT (92.9%) and TOC (81.7%).

The data in Tables 19 and 20 are limited for evaluation of patients with amoxicillin/clavulanate MICs of ≥ 4.0 µg/mL because there are only five patients/isolates for evaluation at the EOT and only four patients/isolates at the TOC. Never the less the same trend as for PRSP is observed since the clinical and microbiological success rates decrease from 100% at the EOT to 75% at the TOC.

For PRSP the rate of clinical failures at the TOC (37.0%, Table 20), despite the bacteriological success is disturbing. Even if the data for isolates with amoxicillin/clavulanate MICs of ≥ 4.0 µg/mL is limited; the same trend can be observed (25%. Table 20) for these isolates as well. The reason for negative culture results could stem from sample mishandling and *S. pneumoniae* autolysis or the presence of amoxicillin/clavulanate in the MEF at the on-therapy period when the samples were collected.

4. Breakpoint Determination

The only in vitro susceptibility interpretive break point that will be discussed is the one for amoxicillin clavulanate for *S. pneumoniae*.

Unfortunately the in vitro data presented through out this submission did not present the MIC_{50} nor did it present the MIC range for *S. pneumoniae* isolates against amoxicillin clavulanate. Instead, the sponsor had concentrated on presenting percent susceptible isolates based on two unapproved susceptible break points of 2.0 and 4.0 μg/mL.

The MIC_{90} values against amoxicillin clavulanate for the US isolates has increased from 2 in 1997 to 4 μg/mL in 1998 and had remained the same, at 2 μg/mL for the global isolates (Table 2, Alexander project). The MIC_{90} values from the International Surveillance Study (ISS); the Clinical Microbiology Institute (CMI), and the Consultants in Anti-Infectives Surveillance and Testing (CAST) studies were reported at 1-2 μg/mL for the US isolates between years 1997 and 1999 (Table 3). The MIC_{90} for PISP isolates against amoxicillin clavulanate is 1 μg/mL (Table 4). This means that if a susceptible breakpoint of 1 μg/mL is given for amoxicillin clavulanate all the PISP isolates would be correctly categorized as susceptible to amoxicillin clavulanate. The PRSP isolates have MIC_{90}s of 4-8 μg/mL against amoxicillin clavulanate (Table 4). If one gives a susceptible breakpoint of 2 μg/mL for amoxicillin clavulanate then 64.6% to 80.2% (Table 4, Alexander project 1997 & 1998, ISS, and CAST data) of the PRSP isolated would be incorrectly categorized as amoxicillin clavulanate susceptible. Finally, If one gives a susceptible breakpoint of 4 μg/mL for amoxicillin clavulanate then 79.9 % to 95.7% (Table 4, Alexander project 1998, ISS, CAST and Alexander project 1997 data) of the PRSP isolated would be incorrectly categorized as amoxicillin clavulanate susceptible. With this information this reviewer believes that the in vitro data would not support an MIC break point of greater than 1 μg/mL.

The frequency distribution histograms for the US and global clinical isolates recovered from clinical study 536 (Figures 19 and 20) are very similar to the frequency distribution histograms from the in vitro studies presented in Figures 1-4 earlier in this review. From these histograms one can see that MIC of 1.0 μg/mL nicely separates the two populations in this bimodal population distribution.

Figure 19. Frequency distribution of amox./clav. MICs for *S. pneumoniae* from Study 536-US (N=75)

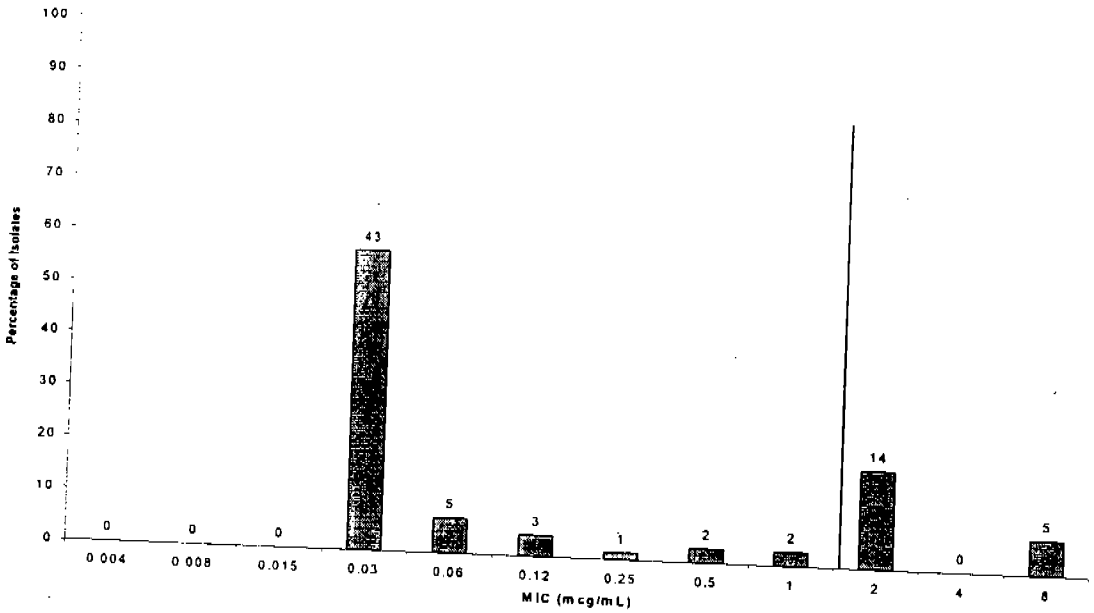
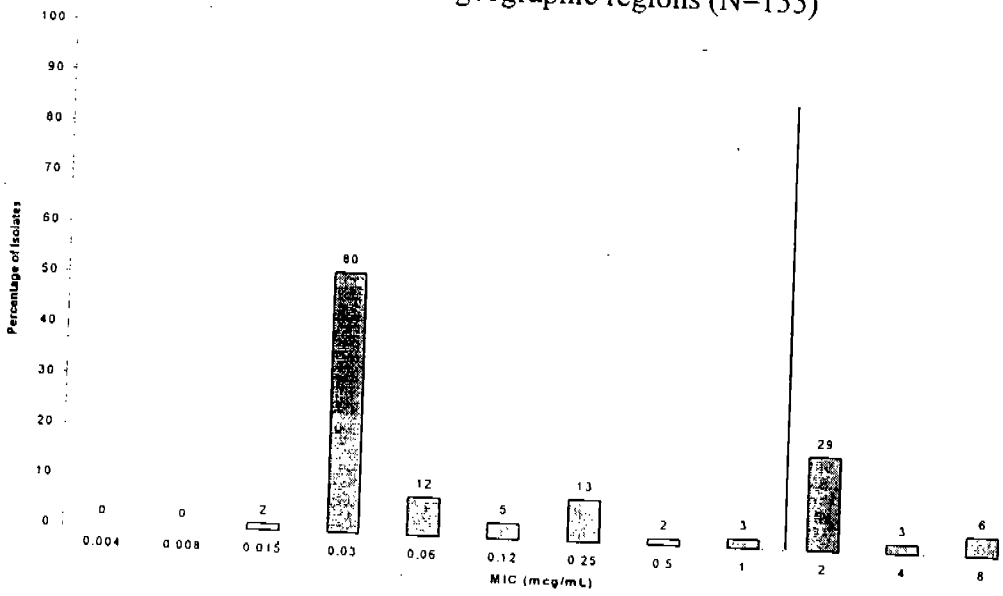


Figure 20. Frequency distribution of amoxicillin/clavulanic acid MICs for *S. pneumoniae* from Study 536 - all geographic regions (N=155)



The pharmacodynamic studies in the neutropenic Murine thigh model indicated that there was a correlation between therapeutic efficacy and the duration that the serum levels of amoxicillin exceeded the MIC. Good efficacy was observed if levels exceeded the MIC for at least 30% of the dosing interval. Similar results were obtained when the neutropenic Murine pneumonia model was used. In this study, when T > MIC exceeded 40% the decrease in bacterial counts was maximal and efficacy correlated directly with T > MIC irrespective of the dosing interval.

The sponsor submitted extrapolated results from pharmacokinetic and pharmacodynamic studies in human seam to indicate that Augmentin ES concentration would remain above MIC of 4 μg/mL 38- 41% of the dosing interval. However Dr. F. Pelsor who is the Biopharmacology reviewer of this application indicated that even if the extrapolation by the sponsor is a conservative one, currently the Office of Clinical Pharmacology and Biopharmaceuticals does not accept extrapolated data and would like to see real data from patients who received the formulation to be marketed. Knowing Dr. Pelsor's view this reviewer had asked the sponsor to recalculate the T>MIC for a MIC of 2 μg/mL during the dosing interval to see the feasibility of a susceptible breakpoint of 2 μg/mL. The results of recalculation received on 10-2-00 follows:

The same methodology as previously described in the submission was used to derive the T>MIC for an amoxicillin MIC of 2 mcg/mL and a dosing interval of 12 hours. For study 25000/382, the derived mean T>MIC is approx. 50% (approx. 6.0 hours). The individual values are:

Subj. No.	***T>MIC (h)***	***(%)***
117	*6.9*	*57.5*
120	*4.9*	*40.8*
218	*6.6*	*55.0*
219	*5.9*	*49.2*
407	*5.8*	*48.3*

For study 25000/446, the derived value is approximately 51% (approx. 6.1 hours).

With this information this reviewer believes that the PK/PD data would probably support an MIC break point of 2 μg/mL and not an MIC break point of 4 μg/mL.

The clinical study that would have been the proof of concept resulted in 4 patients (by the sponsor's analysis) at TOC visit with PRSP isolates that had amox./clav. MICs of ≥ 4 μg/mL, one of which was clinical failure (sponsors clinical failure rate = 25%). It is important to indicate that the reanalysis of the sponsor's data by Dr. M. Makhene, the medical reviewer, and Dr. E. Brittain, the statistician, resulted in a total of 8 patients whose isolates had amox./clav. MICs of ≥ 4 μg/mL (four with MICs of 8 and four with MICs of 4 μg/mL). All 4 patients with isolates having amox./clav. MICs of 8 μg/mL failed clinically at the TOC and one out of the four patients with isolates having MICs of 4 μg/mL also failed clinically at the TOC. This resulted in a clinical success rate of 3/8, 37.5% for all patients with isolates that had amox./clav. MICs of ≥ 4 μg/mL. This is consistent with the in vitro data where one could predict that PRSP isolates would not be successfully treated with amox/clav Table 4.). The successful clinical response rate for patients with *S. pneumoniae* isolates with amox./clav. MICs of 2 μg/mL was 14/23, 60.9%, which is traditionally not considered a good efficacy rate. The successful clinical response rate for patients with *S. pneumoniae* isolates with amox./clav. MICs of <2 μg/mL (i.e. ≤ 1.0 μg/mL) was 80/101, 79.2% which is traditionally an almost acceptable efficacy rate. With this information this reviewer believes that the clinical trial data would probably support a susceptible MIC break point of 1.0 μg/mL.

In summary, when this reviewer takes into consideration all the evidence provided by the in vitro susceptibility data, the animal and human the PK/PD data, the animal efficacy data, and the clinical outcomes from the clinical trial the susceptible breakpoint seems to fall on 1.0 μg/mL. The breakpoint of 1.0 μg/mL seems a good choice because the T>MIC would certainly be closer to 60% of the dosing interval, the clinical outcome would be at 79.2% and the bimodal population is clearly separated. If one chooses the MIC of 1.0 μg/mL for the susceptible breakpoint then MICs of 2.0 and 4.0 μg/mL would be the obvious intermediate and resistant breakpoints respectively. If one chooses the MIC of 2.0 μg/mL for the susceptible breakpoint then MICs of 4.0 and 8.0 μg/mL would be the obvious intermediate and resistant breakpoints respectively.

5. Recommended labeling

Depending on the approval of this indication by the medical reviewer Dr. M. Makhene and based on the above microbiology review the microbiology section of the product insert should read as follows:

MICROBIOLOGY:

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Amoxicillin is, however, susceptible to degradation by β-lactamases and, therefore, the spectrum of activity does not include organisms, which produce these enzymes. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance.

[redacted] Augmentin protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics. Thus, Augmentin possesses the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic Gram-positive microorganisms

Streptococcus pneumoniae (including penicillin resistant isolates)

Aerobic Gram-negative microorganisms

Haemophilus influenzae (including β-lactamase producing strains)

Moraxella catarrhalis (including β -lactamase producing strains)

The following *in vitro* data are available, **but their clinical significance is unknown**.

At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic acid. However, with the exception of organisms shown to respond to amoxicillin alone, the safety and effectiveness of amoxicillin/clavulanic acid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Staphylococcus aureus (including β-lactamase producing strains)
Streptococcus pyogenes

NOTE: Staphylococci that are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

NOTE: *Streptococcus pyogenes* [redacted] and, therefore, are susceptible to amoxicillin alone. Adequate and well-controlled clinical trials have established the effectiveness of amoxicillin alone in treating certain clinical infections due to *Streptococcus pyogenes*.

Susceptibility Testing
Dilution Techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1,2] (broth) or equivalent with standardized inoculum concentrations and standardized concentrations of amoxicillin/clavulanate potassium powder.

The recommended dilution pattern utilizes a constant amoxicillin/clavulanate potassium ratio of 2 to 1 in all tubes with varying amounts of amoxicillin. MICs are expressed in terms of the amoxicillin concentration in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid. The MIC values should be interpreted according to the following criteria:

For testing *Streptococcus pneumoniae*[a]

MIC (µg/mL)	Interpretation
[redacted]	Susceptible (S)
[redacted]	Intermediate (I)
[redacted]	Resistant (R)

For testing [redacted] *Haemophilus influenza*[b]

MIC (µg/mL)	Interpretation
[redacted]	Susceptible (S)

Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (HTM)[2].

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard amoxicillin/clavulanate potassium powder should provide the following MIC values:

Microorganism	MIC range (µg/mL)[c]
Haemophilus influenzae[d] ATCC 49247	2 to 16
Streptococcus pneumoniae[e] ATCC 49619	0.03 to 0.12

[c] Expressed as concentration of amoxicillin in the presence of clavulanic acid at a constant 2 parts amoxicillin to 1 part clavulanic acid.

[d] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM[2].

[e] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood[2].

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[3,4] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 µg of amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) to test the susceptibility of microorganisms to amoxicillin/clavulanic acid.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) disk should be interpreted according to the following criteria:

For *H. influenzae*[f]

Zone diameter (mm)	Interpretation
≥ 20	Susceptible (S)
≤ 19	Resistant (R)

NOTE: Staphylococci that are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

NOTE: β-lactamase negative, ampicillin-resistant strains of *H. influenzae* must be considered resistant to amoxicillin/clavulanic acid.

[f] These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM.

Susceptibility of *S. pneumoniae* should be determined using a 1-µg oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible to amoxicillin/clavulanic acid. An amoxicillin/clavulanic acid MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤ 19 mm.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for amoxicillin/clavulanic acid.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-µg amoxicillin/clavulanate potassium (20 µg amoxicillin plus 10 µg clavulanate potassium) disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
Haemophilus influenzae[g] ATCC 49247	15-23

[g] This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM[4].

References

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3. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests -Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January 2000.
4. National Committee for Clinical Laboratory Standards. Disk Diffusion Supplemental Tables NCCLS Document M100- S10 (M2) . NCCLS, Wayne, PA, January 2000. National Committee for Clinical Laboratory Standards. MIC Testing Supplemental Tables NCCLS Document M100- S10 (M7) . NCCLS, Wayne, PA, January 2000.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. These revisions are found on pages 37-40 of this review. The sponsor should be notified of the needed changes in the product insert.

/S/

Sousan Sayahtaheri Altaie, Ph.D.
Clinical Microbiology Review Officer

Orig. NDA 50755
HFD-520/Division File
HFD-520/MO/D. Makhene
HFD-520/BioStat/E. Brittain
HFD-520/PharmTox /K. Seethaller
HFD-520/Biopharm TL/F. Pelsor
HFD-520/Micro/S.S. Altaie
HFD-520/Chem/A. Yu
HFD-520/PM/S. Samanta

Concurrence Only:
HFD-520/Dep. Dir./L. Gavrilovich
HFD-520/TL Micro/A. T. Sheldon
Red and Final Initialed 12/08/00 SSA

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4. In vitro activity of gemifloxacin (SB-265805) against contemporary clinical bacterial isolates from eleven North American medical centers, and assessment of disk test interpretive criteria. P. Fuchs, A. Barry and S. Brown. 24 June 1999.
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