CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537 / S-049
20-780 / S-013
19-847 / S-027
19-857 / S-031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Section 14 – Patent Certification

All investigations relied upon by Bayer Pharmaceuticals Corporation in this sNDA were conducted by or for Bayer using drug substance and drug product in accordance with the patents listed in the Patent Information Section.

Please refer to Section 13, Patent Information.

Section 13: The following information is hereby provided pursuant to 21 C.F.R. § 314.53(c).

This application for Pediatric Exclusivity/Pediatric Use Labeling pertains to four currently approved and marketed products. The patent information for each is as follows:

NDA 19-537 100mg, 250mg, 500mg, 750 mg tablets
U.S. Patent No. 4,670,444
U.S. Patent No. 5,286,754

NDA 19-847 10 mg/ml injectable (vials)
U.S. Patent No. 4,670,444
U.S. Patent No. 4,705,789
U.S. Patent No. 4,808,583

NDA 19-857 200mg/100ml (IV flexibags)
U.S. Patent No. 4,670,444
U.S. Patent No. 4,705,789
U.S. Patent No. 4,808,583
U.S. Patent No. 4,957,922

NDA 20-780 250mg/5ml, 500mg/5ml (oral suspension)
U.S. Patent No. 4,670,444
U.S. Patent No. 5,695,784
U.S. Patent No. 6,136,347

Patent Number:	4,670,444
Expiration Date:	9 December 2003
Type of Patent:	drug substance, drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Pharmaceuticals Corporation), residing in the U.S.

The undersigned declares that U.S. Patent No. 4,670,444 covers the formulation, composition, and/or method of use of ciprofloxacin, the product which is the subject of NDA 19-537, 19-847, 19-857, 20-780, and this application for Pediatric Exclusivity for which approval is being sought.

Patent Number:	4,705,789
Expiration Date:	10 November 2004
Type of Patent:	drug product
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Pharmaceuticals Corporation), residing in the U.S.

The undersigned declares that U.S. Patent No. 4,705,789 covers the formulation, composition, and/or method of use of ciprofloxacin, the product which is the subject of NDA 19-847 and 19-857and this application for Pediatric Exclusivity for which approval is being sought.

Patent Number: 4,808,583
Expiration Date: 28 February 2006
Type of Patent: drug product
Name of Patent Owner: Bayer Aktiengesellschaft
Agent: Applicant (Bayer Pharmaceuticals Corporation), residing in the U.S.

The undersigned declares that U.S. Patent No. 4,808,583 covers the formulation, composition, and/or method of use of ciprofloxacin, the product which is the subject of NDA 19-847 and 19-857and this application for Pediatric Exclusivity for which approval is being sought.

Patent Number: 4,957,922
Expiration Date: 18 September 2007
Type of Patent: drug product
Name of Patent Owner: Bayer Aktiengesellschaft
Agent: Applicant (Bayer Pharmaceuticals Corporation), residing in the U.S.

The undersigned declares that U.S. Patent No. 4,957,922 covers the formulation, composition, and/or method of use of ciprofloxacin, the product which is the subject of NDA 19-857and this application for Pediatric Exclusivity for which approval is being sought.

Patent Number: 5,286,754
Expiration Date: 15 February 2011
Type of Patent: drug product
Name of Patent Owner: Bayer Aktiengesellschaft
Agent: Applicant (Bayer Pharmaceuticals Corporation), residing in the U.S.

The undersigned declares that U.S. Patent No. 5,286,754 covers the formulation, composition, and/or method of use of ciprofloxacin, the product which is the subject of NDA 19-537 and this application for Pediatric Exclusivity for which approval is being sought.

Patent Number: 5,695,784
Expiration Date: 9 December 2014
Type of Patent: drug product
Name of Patent Owner: Bayer Aktiengesellschaft
Agent: Applicant (Bayer Pharmaceuticals Corporation), residing in the U.S.

The undersigned declares that U.S. Patent No. 5,695,784 covers the formulation, composition, and/or method of use of ciprofloxacin, the product which is the subject of NDA 20-780 and this application for Pediatric Exclusivity for which approval is being sought.

Patent Number:	6,136,347
Expiration Date:	9 December 2014
Type of Patent:	drug product, method of use
Name of Patent Owner:	Bayer Aktiengesellschaft
Agent:	Applicant (Bayer Pharmaceuticals Corporation), residing in the U.S.

The undersigned declares that U.S. Patent No. 6,136,347 covers the formulation, composition, and/or method of use of ciprofloxacin, the product which is the subject of NDA 20-780 and this application for Pediatric Exclusivity for which approval is being sought.

Mary Taylor, MPH
Vice President, Regulatory Affairs
Bayer Pharmaceuticals Corporation

EXCLUSIVITY SUMMARY for sNDA # 19-537/S-049, 19-847/S-027, 19-587/S-031, 20-780/S-013

Trade Name Cipro **Generic Name** ciprofloxacin HCL

Applicant Name Bayer Pharmaceuticals Corporations **HFD-590**

Approval Date March 25, 2004

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 /_x__/

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

      If yes, what type(SE1, SE2, etc.)? SE5

   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.

      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 /_x__/NO /___/

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

The applicant requested a determination of 6-month pediatric exclusivity.

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

YES /_x__/ 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 /_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).

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 /_x__/ NO /___/

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

NDA # 19-537 Cipro® (ciprofloxacin hydrochloride) Tablets, 100 mg, 250 mg, 500 mg and 750 mg
NDA # 19-847 Cipro® IV (ciprofloxacin) 1% Solution Vials, 200 mg, 400 mg and 1200 mg
NDA # 19-857 Cipro® IV (ciprofloxacin) 0.2% Solution in 5% Dextrose, 200 mg and 400 mg
NDA # 20-780 Cipro® (ciprofloxacin) Oral Suspension, 5 % and 10%

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 #

NDA #

NDA #

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 /_x__/ 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 /_x_/ 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 /_x__/

(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 /_x__/

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 # 100169

Investigation #2, Study # 100201

Investigation #3, Study #

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 /_x__/
Investigation #2	YES /___/	NO /_x_/
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 /_x__/

Investigation #2 YES /___/ NO /_x__/

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 # __100169

Investigation #_2_, Study # __100201

Investigation #__, Study #

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 # ~ YES /_x_/	NO /___/ Explain:
Investigation #2	
IND # ~ 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?

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: _____

_____

_____

Yon Yu
Signature of Preparer

March 22, 2004
Date

Title: Regulatory Project Manager

Signature of Office or Division Director Date
{See appended electronic signature page}

cc:
Archival NDA
HFD-590/Division File
HFD-590/RPM
HFD-610/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

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
3/24/04 10:11:52 PM

Debarment Certification

Bayer Pharmaceuticals Corporation certifies under the FD&C Act, Section306(k)(1) that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application*.

Mary E. Taylor, MPH
Vice President, North America Regulatory Affairs