CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-755

ADMINISTRATIVE DOCUMENTS

SmithKline Beecham

TO: Deneen Stewart
US Regulatory Affairs

FROM: Dara L. Dinner
Associate Patent Counsel
SB Corporate IP - US

DATE: 30 March 2000

RE: Patent Information Respecting Augmentin ES New Drug Application (# 50-755) for Management of Specific Bacterial Infections

Please find below the patent information that SB is required to submit to the U.S. FDA under the provisions of 21 C.F.R. § 314.53 for the "Description" and "How Supplied" sections of the labeling.[1]

The composition for which approval is being sought (AUGMENTIN ES ™) is a formulation having a ratio of 14:1 of amoxicillin trihydrate and potassium clavulanate in suspension form.

[1] FDA recently issued a proposed rule entitled "Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs" (65 Fed. Reg. 3623, Jan. 24, 2000) which the agency attempted to bring its regulations into conformance with certain transitional provisions of the Food and Drug Administration Modernization Act (Section 125 (d) of FDAMA (1997)). In this proposed rule, FDA would exempt marketing applications for certain antibiotic drug products from regulatory provisions governing exclusivity and patents based on a comparison of active moieties. SB disagrees with this proposed rule because it does not reflect Congress's intent for repealing Section 507 of the FD&C Act. SB intends to provide comments to the docket expressing our disagreement with this proposed rule and believes the rule should be changed to reflect these comments. SB was required to perform clinical studies on *Augmentin ES* to show that it is safe and effective for its intended use. Therefore, the product should receive three years exclusivity under the Hatch-Waxman Act, which is the same period that is available to non-antibiotic drugs and purely synthetic antibiotic drugs. For this reason, we are submitting the patent information on *Augmentin ES* to receive three years exclusivity and to be listed in The Orange Book.

Patent Information for NDA Filings (5 Patents)

Patent 1: U.S. Patent No. 6,031,093

a. Expiration Date

The 17 year term expires on 28 February 2017.

b. Type of Patent

This patent claims:

1) a solid pharmaceutically acceptable salt of clavulanic acid which is a component of the formulation for which approval is being sought.

c. Name of Patent Owner

SmithKline Beecham p.l.c.

Patent 2: U.S. Patent Number 4,529,720

a. Expiration Date

The 17 year term expires on July 16, 2002.

b. Type of Patent

This patent claims:

1) generically, a method of effecting β-lactamase inhibition in a human [with β-lactamase producing bacteria] with clavulanic acid or a pharmaceutically acceptable salt thereof, which claims contain a component of the formulation for which approval is being sought.

2) specifically claims the administration of the potassium salt of clavulanic acid, and also oral administration of clavulanic acid or salt thereof, which claims cover a component of the formulation for which approval is being sought.

c. Name of Patent Owner

Beecham Group, p.l.c.

Patent 3: U.S. Patent Number 4,560,552

a. Expiration Date

The 17 year term expires on December 24, 2002

b. Type of Patent

This patent claims:

1) a generic pharmaceutical composition for treating bacterial infections in a human with a synergistically effective amount of clavulanic acid, or a pharmaceutically acceptable salt thereof, and an antibacterially effective amount of a penicillin, or a pharmaceutically acceptable salt or ester thereof, which claims cover the both active ingredients in the formulation for which approval is being sought.

c. Name of Patent Owner

Beecham Group p.l.c.

Patent 4: U.S. Patent Number 4,525,352

a. Expiration Date

The 17 year term expires on June 25, 2002

b. Type of Patent

This patent claims:

1) a generic pharmaceutical composition for treating bacterial infections in a human with a synergistically effective amount of a pharmaceutically acceptable salt of clavulanic acid, and an antibacterially effective amount of amoxicillin, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof, in combination with a pharmaceutically acceptable carrier, which claims cover both of the active ingredients in the formulation for which approval is being sought.

2) specifically claims the potassium salt of clavulanic acid, as a component of the formulation for which approval is being sought.

3) specifically claims the trihydrate form of amoxycillin, as a component of the formulation for which approval is being sought.

4) a generic method of treating bacterial infections in humans with a synergistically effective amount of a pharmaceutically acceptable salt of

clavulanic acid, and an antibacterially effective amount of amoxicillin, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof, in combination with a pharmaceutically acceptable carrier, which claims a use for which approval is being sought.

5) specifically claims the potassium salt of clavulanic acid and amoxicillin trihydrate, which claims cover use of both active agents in the formulation for which approval is being sought.

c. Name of Patent Owner

Beecham Group p.l.c.

Patent 5: U.S. Patent Number 4,454,069

a. Expiration Date

The 17 year term expires on June 12, 2001.

b. Type of Patent

This patent claims:

1) a method for the production of clavulanic acid, or a pharmaceutically acceptable salt thereof, which claims cover production of a component of the formulation for which approval is being sought.

c. Name of Patent Owner

Beecham Group Limited

EXCLUSIVITY SUMMARY for NDA # 50-755 **SUPPL #** NA

Trade Name Augmentin ES-600™ **Generic Name** Amoxicillin/clavulanate Potassium

Applicant Name GlaxoSmithKline **HFD-** 520

Approval Date June 22, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ ✓ / NO / ___ /

   b) Is it an effectiveness supplement? YES / ___ / NO / ✓ /

   If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES / ✓ / NO / ___ /

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 50-564 Tablet amoxicillin/clavulate 250/125 500/125

NDA # 50-575 Oral Suspension 125/31.25, 250/62

NDA # 50-597 Chewable Tablet " "
50-720 Tablet 875/125
50-725, 50-726

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 25000/536

Investigation #2, Study # 25000/446

Investigation #3, Study # 25000 447

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 25000/536

Investigation #2, Study # 25000/446

Investigation #3, Study # 25000/447

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /X/ NO /___/ Explain: _____

Investigation #2

IND # [redacted] YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? not applicable

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

/S/
Signature of Preparer
Title: Regulatory Project manager

6-22-01
Date

/S/
Signature of Office or Division Director

7/16/01
Date

cc:
Archival NDA
HFD-520/Division File
HFD-520/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

SB
SmithKline Beecham
Pharmaceuticals

NDA 50-755
Debarment Certification

Pursuant to Section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to Section 306(e) as debarred under subsections 306(a) or (b) of the Act.

(See cover letter of NDA 50-755)

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 050755
Trade Name: AUGMENTIN(AMOXICILLIN/CLAVULANATE POTASS
Generic Name: AMOXICILLIN/CLAVULANATE POTASSIUM
Supplement Number: 000 **Supplement Type**: N
Dosage Form:
Regulatory Action: NA **Action Date**: 10/26/98
COMIS Indication: TREATMENT OF PEDIATRIC PATIENTS WITH OTITIS MEDIA IN WHOM S. PNEUMONIAE OF REDUCED SUSCEPTIBILITY TO PENICILLIN IS SUSPECTED AND B-LACTAMASE-PRODUCING STRAINS O

Indication #1: Treatment of pediatric patients with recurrent or persistent acute otitis media due to S. pneumoniae (penicillin MICs less than or equal to 2 microgram/mL), H. influenzae (including beta-lactamase producing strains), or M. catarrhalis (including beta-lactamase producing strains) characterized by the following risk factors: antibiotic exposure for acute ottis media within the preceding 3 months, and either of the following: age less than or equal to 2 years or daycare attendance.

Label Adequacy: Adequate for some pediatric age groups
Formulation Needed: New formulation developed with this submission
Comments (if any) approval (6/22/01)

	Lower Range	Upper Range	Status	Date
	3 months	12 years	Completed	
	0 months	3 months	Waived	
	12 years	16 years	Waived	

This page was last edited on 6/20/01

/S/
Signature

6-21-01
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CRF 54.2(f).

Clinical Investigators	
Please see two attached lists	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 542(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David E. Wheadon, M.D.	**V.P. and Director, Regulatory Affairs-NA and Product Proffesional Services**
FIRM/ORGANIZATION: **SmithKline Beecham Pharmaceuticals**	
SIGNATURE: David E Wheadon, MD	DATE: **22 March 2000**

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Division Director's Memorandum for NDA 50-755
Augmentin ES 600 Oral Suspension (14:1 ratio of amoxicillin and clavulanate)

In April, 2000, SmithKline Beecham Pharmaceuticals submitted a new drug application for Augmentin ES-600 Oral Suspension in the treatment of pediatric patients with acute otitis media (AOM). Augmentin ES-600 (also referred to in this document as Augmentin 14:1) is a pediatric suspension for dosing at 90 mg/kg/day (amoxicillin component) to be dosed every 12 hours. The clavulanate dose is identical to that in the already-marketed 7:1 Augmentin formulation. The rationale for development of a higher strength Augmentin suspension was to provide coverage, in the empiric treatment of children afflicted with AOM, for penicillin-resistant strains of *Streptococcus pneumoniae* (PRSP), as well as coverage for beta-lactamase producing pathogens like *Haemophilus influenzae* and *Moraxella catarrhalis*. This memorandum will serve to summarize the basis for approval of this NDA, focusing on the results of the pivotal trials, as well as the recommendations of the Anti-Infective Advisory Committee to whom the data were presented in January, 2001.

The company conducted studies evaluating Augmentin ES-600 using the following approach: 1) a pharmacokinetic study of the 14:1 formulation was conducted; 2) a "clinical only" study (no baseline tympanocentesis) was performed comparing Augmentin 14:1 to the 7:1 formulation in children with AOM; and 3) an open-label, non-comparative double tympanocentesis ("double tap") study was undertaken in children with AOM, including those with PRSP.

A pharmacokinetic (PK) study was conducted at a single center in 19 pediatric patients with AOM, aged 3 months to 12 years. Middle-ear fluid and plasma concentrations of amoxicillin were determined at 1, 2, and 3 hours post-dose (six patients per time point) after a single oral dose of Augmentin 14:1 (i.e., 45/3.2 mg/kg). The goal of the study was to provide evidence for time (T) over the minimum inhibitory concentration (MIC) as a surrogate for bacteriologic activity. Results of the mean plasma concentrations of amoxicillin from this study were available for up to 3 hours only. (Beyond 3 hours, plasma amoxicillin concentrations were calculated based on results of another PK study of the Augmentin 7:1 formulation.) While the outcome yielded a T>MIC of 40%, these results must be interpreted with some caution, since the full concentration-time profile for Augmentin 14:1 was extrapolated from 7:1 data, and observed concentrations showed large inter-patient variability.

The clinical only study (randomized, double-blind, multicenter comparative study of Augmentin 14:1 versus Augmentin 7:1) was conducted in pediatric patients aged 3 months to 12 years with AOM. Four hundred fifty-three patients were enrolled and received 10 days of either Augmentin 14:1 or 7:1. The trial enrolled "all comers" and did not specifically enrich for patients with PRSP. Clinical safety and efficacy evaluations were performed at study days 12-14 and 22-28. Clinical cure rates at the later follow-up for Augmentin 14:1 were 83% (96/116) compared to 78% (94/120) for the 7:1

formulation (95% confidence interval –6.5%, 15.4%). Diarrhea was more common with 14:1 (11% v. 9%). Because of the need for microbiologic information, the Division requested a confirmatory study of the 14:1 formulation in children with AOM due to documented PRSP.

The open-label, non-comparative double-tap study (tympanocentesis at baseline and on-therapy) was conducted in children with AOM treated with Augmentin 14:1 for 10 days. It is important to note, this study was enriched for pediatric patients more likely to have PRSP (younger age, previous antibiotic therapy for AOM, daycare attendance, etc.). Five hundred twenty-one (521) children, aged 3-48 months, were enrolled and underwent tympanocentesis at baseline and on study day 4-6. Efficacy endpoints included bacteriologic assessment at the on-therapy visit in patients infected with *S. pneumoniae*; and clinical response after therapy on study day 12-14, referred to as end-of-therapy (EOT) and study day 25-28, referred to as the test-of-cure (TOC) in the current Guidance on AOM. It should be noted that Advisory Committee (AC) members recommended that the primary clinical endpoint in AOM trials be determined at EOT, while the primary microbiologic endpoint be assessed on therapy in double-tap studies. Some committee members stressed that they did not expect an antibiotic to have an effect in children three to fours weeks post-therapy for AOM, especially on a mucosal surface known to recolonize, and in the setting of intrinsic factors like eustachian tube dysfunction that naturally lead to new infections. At the same time, most panel members recommended assessing children at the later follow-up, approximately two to three weeks after completion of therapy, as a secondary endpoint. With these AC recommendations in mind, then, the microbiologic and clinical results of the double-tap study are reviewed below.

A total of 521 pediatric patients with AOM, aged 3-48 months, were enrolled, of whom 359 had a baseline pathogen. Of these 359 patients, 157 had *Streptococcus pneumoniae,* including 41 with penicillin-resistant strains (MIC $\geq$ 2 µg/mL). Microbiologic and clinical outcomes for patients infected with *Streptococcus pneumoniae* given Augmentin ES-600 were as follows:

Microbiologic Eradication Rates On-Therapy (*Study Day 4-6*)
(FDA Briefing Document January 30, 2001)

	Intent-to-Treat n /N (%)	Per Protocol n /N (%)
Streptococcus pneumoniae (all)	149/157 (94)	121/123 (98)
Penicillin MIC < 2 µg/mL	103/109 (95)	84/84 (100)
Penicillin MIC $\geq$ 2 µg/mL	38/41 (93)	31/33 (94)
Penicillin MIC = 2 µg/mL	22/23 (96)	19/19 (100)
Penicillin MIC = 4 µg/mL	16/18 (89)	12/14 (86)

Clinical Response at End of Therapy (*Study Day 12-14*)
(SmithKline Beecham Briefing Document January 30, 2001)

	S. pneumoniae	Penicillin MICs ≥ 2 μg/mL	Penicillin MICs < 2 μg/mL
Per Protocol	**n/N**	**n/N**	**n/N**
Success, n (%)	125/140 (89)	28/34 (82)	91/99 (92)
Failure, n (%)	15/140 (11)	6/34 (18)	8/99 (8)
Intent-to-Treat	**n/N**	**n/N**	**n/N**
Success, n (%)	131/159 (82)	29/41 (70)	96/111 (86)
Failure, n (%)	17/159 (11)	6/41 (15)	10/111 (9)
Missing Clinical Response, n (%)	11/159 (7)	6/41 (15)	5/111 (5)

Note: In the clinical PP population, 7 patients are missing penicillin MICs. They are counted as missing when displayed by MIC and are thus not included in tabulations by MIC.

Safety data analysis for Augmentin ES-600 showed diarrhea as the most common adverse event. A total of 70/521 children (13%) had "protocol defined diarrhea" (3 or more watery stools in a day, 2 watery stools on 2 consecutive days, or reported an adverse event of diarrhea).

Advisory Committee members discussed the question of whether the data supported the safety and efficacy of Augmentin ES-600 for the treatment of AOM due to PRSP. They voted against a "blanket approval" of Augmentin ES for PRSP, citing too few isolates with MICs equal to 4 or 8, as well as pharmacokinetic data, animal model data, and clinical data with other beta-lactams and with meningitis and penicillin, that raised concerns about using amoxicillin for strains of *S. pneumoniae* with higher amoxicillin MICs. (A total of 8 patients had amoxicillin MICs greater than 2 μg/mL; the clinical success rate dropped to 38% (3/8) for such patients.) When AC members modified the question, restating it as "Do the data support the safety and efficacy of Augmentin ES for the treatment of AOM due to PRSP based on an amoxicillin MIC ≤ 2 μg/mL", they endorsed approval of Augmentin ES (13 "yes" votes, 1 abstention).

In conclusion, SmithKline Beecham Pharmaceuticals has presented substantial evidence that Augmentin ES-600 is safe and effective in the treatment of pediatric patients with acute otitis media (AOM). The approval includes those at risk for infection due to *Streptococcus pneumoniae* with reduced susceptibility to penicillin as defined by an MIC ≤ 2 μg/mL. These conclusions are based on the microbiologic outcome determined at the on-therapy tympanocentesis, as well as clinical assessment at the end of therapy. The Advisory Committee felt the Agency could successfully describe in product labeling the high-risk population (the "enriched" population in study 3) most likely to benefit from using an empiric therapy which would treat infections caused by *Streptococcus pneumoniae* with MIC ≤ 2.

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/s/

Susmita Samanta
12/17/01 01:52:09 PM
CSO

Janice Soreth
12/17/01 02:02:43 PM
MEDICAL OFFICER

MEMORANDUM

Date: January 23, 1998

To: Sharon Shapowal, R.Ph.
Associate Director, U.S. Regulatory Affairs
SMITH KLINE BEECHAM PHARMACEUTICALS
Philadelphia, PA
215-751-3468

From: M. Makhene, M.D.
Medical Reviewer
Division of Anti-Infective Drug Products

Re: NDA 50-755 Augmentin 14:1 formulation

The following memorandum summarizes the issues raised during and following a face-to-face meeting last month with representatives of SB.

1. REGULATORY GUIDANCE AND PRECEDENCE

Is the single clinical only study adequate to support the claim of efficacy for acute otitis media due to resistant S. pneumoniae?

- The Points to Consider document and the IDSA guidelines ask for a microbiologic study in addition to the clinical study to support claim of efficacy.

2. EFFICACY

What is the rationale for the higher dose?

- based on the applicant's analysis, the efficacy from the SB study 25000/447 is the same for Augmentin 90mg/kg/day and Augmentin 45 mg/kg/day
- what is the appropriate interpretation of these efficacy data (without supporting bacteriologic study) in the face of spontaneous resolution of acute otitis media
- no information on which failures in SB clinical study were due to resistant *S. pneumoniae*

How are the effects of *host factors and concurrent viral infections on response rates accounted for without supporting bacteriologic data?*

3. EMPIRIC TREATMENT AND OVERUSE OF ANTIBIOTICS

Can empiric treatment be appropriate in the face of increasing pneumococcal resistance to antimicrobial agents?

- low proportion of treatment failures (2-3%) in patients with AOM due to penicillin resistant pneumococci (Klein and Bluestone, Advances in Ped Infect Dis 1996)
- overwhelming concern in the medical community about antibiotic resistance
- young children are at greatest risk for acute otitis media from overuse of antibiotics and day care attendance
- concern about empiric treatment with new formulation with report of bacteriologic failures of Augmentin in the treatment of acute otitis media with *H. influenzae* (Patel J, Reisner B, Vizirinia N, et al, J Pediatr 1995; 126:799-806)

4. PHARMACOKINETIC/PHARMACODYNAMIC ARGUMENTS

a) Is time over MIC (T_{MIC})an adequate surrogate marker to support the claim for efficacy?

- From the pharmacology literature, when T_{MIC} is in the [redacted] range for the dosing interval or for 24 hours, favourable clinical outcomes in the [redacted] range can be expected
- Amoxicillin 40mg/kg/day alone appears to provide adequate drug concentration for the treatment of penicillin resistant strains

b) Clinical Data to support T_{MIC} as surrogate marker for efficacy are limited

- PK/PD surrogates have been studied mainly *in vitro* and animal models
- human studies have confirmed a relationship between T_{MIC} and microbiologic efficacy of beta lactams are few

c) What is the role of peak MIC, AUC and AUC/MIC (as surrogates) in predicting the efficacy of beta lactams?

- contribution to overall efficacy
- dosing interval may affect the role of T_{MIC} as the major surrogate for efficacy
- role of covariance in the models of peak MIC, T_{MIC} and AUC/MIC and the interpretation of these surrogates

d) antibiotic concentrations in the middle ear

- consideration of interpatient variability in the antibiotic concentration and penetration rates in the middle ear

5. MICROBIOLOGY

- *What is the role of the clavulanate, as supported by microbiologic data, against S. pneumoniae?*

cc: NDA file 50-755
HFD-520/TL/Albuerne
HFD-520/CSO/Trostle
mkm/01/23/98

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 27, 2001

TO: HFD-520 Division Files

FROM: Janice M. Soreth, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV

SUBJECT: Name Selection for NDA 50-755

The proprietary name, Augmentin ES-600, was approved by the Division, in agreement with the sponsor. The sponsor requested approval for the name Augmentin ES in the submission, dated May 15, 2000. The Office of Post-Marketing Drug Risk Assessment (OPDRA) was consulted and did not recommend use of the modifier ES, because the "extra strength" modifier was misleading when an 875 mg tablet was available. Policy concerns as indicated by OPDRA are that modifiers are used: a) for extended-release formulations with different pharmacokinetic performances and different dosing recommendations and, b) that a 1000 mg tablet currently under review had the same proposed name. OPDRA recommended that the product be named Augmentin 600 mg/5mL, consistent with "Augmentin's current nomenclature... Augmentin 125, Augmentin 200, Augmentin 250, Augmentin 400, Augmentin 500, Augmentin 875".

In selecting the name Augmentin ES-600, the Division attempted to address the issues brought forth by OPDRA, the Sponsor, and the Division:

1. The modifier ES, meaning extra strength, was appropriate for this product because this suspension was designed to provide a greater amount of amoxicillin in a higher ratio of amoxicillin to clavulanate (14:1) than the prior suspension formulations (4:1 and 7:1 ratios). The product does provide different pharmacokinetic performance in that previous formulations cannot provide similar high concentrations of amoxicillin without also increasing clavulanate exposure. The product has a different dosage regimen based on weight. These facts are consistent with the policy stated by OPDRA for use of a modifier.

2. The Division considered it important to distinguish between the new product and the 200 mg/5 mL and 400 mg/5 mL suspensions to discourage attempts to substitute these older formulations for the new product. Augmentin ES-600 contains 42.9 mg of clavulanic acid per 5mL whereas Augmentin 200mg/5mL suspension contains 28.5mg of clavulanic acid per 5mL and the 400mg/5mL suspension contains 57mg of clavulanic acid per 5mL. Therefore,

the Augmentin 200mg/5mL and 400mg/5mL suspensions should not be substituted for Augmentin ES-600, as they are not interchangeable. The name proposed by OPDRA, Augmentin 600 mg/5 mL, does not sufficiently distinguish the new suspension from the prior formulations.

3. The Division acknowledged OPDRA's concern that ES was misleading when a formulation of Augmentin with 875 mg of the amoxicillin component is available. However, "Augmentin 875" has a lower amoxicillin to clavulanate ratio (7:1), equivalent to the 200 mg/5 mL and 400 mg/5 mL suspensions. Further, the 875 mg formulation is a tablet, unlikely to be used as an alternative to the Augmentin ES-600 formulation, since the majority of the target population are unable to swallow tablets. The Division considered the need to distinguish between Augmentin ES 600 and other suspensions as more important than avoiding a "misleading" comparison to the 875 mg tablet.

4. The Sponsor noted that previous formulations are not numbered and all have the proprietary name of Augmentin® alone.

5. The Division agrees with OPDRA that use of the same name, Augmentin ES, for the 1000 mg tablet, under review, could create confusion. The Sponsor agreed not to use the name Augmentin ES for this tablet.

6. The Sponsor is attempting to develop another suspension with a similar amoxicillin to clavulanate ratio (14:1) in a more concentrated suspension, 800 mg/5 mL. The use of Augmentin ES alone would not provide sufficient distinction between this product and potential future formulations.

The name Augmentin ES-600 offered the best option for distinguishing this product from currently marketed and potential future formulations.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Susmita Samanta
7/23/01 09:44:54 AM
CSO

Maureen Dillon-Parker
7/26/01 08:39:11 AM
CSO
MDParker for FVLeSane

Janice Soreth
8/29/01 10:55:14 AM
MEDICAL OFFICER

M. Trostle

MEMORANDUM-OF-MEETING

NDA 50-755 **Date:** December 18, 1998

Applicant: SmithKline Beecham Pharmaceuticals (SB)

Drug: Augmentin 600 mg/42.9 mg per 5 mL (amoxicillin/clavulanate potassium) Powder for Oral Suspension

Meeting Type: End of review conference

Meeting Chair: Dr. Gary Chikami **Applicant Lead:** Dr. Robert Pietrusko

Meeting Recorder: Mr. Stephen Trostle

FDA Attendees, Titles, and Offices:

Dianne Murphy, M.D., Office Director, Office of Drug Evaluation IV, HFD-104
Gary Chikami, M.D., Division Director, Division of Anti-Infective Drug Products (DAIDP), HFD-520
Mercedes Albuerne, M.D., Team Leader, Medical Officer, DAIDP, HFD-520
Mamodikoe Makhene, M.D., Medical Officer, DAIDP, HFD-520
Albert Sheldon, Ph.D., Team Leader, Microbiologist, DAIDP, HFD-520
James King, Ph.D., Microbiologist, DAIDP, HFD-520
Andrew Yu, Ph.D., Chemist, Division of New Drug Chemistry III (DNDCIII), HFD-520
Li Ming Dong, Ph.D., Statistician, Division of Biometrics III (DOBIII), HFD-725
Frank Pelsor, Ph.D., Team Leader, Biopharmaceuticist, Division of Pharmaceutical Evaluation III (DPEIII), HFD-880
He Sun, Ph.D., Biopharmaceuticist, DPEIII, HFD-880
Stephen Trostle, Regulatory Health Project Manager, DAIDP, HFD-520

Applicant Attendees and Titles:

Dr. Robert Pietrusko, Vice President and Group Director, U.S. Regulatory Affairs
Dr. Daniel Burch, Group Director, Clinical Research & Development and Medical Affairs
Dr. Linda Miller, Senior Investigator, Microbiology
Ms. Sharon Shapowal, Associate Director, U.S. Regulatory Affairs

FDA's Objectives:

To respond to SB's request for the following (as presented in SB's background material for the meeting):

1. What further steps need to be taken by the applicant before the application can be approved.
2. Does the Division concur that Subpart H is applicable to this product registration, especially in light of recent Advisory Committee discussion/endorsement?
3. Has the Division taken a position against empiric antibiotic use in acute otitis media (AOM)?

Discussion:

After the attendees introduced themselves, SB presented overheads (a copy of the overheads is attached). During the presentation of their overheads, SB requested for the Agency to respond to the following three questions:

1. Was the application accepted and filed under Subpart H?
2. Was the application reviewed under Subpart H?
3. What will it take for SB to get the approval of the application under Subpart H?

The Agency provided a response to each of the questions asked during SB's presentation.

The Agency's response to Question 1 is as follows:

After reviewing the regulatory history for development of the drug product, the Agency honored the previous commitment to accept and file the application under Subpart H but expressed concerns to the applicant in a meeting on December 18, 1997, about using Time Above Minimum Inhibitory Concentration (T>MIC) as a surrogate for bacteriologic efficacy.

The Agency's response to Question 2 is as follows:

During the review of the application after it was filed, the Agency determined that the application did not meet Subpart H criteria.

Regarding the application not meeting Subpart H criteria:

- The intent of Subpart H is to provide drug products, for serious and life-threatening illnesses, that provide therapeutic benefit over existing products. Otitis media (OM) is a common illness; it does not equal a serious or life-threatening illness as does meningitis or bacteremia.
- A surrogate endpoint should be in a serious or life-threatening illness such as meningitis or bacteremia not OM.
- There is more risk at approving a drug in development compared to less risk of evaluating a drug based on clinical trial data.

Regarding the application not meeting surrogate criteria:

- Consistent with the recommendations made by the Anti-Infective Drugs Advisory Committee in July and October, 1998, the Agency has not accepted T>MIC as a surrogate for efficacy.
- Pharmacokinetic/pharmacodynamic parameters show *in vitro* susceptibility while surrogates are used to predict clinical benefit, i.e., survival, disease progression, etc.
- T>MIC for the 14:1 product in Study 25000/496 was an extrapolated value. The use of T>MIC as a surrogate was not adequately demonstrated in the application.

The Agency's response to Question 3 is as follows:

- The application's deficiencies are contained in the not approvable letter dated October 26, 1998.
- In order to satisfactorily assess the drug product, an adequate and well-controlled clinical study including bacteriology endpoints should be conducted. The Agency will assist SB in designing the study. Although drugs for AOM are used empirically in clinical practice, their approval is not based on an empiric claim. Therefore, any product seeking approval for treatment of AOM must have demonstrated efficacy against the major pathogens associated with AOM.

Also discussed in the meeting:
The Advisory Committee examines the scientific issues regarding an application not the regulatory issues. The Agency examines the regulatory issues, i.e., whether or not an application meets the combination drug policy or Subpart H criteria.
In order to establish if it is clinically effective, the proposed drug should be compared to the standard of care, i.e., amoxicillin. For the proposed indication, 80 - 90% of patients having AOM would receive twice the amount labeled for the amoxicillin in order to cover 10 - 20% of those patients who have drug resistant *Streptococcus pneumoniae* (DRSP). Although untreated OM can result in meningitis or bacteremia, OM has a significantly high resolution rate.
SB also presented in the meeting that the MIC spread is bimodal; therefore, the Agency recommends that SB include serotyping in its surveys for DRSP. In addition, the source of the isolate should be identified.
The utility or appropriateness of applying the combination drug policy in this situation was discussed.

Conclusions:

- This application is not acceptable under Subpart H because of the lack of evidence of T>MIC as an adequate surrogate for clinical outcomes in the application and OM is a common illness; as such, it does not equal a serious or life-threatening illness as does meningitis or bacteremia. Subpart H is reserved for serious or life-threatening illnesses.
- SB will have to demonstrate the bacteriologic efficacy of Augmentin 90 mg/kg/day to register it for the treatment of AOM.
- There is no evidence of the effect of clavulanate against *S. pneumoniae*, nor is there expected such will become available.

Action Items:

- SB is to provide to the Agency a draft protocol for an adequate and well-controlled clinical study including bacteriology endpoints.
- The Agency will assist SB in designing the study.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

Attachment: Copy of SB's overheads.

(b5)

5 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

MEMORANDUM-OF-MEETING

Date: January 14, 1998

Augmentin -- NDAs 50-564, 50-575, 50-597, 50-720, 50-725, 50-726 [50-755 (pending)]
Timentin -- NDAs 50-590, 50-658
Sponsor: SmithKline Beecham Pharmaceuticals

Unasyn -- NDA 50-608
Sponsor: Pfizer Inc.

Zosyn -- NDA 50-684 [50-750 (pending)]
Sponsor: Wyeth-Ayerst Laboratories

Meeting Type: Review Management Team, Clinical Review Team, and Microbiology Review Team Meeting to define the Division's penicillin combination drug product policy.
Meeting Chair: Dr. Gary Chikami
Meeting Recorder: Mr. Stephen Trostle

FDA Attendees, Titles, and Offices:
Gary Chikami, M.D., Division Director, Division of Anti-Infective Drug Products (DAIDP), HFD-520
Lillian Gavrilovich, M.D., Deputy Division Director, DAIDP, HFD-520
Mercedes Albuerne, M.D., Team Leader, Medical Officer, DAIDP, HFD-520
Mamodikoe Makhene, M.D., Medical Officer, DAIDP, HFD-520
Albert Sheldon, Ph.D., Team Leader, Microbiologist, DAIDP, HFD-520
James King, Ph.D., Microbiologist, DAIDP, HFD-520
Sousan Altaie, Ph.D., Microbiologist, DAIDP, HFD-520
Harold Silver, Microbiologist, DAIDP, HFD-520
Stephen Trostle, Regulatory Health Project Manager, DAIDP, HFD-520

Background:
Combination drug policy under 21 CFR 300.50
DAIDP's Points to Consider
ALL NDA HOLDERS letter dated January 26, 1993

Discussion:
First List of the Microbiology subsection

- Remove non-beta-lactamase producing strains.
  Reason #1: Based on the combination drug policy, both components must contribute to the efficacy of the product, *in vivo* and *in vitro*.
  Reason #2: These products are only indicated for beta-lactamase producing strains.

Second List of the Microbiology subsection

- Remove non-beta-lactamase producing strains.
  Reason: Based on the combination-drug policy, both components must contribute to the efficacy of the product, *in vivo* and *in vitro*.

- Grant beta-lactam in combination with beta-lactamase inhibitor indications only for the treatment of beta-lactamase producing bacterial pathogens.
  Reason: This combination is only necessary for beta-lactamase producing organisms. The non-beta-lactamase producing organisms do not need the combination.

- No indication - no microorganism.
  Reason: Please refer to the January 23, 1993 ALL NDA HOLDERS letter.

Conclusions:

- Based on the combination drug policy, all components of the combination drug must contribute to both *in vivo* and *in vitro* activity; thus, for drug combinations containing a beta-lactamase inhibitor, non-beta-lactamase producing strains should not be included in the First or the Second List of the Microbiology subsection. Only beta-lactamase producing organisms which are resistant to the beta-lactam antibiotic are to be included in the First and the Second List of the Microbiology subsection.

Action Items:

- All labels of beta-lactam antibiotic, combined with a beta-lactamase inhibitor should be reviewed and updated according to the policy statement contained in the Conclusions.

- The policy statement should be written to reflect this concept of antibiotic/inhibitor in a generic fashion, since molecules may be developed to inhibit the action of other mechanisms of resistance.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2003
See OMB Statement on page 2.

NC

FOR FDA USE ONLY

APPLICATION NUMBER

PLICANT INFORMATION

IE OF APPLICANT
SmithKline Beecham Pharmaceuticals

DATE OF SUBMISSION
June 18, 2001

TELEPHONE NO. *(Include Area Code)*
(215) 751-3468

FACSIMILE (FAX) Number *(Include Area Code)*
(215) 751-4926

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Cynthia D'Ambrosio, Ph.D.
Associate Director, U.S. Regulatory Affairs

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **NDA 50-755**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
amoxicillin/clavulanate potassium

PROPRIETARY NAME *(trade name)* IF ANY
Augmentin ES™

CHEMICAL/BIOLOGICAL/BLOOD PRODUCT NAME *(If any)*
(2S,5R,6R)-6-[-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid as the trihydrate and monosodium salts/clavulanate potassium

CODE NAME *(If any)*

DOSAGE FORM:
Powder for oral suspension

STRENGTHS:
600 mg/42.9 mg

ROUTE OF ADMINISTRATION:
Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of acute otitis media caused by susceptible strains of designated organisms.

APPLICATION INFORMATION

APPLICATION TYPE
(check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

N NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug
Holder of Approved Application

TYPE OF SUBMISSION
(check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to request for information on proposed proprietary name

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

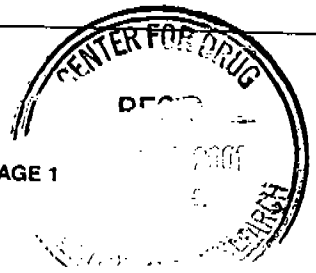
THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 50-564; NDA 50-575; NDA 50-597; NDA 50-720; NDA 50-725; NDA 50-726; NDA 50-765



This application contains the following items: *(Check all that apply)*

	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (l), 21 CFR 601.2(a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER (Specify) - see cover letter

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Cynthia D'Ambrosio	Cynthia D'Ambrosio, Ph.D. Associate Director, U.S. Regulatory Affs.	June 18, 2001

ADDRESS *(Street, City, State and ZIP Code)*	Telephone Number
One Franklin Plaza, P.O. Box 7929 Philadelphia, PA 19101-7929	(215) 751-3468

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99,
1401 Rockville Pike
Rockville, MD 20852-1448

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
SmithKline Beecham Pharmaceuticals

DATE OF SUBMISSION
May 22, 2001

TELEPHONE NO. *(Include Area Code)*
(215) 751-3868

FACSIMILE (FAX) Number *(Include Area Code)*
(215) 751-4926

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One Franklin Plaza, P.O. Box 7929
Philadelphia, PA 19101-7929

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Deneen Stewart, Ph.D.
Senior Regulatory Associate, U.S. Regulatory Aff.

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued).* **NDA 50-755**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
amoxicillin/clavulanate potassium

PROPRIETARY NAME *(trade name)* IF ANY
Augmentin ES™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:
Powder for Oral Suspension

STRENGTHS:
600 mg / 5 mL

ROUTE OF ADMINISTRATION:
Oral

The treatment of pediatric patients with otitis media in whom *S. pneumoniae* of reduced susceptibility to penicillin is suspected and β-lactamase-producing strains of *H. influenzae* or *M. catarrhalis* have not been ruled out as an etiology.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b) (2)

IF AN ANDA, OR 505 (b) (2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUAFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMETN TO PARTIAL SUBMISSION: _____

IFA SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Revised Draft Package Labeling

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

RECD FOR DRUG
MAY 23 2001
MEGA DOC RM
AND RESEARCH

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 50-564; NDA 50-575; NDA 50-597; NDA 50-720; NDA 50-725; NDA 50-726; ; NDA 50-765, NDA 50-785

000003

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbioblogy (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
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	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial information (21 CFR Part 54)
	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by the FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Deneen R. Stewart	Deneen Stewart, Ph.D. Senior Regulatory Affairs, U.S. Regulatory Affairs	05/22/2001

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Franklin Plaza, P.O. Box 7929 Philadelphia, PA 19101-7929	(215) 751-6318

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT
SmithKline Beecham Pharmaceuticals

DATE OF SUBMISSION
April 19, 2001

TELEPHONE NO. *(Include Area Code)*
(215) 751-3468

FACSIMILE (FAX) Number *(Include Area Code)*
(215) 751-4926

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Cynthia D'Ambrosio, Ph.D.
Associate Director, U.S. Regulatory Affairs

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* **NDA 50-755**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*
amoxicillin/clavulanate potassium

PROPRIETARY NAME *(trade name)* IF ANY
Augmentin ES™

CHEMICAL/BIOLOGICAL/BLOOD PRODUCT NAME *(If any)*
(2S,5R,6R)-6-[-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid as the trihydrate and monosodium salts/clavulanate potassium

CODE NAME *(If any)*

DOSAGE FORM:
Powder for oral suspension

STRENGTHS:
600 mg/42.9 mg

ROUTE OF ADMINISTRATION:
Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of acute otitis media caused by susceptible strains of designated organisms.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Revised Draft Labeling/Request for teleconference

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