CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-473

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-473	Efficacy Supplement Type SE-	Supplement Number	
Drug: **CIPRO® XR**		Applicant: **Bayer Corporation**	
RPM: **Jouhayna Saliba, Pharm.D.**		**HFD-590**	Phone # 301-827-2127
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**January 3, 2003**
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	February 13, 2001 (CMC) & May 2, 2001
• Pre-NDA meeting (indicate date)	January 15, 2002 & February 15, 2002 (CMC)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	June 6, 2002

Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	**N/A**
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	**N/A**
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**N/A**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**January 7, 2003**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**June 4, 2002**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**January 7, 2003**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**X**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**December 2, 2002**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**December 16, 2002**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**X**
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**December 10, 2002**
❖ Environmental Assessment – **See CMC review**	
• Categorical Exclusion *(indicate review date)*	**December 10, 2002**
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**N/A**
❖ Facilities inspection (provide EER report) **See CMC review**	Date completed: **December 3, 2002** **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation – **Not completed at time of review**	**( )** Completed **(X)** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**October 2, 2002**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**

7/2/02

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

/s/

Jouhayna Saliba
5/14/03 02:58:09 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

2. TELEPHONE NUMBER *(Include Area Code)*

(203) 812-5172

3. PRODUCT NAME
Cipro

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N #21-473

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4265

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, on reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Andrew L. Vesterman	Deputy Director, Regulatory Affairs	3/4/02

FORM FDA 3397 (3/01)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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400 Morgan Lane
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(203) 812-5172

3. PRODUCT NAME
Cipro

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N #21-473

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

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(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Andrew L. Vesterman	Deputy Director, Regulatory Affairs	3/4/02

FORM FDA 3397 (3/01)

Section 16: Debarment Certification

Bayer hereby certifies under FD&C Act, Section 306 (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 American Regulatory Affairs
Bayer Corporation

APPEARS THIS WAY
ON ORIGINAL

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

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

The undersigned declares that the U.S. Patent Number 4,670,444 covers the formulation, composition and method of use of ciprofloxacin. This product is the subject of this application for which approval is being sought.

Mary Taylor
Vice President, North American Regulatory Affairs
Bayer Corporation

APPEARS THIS WAY
ON ORIGINAL

Section 14 – Patent Certification

All investigators relied upon by Bayer in this NDA 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.

EXCLUSIVITY SUMMARY for NDA # 21-473 SUPPL #

Trade Name CIPRO® XR Generic Name ciprofloxacin extended release tablets
Applicant Name Bayer Corporation HFD- 590
Approval Date December 13, 2002

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 /_X__/

      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.

      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 /_X_ /

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 /_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).

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® tablets

NDA # 20-780 Cipro® oral suspension

NDA # 19-847, 19-857, 19-858 Cipro® I.V.

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/___/N/A_X_

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 /X__/

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 # 100346

Investigation #2, Study #

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 /___/
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 /___/
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 # ___100346

Investigation #__, Study #

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 # [redacted] YES /_X_/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ 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: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /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

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
2/14/03 03:58:09 PM

Jouhayna Saliba
2/10/03 03:11:58 PM

APPEARS THIS WAY
ON ORIGINAL

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 21-473
Trade Name: Cipro
Generic Name: Ciprofloxacin / Ciprofloxacin HCL
Strength: 500mg tablets

Applicant: Bayer Corporation

Date of Application: March 4, 2002
Date of Receipt: March 5, 2002
Date of Filing Meeting: April 17, 2002
Filing Date: May 4, 2002

Indication requested: Uncomplicated UTI

Type of Application: Full NDA _X_____ Supplement _____
(b)(1) ____X____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S____X___ P_____
Resubmission after a withdrawal or refuse to file _____
Chemical Classification: (1,2,3 etc.)_3_____
Other (orphan, OTC, etc.)_____

Has orphan drug exclusivity been granted to another drug for the same indication? YES X NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain. N/A

User Fee Status: Paid ____X____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES__X_____ NO_____
User Fee ID#_4265___
Clinical data? YES ___X____ NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: **January 3, 2003**

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? X YES NO
- Form 356h included with authorized signature? X YES NO

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? **X** YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? **X** YES NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? YES NO , **X** NA

- Patent information included with authorized signature? **X** YES NO

- Exclusivity requested? YES; If yes, _____years **X** NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? **X** YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? **X** YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES **X** NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:
  Waiver requested for all ages of pediatric population
- Field Copy Certification (that it is a true copy of the CMC technical section)? **X** YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? **X** YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers:

End-of-Phase 2 Meeting? Date **2/14/2001** NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) **1/15/2002** NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? X YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
X YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO X N/A

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO X N/A

Advisory Committee Meeting needed? YES, date if known _____ X NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES NO X N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? X YES NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? X YES NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? N/A

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: Held virtually 4/17/02

BACKGROUND
Cipro was already approved and this NDA is for a modified release formulation

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Regina Alivisatos
Statistical:	Ruthanna Davi
Pharmacology/Toxicology:	Stephen Hundley
Chemist:	Dorota Matecka
Environmental Assessment (if needed):	
Biopharmaceutical:	Joette Meyer
Microbiology, clinical (for antimicrobial products only):	Pete Dionne
Project Manager:	Jouhayna Saliba

Per reviewers, all parts in English, or English translation? YES_X___ NO___

CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES_____ NO___ X _____

MICROBIOLOGY CLINICAL – File_____ X _____ Refuse to file_____

STATISTICAL – File _____ X _____ Refuse to file _____

BIOPHARMACEUTICS – File ____ X _____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ____ X _____

PHARMACOLOGY – File ___ X _____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__X___NO_____ File__ X ___ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

____ X ___The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
_____ The application is unsuitable for filing. Explain why:

__Jouhayna Saliba_____
Regulatory Project Manager, HFD-590

Version: 3/27/2002

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

/s/

Jouhayna Saliba
2/13/03 10:56:32 AM

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ON ORIGINAL

Number of Pages Redacted 49

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Draft Labeling
(not releasable,

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

DATE: May 24, 2002

TO: Jouhayna Saliba, Project Manager, HFD-510

FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., Director
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety

SUBJECT: Label Comprehension Study for Cipro
NDA 21-473

The attached memorandum summarizes the most important points DSRCS wishes to make about the label comprehension study.

{See appended electronic signature page}

MEMORANDUM

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

DATE: May 24, 2002

TO: Jouhayna Saliba, Project Manager, HFD-590

FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support (DSRCS), HFD-410
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., Director
Division of Surveillance, Research,
and Communication Support (DSRCS), HFD-410
Office of Drug Safety (ODS)

SUBJECT: DSRCS Label Comprehension Comments for Cipro
NDA 21-473

These comments will cover the portion of the label comprehension study that deals with the questions to physicians about how Cipro — is to be used and how distinguishable Cipro — is from Cipro. We are not commenting here on responses from the pharmacists or on physicians' responses about useful sources of information. We are sending these comments without a complete written review so you will have our thoughts before the meeting with the sponsor.

Open-ended question about the indication

The results show that when asked what the product is used for, 36% of physicians in the study correctly stated it is for uncomplicated UTI's. Sixty-one percent (61%) said UTI's without specifying uncomplicated.

Direct questions

When asked direct questions about using the product for specific conditions, the percentages of **incorrect** responses ranged from 8% to 10%. Incorrect responses were those that did **not** say the product should **not** be used. They did not necessarily say that the product **could** be used, but they did not say it should not. Incorrect responses included mentions of bacteria or organisms that could be treated, as well as other unspecified responses.

	Incorrect
complicated UTI's	18%
lower respiratory tract infections	10%

sinusitis	8%

Hypothetical cases

In a series of hypothetical cases, incorrect percentages for uses that are not indicated ranged from 2% to 17%. Incorrect responses said that Cipro [redacted] **could** be used, or they were incorrect for unspecified reasons.

	Incorrect
intra-abdominal infection	5%
prostatitis	11%
pharyngitis/tonsilitis	2%
uncomplicated UTI	0%
pyelonephritis	17%
gonococcal urethritis	4%

Dosing and administration questions

When the physicians were asked about dosing and whether the product could be broken or chewed, the incorrect responses were as follows:

	Incorrect
Q. 17- dosage, frequency, and duration—uncomplicated UTI	11%
Q. 25- dosage, frequency, and duration—uncomplicated UTI	6%
Q. 32- dosage, frequency, and duration—uncomplicated UTI	3%
Q. 30—dosage, frequency, duration for conventional Cipro (not clear which responses were correct) ?	
Q. 23/24—which is a once a day product? (Cipro [redacted] Cipro, both, neither?)	5%
Q. 28/29/31—which appropriate for uncomplicated UTI? (Cipro [redacted] Cipro, both, neither?)	1%
Q. 26—can the medicine be crushed?	13%
Q. 34—take more than 1/day if you miss a day?	7%
Q. 36—what to tell patient who misses a day?	4%

Distinguishable ratings

On a scale of 1-10, with 1 being not at all distinguishable and 10 being extremely distinguishable, 86% of physicians said the packages of Cipro and Cipro [redacted] were distinguishable from each other at a level of 8 or above. However, on the same scale, only 55% said the names were distinguishable with a rating of 8 or above. This suggests that the names may not be well differentiated by physicians.

Discussion

Although the correct results are relatively high for most questions, we have some methodological concerns that may have contributed to the high scores. Some of these concerns were raised in our comments on the original protocol; others are new. While some of our recommendations were followed, others were not.

We had recommended that the series of three direct questions about using the product for different conditions be presented in a different manner. We recommended scenario

(hypothetical) questions or a checklist containing a number of conditions instead of the direct questions. Furthermore, all three questions presented situations in which the product should not be used, potentially establishing a nay-saying bias by which the pattern of the questions influences the responses.

It is not good practice to alert participants to the purpose of a study. Doing so detracts from the realism of the situation, which, already, is far from perfect. If we wanted to study how physicians would use the new product in the course of their practice, it would have been better not to tell them that fact. In this study, the interviewer stated "The manufacturer of ciprofloxacin wants to make sure that they have made clear to physicians the differences between this new product and the conventional Cipro tablets." This statement alerts participants to look for differences they might not ordinarily notice.

The interviewer provided participants specifically with pages from the PDR for conventional Cipro. This made conventional Cipro and all of its labeling more salient to the participants. In an actual patient situation, we do not know if physicians would bother to check the conventional Cipro labeling. Participants also had a PDR for reference. They could have used that if they wanted to look up conventional Cipro. Using the PDR better simulates what they would do in their offices if they needed information on conventional Cipro. It would have been better not to give participants conventional Cipro labeling separate from the PDR.

We recommended that when the participants examined the package insert that they not be given 10 minutes to do so. We believed that may have been too long. Instead, we suggested having the participants signal when they had finished examining the insert. The sponsor, however, gave them all 10 minutes. It is possible this gave participants much more time to think about the product than they would in a normal practice situation.

Recommendations

The sponsor provided a report from [redacted] which made some useful recommendations about how to improve the label communication in some of the areas in which there were higher percentages of incorrect responses. However, for some issues, [redacted] had no specific suggestions.

His suggestions include the following, and appear to be appropriate:

- The initial topic sentence in the indications section should emphasize the product is for uncomplicated UTI's.
- Explicitly state that the product has not been shown to be effective in infections other than uncomplicated UTI's.
- The wording about not crushing, chewing, or breaking the product should be highlighted.
- Promotional material should emphasize the dosing regimen.
- Perhaps more conventional brand name testing should be conducted for further data on the sufficiency of differences in the brand names of Cipro [redacted] and Cipro.

DSRCS has the following additional suggestions:

- Edit the PPI so it is in the format the agency now recommends. Change wording that is in all capitals to bolded upper and lower case. All capitals is hard to read.
- If appropriate, clarify in the PI what "uncomplicated UTI" means.

Conclusion

There is evidence that some messages about Ciprc[redacted] are not well understood by physicians and that the product name may not be very distinguishable from conventional Cipro. Problems with the methodology somewhat reduce our confidence in the validity of the results that show generally high levels of understanding. The sponsor's consultant has provided some useful recommendations to strengthen the weak messages, however, we cannot be sure that they will help unless further study is done. DSRCS has provided some additional suggestions.

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

/s/

Karen Lechter
5/24/02 10:54:38 AM
UNKNOWN

Anne Trontell
5/28/02 06:59:25 AM
MEDICAL OFFICER

APPEARS THIS
ON ORIGI

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 06/05/01	DUE DATE: 07/31/01	OPDRA CONSULT #: 01-0125

TO:
Renata Albrect, MD
Acting Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH:
Jouhayna Saliba
Project Manager
HFD-590

PRODUCT NAMES:	SPONSOR:
[redacted] (Ciprofloxacin Extended-release Tablets) **500 mg** **and** [redacted] (Alternate name)	Bayer Corporation Pharmaceutical Division
NDA: 21-473 and IND: [redacted]	

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), DMETS has commented on the proposed names [redacted] and the Division of Risk Evaluation has evaluated and commented on the proposed "Package Insert Comprehension/Package and Brand Name Assessment Study" for each proposed proprietary name.

DMETS RECOMMENDATION:
The Division of Drug Risk Evaluation reviewed the proposed study protocols and determined the sponsor does not completely address their stated study objectives (see attachment A for complete review). The Division of Medication Errors and Technical Support does not recommend the use of the proprietary names [redacted]

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 480-8173

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 26, 2001

NDA NUMBER: 21-473
IND NUMBER: [redacted]

NAME OF DRUG: [redacted] (Ciprofloxacin Extended-release Tablets) 500 mg
[redacted] (Ciprofloxacin Extended-release Tablets) 500 mg

NDA/IND HOLDER: Bayer Corporation Pharmaceutical Division

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), for assessment of the sponsors protocols entitled " [redacted] Package Insert Comprehension/Package and Brand Name Assessment Study" and " [redacted] Package Insert Comprehension/Package and Brand Name Assessment Study". DMETS was recently informed by the Division that [redacted] will not be submitted as an NDA. However, the review provided by the Division of Risk Evaluation were completed prior to this knowledge and therefore contain content relating to [redacted] Additionally, DMETS has also reviewed the proposed proprietary names [redacted]

PRODUCT INFORMATION
The sponsor states that [redacted] is a [redacted] formulation of the currently marketed Cipro. [redacted]' will be available as 500 mg tablets for once daily administration. Both are indicated for the treatment of uncomplicated urinary tract infections caused by *Escherichia coli,* [redacted] *. Proteus mirabilis, or Staphylococcus saprophyticus.* The usual dosage is 500 mg once daily for 3 days.

II. SAFETY EVALUATOR RISK ASSESSMENT

A. ESTABLISHED NAME/FORMULATION ISSUES

The sponsor describes Cipro [redacted] is a [redacted]. According to the sponsor, the tablet is designed as a two-layer tablet in which the first layer contains 35% of the drug substance and releases the drug within a short period of time after administration. The second layer contains 65% of the drug and has slower release characteristics for the drug substance than the immediate release tablet.

Upon review of the DESCRIPTION section of the Cipro [redacted] package insert labeling we noted that Cipro [redacted] contains ciprofloxacin hydrochloride and ciprofloxacin betaine hydrate. The currently marketed Cipro contains ciprofloxacin hydrochloride alone. The addition of the second active ingredient raises several questions. First, is "ciprofloxacin betaine hydrate" another salt of the active moiety ciprofloxacin? Alternatively, can "ciprofloxacin betaine hydrate" be considered a water of hydration or polymorph of ciprofloxacin? The answers to these questions will inevitably affect the established name of the product and discussion would follow regarding whether or not this new formulation could use "Cipro" as part of the proprietary name if deemed a different product. Finally, the term ' [redacted] ' is not an approved dosage form descriptor according to the United States Pharmacopeia (USP). DMETS recommends this issue be forwarded to the CDER Labeling and Nomenclature Committee (LNC) for review and comment.

B. PROPRIETARY NAMES

"Cipro" is an approved proprietary name for ciprofloxacin hydrochloride and has been marketed by Bayer under NDA 19-537 since April 18, 1996. Therefore, ' [redacted] ' were the only portions of the proposed proprietary names that were evaluated. DMETS does not recommend the use of the modifiers [redacted] for the following reasons:

1. The Agency has reconsidered their approach in approving alternate proprietary names. Pursuant to a December 1, 2000, CDER policy meeting with the Center Director, Janet Woodcock, M.D. and senior management, DMETS will no longer recommend approval of different proprietary names by the same applicant or manufacturer for products that are essentially identical unless there is a public health risk or stigma associated with the use of the drug product. The Agency is concerned that the proliferation of proprietary names may be misleading and may also lead to product confusion resulting in medication errors and/or patient harm for the following reasons:

   Safety Concerns:

   •*Overdose:* Practitioners may become confused and not understand that the two products (with two different trade names) are identical. This may increase the risk of a patient being prescribed the same drug product by different physicians, resulting in an overdose or inadvertent exposure.

   •*Confusion/Misleading*: Trivialization of the adverse events and risks associated with the use of different proprietary names for the same active moiety. Patients may be falsely assured that the medication does not carry significant risks because the FDA has allowed its use for a relatively benign condition.

•*Medication errors:* The creation of a new proprietary name for a new indication of an essentially identical drug product adds unnecessarily to the growing number of proprietary names in the United States. This proliferation of numerous proprietary names may increase the likelihood of occurrence of medication errors resulting in patient injury due to sound-alike and/or look-alike confusion between products.

Other Concerns:
•*Management of ADE:* The increasing complexity to manage (regulatory) reports of adverse drug events associated with one active ingredient with two or more proprietary names.

2. The currently approved Cipro tablets can be utilized to treat severe complicated urinary tract infections and mild to moderate urinary tract infections dependent on the dosage. According to the package insert labeling, Cipro [redacted] is *only* indicated for use in the treatment of uncomplicated urinary tract infections. [redacted] is broad, does not clearly convey "Uncomplicated Urinary Tract Infections", and is therefore misleading.

3. "UTI" is a common medical abbreviation for urinary tract infection and urinary trypsin. "QD" is a standard medical abbreviation for "every day". The Agency has always considered the use of coined abbreviations in conjunction with proprietary names objectionable since they can be misinterpreted. We refer you to ASHP Guidelines on Preventing Medication Errors in Hospitals (Am J Hosp Pharm., Vol. 50, Feb 1993) and The CDER Labeling and Nomenclature Committee, Structure, Function, and Process (Drug Information Journal, Vol. 31, Nov 1997).

4. "QD" is a dangerous abbreviation to use because it is often misinterpreted as "QID" or "4 times a day". DMETS also believes the proposed proprietary name poses a significant risk for potential confusion between the immediate release dosage form and the proposed extended release formulation. The immediate release formulation is utilized to treat severe complicated urinary tract infections and mild to moderate urinary tract infections dependent on the dosage. Prescriptions for Cipro [redacted] x 3 days could easily be misinterpreted as simply ciprofloxacin daily and filled with the immediate release dosage form which is not approved for a 24 hour dosing interval or three day treatment regimen.

5. We discourage including the dosage regimen in the proprietary name. As the product evolves, newer dosing schedules may be approved, which might conflict with the a once a day modifier.

6. It is not clear if this proposed formulation could be considered a delayed or extended release formulation of the currently marketed Cipro or classified as a different chemical entity. If it is considered a delayed or extended release formulation of Cipro, then current nomenclature standards would include an extended-release modifier to the CIPRO name (CIPRO [redacted], etc.) rather than an indication of use or dosing interval.

C. PROTOCOLS

The Division of Drug Risk Evaluation in the Office of Drug Safety reviewed the proposed protocols for Cipro [redacted]. The following represents the "Executive Summary" comments only. See attachment A for the complete review.

Executive Summary:

The studies proposed by the sponsors do not completely address their stated study objectives. However, these studies may provide some insight about the comprehensibility of the label without measuring the extent of the problem. The limitations of their studies are as follows:

- The study population may not be representative of the targeted population.
- Conditions in which study populations are tested may not resemble real-life situations.
- Survey participants will be aware of study objectives.
- Questionnaire skip patterns may result in biased responses.
- There is not enough detail on the definition of "acceptable" responses.
- Sample size is not adequate to detect the label miscomprehension rate.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

DMETS reviewed the proposed Cipro container labels and carton labeling and have identified several areas of possible improvement, which might minimize potential user error.

1. DMETS does not recommend the use of the nomenclature " " for the following reasons:

   appears to be the most prominent name on the labeling inferring it is another proprietary name for the product and is misleading.

   ♦ The use of the " nomenclature" is similar to that utilized by Pfizer for Zithromax Z-Pak. Health care providers prescribe Zithromax Z-Pak simply as OPDRA has safety concerns regarding the use of this unapproved nomenclature. is not an approved proprietary name and if a practitioner is unfamiliar with and attempts to find a reference to this name, they will be unsuccessful. Since is not an approved name, it does not exist in any reference text. OPDRA searched the PDR, Medline, Micromedex, Facts and Comparisons and American Drug Index for reference to and was unsuccessful.

2. The established name and expression of strength may need to be revised based on the outcome of the salt issue. In addition, 21 CFR 201.10 states "the established name shall be in letters that are at least ½ as large as the letters comprising the proprietary name and shall have a prominence with such proprietary name". We recommend the prominence of the established name be increased and revised to appear in the same font and appearance as Cipro on all labels and labeling.

3. Delete "Cipro which appears in red print.

4. Include the following on the principal display panel "ONCE DAILY".

5. Revise the Dosage section to read "Usual Dosage: One tablet daily for three days.".

6. A statement should be included as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed outpatient, it should be with a child-resistant container. For example:

   This unit-dose package is not child resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

   [Note: The second sentence is optional.]

7. f

8. The full text of the patient information section of the insert labeling should be reprinted at the end of the labeling to be in accordance with 21 CFR 201.57(f)(2).

9. We note the sponsor has proposed [redacted]. We request the sponsor provide clarification.

IV. RECOMMENDATIONS

The Division of Drug Risk Evaluation has reviewed the proposed study protocols and determined the sponsor does not completely address their stated study objectives (see attachment A for complete review). The Division of Medication Errors and Technical Support does not recommend the use of the proprietary names [redacted].

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3242.

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT A

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 1, 2002

FROM: Parivash Nourjah, PhD
Division of Drug Risk Evaluation, HFD-430

THROUGH: Julie Beitz, MD
Division of Drug Risk Evaluation , HFD-430

TO: Jerry Phillips, R.Ph.
Division of Medical Errors and Technical Support, HFD-430

SUBJECT: Bayer study protocol review: [redacted] ™Package Insert Comprehension/Package and Brand Name Assessment Study

PID# D010624,D010625

Executive Summary:

The studies proposed by the sponsors do not completely address their stated study objectives. However, these studies may provide some insight about the comprehensibility of the label without measuring the extent of the problem. The limitations of their studies are as follows:

- The study population may not be representative of the targeted population.
- Conditions in which study populations are tested may not resemble real-life situations.
- Survey participants will be aware of study objectives.
- Questionnaire skip patterns may result in biased responses.
- There is not enough detail on the definition of "acceptable" responses.
- Sample size is not adequate to detect the label miscomprehension rate.

Introduction:

This Memorandum is prepared in response to a request from the Division of Medical Errors and Technical Support to review the study protocol for package insert comprehension/package and brand name assessment submitted by Bayer Corporation. The products names are Cipro® [redacted] ciprofloxacin 500 mg tablet) and [redacted] extended release ciprofloxacin 500 mg tablet). Both studies have identical objectives except for the [redacted] protocol which includes an additional group (i.e. potential consumers for this product) for assessment of package insert comprehension.

This review will concentrate on the [redacted] protocol for Package Insert Comprehension/Package and Brand Name Assessment Study. However, these comments are also applicable for the Cipro [redacted] study protocol.

The [redacted] protocol includes the following objectives:

1. To evaluate physicians', pharmacists', and consumers' understanding of the draft [redacted] labeling (package insert) and how to safely prescribe, dispense, and use [redacted]

2. To measure how well physicians and pharmacists distinguish the [redacted] brand name and package from the conventional Cipro brand name and package.
3. To assess how pharmacists will differentiate [redacted] from the current Cipro products when viewing a mock physician prescription of the various currently prescribed Cipro regimens.

Study populations:

The protocol outlines a sample to consist of 200 physicians: 150 primary care physicians (family practitioners, general practitioners, internists, OB/GYNs) and 50 urologists; and 150 pharmacists. Both pharmacists and physicians are recruited over the telephone by using purchased lists of health care professionals as well as databases from approximately 12 marketing research sites.

Comments:

The sampling selection is a quota sampling. Since this is not a probability sampling, the response rate may not be calculated in the conventional manner. To better understand the response rate, the sponsor needs to keep a log of the number of telephone contacts, number of telephone contacts who agree to participate, and number of those who attend the testing sites. In my experience, the response rate will be quite low (i.e. 1% to 10%), therefore participants in this study may not be representative of the targeted population. Moreover, it is not clear what kind of sampling frame the sponsor is using (i.e., a list of physicians working for a specific HMO, American Physicians Association, or etc.)
It is also noteworthy to know where the locations of the 12 marketing research sites are in the United States. Are they geographically dispersed or mainly located in one or two regions in the U.S.?

The protocol outlines a sample of 150 female consumers who are 18 years or older from the general population and another 150 females from low literacy populations recruited from 6 shopping malls across the United States. Low literacy is defined as a reading skill at a maximum 7th-8th grade equivalency level.

Comments:

Type of sampling is convenience, thus those who participate in this study may not be representative of the typical users of this drug. The level of low literacy is still high. Approximately 20% of the U.S. adult population has a literacy level at or below 5th grade but among elderly, this percentage is about 40% (Pfeiser Health Literacy Principal, 2nd edition, 1989.) Given the indication of this drug, we recommend a level of literacy at a maximum 5th-6th grade equivalency level for low literacy consumers.

Method of data collection

Package insert comprehension assessment:

Physicians and pharmacists who agree to participate in the study will be invited to the marketing research sites for the interview. Physicians, pharmacists, and consumers will be asked to read package labels after they are briefed about the objective of the study. All the subjects can spend as much time as needed to read the label. During the questioning, both physicians and pharmacists can refer to the PDR or any other tool if they need to.

Comments:

The environment under which the subjects are interviewed may not be similar to real-life situations. For example, it is common for pharmacists to work under poor lighting and high background noise, which subsequently influence their comprehension.

Also, all subjects are aware of the objective of the study, which also may influence their reading and understanding of the labels. Another limitation of the data collection methodology is that the subjects could spend as much time reading the label as needed to understand it whereas in real-life the subjects may have limited time to read the label.

Assessment of differentiation of the [redacted] brand name and package from conventional Cipro tablets:

In addressing Objective 3, mock physician prescriptions of the various currently prescribed cipro dosage forms are used.

Comments:

The sponsor does not provide a sample of mock physician prescriptions. Variations in handwriting should be included in this study.

Questionnaire design:

There are consistent skip patterns based on initial "correct" or "incorrect" answers.

For example as it is currently proposed, Question 4: Based on the package and drug label, should you prescribe this drug to treat a lower respiratory tract infection? The interviewer skips to question 5 if the subject's response is correct (i.e., NO.) However, if the subject's response was not correct (i.e., YES), the interviewer should ask: Why do you say that?

Comments:

Skip patterns may influence the subject's response. I recommend the follow-up question should be asked of all subjects regardless of whether their responses are correct or not.

Coding:

The questionnaire is pre-coded for the most part. In situations where there are verbatim responses, one coder creates codes based on 20% of the verbatim responses. Additional codes would be added as needed, and also more coders would be assigned if it becomes necessary. After the completion of the coding process, the final code sheet for each question will be sent to Bayer. [redacted] and Bayer will work together to divide these codes into "correct," "acceptable," and "incorrect" responses.

Comments:
There are several issues with the coding process of verbatim responses. The verbatim comments are taken when the subject's answer is not the "correct" answer. For example, the physicians are asked "Based on the package and drug label, should you prescribe this drug to treat a complicated urinary tract infection?" If their response is not "NO", then the interviewer would ask "why do you say that? RECORD VERBATIM..."

My concerns about coding the verbatim responses are as follow:

1. The coding of the verbatim responses requires clinical knowledge; do coders have a clinical background?

2. Although using one coder results in consistency of the coding, it does not prevent systematic errors in coding. I recommend at least 2 coders to generate a consensual coding procedure.

3. Coders should be blinded to the objective of the study since it may influence their coding procedure. I recommend that the sponsor also submit the verbatim responses to FDA for review.

4. The list of "correct" and "acceptable" responses should be provided to FDA for review since there could be a disagreement between FDA and Bayer reviewers on the "acceptable" response.

Sample size:

The outcome measurement proposed for addressing the comprehension of label and packaging is based on the percent of correct responses (comprehension proportion). Although this measurement is equal to 1 minus percent of miscomprehension, it affects our interpretation of the study findings. Using this outcome measurement also leads to a different sample size requirement.

Using percent miscomprehension as an outcome measurement helps us to have a better feel for the extent of the problem. For example, if the percent of correct answers (i.e. proportion of comprehension) is computed to be 99%, it means 1% of respondents did not understand the label. Although 1% seems to be small and trivial, when it is applied to the overall targeted population, it results in a substantial number of misunderstanding events. For example, a misunderstanding percent of 1% in a population of 100,000 physicians means that 1000 physicians miscomprehend the label.

In calculating the sample size, when the point estimate is expected to be small, it is better to use relative precision rather than absolute precision. For example, the sample size needed to detect at least 1% miscomprehension should be sufficient to distinguish 1% from 0% miscomprehension. A sample size of 200 has an absolute precision of 1.3% and a 95% C.I of: -0.3% to 2.3%. Thus we could conclude erroneously that there is no problem with the label when there is indeed 1% misunderstanding. So, the sample size of 200 is not large enough to detect a 1% error with adequate precision. We suggest that the sample size be based on the relative precision of at least 30% of the point estimate. In that case, a sample size of 4200 is needed if one wants to detect a miscomprehension level of 1% with ± (30% of 1%).

The alternative approach to what I have suggested above is to use the lower bound of the 95% confidence interval for percent compreshension. For example if the percent comprehension is 99% (95% C.I.:97.7% - 100%), we should considered that the comprehenshion level can be as low as 97.7% and our policy toward label change should be based on this level.

Statistical Analysis

The sponsor would compute the number of and the percentage of "correct" and "acceptable," responses to each question. They propose that adequate label comprehension would be a summation of "correct" and "acceptable" responses.

It is important to know exactly what criteria the sponsor is using to determine the "acceptable" responses and the threshold at which the sponsor believes a change to the label is required.

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/s/

Carol Holquist
3/27/02 12:21:43 PM
PHARMACIST

Jerry Phillips
3/27/02 12:29:41 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Associate Director, Medication Error Prevention
Office of Drug Safety, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM:
Division of Special Pathogen and Immunologic Drug Products
HFD-590

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 29, 2002		21-473	NDA	July 18, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cipro XR	Standard review	Quinolone	August 31, 2002

NAME OF FIRM: Bayer

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
Bayer submitted [redacted] as their trade name with the NDA. This was reviewed and was found unacceptable. A meeting was held between the Agency and Bayer and the Agency requested a submission of a different trade name.
I'm attaching the cover letter to the consult. If you have any questions please contact Jouhayna Saliba or Susan Peacock at 72127.

PDUFA DATE: January 3, 2002
ATTACHMENTS: Draft Package Insert, Container and Carton Labels (these will be submitted once name is approved)
CC: Carol Holquist, Sammie Beam, Karen Lechter
Archival NDA 21-473
HFD-590 RPM Jouhayna Saliba and Susan Peacock
HFD-590 Reviewers and Team Leaders Rigoberto Roca, Maria Ruiz, Regina Alivisatos, Norman Schmuff, Dorota Matecka

SIGNATURE OF REQUESTER Jouhayna Saliba and Susan Peacock	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Bayer

Pharmaceutical
Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone 203 812-2000

July 18, 2002

Renata Albrecht, M.D., Acting Director
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV (HFD-590)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 21-473
CIPRO® XR (ciprofloxacin hydrochloride and ciprofloxacin extended release tablets)
General Correspondence – Change in Tradename

Dear Dr. Albrecht,

Bayer Corporation references the June 6, 2002 meeting held between Bayer and the Division concerning the review of NDA 21-473. During this meeting the Division and other Agency representatives expressed concern for the proposed tradename of the product – Cipro – Bayer committed to revise the tradename based on these concerns and to quickly communicate a new name to the Division.

We also reference previous discussion with the Project Manager concerning a revision to the established or "generic" name for this product. Therefore, the name for this product is now formally proposed to be:

CIPRO® XR (ciprofloxacin hydrochloride and ciprofloxacin extended release tablets)

Note that this was the name discussed briefly at the June 6 meeting, and was verbally endorsed by some of the Agency representatives in attendance. Please commence the review of this name as soon as possible. Bayer would like to be contacted immediately once this process has completed. Formal submissions of revised bottle labels and the package insert will be made at that time. If any questions or concerns arise from this information, do not hesitate to contact me at (203) 812-5172 or at andrew.verderame.b@bayer.com.

Sincerely,

Andrew S. Verderame
Director, Regulatory Affairs

Desk Copy: Jouhayna Saliba, Pharm.D., Project Manager

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/s/

Jouhayna Saliba
7/29/02 10:28:36 AM

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ON ORIGINAL

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 29, 2002	**DUE DATE:** August 31, 2001	**ODS CONSULT #:** 01-0125-1

TO: Renata Albrect, M.D.
Acting Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH: Jouhayna Saliba
Project Manager
HFD-590

PRODUCT NAME: **Cipro XR** (Ciprofloxacin Hydrochloride and Ciprofloxacin Extended-Release Tablets) 500 mg **NDA #:** 21-473	**SPONSOR:** Bayer Corporation Pharmaceutical Division

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Special Pathogen and Immunologic Drug Products (HFD-590), the Division of Medication Errors and Technical Support (DMETS) has conducted a review of the proposed proprietary name "Cipro XR" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proprietary name Cipro XR.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)
HFD-420; Parklawn Building Room 15B-32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 15, 2002

NDA NUMBER: 21-473

NAME OF DRUG: **Cipro XR**
(Ciprofloxacin Hydrochloride and Ciprofloxacin Extended-Release Tablets)
500 mg

NDA SPONSOR: Bayer Corporation Pharmaceutical Division

I. INTRODUCTION

This consult was written in response to a request from the Division of Special Pathogens and Immunologic Drug Products (HFD-590) for assessment of the proprietary name, *Cipro XR*.

The sponsor, Bayer Pharmaceuticals, previously proposed the proprietary names "Cipro [redacted]" and "Cipro [redacted]" for this drug product. On June 26, 2001, DMETS did not recommend the use of these names and also recommended that the sponsor consult with the CDER Labeling and Nomenclature Committee (LNC) with regard to the established name.

Subsequent to a meeting held on June 6, 2002 between the Division and the sponsor, the established name was revised to ciprofloxacin hydrochloride and ciprofloxacin extended-release tablets. In addition, the sponsor proposed the proprietary name Cipro XR.

PRODUCT INFORMATION

Cipro XR is the proposed proprietary name for ciprofloxacin hydrochloride and ciprofloxacin extended-release tablets. Cipro XR will be available as 500 mg tablets for once daily administration. Cipro XR indicated for the treatment of uncomplicated urinary tract infections caused by *Escherichia coli*, [redacted] *Proteus mirabilis, or Staphylococcus saprophyticus*. The usual dosage is 500 mg once daily for 3 days.

II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name "Cipro" has been utilized in the U.S. marketplace since June 1994. An Expert Panel discussion was conducted to address concerns with the use of the modifier "XR". In addition, the Adverse Event Reporting System (AERS) database was searched to determine if there is any confusion with the use of the proprietary name "Cipro."

A. EXPERT PANEL DISCUSSION

A discussion was held by DMETS to gather professional opinions on the safety of the proprietary name *Cipro XR*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel did not object to the modifier "XR", because "XR" has been commonly used for similar "extended-release" dosage forms marketed in the U.S. (e.g., *Tegretol XR, Voltaren XR, Dilacor XR, Glucophage XR,* and *Effexor XR).*

2. DDMAC did not object to the proprietary name Cipro XR in regard to promotional claims.

B. AERS DATABASE SEARCH

1. DMETS searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Cipro. The Meddra Preferred Term (PT), "Medication Error" and the drug names, "Cipro%," and "ciprofloxacin%", were used to perform the search.

   A total of 42 reports from the AERS search were retrieved and reviewed. Of the 42 reports reviewed, two accounts involved name confusion with Cipro (See Attachment I, Table 1).

2. DMETS also searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with "XR." The Meddra Preferred Term (PT), "Medication Error" and the drug names, "Adderall%", "Dilacor%", "Effexor %", "Glucophage%", "Tegretol%" and "Voltaren%" were used to perform the search.

   A total of 69 reports from the AERS search were retrieved and reviewed. Of the 69 reports reviewed, 7 accounts involved confusion with "XR" (See Attachment I, Table 2).

C. SAFETY EVALUATOR RISK ASSESSMENT

To date, the Agency has received two medication error reports involving name confusion with Cipro. One report involved a medication error between Cipro and Naproxen while another report involved a pharmacist dispensing Cipro tablets but labeling the bottle as generic Lortab 5 mg. Although Cipro products have been available since October 1987, only two medication error reports between Cipro and Naproxen and generic Lortab were received by the Agency. Therefore, there is insufficient evidence at this time to conclude that the proprietary name, Cipro, has significant potential for name confusion. DMETS will continue to monitor post-marketing medication errors in association with the proprietary name, Cipro.

Cipro XR contains the same active ingredient, Ciprofloxacin, as the currently marketed Cipro tablets. However, Cipro XR will be available as extended-release tablets. We recognize the need to differentiate the currently marketed Cipro tablets from this new product, Cipro XR; Cipro tablets are dosed twice daily while Cipro XR will be dosed once daily. DMETS does not object to the use of the modifier "XR" for this proposed product, since this is a common practice for similar "extended-release" dosage forms marketed in the U.S. (e.g., Tegretol XR™, Dilacor XR™, Glucophage XR™, Effexor XR™, and Adderall XR™). From the names listed above, all but Tegretol XR is dosed once daily; Tegretol XR is dosed twice daily. Based on the once a day dosing schedules, the modifier "XR" would be appropriate to identify the extended-release characteristic of Cipro XR.

According to a search in the Adverse Event Reporting System (AERS) for medication error reports with "XR", five medication error reports of confusion between Effexor and Effexor XR, one medication error report of confusion between Glucophage and Glucophage XR, and one medication error report of confusion between Adderall and Adderall XR were identified. In each case, the overlapping strength between the "non-extended release" and the "extended-release" formulations was the confounding factor that contributed to a medication error (See table 1). Overlapping strengths exist between the extended release and non-extended release formulations for Effexor XR/Effexor, Glucophage XR/Glucophage, and Adderall XR/Adderall.

Table 1

	Source AERS	Intended Product	Dispensed Product
1	3208763-8 (USP 52081)	Effexor XR 75 mg	Effexor 75 mg
2	3332283-3	Effexor 75 mg	Effexor XR 75 mg
3	3332288-2	Effexor 150 mg	Effexor XR 150 mg
4	3460522-7	Effexor XR 150 mg	Effexor 150 mg
5	3762570-6	Effexor 37.5 mg	Effexor XR 37.5 mg
6	3824270-3 (USP 54575)	Glucophage XR 500 mg	Glucophage 500 mg
7	3895548-2 (USP 54804)	Adderall XR 20 mg	Adderall 20 mg

In regards to Cipro and Cipro XR, a safety concern regarding the overlapping strength does exist. Cipro is available as 100 mg, 250 mg, 500 mg, and 750 mg tablets while Cipro XR will be available as 500 mg tablets. Therefore, we recommend careful monitoring and sufficient education regarding the difference between Cipro and Cipro XR tablets upon the launch of this product.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

Refer to ODS consult 01-0125.

IV. RECOMMENDATIONS:

DMETS has no objections to the use of the proprietary name Cipro XR.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

Alina R. Mahmud, RPh.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

Attachment I

Table 1

	Source AERS	Date of Event/ Report	Intended Product	Dispensed Product	Outcome/Description
1	3760235-8	07/08/01	Cipro	Cipro 500 mg but mislabeled bottle as generic Lortab	A pharmacist dispensed Cipro 500 mg tablets to a patient and mislabeled the prescription container as being filled with hydrocodone/ASAP 5 mg/500 mg (generic Lortab).
2	3450729-7	02/03/00	Naproxen 500 mg	Cipro 500 mg	A prescription for Naproxen 500 mg tablets was incorrectly filled with Cipro 500 mg tablets.

Table 2

	Source AERS	Date of Event/ Report	Intended Product	Dispensed Product	Outcome/Description
1	3208763-8 (USP 52081)	2/10/99	Effexor XR 75 mg	Effexor 75 mg	Actual Error. A prescription for Effexor XR 75 mg was dispensed with Effexor 75 mg. The patient discovered the error prior to ingestion.
2	3332283-3	3/99	Effexor 75 mg	Effexor XR 75 mg	Actual Error. A patient received Effexor XR 75 mg instead of Effexor 75 mg. She experienced dizziness, diarrhea, and fell down without any muscle coordination.
3	3332288-2	5/4/99	Effexor 150 mg	Effexor XR 150 mg	Actual Error. A patient received Effexor XR 150 mg instead of Effexor 150 mg. She took Effexor XR 600 mg daily for an unknown amount of time.
4	3460522-7	4/13/99	Effexor XR 150 mg	Effexor 150 mg	Actual Error. A patient received Effexor 150 mg instead of Effexor XR 150 mg. Within a week of taking Effexor 300 mg daily, she experienced increased blood pressure.
5	3762570-6	6/11/01	Effexor 37.5 mg	Effexor XR 37.5 mg	Actual Error. A physician dispensed samples of Effexor XR 37.5 mg instead of Effexor 37.5 mg. The error was discovered prior to ingestion
6	3824270-3 (USP 54575)	10/25/01	Glucophage XR 500 mg	Glucophage 500 mg	Actual Error. A refill for Glucophage XR 500 mg was filled with Glucophage 500 mg. A patient discovered the error prior to ingestion.
7	3895548-2 (USP 54804)	3/12/02	Adderall XR 20 mg	Adderall 20 mg	Actual Error. A prescription for Adderall XR 20 mg was dispensed with Adderall 20 mg. The pharmacist did not realize that an extended release form of Adderall was available. The patient experienced no adverse outcome.

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/s/

Alina Mahmud
8/29/02 04:11:34 PM
PHARMACIST

Carol Holquist
8/29/02 04:25:58 PM
PHARMACIST

Jerry Phillips
8/31/02 08:55:54 AM
DIRECTOR

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 6, 2002

To: Andrew Verderame	**From:** Jouhayna Saliba
Company: Bayer Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 203-812-5029	**Fax number:** 301-827-2475
Phone number: 203-812-5172	**Phone number:** 301-827-2387

Subject: Request for additional clin/pharm information

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Services
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

DATE: December 6, 2002

TO: Andrew Verderame
Deputy Director, Regulatory Affairs

ADDRESS: Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

TELEPHONE: 203-812-5172
FAX: 203-812-5029

FROM: Jouhayna Saliba

APPLICATION: NDA 21-473

SUBJECT: Request for additional information

We refer to your submission dated December 6, 2002, where you provided additional information to support certain labeling statements regarding renal insufficiency. We would like to thank you for providing that information and would like to request the following additional information:

- Please perform Monte-Carlo simulations of plasma ciprofloxacin concentration-time profiles in the following groups:

  1. Patients with severe renal impairment (CLcr < 30mL/min) given CIPRO XR 500 mg given once-daily for three days.
  2. Patients with mild to moderate renal impairment given immediate-release CIPRO 500 mg given twice-daily for three days.
  3. Patients with severe renal impairment given immediate-release CIPRO 500 mg given once-daily or once every 18 hours for three days.
  4. Subjects with normal renal function given immediate-release CIPRO 750 mg given twice-daily (bid) for 14 days.

- Please provide plots and a tabular list comparing the predicted daily peak and 24-hour exposures following these administrations.

- Please also provide your assumptions when conducting the above simulations.

NDA 21-473
CIPRO® XR
December 6, 2002

If you have any questions, please contact me at (301) 827-2387.

Jouhayna S. Saliba, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Immunologic Drug Product

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/s/

Jouhayna Saliba
12/12/02 11:53:19 AM
CSO

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-473

Bayer Corporation Pharmaceutical Division
ATTN: Mr. Andrew S. Verderame
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

Dear Mr. Verderame:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	CIPRO® (ciprofloxacin hydrochloride and ciprofloxacin) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	March 4, 2002
Date of Receipt:	March 5, 2002
Our Reference Number:	NDA 21-473

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 4, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 3, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products, HFD-590
Attention: Document Room
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Jouhayna Saliba, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
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/s/

Ellen Frank
4/22/02 06:26:07 PM
NDA 21-473

MEETING MINUTES

MEETING DATE: June 6, 2002
TIME: 1:00 p.m.
LOCATION: S400
NDA: 21-473
DRUG: Cipro [redacted]
SPONSOR: Bayer
CONTACT NAME: Andrew Verderame
FAX NUMBER: 203-812-5029
PHONE NUMBER: 203-812-5172
PROJECT MANAGER: Jouhayna Saliba
DIVISION OF: Special Pathogen and Immunologic Drug Products, HFD-590
FORMAT: FACE TO FACE
TYPE of MEETING: B
MEETING REQUEST RECEIPT DATE: March 5, 2002
MEETING DATE CONVEYED TO SPONSOR: March 5, 2002 **VIA;** Telephone
BRIEFING DOCUMENT RECEIPT DATE: May 6, 2002 **ON TIME:** YES

FDA PARTICIPANTS, DIVISIONS, AND TITLES:

Renata Albrecht, M.D., Acting Division Director
Rigoberto Roca, M.D., Medical Team Leader
Eileen Navarro, M.D., Medical Reviewer
Ruthanna Davi, M.S., Statistical Reviewer
Joette Meyer, Pharm.D., Clinical Pharmacology & Biopharmaceutics Reviewer
Carol Holquist, R.Ph., Office of Drug Safety
Ellen Frank, R.Ph., Chief, Project Management Staff
Andrew Cheung, pharmacy student
Jouhayna Saliba, Pharm. D., Project Manager

INDUSTRY PARTICIPANTS AND TITLES:

Mary E. Taylor, M.P.H.
Paul MacCarthy, M.D.
Lawrence Posner, M.D.
Deborah Church, M.D.

Daniel Haverstock, Ph.D
Steven Kowalsky, Pharm.D
Gabriele Fischer
John Lettieri, Ph.D.
Andrew Verderame
Robin Christoforides
Kamal Hamed, M.D.
Kathleen Gondek, Ph.D.
[redacted]
Joseph Carofano
Tig Conger
Jonathan Harris, Ph.D.
Jennifer Stahl

BACKGROUND INFORMATION:

This meeting was requested by Bayer to discuss the trade name Cipro [redacted] and to discuss the results and conclusions of the Cipro [redacted] label comprehension study.

MEETING OBJECTIVES:

- Bayer will present the results and conclusion of the Cipro [redacted] label comprehension study
- Discussion between the Agency and Bayer with regard to the Cipro [redacted] trade name
- Discussion of strategies to support the appropriate use of the product

QUESTIONS FOR DISCUSSION WITH RESPONSES AND DECISIONS REACHED:

1. We believe that the label comprehension study generated information that helped Bayer to identify labeling issues that had potential to cause confusion. We improved our package insert to enhance the understanding of the product and now expect increased assurance of the appropriate use of the product. Could the Division please comment?

   The Division commented that labeling modifications would be considered later during the review period of this NDA.

2. As per the discussions held prior to the NDA submission, we anticipate marketing this product in the US with the trade name ***Cipro*** [redacted] Based on the outlined rationale, which is that this name most clearly supports and communicates the objective of appropriate use, does DSPIDP or the other invited Divisions have any comment on the name at this point?

   The Division along with the Office of Drug Safety strongly discouraged the inclusion of an indication in the trade name. Some concerns that were raised are the use of this name in hospital setting where standard medical abbreviations are used on prescriptions and can include the indication along with the trade name. Also, problems with verbal orders may

arise. Off label use maybe a problem also, since this product should be used for uncomplicated UTI.
The Division commented that the proposed new name may include the current Cipro prefix and the Division would consider an alternative suffix that refers to the kinetics of the alternative formulation, such as extended release.

3. We believe the label comprehension study supports that pharmacists can successfully differentiate the products. As stated previously, Bayer intends to package this product for distribution in bottles. Can the Division comment?

   The bottles will be an acceptable packaging option while Bayer looks at retesting and proposing an alternative trade name to the Cipro — name.

4. Is the Agency in agreement that the proposed initial marketing and branding activities form the basis of an effective plan to adequately address concerns about potential off label use?

   The Division was encouraged with Bayer's educational plans and Bayer stated that they would also share their plans of an educational campaign for physicians, nurses or nurse practitioners. The Division encouraged Bayer to continue with their educational plans and have them submitted during the NDA review time so that the Division may offer comments or suggestions.

5. Within the development of this product, we have communicated and cooperated closely with the Division to address all requests received from FDA, including those made at the pre-phase III meeting and the pre-NDA meeting. We believe that we have provided everything that the Division needs to adjudicate on the uUTI NDA within the ten-month review cycle. Is there agreement on this point?

   The Division had no objection to a ten-month review cycle for the uUTI NDA.
   Bayer stated that the —
   The Division was in agreement with Bayer's proposal not —

ACTION ITEMS:

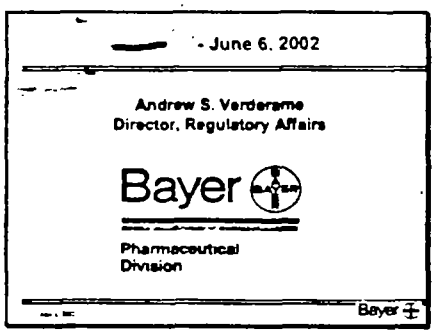
1. The Division will send Bayer details on the format of the electronic submission —
2. —
3. Bayer will share their plans with the Division for an educational campaign for physicians, nurses, and nurse practitioners.

Jouhayna Saliba, Pharm.D. Regulatory Project Manager
Minutes Preparer

Renata Albrecht, M.D., Acting Division Director
Meeting Chair

Attachment/Handouts: Overhead slides

Slide 1



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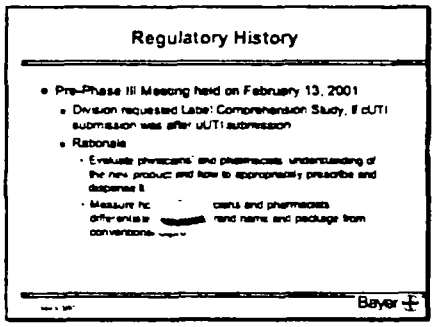

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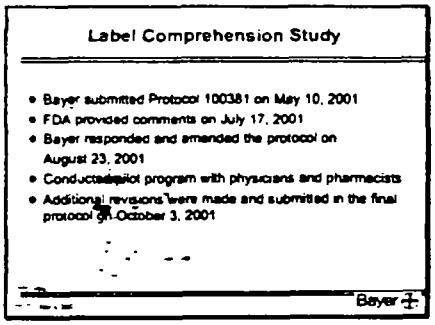

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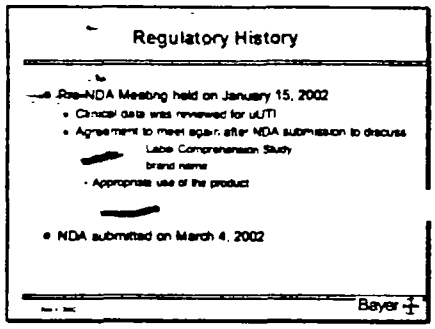

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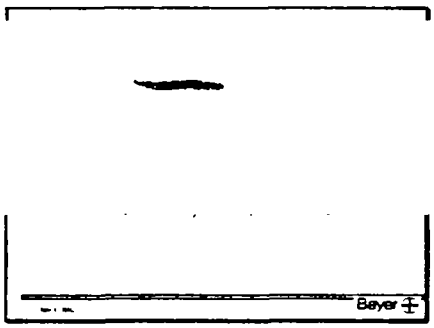

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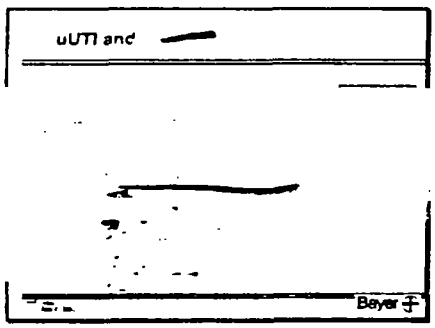

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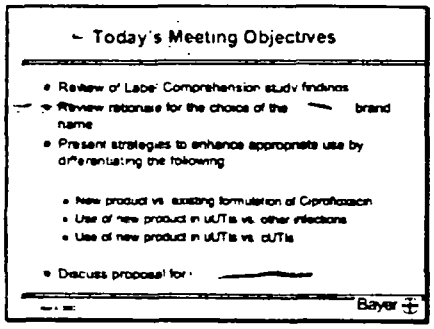

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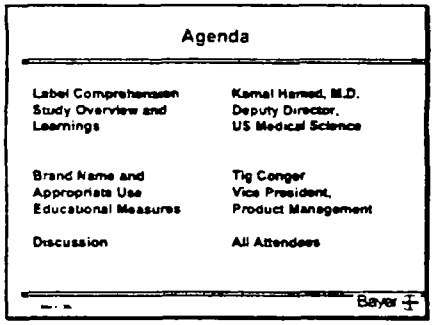

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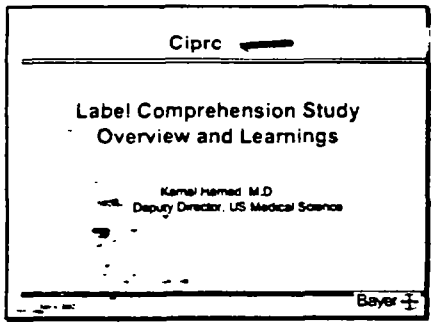

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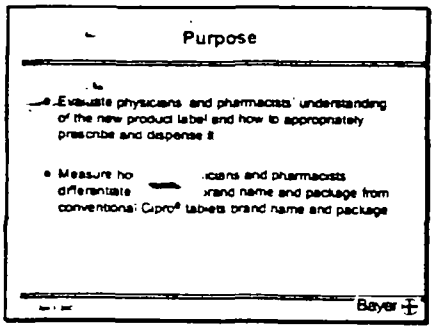

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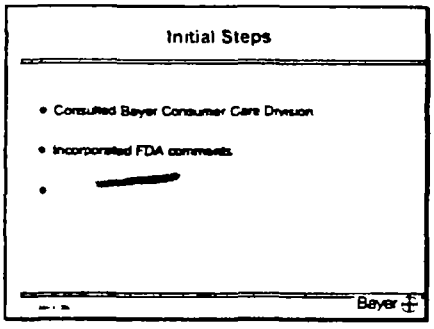

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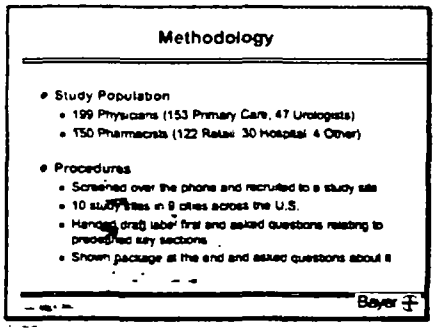

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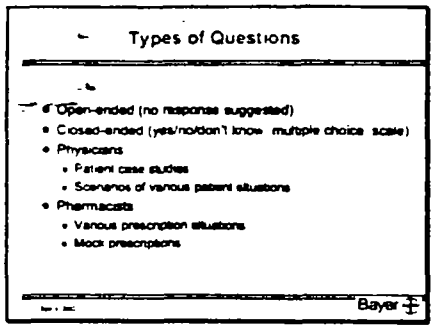

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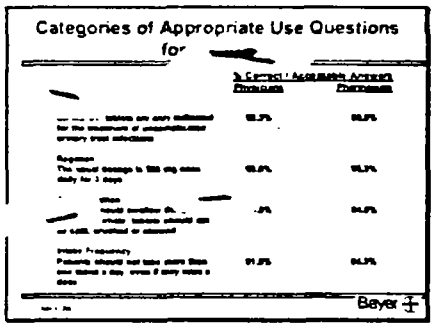

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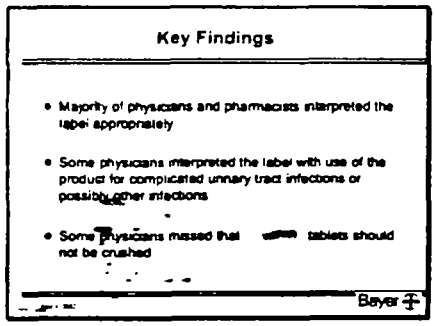

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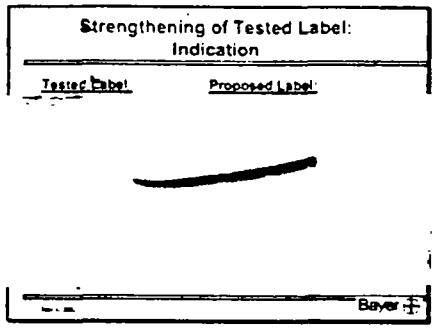

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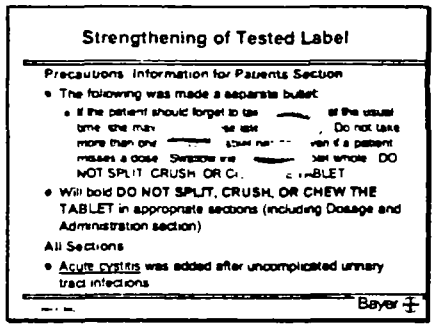

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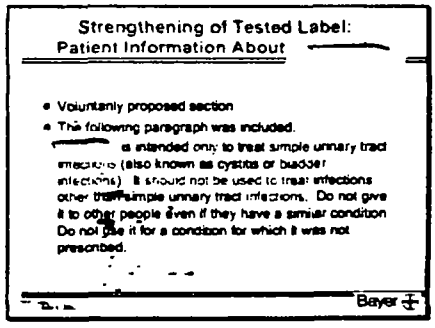

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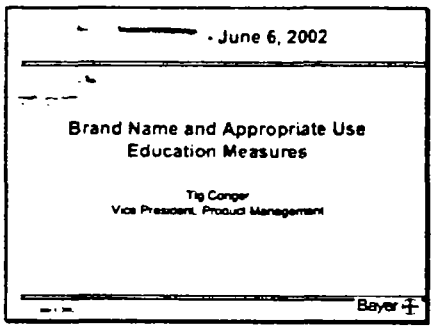

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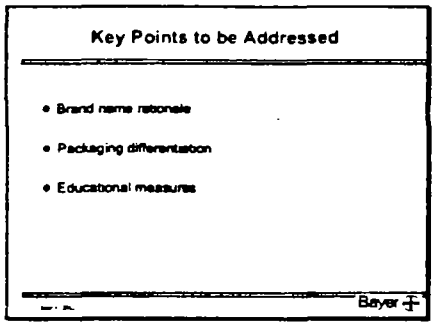

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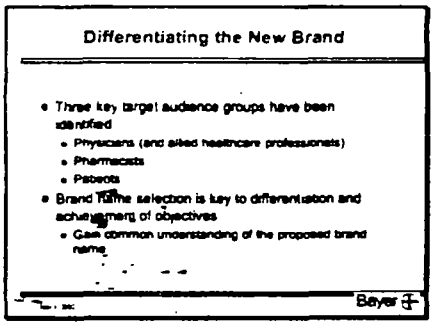

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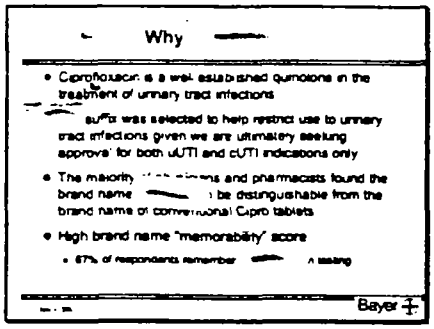

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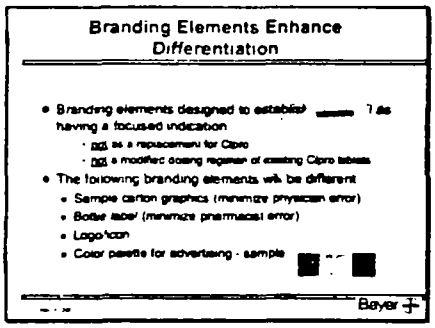

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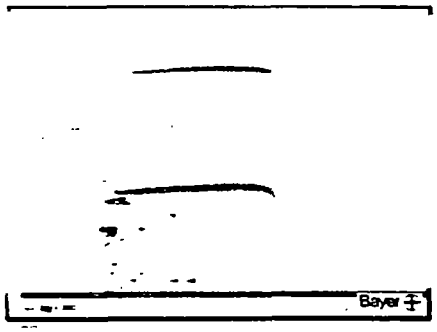

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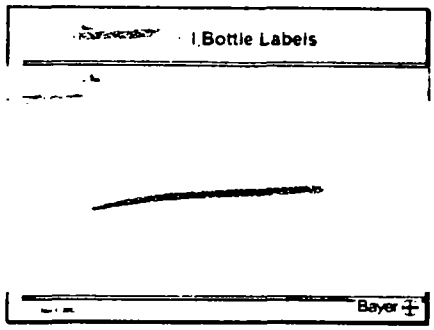

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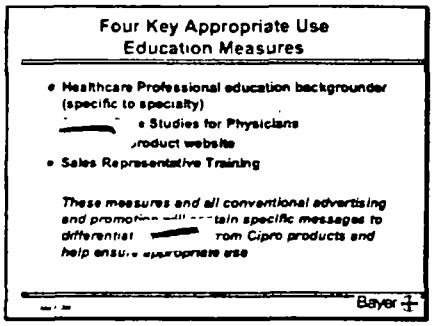

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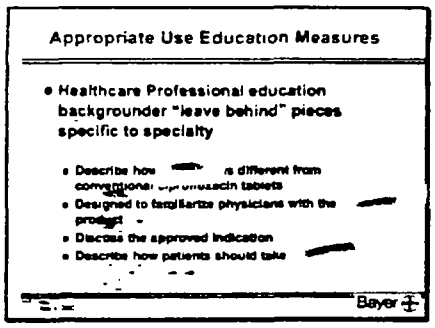

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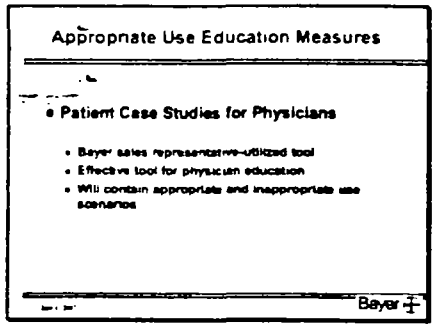

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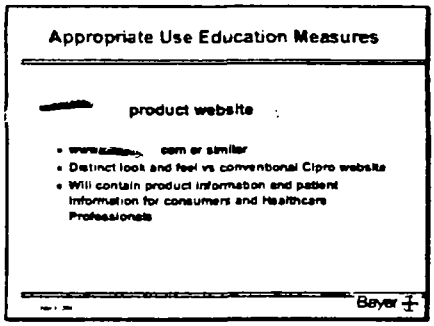

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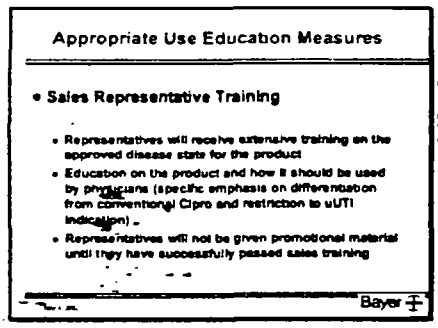

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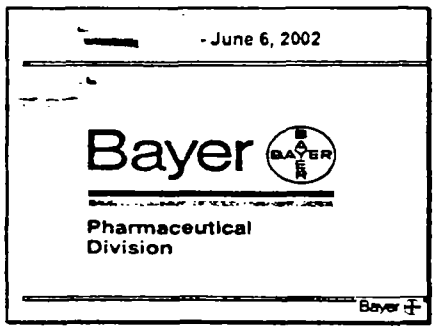

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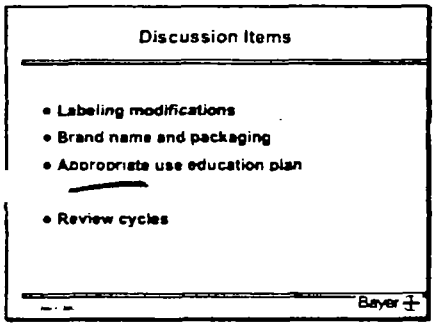

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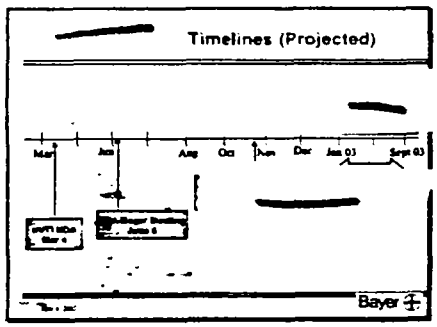

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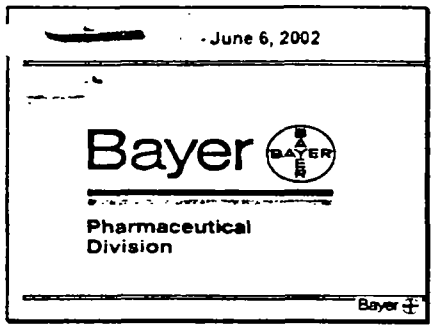

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/s/

Renata Albrecht
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Jouhayna Saliba
2/11/03 07:29:42 AM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF MEETING

DATE: February 15, 2002

MEETING TYPE: Pre-NDA CMC meeting

IND: [redacted]

DRUG: Cipro [redacted]

BAYER ATTENDEES:
Shelina Bhojani, Associate Development Program, Regulatory Affairs
Gabrielle Fischer, Deputy Director, Project Management
Robin Christoforides, Assistant Director, Regulatory Affairs
Andrew Verderame, Deputy Director, Regulatory Affairs
Horst-Dieter Friedel, Quality Control Development
Maryann Graham, Quality Assurance Development
Andreas Ohm, Pharmaceutical Technology
Hans Scholl, Quality Assurance Development
Fritz Schueckler, Quality Control Development
Wolfgang Weber, Quality Control Development
Max Wegner, Global Regulatory Affairs

FDA ATTENDEES:
Norman Schmuff, Ph.D., Chemistry Team Leader
Dorota Matecka, Ph.D., Chemistry Reviewer
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Jouhayna Saliba, Pharm.D., Project Manager

BACKGROUND:
A meeting request for a teleconference dated December 6, 2001 was submitted by Bayer regarding [redacted]. This meeting request was received by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) on December 7, 2001. This meeting is considered a Pre-NDA CMC meeting for the [redacted] of ciprofloxacin studied under [redacted]. A background package for this Pre-NDA CMC teleconference was submitted January 18 and February 8, 2002.

Discussion items during this meeting are duplicated below. Division comments are duplicated below in italics.

Discussion Item (1)
As discussed with the Division during the End of Phase II CMC Teleconference, Bayer will submit 9 months of stability data on three primary stability batches of Ciprofolxacin [redacted]

Tablets 0.5 G. Stability studies will continue and Bayer will submit and update of the stability data for 52 weeks during the NDA review. Comparative dissolution data from embossed tablets will also be included in the NDA, as agreed during the End of Phase II CMC Teleconference.

The Division was in agreement with the above.

With regard to comparative dissolution, a bioequivalence study would not be required if the comparability of the products is demonstrated by dissolution profiles.

Bayer questioned

Discussion Item (2)

As mentioned in Section 10, Stability, formation of trace amounts of was observed on tablets during long-term stability studies. Bayer is currently investigating the effect, which is considered a cosmetic defect that does not impact on efficacy and safety of the product. Bayer will provide additional information to the Division (no later than February 8, 2002) prior to the CMC Teleconference.

The Division had no comments

Discussion Item (3)

Because the active ingredient in Ciprofloxacin Tablets 0.5 G is a combination of two forms of Ciprofloxacin drug substance, Ciprofloxacin HCl, and ciprofloxacin (Ciprofloxacin betain), Bayer proposes to use "Ciprofloxacin" as the generic chemical name for the drug substance for all drug product labeling (e.g. package insert, bottle label). The proposed package insert (see Appendix 3 for an in-process draft PI) will contain a more detailed description of the two forms of ciprofloxacin.

Since the product contains both ciprofloxacin and ciprofloxacin HCl, the established name should include both names in order to comply with Section 501(b) of the Federal Food Drug and Cosmetic Act (the Act). Furthermore, in compliance with the Act, if either drug does not comply with the existing monograph, it should be clearly stated in the label in what specific regard it differs from the monograph. It was noted that this labeling requirement also applies to other ciprofloxacin products, and they should be revised to comply. .

Signature, minutes preparer: _____ Date: _____
Jouhayna Saliba, PharmD, Project Manager
Conference Chair (or designated signatory): _____ Date: _____
Norman Schmuff, Ph.D., Chemistry Team Leader

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/s/

Norman Schmuff
3/12/02 11:35:36 AM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF MEETING

DATE: January 15, 2002

MEETING TYPE: Pre-NDA meeting

IND: [redacted]

DRUG: Cipro [redacted]

BAYER ATTENDEES:

Lawrence Posner, M.D., Senior Vice President, Pharmaceutical Development and Head of Worldwide Regulatory Affairs
Mary E. Taylor, MPH, Vice President, Regulatory Affairs
Deborah Church, M.D., Director Medical Affairs, Anti-Infective
Shelina Bhojani, Associate Development Program, Regulatory Affairs
Mark Kunkel, M.D., Director, Strategic Marketing, Anti-Infectives
Daniel Haverstock, Ph.D., Deputy Director, Statistics
Steven Kowalsky, Pharm.D., Global Clinical Project Leader, Global Project Management
John Lettieri, Ph.D., Deputy Director, Clinical Pharmacology
Barbara Painter, Ph.D., Deputy Director, Medical Affairs, Anti-Infectives
Kamal Hamed, M.D., Associate Director, Medical Affairs, Anti-Infectives
Gabrielle Fischer, Deputy Director, Project Management
Robin Christoforides, Assistant Director, Regulatory Affairs
Andrew Verderame, Deputy Director, Regulatory Affairs

FDA ATTENDEES:

Rigoberto Roca, M.D., Medical Team Leader
Eileen Navarro, M.D., Medical Reviewer
Funmi Ajayi, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Peter Dionne, M.S., Microbiology Reviewer
Karen Higgins, Ph.D., Statistical Team Leader
Ruthanna Davi, M.S., Statistical Reviewer
Kenneth Hastings, Ph.D., Pharm-Tox Team Leader

Stephen Hundley, Ph.D., Pharm-Tox Reviewer
Karen Lechter, J.D., Ph.D., Office of Drug Safety
Jouhayna Saliba, Pharm.D., Project Manager

BACKGROUND:

A meeting request for a Type B meeting dated November 14, 2001 was submitted by Bayer regarding [redacted]. This meeting request was received by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) on November 16, 2001. Bayer sent a letter dated December 21, 2001 agreeing to a January 15, 2002 meeting date regarding this IND. This meeting is considered a Pre-NDA meeting for the modified release formulation of ciprofloxacin studied under [redacted]. A background package for this Pre-NDA meeting was submitted December 21, 2001.

Discussion items during this meeting are duplicated below. Division comments are duplicated below in italics.

Discussion Item (1)

As discussed with the Division during the End-of-Phase II meeting held on February 13, 2001, the Cipro [redacted] NDA will contain one pivotal clinical study for the indication of uncomplicated urinary tract infections. In addition, the results from eight clinical pharmacology studies will also be submitted. Bayer has incorporated the Division's recommendations into the design of these studies. It is our intention to submit this NDA in March 2002.

The Division inquired about the format of the datasets for the pivotal clinical study, which will be submitted with the NDA. Bayer will submit the NDA electronically according to the Guidance. The Division requested an additional dataset containing one row of data per subject and including all variables used in the primary and secondary efficacy analyses. Bayer agreed to submit such a data set.

Discussion Item (2)

Two label comprehension studies were performed, one using "Cipro [redacted], the other using "Cipro [redacted]' as the trade name. Data collection is completed and is being reviewed for analysis. Based on the results, Bayer may choose to revise the package insert or bottle labeling. In addition, Bayer will use these results in the development of the advertising and promotional materials.

The two label and package comprehension studies are completed and the data is being analyzed and will be included in the NDA. The analysis for these studies will be further discussed with the Division.

Discussion Item (3)

Bayer is also conducting a large, Phase III trial in complicated urinary tract infections using the 1 gram tablet. The "Ongoing Clinical Studies" section in the uUTI NDA will contain safety information from the cUTI trial. We will also provide updated safety information for [redacted] It is anticipated that a [redacted]

The Division requested that periodic updates of the complicated UTI study be submitted to help make a decision on the uncomplicated UTI NDA. The Division inquired about the number of patients enrolled in the complicated UTI study. Bayer responded that approximately 475 patients are now enrolled and that the expected number of enrollment is 940 patients. Bayer told the Division that the

The Division also commented that the range of severity of patients in the complicated UTI study must include those patients in whom more severe disease is present to evaluate that off-label use in complicated UTI would be safe.

Discussion Item (4)

Discussion Item (5)

The trade name for this product has not yet been finalized. It is Bayer's intention to choose a "Cipro" containing name for this product, such as "Cipro or "Cipro or a Cipro-derivative of our choice.

The trade name submitted will be discussed with the Division of Drug Marketing, Advertising and Communications (DDMAC) as well as, the Office of Drug Safety (ODS).

Additional comments:

Signature, minutes preparer: _____ Date: _____
Jouhayna Saliba, Pharm.D., Project Manager

Conference Chair (or designated signatory): _____Date: _____
Rigoberto Roca, M.D., Medical Team Leader

Attachment/Handouts: Overhead slides

Introduction

- November 29, 2000 - Bayer submitted the Cipro —
- February 13, 2001 - End of Phase II meeting
  - agreement on Clinical Pharmacology studies
  - agreement on one uUTI clinical study for submission of this indication
  - agreement on one cUTI clinical study for (Division suggested 10% delta)
  - Division requested label comprehension study if uUTI was to be submitted —

Introduction

- March 1, 2001 - Division agrees with Bayer's proposal —
- May 17, 2001 - Division agrees that the preclinical sections of the Cipro — NDA contain only a cross-reference statement to already-approved Cipro NDAs
- December 20, 2001 - NDA # 21-473 is assigned to the uUTI submission

Discussion Item # 5

- The trade name for this product has not yet been finalized. It is Bayer's intention to choose a "Cipro" containing name for this product, such as "Cipro ——" "Cipro —" or a Cipro-derivative of our choice.

Discussion Item # 6

- Any items that the Division would like to discuss.

Discussion Item # 3

- Bayer is also [redacted] he "Ongoing Clinical Studies" section in the uUTI NDA will contain safety information from the cUTI trial. We will also provide updated safety information for cUTI in the 4-Month Safety Update. It is anticipated [redacted]

Discussion Item # 4

- Bayer is currently conducting pediatric studies with the approved ciprofloxacin formulations (tablet, i.v., oral suspension). The development of a pediatric modified-release formulation is not feasible. We will be requesting a waiver for pediatric use information for this submission. It is our intention to include the relevant information gathered from the ongoing pediatric trials into the package insert for the once-daily product.

Discussion Item # 1

- As discussed with the Division during the End-of-Phase II meeting held on 2/13/01, the Cipro — NDA will contain one pivotal clinical study for the indication of uUTI. In addition, the results from eight clinical pharmacology studies will be submitted Bayer has incorporated the Division's recommendations into the designs of these studies. It is our intention to submit this NDA in March 2002.

Discussion Item # 2

- Two label comprehension studies were performed, one using "Cipro — the other using "Cipro — as the trade name. Data collection is completed and is being reviewed for analysis. Based on the results, — In addition, Bayer will use these results in the development of the advertising and promotional materials.

Clinical Pharmacology - Drug Interaction Studies

- End-of-Phase II meeting February 13,2001
  - FDA request to complete 2 drug interaction studies
    - Proton pump inhibitor study
    - Antacid study

Cipro → Results of Interaction Studies

- Omeprazole: 20% decrease in AUC when 1g Cipro was dosed with 40 mg omeprazole
- Maalox 70*: approximately 25% decrease in AUC when 1g Cipro was given 2 hours before, or 4 hours after 10 ml Maalox 70

*formulation not available in US

Label Comprehension Study

- Study Population
  - Physicians (N = 200)
    - PCPs (FPs, GPs, Internists, OB/GYNs)
    - Urologists
  - Pharmacists (N = 150)
    - Hospital
    - Independent retail pharmacy
    - Chain pharmacy
    - Other
- Analysis plan
  - The questions asked both MDs and RPhs were incorporated into an overall test score (domain score)

Format of Label Comprehension Report

Physician and Pharmacist Domain Scores

	Objectives	Physician Domain Scores (% Correct/Acceptable)
1	Cipro ___ tablets are indicated for the treatment of uncomplicated UTI	(Average) (95%CI)
2	The usual dosage is 500 mg once daily for three (3) days	(Average) (95%CI)
3	Patients should swallow the Cipro ___ tablet whole; they should not split, crush or chew the tablet	(Average) (95%CI)
4	Patients should not take more than one (1) tablet a day, even if they miss a dose	(Average) (95%CI)

Conclusions (Study 100346)

- Efficacy
  - Cipro – 500 mg QD was equivalent to the control regimen (conventional Cipro 250 mg BID)
- Safety
  - The adverse event profile was similar between Cipro – 500 mg and conventional Cipro 250 mg BID

Bayer

Label Comprehension Study

- Objective
  - To evaluate physicians' and pharmacists' understanding of the Cipro – labeling (PI) and how to safely prescribe or dispense Cipro –
- Design
  - MDs & RPhs were asked to read the following sections of the PI for Cipro –
    - **Indications**
    - **Dosage and Administration**
    - **Patient Information About Cipro – Tablets**
  - Asked questions about the PI to determine their comprehension of the Cipro – label using:
    - **Patient case studies or scenarios**
    - **Scenarios for various patient prescription situations**

Bayer

100346: Response Rates (Population Valid for Efficacy)

Primary efficacy variable: rate of microbiological eradication at the Test-of-Cure visit

	Cipro 500 mg QD	Cipro 250 mg BID	95% CI
Bacteriological Response at TOC*	186/197 (94.4%)	205/219 (93.6%)	-3.5%, 5.2% (MH)
Clinical response at TOC**	187/197 (94.9%)	200/219 (91.3%)	-1.6%, 7.2% (MH)

* Eradication vs. Persistence + New Infection

** Cure vs. Failure

January 15, 2002

Bayer

100346 Overview of Safety Events

	Cipro 500 mg QD (N = 444)	Cipro 250 mg BID (N = 447)
Adverse Event (AE)	121 (27%)	105 (24%)
Serious AE	6 (1.4%)	6 (1.3%)
Discontinuation due to AE	2 (0.5%)	2 (0.4%)
Deaths	0	0

January 15, 2002

Bayer

Study 100346: Uncomplicated UTI

- Design: Prospective, randomized, double blind, comparative trial
- Countries: United States (58 centers)
- Study Regimens*
  - Ciprofloxacin Once Daily — Tablet Arm
    - PO Cipro — . 500 mg QD
  - Conventional Ciprofloxacin Tablet Arm
    - PO Cipro 250 mg BID
- Duration of Therapy: short-course therapy (3 days)

*2-bottle system for blinding

January 15, 2002

Bayer

Study 100346: Patient Validity

	Cipro — . 500 mg (N = 452)	Cipro 250 mg BID (N = 453)
Valid for Safety	444 (98%)	447 (99%)
Valid for Efficacy	197 (43%)	219 (48%)

Most common reason for exclusion from efficacy population - " No causative organism isolated pre-Rx"
(221 Cipro — d 201 Cipro —

January 15, 2002

Bayer

Ciprofloxacin Once Daily — Tablet Development Program
Pre-NDA Meeting

Steven F. Kowalsky, PharmD
Director,
Global Clinical Project Management, Anti-infectives
Bayer Corporation

Ciprofloxacin — NDA Submission Package

The NDA submission (11/Mar/2002) will consist of:

- Single, pivotal Phase III clinical trial in uncomplicated urinary tract infection (Study 100346); plasma/urine samples incorporated as requested by FDA
- Label comprehension study
- Clinical Pharmacology program
  - Basic program: food effect studies, S-D and M-D pharmacokinetic studies compared to IR formulation
  - Drug interaction studies: antacid and omeprazole

Bayer

Pharmaceutical Division

January 15, 2002

Bayer

Ciprofloxacin Tablets

Agenda

Introduction :	***Andrew S. Verderame***
Clinical :	***Steven Kowalsky, Pharm.D.***
Discussion :	***All***

January 15, 2002

Bayer

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/s/

Rigoberto Roca
3/11/02 09:49:57 AM

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING

DATE: May 2, 2001

MEETING TYPE: End of Phase 2 Meeting

IND: —

DRUG: Cipro® —

BAYER ATTENDEES:
Anja Dingler, Quality Control Development
Horst-Dieter Friedel, Quality Control Development
Fritz Scheuekler, Quality Control Development
Wolfgang Weber, Quality Control Development
Austin Bebyn, Pharmaceutical Technology
Maryann Graham, Quality Assurance
Kim Parthum, Quality Assurance
Hans Scholl, Quality Assurance
John Lettieri, PhD, Deputy Director, Clinical Pharmacology
Gabriele Fischer, Associate Director, Project Management
Robin Christoforides, Assistant Director, Regulatory Affairs
Andrew Verderame, Deputy Director, Regulatory Affairs

FDA ATTENDEES:
Norman Schmuff, Ph.D., Chemistry Team Leader
Joette Meyer, Pharm D, Clinical Pharmacology and Biopharmaceutics Reviewer
Dorota Matecka, PhD, CMC Reviewer
Jouhayna Saliba, R Ph, Project Manager

BACKGROUND: An End of Phase II teleconference meeting with Bayer to discuss their CMC plans for Cipro® —

Discussion Items:

1. Bayer plans to submit 9 months of stability data on three primary stability batches for Cipro® — Tablets, 0.5 g and — Stability studies will continue and Bayer commits to provide updated stability reports upon request.

   The Division asked for clarification on the nine months stability data being submitted for Cipro® — Tablets, 0.5g and —

   Bayer plans to submit the nine months stability data for the 500mg tablets under the uncomplicated UTI indication and the —
   indication. Bayer will provide the updated stability reports without the Division's request.

2. The Primary stability data to be included in the future NDA are being generated on tablets without embossing and without printing. Product for the market will most likely be embossed with a unique identity mark. Based on the retardation principle of Cipro® tablets (as discussed in the briefing summary in section 3), Bayer considers this change minor, which would be covered by providing data from the first production batches for the commercial product with unique identity markings. Therefore, Bayer believes a bioequivalence study is not required and equivalency between the tablets with and without embossing will be demonstrated by in vitro dissolution testing.

   The Division is in agreement that a bioequivalence study is not required. In addition, we agree to the proposal for in vitro dissolution testing between the tablets with or without embossing. The Division also requested that full dissolution profiles using the F_2 similarity factor be submitted.

3. *The Division inquired about the dates of when the NDAs will be submitted.*

   Bayer will be submitting the NDA for the uncomplicated UTI by December 2001

Signature, minutes preparer: _____ **Date:** _____
Jouhayna Saliba R.ph., Project Manager

Conference Chair (or designated signatory): _____ **Date:** _____
Norman Schmuff, Ph.D., Chemistry Team Leader

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/s/

Norman Schmuff
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Rockville MD 20857

MEMORANDUM OF MEETING

DATE: February 13, 2001

MEETING TYPE: End of Phase 2 Meeting

IND: [redacted]

DRUG: Cipro [redacted]

BAYER ATTENDEES:

Carl Calcagni, R.Ph., Vice President, Regulatory Affairs
Paul MacCarthy, M.D., Vice President, Medical Affairs
Deborah Church, M.D., Director Anti-Infective Medical Affairs
Steven Kowalsky, Pharm.D., Ciprofloxacin Global Clinical Project Leader
Pavur Sundaresan, M.D., Director, Clinical Pharmacology
John Lettieri, Ph.D., Deputy Director, Clinical Pharmacology
Barbara Painter, Ph.D., Microbiology
Gabrielle Fischer, Project Management
Kim Parthum, Ph.D., Quality Assurance
Robin Christoforides, Regulatory
Andrew Verderame, Regulatory
John Warner, Statistics
Heino Stass, Ph.D., Clin. Pharmacology, Bayer Germany
Hans Diter Freidl, Ph.D., Chemistry, Bayer Germany

FDA ATTENDEES:

Mark Goldberger, M.D., M.P.H., Division Director, DSPIDP
Renata Albrecht, M.D., Deputy Director, DSPIDP
Rigoberto Roca, M.D., Medical Team Leader
Eileen Navarro, M.D., Medical Reviewer
Funmi Ajayi, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Peter Dionne, M.S., Microbiology Reviewer
Karen Higgins, Ph.D., Statistical Team Leader
Ruthanna Davi, Ph.D., Statistical Reviewer
Stephen Hundley, Ph.D., Pharm-Tox Reviewer

Shukal Bala, Ph.D., Microbiology Team Leader
Dorota Matecka, Ph.D., CMC Reviewer
Rosemary Johann-Liang, M.D., Medical Reviewer
Fonda Chen, Pharm.D., Clin. Pharm.& Biopharm Fellow
Valerie Jensen, R.Ph., Project Manager

BACKGROUND:
A meeting request for a Type B meeting dated November 28, 2000 was submitted by Bayer regarding —. This meeting request was received by the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) on November 29, 2000. Bayer sent a letter dated December 5, 2000 agreeing to a February 13, 2001 meeting date regarding this IND. This meeting is considered an End of Phase 2 meeting for the modified release formulation of ciprofloxacin studied under — A background package for this End of Phase 2 meeting was submitted January 23, 2001.

Discussion items during this meeting are duplicated below. Division comments are duplicated below in italics.

Discussion Item (1)
Since CIPRO — is bioequivalent in terms of AUC and the PK/PD parameters (e.g. AUIC and C_{max}/MIC) appear acceptable to achieve satisfactory efficacy and safety, then clinical pharmacology studies may be sufficient for approval of all urinary tract indications (including chronic bacterial prostatitis) without a need for large scale Phase III studies.

The Division stated that rate and extent of absorption are the required criteria for bioequivalence and that the trough (C_{min}) is an important consideration for antiinfective indications. The Division pointed out that although the AUCs of the immediate release (IR) ciprofloxacin and the modified release ciprofloxacin (MR) are comparable, there is a significant difference in the concentration at the end of the dosing interval which may be of clinical importance. Also the implications for clinical efficacy of a second peak concentration during a twenty-four hour period (as is obtained with the IR formulation dosed twice daily and is not obtained with the MR formulation) are unknown.

Bayer raised the issue of intravenous (IV) ciprofloxacin (the IV formulations were approved in 1990) being approved based solely on the fact that it demonstrated a comparable extent of systemic absorption (i.e., AUC) to the oral (IR) formulation.

The Division stated that 1) the pharmacokinetic profiles are comparable with the exception of a slight increase in C_{max} (which was considered not to pose a safety concern), and 2) the regimens for both the IV and oral immediate release ciprofloxacin formulations are the same. The Division has not found a precedent where a new formulation was approved based on bioequivalence to an approved formulation when the dosing frequency of the new formulation is not the same as the already approved formulation. Approvals for modified release formulations have in the past always relied on clinical confirmation of efficacy. The Division will require clinical data to confirm efficacy for the modified release formulation of ciprofloxacin.

Discussion Item (2)

Pharmacokinetic data from conventional CIPRO Tablets are considered to be relevant to special patient populations such as the renally impared, hepatically impaired, and elderly. Therefore, no additional special population PK studies are planned.

The Division agreed with Bayer's plan but asked for an interactions study with antacids due to the broader absorption window seen with the MR formulation.

Bayer agrees to perform an antacids study with this formulation.

The Division stated that the need for an interaction study involving proton pump inhibitors will be evaluated after review of literature information and/or data from Bayer.

Discussion Item (3)

If the Agency disagrees with item (1), Bayer would propose that a single clinical trial in both uncomplicated and
safety and efficacy data to support approval f

Bayer proposes submitting the NDA for the 500 mg tablet for uncomplicated UTI (uUTI) in December 2001 and

The Division commented that the cUTI data will be valuable in the decision to
The Division stated that the Division
n. The Division agreed to explore options, including the possibility of
o administratively handle

Discussion Item (4)

Bayer stated that the formulation will have a separate label (PI) from the already approved ciprofloxacin formulations.

Discussion Item (5)

As per the Statistical Considerations in the Guidance Document entitled, "Complicated Urinary Tract Infections and Pyelonephritis", a delta of 15% would be used.

The Division stated that there would be concerns if the formulation had a lower cure rate than the IR formulation and the lower limit of the 95% confidence interval of the difference was between 10-15%. The Division recommended that if Bayer thinks the lower limit will be close to 15%, they may want to consider increasing the sample size.

Discussion Item (6)

A labeling comprehension study would not be necessary for approval in light of:

- **Bioequivalent AUC**
- **Serum concentrations that are unlikely to be influenced by posture or ranitidine**

- **Potential off-label use would not pose an undue safety concern**
- **Bayer's plan to label the product appropriately for use only in UTI**

The Division stated concerns regarding a situation where the uncomplicated UTI indication may be approved before [redacted] indication and there would be the risk of a physician prescribing this formulation for [redacted] indication before the product has been approved [redacted]. The Division would request a physician labeling comprehension study if the [redacted] will not be approved at the same time as the uUTI indication. A labeling comprehension study is also requested by the Division in order to decrease the risk of this [redacted] formulation being [redacted]

Once Bayer has draft labeling and a proposed name and packaging for this product, the Division requests that these be submitted so that the Office of Post MarketingDrug Risk Assessment can be consulted. The Division discussed with Bayer what we meant by a "labeling comprehension study" and stated that this type of study would involve the proposed package and package insert and may involve focus groups of physicians and pharmacists to see if they understand the product's labeling. A pharmacist portion of this study may involve product name recognition and the assessment of whether a pharmacist realizes from a mock prescription for the [redacted] formulation that the [redacted] ciprofloxacin is a different formulation from conventional ciprofloxacin tablets. Such a study may also involve case studies which would test physicians' comprehension of what the [redacted] product is labeled for and assess the likelihood of whether a physician would use the product off-label after reading the product's proposed label.

<u>Discussion Item (7)</u>
Bayer proposed [redacted]

[redacted]

Signature, minutes preparer: _____ Date: _____

Conference Chair (or designated signatory): _____ Date: _____
Attachment/Handouts:
Overhead slides :

/s/

Mark Goldberger
3/1/01 03:08:36 PM

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Number of Pages Redacted 103

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103

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-473 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: March 5, 2002 Action Date: December 13, 2002

HFD-590 Trade and generic names/dosage form: CIPRO® XR (ciprofloxacin extended release tablets)

Applicant: Bayer Corporation Therapeutic Class: quinolone

Indication(s) previously approved: uncomplicated urinary tract infection

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Uncomplicated urinary tract infection

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: ___Partial Waiver __X__Deferred ___Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: 0-16 years

Min ____	**kg____**	**mo.____**	**yr. 0____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr. 16___**	**Tanner Stage____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- **X There are safety concerns**
- **X Adult studies ready for approval**
- **X Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): December 31, 2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jouhayna S. Saliba, Pharm.D.
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ction D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Jouhayna Saliba
2/10/03 03:08:24 PM

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Pediatric Studies Waiver Request

Pursuant to 21 CFR 314.55 (c), Bayer Corporation Pharmaceutical Division requests a full waiver of the assessment of the efficacy and safety of Cipro — Tablets in the pediatric population.

Cartilage lesions have been demonstrated in the weight bearing joints of immature dogs given ciprofloxacin. This is a class effect of all quinolones. The WARNINGS section of the proposed package insert cautions against the use of this product in pediatric patients. Definitive statements concerning if this effect manifests itself in human pathology cannot be made presently. Ongoing ciprofloxacin trials (reference Ciprofloxacin Oral Suspension ———) being conducted by Bayer should provide additional information on this subject. It is anticipated that Bayer will report the results of these studies to the Division in September, 2003.

Ciprofloxacin is an extremely bitter drug substance. —

Therefore, Bayer requests a full waiver for the assessment in pediatric patients for this NDA. We do commit, however, to include the relevant information gained from the ongoing studies being conducted under ——— ' in the Cipro — package insert.