ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 50785/000** Priority: **3S** Org Code: **520**
Stamp: **20-DEC-2000** Regulatory Due: **29-SEP-2002**
Action Goal: District Goal: **31-JUL-2002**
Applicant: **GLAXOSMITHKLINE** Brand Name: **AUGMENTIN XR**
5 MOORE DR **(AMOXICILLIN/CLAVULANATE POT)**
RESEARCH TRIANGLE PARK, NC 27709 Established Name:
Generic Name: **AMOXICILLIN/CLAVULANATE POTASSIUM**
Dosage Form: **TAB (TABLET)**
Strength: **1000MG/62.5MG**

FDA Contacts:

S. SAMANTA	**(HFD-520)**	**301-827-2125 , Project Manager**
S. PAGAY	**(HFD-520)**	**301-827-2179 , Review Chemist**
D. KATAGUE	**(HFD-520)**	**301-827-2184 , Team Leader**

Overall Recommendation:

ACCEPTABLEon 30-AUG-2001 by J. D AMBROGIO (HFD-324)301-827-0062

Establishment: **2218963** DMF No:
BEECHAM DIV SMITHKLINE BEECHAM AADA No:
101 POSSUMTOWN RD
PISCATAWAY, NJ 08854

Profile: **CFN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER** Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-AUG-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9611207** DMF No:
BEECHAM PHARMACEUTICALS PTE LTDAADA No:

2261 JURONG INDUSTRIAL ESTATE, JURONG

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER** Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-MAR-2001**

CHEMISTRY REVIEW

Chemistry Assessment Section

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted] DMF No:
[redacted] AADA No: [redacted]

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
[redacted] Last Milestone: **OC RECOMMENDATION**

Milestone Date: **02-FEB-2001**
Decision: **ACCEPTABLE** Reason: **BASED ON PROFILE**

Establishment: [redacted] DMF No:
[redacted] AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: [redacted]
[redacted] Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-FEB-2001**
Decision: **ACCEPTABLE** Reason: **BASED ON PROFILE**

Establishment: **9610449** DMF No:
SMITHKLINE BEECHAM CHEMICALS AADA No:
AYRSHIRE, SCOTLAND
IRVINE, UK

Profile: **CFN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER** Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-APR-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

CHEMISTRY REVIEW

Chemistry Assessment Section

Establishment: **1047293** DMF No:
SMITHKLINE BEECHAM PHARMACEUTI AADA No:
201 INDUSTRIAL DR
BRISTOL, TN 37620

Profile: **TCT**

OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE MANUFACTURER** Last Milestone: **OC RECOMMENDATION**
Milestone Date: **30-AUG-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9610412** DMF No:
SMITHKLINE BEECHAM PHARMACEUTI AADA No:

WORTHING, WEST SUSSEX, , UK

Profile: **CFN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Last Milestone: **OC RECOMMENDATION** Milestone Date: **05-MAR-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-785

GlaxoSmithKline
Attention: Cynthia D'Ambrosio, Ph.D.
Associate Director, U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pennsylvania 19101-7929

Dear Dr. D'Ambrosio:

Please refer to your new drug application (NDA) dated December 20, 2000, received December 20, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Augmentin XR™ (amoxicillin/clavulanate potassium) tablet, 1000mg/62.5 mg.

We acknowledge receipt of your submissions dated January 11; March 19 and 23; April 13 and 18; July 20; August 7, 10, 15, 22 (2), 24 and 29; September 14; October 31 and November 19, 2001.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

- Data are insufficient to support the efficacy of Augmentin XR™ in patients with community acquired pneumonia (CAP) due to penicillin resistant *Streptococcus pneumoniae* (PRSP). Data are deficient both in the number of cases as well as severity of illness in these patients. The patient population should include experience in CAP patients with bacteremia due to PRSP. Prior to getting a claim for sinusitis due to *S. pneumoniae* with reduced susceptibility to penicillin, you will need to establish efficacy in patients with more severe disease (e.g. CAP). Submission of additional data in patients with acute bacterial sinusitis due to PRSP is encouraged.

- The draft labeling does not clearly identify the characteristics of the intended patient population for Augmentin XR™, in contrast to the Augmentin® (7:1) formulation. The population so defined should be reflective of pneumonia and sinusitis trials conducted with Augmentin XR™, including those with *Streptococcus pneumoniae* with reduced susceptibility to penicillin. The components of such identification could include age, prior antibiotic use, or other co-morbidities, and should be readily recognizable to the clinician at the onset of treatment.

- Augmentin XR™ would not provide additional benefit in the treatment of _____ _____, over Augmentin® formulations with less amoxicillin. At this time, we do not think there are sufficient data to warrant labeling of an _____. Therefore, we recommend that you withdraw this indication from your application.

As part of your planning any additional trial or further versions of labeling, we strongly recommend that you meet with us to formulate a mutually acceptable plan.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the tabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a tabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Susmita Samanta, M.D., Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Janice Soreth
12/12/01 03:50:04 PM

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