

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-158

ADMINISTRATIVE DOCUMENTS

Confidential



Factive

SB-265805

Item 16 Debarment Certification

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

Edward M. Yuhas, Ph.D.*

*US Regulatory Affairs

SB Document Number: SB-265805/RSD-101RK2/1

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ON ORIGINAL

DEBARMENT CERTIFICATION

Pursuant to section 306(K)(1) of the Federal Food, Drug and Costmetic 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.

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NDA 21-158

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FACTIVE[®] (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

**APPEARS THIS WAY
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MIC: Dionne

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

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Item 16. Debarment Certification

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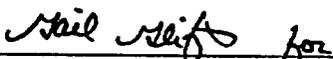
Patent 1: U.S. Patent No. 6,262,071
i. Expiration Date:
The 20 year term expires on September 21, 2019
ii. Type of patent:
Method of Use
iii. Name of patent owner:
SmithKline Beecham Corporation, Philadelphia, PA

Patent 2: U.S. Patent No. 6,331,550
i. Expiration Date:
The 20 year term expires on September 21, 2019
ii. Type of patent:
Method of Use
iii. Name of patent owner:
SmithKline Beecham Corporation, Philadelphia, PA

Patent 3: U.S. Patent No. 6,340,689
i. Expiration Date:
The 20-year term expires on September 14, 2019
ii. Type of patent:
Method of Use
iii. Name of patent owner:
SmithKline Beecham Corporation, Philadelphia, PA

Patent 4: U.S. Patent No. 6,455,540
i. Expiration Date:
The 20-year term expires on September 21, 2019
ii. Type of patent:
Method of Use
iii. Name of patent owner:
SmithKline Beecham Corporation, Philadelphia, PA

Under the provisions of 21 CFR §314.53 (c)(2), the undersigned declares that the above referenced patents cover methods of use for gemifloxacin. This product is the subject of the application (NDA 21-158) for which approval is being sought.



Alberto Grignolo, Ph.D.
President, Worldwide Regulatory Affairs
PAREXEL International Corporation
Authorized U.S. Agent for LG Life Sciences, Ltd.

April 1, 2003
Date

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NDA 21-158

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SmithKline Beecham

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SB-265805

Item 13/14. Patent Information

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Edward R. Grimmi*

*Corporate Intellectual Property - US

SB Document Number: SB-265805/RSD-1015M7/1

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DATE: 29 October 1999

APPEARS THIS WAY
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TO: Edward Yuhas
US Regulatory Affairs

FROM: Edward R. Gimmi 
Assistant Patent Counsel
Corporate Intellectual Property - US

Re: Patent Information Respecting LG's (FACTIVE ®)
New Drug Application (#21-158) for Management of Specific Bacterial
Infections

Please find below the patent information which 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.

The compound for which approval is being sought (FACTIVE ®) is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-1-pyrrolidiny)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid methanesulfonate, also known as gemifloxacin mesylate. An alternative chemical name is (Z)-7-[3-Aminomethyl)-4-(methoxyimino)-1-pyrrolidiny]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid monomethanesulfonate.

Patent Information for NDA Filings (3 Patents)

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ON ORIGINAL

Patent 1: U.S. Patent No. 5,633,262

a. Expiration Date

The 20 year term expires on June 15, 2015.

b. Type of Patent

This patent claims:

1) generic claims to a naphthyridine carboxylic acid compound that covers the active ingredient for which approval is being sought.

2) a generic claim to an antibacterial composition comprising a naphthyridine carboxylic acid compound that covers the active ingredient for which approval is being sought.

- c. Name of Patent Owner
LG Chemical Ltd., Seoul, Republic of Korea

Patent 2: U.S. Patent Number 5,776,944

**APPEARS THIS WAY
ON ORIGINAL**

- a. Expiration Date
The 20 year term expires on June 15, 2015.

- b. Type of Patent

This patent claims:

1) claims that cover the active ingredient for which approval is being sought, hydrates, racemate and isomeric forms thereof.

2) claims to antibacterial compositions that cover the active ingredient for which approval is being sought, hydrates, racemate and isomeric forms thereof.

- c. Name of Patent Owner
LG Chemical Ltd., Seoul, Republic of Korea

Patent 3: U.S. Patent Number 5,962,468

**APPEARS THIS WAY
ON ORIGINAL**

- a. Expiration Date
The 20 year term expires on June 15, 2015.

- b. Type of Patent

This patent claims:

1) claims to methods for prophylaxis or treatment of bacterial infections in a warm blooded animal that cover the active ingredient for which approval is being sought, hydrates, racemate and isomeric forms thereof.

- c. Name of Patent Owner
LG Chemical Ltd., Seoul, Republic of Korea

EXCLUSIVITY SUMMARY for NDA # 21-158 SUPPL #

Trade Name Factive Generic Name gemifloxacin

Applicant Name LG Life Sciences HFD- 590

Approval Date April 4, 2003

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/ x / 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 / x / 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.

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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:

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d) Did the applicant request exclusivity?

YES /___/ NO /_x_/

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

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

YES /___/ NO /_x_/

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 /_x_/

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 /_x_/

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).

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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 /_x_/

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

NDA #

NDA #

NDA #

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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 /___/

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

NDA #

NDA #

NDA #

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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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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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:

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(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 #
- Investigation #2, Study #
- Investigation #3, Study #

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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:

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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 #

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- (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 #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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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.

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**APPEARS THIS WAY
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(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 # _____ YES /___/ NO /___/ Explain:

Investigation #2
IND # _____ YES /___/ NO /___/ Explain:

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(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?

Investigation #1
YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2
YES /___/ Explain _____ NO /___/ Explain _____

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(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 /___/

If yes, explain: _____

Yon Yu
Signature of Preparer
Title: Regulatory project Manager

April 3, 2003
Date

Renata Albrecht
Signature of Office or Division Director

April 3, 2003
Date

**APPEARS THIS WAY
ON ORIGINAL**

cc:
Archival NDA
HFD-590/Division File
HFD-590/DivDir/Albrecht
HFD-590/CPM/Frank
HFD-590/RPM/Yu
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

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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/

Renata Albrecht
4/4/03 01:44:00 PM

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N/A for unapproved NDAs

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Item 19 Financial Information

Form 3454 000002
Attachment 1 Investigators Who Completed Financial Disclosure Forms 000003
Attachment 2 Investigators Who Did Not Completed Financial
Disclosure Forms 000046
Attachment 3 List of Investigators Disclosing Financial Information ... 000049
Form 3455 for _____ 000050
 _____ Disclosure: Financial Interests and Arrangements of Clinical
 Investigators 000051
Form 3455 for _____ 000052
 _____ Disclosure: Financial Interests and Arrangements of Clinical
 Investigators 000053
Form 3455 for _____ 000054
 _____ Disclosure: Financial Interests and Arrangements of Clinical
 Investigators 000055

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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							
<i>TO BE COMPLETED BY APPLICANT</i>							
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.							
<input checked="" type="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 CFR 54.2(f).							
Clinical Investigators	<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%; padding: 5px;">Please see three attached spreadsheets</td> <td style="width:50%;"></td> </tr> <tr> <td style="height: 20px;"></td> <td></td> </tr> <tr> <td style="height: 20px;"></td> <td></td> </tr> </table>	Please see three attached spreadsheets					
Please see three attached spreadsheets							
<input type="checkbox"/> (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 54.2(f)).							
<input type="checkbox"/> (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.							
<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%; padding: 5px;"> NAME David E. Wheadon, M.D. </td> <td style="width:50%; padding: 5px;"> TITLE Senior Vice President, U.S. Regulatory Affairs </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> FIRM/ORGANIZATION GlaxoSmithKline </td> </tr> <tr> <td style="padding: 5px;"> SIGNATURE </td> <td style="padding: 5px;"> DATE 3/18/02 </td> </tr> </table>		NAME David E. Wheadon, M.D.	TITLE Senior Vice President, U.S. Regulatory Affairs	FIRM/ORGANIZATION GlaxoSmithKline		SIGNATURE 	DATE 3/18/02
NAME David E. Wheadon, M.D.	TITLE Senior Vice President, U.S. Regulatory Affairs						
FIRM/ORGANIZATION GlaxoSmithKline							
SIGNATURE 	DATE 3/18/02						
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							

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47 Pages have been redacted in full
from this document

Reason:

b(2) 'low'

b(4) CCI

b(4) TS

b(5) Deliberative Process:

Attorney Client and Attorney Work
Product Privilege

b(6) Personal Privacy

b(7) Law Enforcement Records

6 Pages have been redacted in full
from this document

Reason:

_____ b(2) 'low'

_____ b(4) CCI

_____ b(4) TS

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date: December 5, 2000

From: Edward Cox, MD MPH */S/*
 Medical Officer
 Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Through: Brad Leissa, MD */S/12/5/00*
 Medical Team Leader
 Division of Special Pathogen and Immunologic Drug Products (HFD-590)

To: Renata Albrecht, MD */S/12/5/00*
 Acting Division Director
 Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Subject: Financial Disclosure for NDA 21-158

The Applicant certified or exercised due diligence in attempting to certify if any financial relationship existed between investigators and SmithKline Beecham Pharmaceuticals. The certification process requested that investigators complete Form FDA 3455 in order to disclose if they had or had received any of the following:

1. Any financial arrangement entered into between the sponsor or the covered study and the clinical investigator involved in the conduct of the study, whereby the value of the compensation to the clinical investigator from conducting the study could be influenced by the outcome of the study.
2. Any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria
3. Any proprietary interest in the product tested in the covered study held by the clinical investigator
4. Any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Three individuals involved in the clinical studies for NDA 21-158 disclosed a significant equity interest in SmithKline Beecham as defined in 21 CFR 54.2(b). These three individuals were involved with Protocol SB-265805/008, one of the non-pivotal, non-supportive AECB studies. Within Protocol SB-265805/008, 6

patients were randomized into study from this study center (Center 008). There were a total of 586 patients randomized into Protocol SB-265805/008. Given the small number of patients that were enrolled from this study center and because Protocol SB-265805/008 was a non-pivotal and non-supportive study within the indication of acute bacterial exacerbations of chronic bronchitis, no additional analyses were performed excluding this study center.

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MEETING MINUTES

MEETING DATE: February 27, 2002
TIME: 12:00-3:00pm
LOCATION: 9201 Corporate Blvd.,
Rockville, MD. 20850
APPLICATION: NDA 21-158
DRUG: Factive (gemifloxacin mesylate) tablets
SPONSOR/APPLICANT: GlaxoSmithKline
CONTACT NAME: Edward Yuhas
FAX NUMBER: (215) 751-4926
PHONE NUMBER: (215) 751-3836
PROJECT MANAGER: Michael Bourg
DIVISION OF: Special Pathogen and Immunologic Drug Products, HFD-590
TYPE: A
FORMAT: Face To Face
TYPE of MEETING: NDA Resubmission

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ON ORIGINAL**

MEETING REQUEST RECEIPT DATE: January 9, 2002
MEETING DATE CONVEYED TO SPONSOR: via fax on January 15, 2002
BRIEFING DOCUMENT RECEIPT DATE: January 9, 2002; February 19, 2002

FDA PARTICIPANTS AND TITLES:
Mark Goldberger, M.D., M.P.H., Acting Director, ODE IV
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Shukal Bala, Ph.D., Microbiology Team Leader
Karen Higgins, Ph.D., Statistical Team Leader

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Philip Colangelo, Pharm.D., Ph.D.,
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Stephen G. Hundley, Ph.D., DABT, Pharmacology/Toxicology Reviewer
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Michael Bourg, Pharm.D., Project Manager
Norman Schmuft, Ph.D., Chemistry Team Leader
Milton Sloan, Ph.D., Chemistry Reviewer
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Development and Program Initiative
Barbara Davit, Ph.D., Clinical Pharmacology & Biopharmaceutics
Team Leader

INDUSTRY PARTICIPANTS AND TITLES:

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US Regulatory Affairs, Research & Development
Reink Pypstra, M.D., Vice President, Clinical Pharmacology,
Research & Development
Elyse Seltzer, M.D., Senior Director, Antibacterials, Clinical
Development & Medical Affairs, Research & Development
Jacquie Warner, Principal Statistician, Biostatistics & Data
Management, Research & Development
Clarence Young, M.D., Vice President, Antibacterials, Clinical
Development & Medical Affairs, Research & Development
Edward Yuhas, Ph.D., Senior Director, Antibacterials, US Regulatory
Affairs, Research & Development
Lynn Marks, M.D., Clinical Development and Product Strategy
David Wheadon, M.D., US Regulatory Affairs, Research &
Development

BACKGROUND INFORMATION:

NDA 21-158 for Factive (gemifloxacin mesylate) tablets was received December 15, 1999. A not approvable letter was issued December 15, 2000. The Agency described the deficiencies in the application and provided suggestions as to how the deficiencies could be addressed. In particular, the Agency requested additional clinical information on gemifloxacin-associated rash. GlaxoSmithKline's (GSK) requested this meeting to present additional safety and efficacy data they had gathered on *Factive*® tablets.

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MEETING OBJECTIVES:

- Presentation of the new safety and efficacy data.
- Discussion of the benefit/risk associated with use of *Factive*® to assist GSK in deciding whether to amend NDA 21-158 with this new data.

MEETING SUMMARY:

Dr. Elyse Seltzer presented an overview of new efficacy data for *Factive*® in CAP and an update of the *Factive*® safety data. Dr. Rienk Pypstra presented an overview of the rash characterization study (Study 344). (See attached slides for details of all presentations.)

QUESTIONS FOR DISCUSSION WITH RESPONSES:

At the start of the meeting, the Agency mentioned that the questions GSK asked are questions that the Agency would typically expect to address during the review of GSK's proposed re-submission for NDA 21-158. GSK requested some feedback from the Agency at this time to allow GSK to make decisions regarding the proposed re-submission for *Factive*®. Therefore the Agency provided the following comments at GSK's request, but stated that the final recommendations would be based on a complete review of the re-submission.

1) *Does the Division agree that efficacy has been established for Factive® _____ in community-acquired pneumonia (CAP) for:*

a) *Severe CAP*

The quantity of data on patients with severe CAP that GSK described appears at face value to be sufficient for the Agency to review. The Agency will need to take a careful look at the data that GSK will provide for this oral agent and its proposed use in the treatment of severe CAP.

[_____] d

2) *Did study 344 provide the necessary information the Division needed to better characterize Factive® associated rash?*

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From what the Agency has seen described in the briefing document, the abbreviated report for study 344 suggests that study 344 will provide the necessary information to further characterize gemifloxacin-associated rash, but as the Agency noted previously, the Agency will need to review the data provided by Study 344 in its entirety.

The Agency may also have further questions about the study data once the Agency has the opportunity to review the full study report for Study 344.

3) *Does the Division agree that the rash is consistent with an uncomplicated _____*

From the summary information provided in the background package on study 344, the rash could be consistent with an _____ but the Agency reserves judgement on this issue until the Agency, including the dermatology division, has had the opportunity to fully review the data from Study 344. The Agency noted in table 51 from the briefing document that there was a fair percentage of patients with urticaria, facial edema, and/or mucosal involvement, and there were cases with eosinophilia noted on biopsy. The Agency also noted that, in Figure 5 from the briefing document describing the distribution of body surface area involved in gemifloxacin-associated rash, it appears that about one quarter of the patients with gemifloxacin-associated rash in part A of the study had rash involving >60 percent of body surface area. Some of these patients were also described as having severe rash. While there were no cases of Steven Johnson Syndrome/Toxic Epidermal Necrolysis reported in Study 344; if in fact these more serious dermatologic reactions occur at some low level of frequency, the data may not be sufficient to exclude that such reactions might occur. The Agency is interested in further reviewing the results of Study 344 to learn more about gemifloxacin-associated rash.

4) *Does the Division agree there are no ECG or liver function finding issues associated with Factive® usage?*

The Agency does not agree that there are no ECG or liver function finding issues associated with Factive®. The Agency's current impression is that the effect of Factive® on the QT interval is probably within the range of other typical fluoroquinolones with a small effect on QT. The Agency is also concerned about the number of patients receiving gemifloxacin at a single dose of _____ that experienced LFT abnormalities. This information should be communicated to healthcare providers.

5) *Does the Division agree that the benefit/risk assessment for Factive® appears acceptable to support product approval?*

In addressing this issue, from what the Agency knows about the drug to date, the Agency would be inclined to try to make a benefit/risk assessment for each of the individual proposed indications.

- For community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis it may be possible to support a satisfactory benefit/risk profile.
- _____
- _____

6) *If Factive® has an acceptable benefit/risk profile, would the product labeling have any unusual/specific statements in the Warnings, Precautions or Contraindications sections?*

The Agency believes that appropriate information and risk-management strategies would need to be in place that could effectively advise prescribers and patients and that would successfully mitigate adverse effects, including gemifloxacin-associated rash. The Agency notes that GSK proposes a Mediguide. While Mediguides may be used for products with special safety risk(s) and an accompanying notable efficacy benefit, currently the Agency

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is of the opinion that a Mediguide is probably not appropriate for gemifloxacin because gemifloxacin appears to be lacking the significant benefit that would justify the use of a Mediguide.

Agency representatives had the following questions and comments:

- *Can GSK update the Agency on the regulatory status of gemifloxacin's outside of the U.S.?*

GSK indicated that currently gemifloxacin is approved only in New Zealand but the product has not been marketed there. GSK has no plans to market the drug in one country only.

- The Agency requested that GSK keep the Agency apprised of GSK's timetable for the proposed re-submission to NDA 21-158.
- The Agency would likely take the amended application before the Anti-Infective Drugs Advisory Committee to discuss the issues associated with rash, QT prolongation and potential liver toxicity as well as other issues that may arise during the review.
- The Agency has concerns about the rate of gemifloxacin-associated rash observed in the clinical studies. While the rates of rash vary across patient, age, and sex strata and by indication, gemifloxacin-associated rash occurs more frequently than rash in the comparator arm in all strata.
- The Agency is interested in proposals that GSK may have to manage the risks associated with gemifloxacin-associated rash and the potential for liver toxicity at higher doses.
- The Agency has concerns that one of the public health effects of gemifloxacin-associated rash could be that more patients will be labeled "quinolone-allergic" and thus lose all quinolones from the armamentarium of antimicrobial agents available to them.
- The Agency has concerns that attempts to limit the duration of *Factive*® therapy may be met with limited success and therefore realistically the Agency will consider the likelihood that patients will receive durations of therapy beyond 5 or 7 days.

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Michael Bourg, Regulatory Project Manager, Division of Special Pathogen and Immunologic Drug Products
Minutes Preparer

Mark J. Goldberger, M.D., M.P.H., Acting Director, ODE IV
Meeting Chair

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MEETING MINUTES

MEETING DATE: January 22, 2003
TIME: 10:20-11:40 am
APPLICATION: NDA 21-158
DRUG: Factive® (gemifloxacin)
SPONSOR: PAREXEL International
TYPE OF MEETING: C
FORMAT: Teleconference
BRIEFING DOCUMENT SUBMISSION DATE: December 30, 2002

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FDA PARTICIPANTS:

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Regina Alivisatos, M.D.	Medical Officer
Eileen Navarro, M.D.	Medical Officer
Maureen Tierney, M.D., M.Sc.	Medical Officer
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Stephen G. Hundley, Ph.D., DABT	Pharmacology & Toxicology Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Peter A. Dionne, M.S.	Microbiology Reviewer
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Chung R. Kim, Ph.D.,	Head, Regulatory Affairs and Product Development
Seong Jin Kim	Senior Manager, Regulatory Affairs and Product Development
Hye Jin Choi	Project Manager, Regulatory Affairs and Product Development

GeneSoft Pharmaceuticals, Inc.

Gary Patou, M.D.	President
John Connelly, Ph.D.	Pre-Clinical Consultant

PAREXEL International

Wayne Dankner, M.D.	Senior Medical Director, North American Medical Services
Alberto Grignolo, Ph.D.	President, Worldwide Regulatory Affairs
Gail Glifort	Project Manager, North American Regulatory Affairs

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Consultant
Sandra Patterson, Ph.D.

Regulatory Consultant

BACKGROUND:

The pending New Drug Application 21-158 is a resubmission, submitted on October 4, 2002. The original NDA was submitted on December 15, 1999 which received a not approvable letter from the Agency on December 15, 2000. An Advisory Committee meeting to discuss NDA 21-158 has been scheduled for March 4, 2003. The sponsor, in its preparation for the Advisory Committee, has requested a teleconference to seek the Division's comments on the Sponsor's draft Briefing Document, dated December 20, 2002.

MEETING SUMMARY:

The meeting began with introductions of attendees followed by an opening statement from Dr. Patou regarding the partnership of LG LifeSciences and GeneSoft in the drug development and marketing of Factive. Dr. Cox facilitated the discussion by addressing the sponsor's questions contained in the briefing document. The Agency's responses to the questions are summarized below.

QUESTIONS FOR DISCUSSION WITH THE AGENCY'S RESPONSES:

(the sponsor's questions are reproduced in italicized type below)

1. *Based on the data contained in the resubmission we believe that efficacy has been adequately demonstrated for the 7-day treatment for all categories and severities of CAP. Does the Division concur?*

The Division continues to have questions regarding the adequacy of the data to support the efficacy of gemifloxacin in the treatment of CAP in subjects who are severely ill. These questions are based on a review of the overall CAP populations (ITT and PP) where only approximately 9 – 10% of subjects were categorized as severe based on Fine scores (categories IV and V). Further analysis of these subjects by mortality revealed lower mortality as compared to that in the Fine article, thus raising questions about the application of the scoring system and the overall severity of the patients studied. Additionally, there were small numbers of patients with pathogens that can be associated with more severe or potentially severe pneumonia.

2. *Does the Division plan to discuss the lack of an intravenous formulation for gemifloxacin at the Advisory Committee meeting?*

The Division will probably not refer directly to this issue although indirectly the potential need for an intravenous formulation could be brought up within the context of the discussion around severity.

3. *Will the 7-day versus _____ treatment duration be subject to specific questions and review at the Advisory Committee meeting?*

Yes, this issue will be brought up as approximately 30% of subjects received between 8 and 14 days of treatment.

4. *The sponsor believes that a sufficient number of evaluable patients and isolates with _____ in CAP have been accumulated to receive a labeling claim. Does the Division concur?*

The Division believes that the accumulated data are noteworthy although a final decision regarding a labeling claim has not been made.

5. *The sponsor has provided adequate data to demonstrate efficacy in the treatment of _____*

As above, the Division recognizes that a number of subjects with _____ have been provided for review. At this time, _____ claims remain interdependent. Additionally, the Division is not certain of the validity of a separate _____ claim. This will be one of the issues that will likely be discussed

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at the Advisory Committee meeting

6. *We believe that we have persuasive new data to support our position that the breakpoint for gemifloxacin susceptibility is _____ those data are located in Appendix A. Does the Division concur with our position?*

There were no isolates of *Streptococcus pneumoniae* in the RTI bacteriological intent-to-treat population with MICs greater than 0.06 mcg/mL. There is, therefore, no evidence of isolates with MICs greater than or equal to _____ being eradicated. Many double-mutants of *S. pneumoniae* have gemifloxacin MICs of around _____ There is no clinical evidence that these isolates are eradicated in any clinical trial. In the rat pneumonia model *S. pneumoniae* isolates with gemifloxacin MIC of _____ or less are eradicated (CFU/lung gets to below level of detection) if treated once a day and treatment started 24 hours after infection. When gemifloxacin MICs get to _____ greater then dosing must be twice a day and started early. The number of CFU/lung never gets to limit of detection.

7. *The sponsor believes that evidence of efficacy for the 5-day treatment of _____ has been demonstrated in the recent submission of October 14, 2002 (NDA 21-158, Amendment 1). Does the Division concur with our position?*

The risk benefit for _____ will need to be carefully considered. From the data presented in Appendix A there are potential concerns regarding the age profile for prescribing in ABECB.

8. *The sponsor believes that Study 344 adequately defines the risk related to the rash associated with gemifloxacin usage; we appreciate the input provided by the division during the design of the study. Does the Division concur that the risk has been adequately defined?*

Study 344 provides important information to characterize gemifloxacin-associated rash. However, questions still remain regarding the potential for cross sensitization with ciprofloxacin and other quinolones besides ciprofloxacin and the potential for more serious rashes to occur should larger numbers of persons be exposed to gemifloxacin. Further understanding of the cases with mucus membrane involvement and their significance is also necessary.

9. *The sponsor believes that the data from the overall clinical trial database including study 344 demonstrate that the rash associated with gemifloxacin is benign. Does the Division concur.*

Questions still remain regarding the potential that this rash portends for the development of more severe rashes in the future. We would be interested in reviewing some of the pathology slides of more severe rashes and of cases where IG deposition was seen. A second related issue is that of whether patients who experience gemifloxacin-associated rash will for all practical purposes be labeled quinolone allergic and have quinolones removed from their therapeutic armamentarium.

10. *An assessment of safety as related to liver function written by Professor Paul Watkins, MD was provided in the resubmission. The sponsor believes that this assessment and information in the briefing document demonstrates that gemifloxacin poses little risk to cause clinically significant liver toxicity in patients. Does the Division concur? Will this topic be subject to review at the Advisory Committee Meeting?*

Although the incidence of hepatic elevations is low there are remaining concerns regarding the risk for infrequent more severe hepatotoxicity. Trends towards higher LFTs were noticed in the older more ill population of study 185 and a few cases of marked increase in Bilirubin or ALT were noted especially in clinical study participants with some hepatic impairment at baseline. We also remain concerned regarding the liver function abnormalities observed at doses in excess of 320 mg daily. If the agent were to be approved, this is an area for which additional information gathered as part of a risk management / phase 4 plan may be warranted.

11. *The sponsor has provided in the clinical report for Study 344 and in the data of the intravenous formulations*

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studies (106, 107 and 111) adequate data regarding QT interval issues associated with gemifloxacin usage and believes that they are no longer a concern. Does the division concur?

Again we would not characterize as there being no concern as to risks associated with QT prolongation. The effect on the QT interval appears to be within the range for QT elevation for drugs of the quinolone class and therefore some small but probably not negligible risk exists especially among those with comorbid conditions and on multiple medications. If the agent were to be approved, this is an area for which additional information gathered as part of your from your risk management / phase 4 plan may be warranted.

12. *The analysis on "the retrospective drug utilization study to assess likely prevalence of gemifloxacin-associated rash in females < 40 years of age receiving gemifloxacin for > 7days" has been provided in Appendix B. Does the Division agree with the sponsor's analysis and conclusion that a fixed dosage pack of gemifloxacin is likely to reduce extended duration prescribing of gemifloxacin?*

This is a complex issue in that it involves changing physician practices. While the 5 or 7 day pack may be one step in the process, its not clear that this alone will achieve the goal of limiting scripts to 5 days for ABECB. For example if a physician writes a script _____ for ABECB or _____ for CAP how will that be handled?

The question that the analysis addresses doesn't seem to address the higher rates of gemifloxacin-associated rash across the development program. The data from the clinical studies seems to be a less complex and more easily understood way of describing the rates of rash associated with gemifloxacin.

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13. *The sponsor believes that the risk/benefit ratio for gemifloxacin is favorable and supports the approval for the indications proposed in the resubmission. Does the Division concur?*

There are still some very important issues that the Agency is looking at.

Rash

- More frequent than with other agents
- From a practical standpoint may end up with persons being labeled "quinolone allergic" and quinolones removed from their armamentarium
- The potential for severe infrequent rashes in the setting of broader use

Liver

- Questions still remain regarding the potential for more severe infrequent liver events given what we have seen with doses in excess of 320 mg

CAP

- The data you've provided from a CAP program are most consistent with mild to moderate CAP
- The potential microbiological benefits based upon non-clinical data - The low MIC values for *S. pneumoniae* are largely offset by the levels achieved by the drug. The lack of clinical data to provide evidence to support to the potential microbiological benefit is an element that is lacking.
- The volume of use for ABECB (based upon your Appendix A) in the younger population is concerning when taking the risk factors for gemifloxacin-associated rash into consideration.

Given these elements, under what circumstances gemifloxacin would achieve a satisfactory risk-benefit profile is still an open question.

14. *Does the division have any comment on the draft briefing Document for the Advisory Committee?*
15. *What are the issues that the Division intends to raise with the Advisory Committee?*

Questions 14 and 15 can be grouped together.

In accordance with the questions that we have discussed today the issues that will likely be discussed at the Advisory Committee will likely include the following.

- Rash
- Frequency

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- Potential for less frequent, severe cutaneous reactions
- Patients with gemifloxacin-associated rash being labeled as "quinolone allergic"
- Issue of cross-sensitization to the members of the quinolone class, including drugs other than ciprofloxacin
- We will likely present data from across the safety database beyond just the CAP and ABECB studies
- Liver
 - The potential for more serious hepatic events given what we have seen at doses in excess of 320mg
- CAP
 - the issue of severity of disease
- Drug-resistant *S. pneumoniae* - _____
- Consider the MIC values in light of the achieved drug levels

ADDITIONAL COMMENTS:

In response to the Sponsor's request to submit additional _____ isolates and the incorporation of these data into the Sponsor's Briefing Document to Advisory Committee, the Agency provided the following comments.

- The additional _____ isolates may be submitted under NDA at this time. Under PDUFA III, such a submission may result in a Major Amendment.
- The additional isolates may be incorporated in the Sponsor's Briefing Document to Advisory Committee if they are clearly delineated as additional data with a disclaimer statement that they have not been reviewed by the Division.
- Due to practical consideration of preparing a Briefing document, the additional data will not be included in the Division's Briefing Document.

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Yon Yu
Project Manager, DSPIDP

Date

Renata Albrecht, M.D.
Director, Division of Special Pathogen
and Immunologic Drug Products

Date

cc:
HFD-590/MOTL/Cox

Drafted: 2/3/03 YY; Final: 2/19/03
RD: 2/12/03 EC
2/14/03 PD

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/s/

Renata Albrecht
2/28/03 03:58:22 PM

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NDA 21-158

FACTIVE[®] (gemifloxacin mesylate) 320mg Tablets

Action Date: December 15, 2000

TL: Leissa

MO: Powers, Alivisatos, Cox

CHM: M. Sloan

PCL: Ellis

MIC: Dionne

BPH: Colangelo

STT: Higgins, Dixon, Silliman

RPM: Kimzey

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Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 11, 2000

To: Edward Yuhas, PhD	From: Rene Kimzey
Company: SmithKline Beecham	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (215) 751-4926	Fax number: (301) 827-2326
Phone number: (215) 751-3836	Phone number: (301) 827-2127
Subject: November 7, 2000 meeting minutes for 21-158	

Total no. of pages including cover: 4

Comments:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Attendees

SmithKline Beecham (SB)

(*consultants)

Dr. Vincent Ahonkhai	Mrs. Ann Allen
Dr. John Connelly	Dr. Ruth Dixon
• Dr. Timothy Henkel	Mr. Brian Lortie
Ms. Ruth MacDonald	Dr. John-Paul Ortonne*
Dr. Robert Pietrukso	Dr. Paul Watkins*
Dr. David Wheadon	Dr. Clarence Young
Dr. Edward Yuhas	Dr. James Leyden* (by phone)

FDA

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Dr. Renata Albrecht	Dr. Brad Leissa
Dr. Edward Cox	Dr. John Powers
Dr. Regina Alivisatos	Ms. Linda Gosey
Dr. Cheryl Dixon	Mr. Peter Dionne
Dr. Kenneth Hastings	Dr. Milton Sloan
Dr. Philip Colangelo	Dr. Amy Ellis
Dr. Funmi Ajayi	Dr. Markham Luke
Dr. Amarilys Vega	Ms. Lisa Hubbard
Dr. Alma Davidson	Ms. Sarah Singer
Mrs. Rene Kimzey	

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After participants introduced themselves, the sponsor presented the agenda and purpose of the meeting. The stated purpose was to discuss the pre-clinical and clinical hepatic events, rash, and labeling options related to these safety concerns. (See attached slides for details of all presentations.)

Dr. John Connelly reviewed the preclinical hepatotoxicity of Factive® (gemifloxacin mesylate). His key points were:

- hepatic pathology was consistent with cholate stasis
- hepatic pathology appeared reversible
- due to biliary concentration and solubility differences between dog and man, gemifloxacin biliary deposition is less likely to occur in man
- gemifloxacin's pre-clinical hepatotoxicity differs from that seen with trovafloxacin

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