

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-744

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

DEPOMED, INC.

Enhancing Pharmaceuticals

JULY 14, 2004

DEPOMED, INC.'S SECTION 505(b)(2) PARAGRAPH II CERTIFICATION FOR CIPROFLOXACIN GR™, TABLETS 500 MG

Paragraph II Certification Statement:

Depomed, Inc. is submitting herewith a New Drug Application ("NDA") with the Food and Drug Administration ("FDA") directed to 500 mg oral tablets of gastric retentive ciprofloxacin hydrochloride ("Ciprofloxacin GR").

Depomed's NDA is being filed primarily under Section 505(b)(1) of the Food, Drug, and Cosmetics Act ("the Act") (referred to hereinafter as "505(b)(1) Application"; codified at 21 U.S.C. § 355(b)(1)) and secondarily under Section 505(b)(2) of the Act (referred to hereinafter as "505(b)(2) Application"; codified at 21 U.S.C. § 355(b)(2)). The instant Paragraph II Certification is submitted for Depomed's 505(b)(2) Application to satisfy the requirements of Section 505(b)(2)(A)(vii)(II) of the Act.

The patent at issue in Depomed's Paragraph II Certification is U.S. Patent No. 4,670,444 ("the '444 Patent"), which is listed in the FDAs *Approved Drug Products with Therapeutic Equivalent Evaluations* reference database ("the Orange Book") under the following NDA numbers: NDA No. 019537, which is directed to FDA approved ciprofloxacin hydrochloride oral tablets in 100 mg, 250 mg, 500 mg, and 750 mg doses; and NDA No. 021473, which is directed to ciprofloxacin hydrochloride extended release oral tablets in 500 mg and 1000 mg doses.

To the best of Depomed's knowledge, the '444 Patent is owned by Bayer AG, and the holder of both NDA No. 019537 and NDA No. 021473 is Bayer Pharmaceuticals, a division of Bayer AG.

According to the Orange Book, the '444 Patent expired on December 9, 2003, and the pediatric exclusivity for the '444 Patent expired on June 9, 2004.

In light of the expiration of the '444 Patent and expiration of the pediatric exclusivity of the '444 Patent, Depomed hereby certifies, pursuant to Paragraph II of 21 U.S.C. § 355(b)(2)(A)(vii), that in its opinion and to the best of its knowledge, the '444 Patent does not prohibit Depomed's manufacture, use, or sale of Ciprofloxacin GR.

Pursuant to the Act, it is understood that this Paragraph II Certification only applies in the event that Depomed's NDA is approved as a Section 505(b)(2) Application. Should Depomed's NDA be approved as a 505(b)(1) Application, this Paragraph II Certification will have no legal effect.

Sincerely yours,



Bret Berner, Ph.D
Vice President, Product Development

1360 O'Brien Drive
Menlo Park, CA 94025-1436
T. 650. 462-5900
F. 650. 462-9993

www.depomedinc.com

DEPOMED, INC.

Enhancing Pharmaceuticals

JULY 14, 2004

DEPOMED, INC.'S SECTION 505(b)(2) PARAGRAPH IV CERTIFICATION FOR CIPROFLOXACIN GRTM, TABLETS 500 MG

Paragraph IV Certification Statement:

Depomed, Inc. is submitting herewith a New Drug Application ("NDA") with the Food and Drug Administration ("FDA") directed to 500 mg oral tablets of gastric retentive ciprofloxacin hydrochloride ("Ciprofloxacin GR").

Depomed's NDA is being filed primarily under Section 505(b)(1) of the Food, Drug, and Cosmetics Act ("the Act") (referred to hereinafter as "505(b)(1) Application"; codified at 21 U.S.C. § 355(b)(1)) and secondarily under Section 505(b)(2) of the Act (referred to hereinafter as "505(b)(2) Application"; codified at 21 U.S.C. § 355(b)(2)). The instant Paragraph IV Certification is submitted for Depomed's 505(b)(2) Application to satisfy the requirements of Section 505(b)(2)(A)(vii)(IV) of the Act.

The patent at issue in Depomed's Paragraph IV Certification is U.S. Patent No. 5,286,754 ("the '754 Patent"), which is listed in the Food and Drug Administration's ("FDA's") *Approved Drug Products with Therapeutic Equivalent Evaluations* reference database ("the Orange Book") under NDA No. 019537, which is directed to FDA approved ciprofloxacin hydrochloride oral tablets in 100 mg, 250 mg, 500 mg, and 750 mg dosages.

To the best of Depomed's knowledge, the '754 Patent is owned by Bayer AG and the holder of NDA No. 019537 is Bayer Pharmaceuticals, a division of Bayer AG.

According to the Orange Book, the '754 Patent expires on February 15, 2011, and the pediatric exclusivity for the '754 Patent expires six months later on August 15, 2011.

Depomed hereby certifies, pursuant to Paragraph IV of 21 U.S.C. § 355(b)(2)(A)(vii), that in its opinion and to the best of its knowledge, the '754 Patent is not infringed by Ciprofloxacin GR and therefore, the '754 Patent does not prohibit Depomed's manufacture, use, or sale of Ciprofloxacin GR.

In the event that Depomed's NDA is approved as a 505(b)(2) Application, then pursuant to 21 C.F.R. §§ 314.95(b) and (c), Depomed will provide notice of the filing to Bayer AG, as the owner of the '754 Patent, and Bayer Pharmaceuticals, as the holder of NDA No. 019537, upon receipt of the FDA's acknowledgement letter that Depomed's NDA for Ciprofloxacin GR has been accepted as a 505(b)(2) Application. As provided in the regulations, such notice will be provided with proof of receipt. 21 C.F.R. § 314.95(e).

Pursuant to the Act, it is understood that this Paragraph IV Certification only applies in the event that Depomed's NDA is approved as a Section 505(b)(2) Application. Should Depomed's NDA be approved as a 505(b)(1) Application, this Paragraph IV Certification will have no legal effect.

Sincerely yours,



Bret Berner, Ph.D
Vice President, Product Development

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EXCLUSIVITY SUMMARY

NDA # 21-744

SUPPL #

HFD # 590

Trade Name Proquin XR Tablets, 500 mg

Generic Name ciprofloxacin extended-release tablets, 500 mg

Applicant Name Depomed, Inc.

Approval Date, If Known May 19, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#	19-537	Cipro (ciprofloxacin hydrochloride) Tablets, 250 mg, 500 mg and 750 mg
	20-780	Cipro (ciprofloxacin) Oral Suspension, 250 mg/5 mL and 500 mg/5 mL
NDA#	19-847	Cipro IV (ciprofloxacin) 1% Solution Vials, 200 mg, 400 mg and 120 mg
	19-857	Cipro IV (ciprofloxacin) 0.2% Solution in 5% Dextrose, 200 mg and 400 mg
NDA#	21-473	Cipro XR (ciprofloxacin extended-release tablets), 500 mg and 1 gm

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

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

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

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

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Investigation# 1 Study81-0005: Randomized, Double Blind (Double Dummy), Parallel Group Pilot Study to Assess the Comparative Efficacy, Safety, and Tolerability of Once Daily Extended Release (GR) and Twice Daily Immediate Release (IR) Ciprofloxacin Formulations in Female Patients with Uncomplicated Urinary Tract Infections (UTI)

Investigation#2 Study 81-0015: Randomized, Double Blind, Parallel Group Study to Compare the Safety and Efficacy of Ciprofloxacin Gastric Retentive (GR) QD and Ciprofloxacin Immediate Release (IR) BID in the Treatment of Uncomplicated in Female Urinary Tract Infections

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

IND # 62,386

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

! NO

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! 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

If yes, explain:

Name of person completing form: Yon Yu, Pharm D.

Title: Regulatory Project Manager

Date: May 18, 2005

Name of Office/Division Director signing form: Renata Albrecht, M.D.
Title: Director, Division of Special Pathogen and Immunologic Drug Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**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
5/19/05 04:15:20 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-744 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: July 19, 2004 Action Date: May 19, 2005

HFD-590

Trade and generic names/dosage form: Proquin XR (ciprofloxacin hydrochloride) Extended-Release Tablets, 500 mg

Applicant: Depomed, Inc. Therapeutic Class: Antibacterial-Quinolone

Indication(s) previously approved: None

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

Number of indications for this application(s): 1

Indication #1: Treatment of uncomplicated urinary tract infections caused by *Escherichia coli* and *Klebsiella pneumoniae*

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
- X Too few children with disease to study. (The drug has not been developed for complicated UTI which is the prevalent condition in pediatric patients.)
- X There are safety concerns. (The efficacy in adults is not encouraging for use for more severe disease.)
- X Other: uUTI does not exist in pediatric males (0 to 17 yrs of age) and is rare in pre-menarchal pediatric females. The use of Proquin XR for the treatment of uUTI in post-menarchal pediatric females can support the extrapolation of the clinical trial data from adult women.

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
 - 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.

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}

Regulatory Project Manager

cc: NDA 21-744
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 12-22-03)**

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

/s/

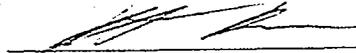
Yon C. Yu
5/19/05 04:57:19 PM

Depomed, Inc.
Debarment Certification

NDA: 21-744

DEBARMENT CERTIFICATION

Depomed, Inc. hereby certifies 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.

 6-25-04

Bret Berner
Vice President, Product Development

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-744	Efficacy Supplement Type: N/A	Supplement Number: N/A
Drug: Proquin XR (ciprofloxacin HCl) Extended-Release Tablets		Applicant: DepoMed, Inc.
RPM: Yon Yu, Pharm.D.		HFD-590 Phone # 301-796-1600
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> Confirmed and/or corrected		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): n/a
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		May 19, 2005
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number <u>4804</u>
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.		<input checked="" type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary 	May 19, 2005
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" 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)	May 19, 2005
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	none
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	(X) Yes () No
<ul style="list-style-type: none"> 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))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	May 18, 2005
<ul style="list-style-type: none"> Original applicant-proposed labeling 	July 18, 2004
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	DMETS September 8, 2004 DSRCS April 4, 2005 DSRCS April 8, 2005
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	n/a
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Applicant proposed 	May 18, 2005 July 18, 2004
<ul style="list-style-type: none"> Reviews 	Please see Labeling Reviews above
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	N/A
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	July 1, 2002
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	February 5, 2004
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	N/A
<ul style="list-style-type: none"> Other 	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	May 19, 2005
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	May 18, 2005
❖ Microbiology (efficacy) review(s) (indicate date for each review)	December 9, 2004
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	N/A
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	March 25, 2005
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	May 19, 2005 (2)
❖ Statistical review(s) (indicate date for each review)	May 4, 2005
❖ Biopharmaceutical review(s) (indicate date for each review)	May 18, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	May 12, 2005
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	May 18, 2005 (2)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	May 18, 2005
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: May 19, 2005 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	May 10, 2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

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

/s/

Rebecca Saville
1/16/2007 08:23:10 AM

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO
 If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? YES NO

• Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

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

• If an electronic NDA, does it follow the Guidance? N/A YES
 NO
If an electronic NDA, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A YES NO

• Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information submitted on form FDA 3542a? YES NO

• Exclusivity requested? YES, _____ years NO
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,

"[Name of applicant] hereby certifies 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." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
 (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? 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: 63,
- End-of-Phase 2 Meeting(s)? Date(s) July 1, 2002
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) February 5, 2004
- If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A YES NO

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

- Name of listed drug(s) and NDA/ANDA #
- 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”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) 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)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). 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? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- 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): The patent on the listed drug is 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. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application,

• 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?

N/A YES NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

• EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to

approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A 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: August 30, 2004

BACKGROUND:

At the time of EOP2 meeting in July of 2002, Depomed's plan for their drug product (an extended-release formulation of ciprofloxacin) was a 505(b)(2) submission. However, subsequent to the EOP2 meeting, on August 16, 2002, the sponsor submitted a letter requesting the Division's comments on their decision to submit a 505(b)(1) NDA for the drug product for the treatment of uncomplicated urinary tract infection. On January 27, 2003, the Division discussed with Depomed via teleconference the requirements for a 505(b)(1) NDA and informed the sponsor of additional studies necessary for their application to be considered under a 505(b)(1) approval.

During the Pre-NDA meeting on February 5, 2004, the issue of 505(b)(1) vs. 505(b)(2) regarding Depomed's planned NDA was raised. It was stated during the meeting that to be considered for a 505(b)(1) NDA, the application must rely exclusively on studies that Depomed conducted, that were conducted for Depoemd, or for which Depomed has the right of reference. It was agreed that the regulatory discussion of 505(b)(1) vs. 505(b)(2) will be tabled for another time to include the participants of the Agency's legal counsel.

Subsequent to the Pre-NDA meeting and again during the NDA filing, the Division sought advice and guidance from Office of Regulatory Policy to accurately determine the type of 505(b) submission Depomed's application is. The Division was advised to delineate the information that is essential to approval and if any portion of the essential information is relied on studies that Depomed did not conduct, that were not conducted for Depoemd, or for which Depomed does not have the right of reference to, the NDA is a 505(b)(2).

Upon review of the NDA submission and discussions, the submitted NDA is being filed as a 505(b)(1).

ATTENDEES:

In addition to the reviewers listed below, Renata Albrecht, Steve Gitterman, David Roeder, Eileen Navarro, Mark Seggel, Phil Colangelo, Shukal Bala, Karen Higgins.

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Meyer
Secondary Medical:	
Statistical:	Dixon
Pharmacology:	Hundley
Chemistry:	Matecka
Environmental Assessment (if needed):	
Biopharmaceutical:	Gieser
Microbiology, sterility:	Dionne
Microbiology, clinical (for antimicrobial products only):	

DSI:
 Regulatory Project Management:
 Other Consults:

Inspection Requested to DSI via Karen Storm
 Yu

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain:

CLINICAL FILE _____ REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY NA _____ FILE X _____ REFUSE TO FILE _____

STATISTICS FILE X _____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE X _____ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE X _____ REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE X _____ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
 Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

X _____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

X _____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Regulatory Project Manager, HFD-590

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/s/

Yon C. Yu
5/19/05 06:59:29 PM
CSO

MEMORANDUM

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

DATE: May 11, 2005

FROM: Karen M. Storms, Consumer Safety Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

THROUGH: Leslie K. Ball, M.D., Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Clinical Inspections Summary - NDA 21-744

TO: Yon Yu, Regulatory Project Manager
Joette Meyer, Ph.D., Medical Officer
Division of Special Pathogens and Immunologic Drug Products, HFD-590

APPLICANT: Depomed, Inc.

DRUG: Proquin (ciprofloxacin HCl)

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment for uncomplicated urinary tract infections (acute cystitis)

ACTION GOAL DATE: May 19, 2005

I. BACKGROUND:

Ciprofloxacin is a fluoroquinolone anti-infective agent with a broad spectrum of efficacy against both gram-negative and gram-positive bacteria. Ciprofloxacin hydrochloride has been marketed by Bayer Corporation under the name CIPRO™ (referred to as ciprofloxacin immediate release [IR]) since its approval in 1987. CIPRO™ is indicated for the treatment of urinary tract infections caused by many strains of microorganisms. A once daily 500 mg tablet of ciprofloxacin in a bilayer formulation combining immediate release and sustained release components has been recently introduced for the treatment of uncomplicated urinary tract infections.

DepoMed's ciprofloxacin gastric retentive (GR™) tablets are an extended release formulation of

ciprofloxacin that delivers 90% of the 500 mg dose to the upper gastrointestinal (GI) tract within 6 hours. The upper GI tract is also where ciprofloxacin is best absorbed. To accomplish the sustained delivery, the tablet is designed to swell in the stomach to allow the _____ e to release the drug. While the digestive system is active (in the fed mode), this combination of polymeric swelling _____ maintains the size of the tablet so that it will be retained in the stomach as the meal is digested. This enables delivery of ciprofloxacin to the upper GI tract throughout the 6 hour duration of this process. A concern associated with extended delivery of any antibiotic, including ciprofloxacin is the delivery of the antibiotic to the colon. The introduction of an antibacterial agent alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one of the primary causes of “antibiotic-associated colitis”.

The potential advantage of ciprofloxacin GR tablets is that dosing may be reduced to 1 dose of ciprofloxacin GR/day compared to 2 doses of ciprofloxacin IR/day.

This is a Phase III, multicenter study designed to compare the efficacy and safety of ciprofloxacin GR, 500 mg qd for 3 days and ciprofloxacin IR, 250 mg bid for 3 days, in the treatment of acute, uncomplicated UTI. The duration of the study was approximately 6 weeks. To obtain 576 evaluable subjects (based on positive urine microbiology and uropathogen susceptibility testing), approximately 960 adult females with the onset of clinical signs and symptoms of acute, uncomplicated UTI within the previous 72 hours were eligible for screening. Subjects enrolled in the study and later determined not to have met the inclusion criteria for positive urine microbiology and uropathogen susceptibility testing were not withdrawn. These subjects were only used for the safety analyses.

The following sites were selected to validate data submitted in support of the pending application.

II. RESULTS (by site):

<u>Name</u>	<u>City</u>	<u>State</u>	<u>IN</u>	<u>Assigned</u>	<u>Action Date</u>	<u>Reviewer</u>	<u>Class</u>
Larsen	Middletown	NJ	DA	14-Feb-05	11-May-05	KMS	NAI
Mazzone	San Luis Obispo	CA	DA	14-Feb-05	10-May-05	KMS	VAI
Rosen	Winston-Salem	NC	DA	14-Feb-05	10-May-05	KMS	NAI

Scott L. Larsen, M.D., FACEP

This site enrolled 49 subjects with 10 subjects lost to follow-up and one subject was a treatment failure. Records reviewed included drug accountability, case report forms; source documents; laboratory reports; medical histories. All subjects received adequate informed consent.

Frank Mazzone, M.D.

This site screened 46 subjects with 41 subjects enrolled and completed the study. There were 2 subjects that withdrew consent; 1 early termination and 2 subjects were lost to follow-up. Twenty subjects' records were reviewed comparing source documents with the corresponding case report form. All records appeared to be in order. All subjects received adequate informed consent.

Although there was no Form FDA 483 issued, the inspection is classified VAI for a minor protocol violation; at least one subject did not have all baseline laboratory tests completed and assessed prior to enrollment.

Robert D. Rosen, M.D.

This site screened 50 subjects with 47 subjects enrolled and 46 completing the study. Records reviewed included drug accountability, case report forms; source documents; laboratory reports; medical histories. All subjects received adequate informed consent.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

No major deficiencies were noted in the three sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable. No subsequent actions or follow up inspections should be undertaken.

There were no limitations to these inspections.

Key to Classification:

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

VAI-r = Deviation(s) from regulations, response requested. Data acceptable

OAI = Significant deviations from regulations. Data unreliable

Karen M. Storms

Concurrence:

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47

cc:

HFD-45

HFD-47 Storms

Page 4 – NDA 21-744 Inspection Summary

HFD-47/rf/cf

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/s/

Karen Storms
5/11/05 01:40:13 PM
TECHNICAL

Leslie Ball
5/12/05 09:58:32 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: April 8, 2005

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

VIA: Yon Yu, Pharm D., Regulatory Project Manager,
Division of Special Pathogen and Immunologic Drug Products,
HFD-590

FROM: Toni Piazza-Hepp, Pharm.D., Deputy Director
Jeanine Best, M.S.N., R.N., P.N.P., Patient Product Information
Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Label Comprehension Study for Proquin
(ciprofloxacin HCL extended-release tablets, 500 mg)
NDA 21-744

Background

Depomed submitted a "proposed outline" for Stage 2 of a Label Comprehension Study as part of the 3rd amendment to the Proquin NDA on November 23, 2004.

A Stage 1 Study was previously completed by the sponsor consisting of interviews with 18 health care professionals (6 pharmacists, 6 private care practitioners, 6 gynecologists). No details were provided in the current submission on the objectives, methodology or results of the Stage 1 study, although the sponsor states that the preliminary information gathered were used as a basis for Stage 2. The Stage 1 format was described as interviews and an explanation of the label.

The focus of the current submission is the Stage 2 Label Comprehension Study, which was in progress at the time of the submission. It is possible that more interviews will be conducted in a Stage 3 study, depending on the consistency of findings in the previous stages.

Methodology

Communication Objectives

Communication objectives are the key messages to be tested (ones that the reader should be able to comprehend). Although not clearly stated as communication objectives for the study, the sponsor states that "it is important that the prescribers, pharmacists and patients understand the appropriate directions for use". The specific directions noted under the "Basis" section of the submission are:

- needs to be taken with a substantial meal;
- should not be taken more than once per day;
- should not be taken with milk products alone;
- should not be taken with aluminum, magnesium or calcium-containing antacids.

Comment: These are appropriate messages to test with regard to proper use of Proquin; the message that Proquin should be taken whole (not crushed or chewed), another important message relating to directions for use, was not tested.

Subjects

Five groups are targeted: 14 patients (with a UTI in the past year), 8 gynecologists, 8 "private care practitioners" (PCPs), 10 gynecologist nurse practitioners and 5 retail pharmacists. Interviews of these groups will be conducted in a research facility in a northern urban city (e.g. Philadelphia).

Comment: It is not stated how these subjects are being recruited or if the interviews are being conducted separately or in focus groups. Further, the sponsor notes that "patients selected for this study should have a relatively low level of health literacy", however, it is not stated how this would be determined, as there is no mention that patients were to be tested for literacy level. The sample of subjects is not designed to be representative of all potential users of Proquin.

Labeling for Testing

There are three versions of "Product X labeling" in the submission: Version M, Version N and an unidentified version. In addition, there are two other pieces of information that presumably were used during the interview process; one titled "Product X Profile" and the other "How product X release mechanism works: Version 2".

Comment: It is not noted which versions were used as label examples for which groups of subjects.

Discussion Guide

A guide for how the interviewers should conduct the session, including the questions to use for each session is included in the sponsor's submission. The questions are open-ended (as opposed to yes/no, multiple choice, etc.). For each group, the following types of questions are asked:

Patients: There are three "background" questions about attitude toward doctors, what the patient suffers from and where do they get their information. Then 14 questions are asked relating to symptoms of UTI, advice they receive from their doctor, the type of doctor they go to, the

medicines that they use, side effects, and others. Then the patients are to be shown two versions of the label, and are to be “probed” on what seven of the instructions mean to them, along with three additional questions addressing preferences for one label or the other.

Pharmacists: There are 20 “background” questions about their pharmacy practice, experiences with explaining information to patients, patients’ medication preferences, information on extended-release formulations (how often dispensed, who prescribes them and perceived advantages) and others. Then seven questions are asked about UTIs (how many patients they see, medications prescribed or recommended OTC, and others). Six questions are specifically asked about a competitor’s product, Cipro XR (impressions for UTI, how many prescriptions, what else it is prescribed for besides UTI, etc.). Four questions are then asked about the Product X Product Profile. Finally, seven questions are asked about the directions for use. These questions relate to the pharmacists’ impressions of the instructions and how comfortable they would be explaining these directions to patients. The interview ends with four questions which do not relate to instructions for use.

Nurse Practitioners and Gynecologists: The questionnaire sequence and content is very similar to the pharmacists with added questions on the patient visit, interaction with patients from a prescriber’s perspective and prescribing habits regarding uncomplicated UTI (including impressions of Cipro XR). As with pharmacists, seven questions are asked about directions for use.

Comments:

- *The majority of questions appear to be tailored at gaining information for marketing purposes, such as patient’s UTI experiences and care-seeking habits, practice and prescribing habits, and use of a competitor’s product. A minority of the questionnaire is focused on gathering information relating to the study’s communication objectives (comprehension of the labeling directions).*
- *Questions posed to the health care professionals about directions for use centered on how they might explain these directions to a patient. It might have been more useful to test alternate labels in a larger group of patients with varying literacy levels if the purpose of the study was to gauge patients’ comprehension of certain words and phrases.*

Summary of Comments

- The majority of this “label comprehension study” appears to be aimed at gaining information for marketing purposes as opposed to achieving the communication objectives related to improving patient understanding of directions for use.
- The study should only be expected to gain some qualitative information that might be used to improve directions for use in future patient labeling, since questions are open-ended, only the minority of questions relate to the communication objectives and the subjects are not representative of potential users of Proquin.
- Patient comprehension questions are asked of the healthcare providers; patient comprehension can only be determined by testing patients of varying demographic and literacy levels.
- The results of the study are not included, so it is not known if information from Stage 1 and 2

have been utilized in any updates of the patient package insert (PPI), since the latest version submitted to the Agency (July 18, 2004) predates this label comprehension study (November 23, 2004).

- Patients will have no chance to comprehend and use important patient information unless it is actually received. As noted in our April 4 review of the patient package insert (PPI), the sponsor should strongly consider a 3-tablet unit-of-use package that includes the PPI.

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/s/

Toni Piazza Hepp
4/8/05 12:48:48 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 7, 2005

To: Ms. Hayley Welton Regulatory Affairs	From: Yon Yu, Pharm D. Regulatory Project Manager
Company: DepoMed, Inc.	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: (650) 462-9997	Fax number: (301) 827-2475
Phone number: (650) 462-5900 ext. 302	Phone number: (301) 827-2195
Subject: NDA 21-744 Request for CMC-related information	

Total no. of pages including cover: 3

Comments: If you have any questions, please contact Yon Yu at 301-827-2195.

Document to be mailed: • YES NO

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We have completed reviewing the Chemistry, Manufacturing, Controls section of ciprofloxacin HCl and have the following request.

Questions to the sponsor:

1. Please indicate if impurity ~~—~~ was monitored in the stability studies and the levels, if any, observed. Please also comment on the origin of the impurity (process impurity vs. degradant).

2. Please clarify if the tablets are debossed
3. Please provide details on dissolution studies which you may have conducted to investigate the effects, if any, on debossing the tablet. Please provide data from these studies.
4. Please provide details on the proposed commercial configurations and the container closure for the same.
5. Please indicate the requested expiry date for the commercial packaging and for the blister pack (physician sample).
6. Please tighten the acceptance level of total known/unknown impurities in the drug product regulatory specification.
7. Please clarify which commercial packaging will be manufactured. In the "How Supplied" section of the proposed package insert, the bottles of 50 are mentioned. However, in the NDA submission bottles of counts are mentioned. We note that stability studies were conducted only on the count bottles and for the blister packs; however the proposed container labels are for 50 counts.

If you have any questions regarding this information request, please call me at 301-827-2195.

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/s/

Yon C. Yu
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MEMORANDUM

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

DATE: April 4, 2005

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

VIA: Yon Yu, Pharm D., Regulatory Project Manager,
Division of Special Pathogen and Immunologic Drug Products,
HFD-590

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review Patient Information for Proquin (ciprofloxacin
HCL extended-release tablets, 500 mg), NDA 21-744

Summary

The patient labeling which follows represents the revised Patient Package Insert (PPI) for Proquin (ciprofloxacin HCL extended-release tablets, 500 mg), NDA 21-744. We have simplified the wording, made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on labeling (PI) submitted by the sponsor on July 18, 2004. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendation

We also have the following comments and recommendations:

1. All patient materials should be written at a 6th to 8th grade reading comprehension level. The

reading ease score should be 60% or greater which corresponds with an 8th grade reading level. Approximately 50% of the U.S. adult population functions at a lower literacy level and reads below an 8th grade reading level. The proposed PPI has a Flesch-Kincaid Reading Level of 10.1 and a Flesch Reading Ease of 49.1 %. To improve these scores, and enhance comprehension to a broader population, including those with lower literacy, we have simplified language, shortened sentences, and removing unnecessary information throughout the document. Our revisions provide a Flesch-Kincaid Reading Level of 7.4 and a Flesch Reading Ease of 62.8 %.

2. The patient is unlikely to receive this patient information unless their prescription is dispensed in unit-of-use packages with the patient information enclosed. PPIs (with the exception of estrogen-containing and Oral Contraceptive products) are voluntary and there is no requirement for their printing or distribution. Proquin XR is indicated for uncomplicated UTI as a once-per-day 3 day regimen. The sponsor should strongly consider a 3 tablet unit-of-use package with the PPI enclosed.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

**APPEARS THIS WAY
ON ORIGINAL**

PATIENT INFORMATION

A

3 Page(s) Withheld

 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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/s/

Jeanine Best
4/4/05 01:59:47 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
4/4/05 04:06:41 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan



MEMORANDUM

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

DATE: March 24, 2005

TO: Renata Albrecht, M.D., Director
Division of Special Pathogen Drug Products, HFD-590

FROM: Claudia B. Karwoski, Pharm.D.,
Scientific Coordinator for Risk Management Programs (detail)
Office of Drug Safety, HFD-400

DRUG: Ciprofloxacin GRTM 500mg (Ciprofloxacin HCL Extended Release
Tablets)

NDA #: 21-744

APPLICANT: Depomed, Inc.

SUBJECT: Review of Proposed Risk Management Plan; submitted July 18, 2004

PID #: D050141

The sponsor's proposed Risk Management Plan for Ciprofloxacin GRTM; NDA 21-774, does not appear to differ substantially from typical new product labeling and routine passive post-marketing safety surveillance.

Ciprofloxacin GRTM (C-GR) is a once-daily extended release tablet that is a new formulation of the immediate release ciprofloxacin; an approved product already on the U.S. market. The proposed indication is for the 3-day treatment of patients with uncomplicated urinary tract infection (UTI). According to the sponsor's submission, C-GR is designed to deliver 90% of the dose to the upper gastrointestinal (GI) tract where ciprofloxacin is absorbed best, which in turn would reduce the amount of drug released in the upper GI tract, thereby reducing the GI adverse events. A reduction in GI AEs was observed in the Phase II and III clinical trials (2.9% for C-GR versus 5.6% for C-IR; p=0.35). The remaining safety profile was consistent with the safety profile of immediate release ciprofloxacin.

To preserve the pharmacokinetic profile of C-GR, patients will be required to adhere to specific instructions for administration. These include 1) taking C-GR with a —

meal; 2) taking no more than 1 tablet per day; 3) swallowing the tablet whole (no cut, crushing, or chewing); 4) not taking with milk or calcium-fortified juices; and 5) avoiding concomitant intake of antacids containing aluminum, magnesium, or calcium.

The Sponsor's submission does not identify any unique safety issues with this extended release product for which a Risk Minimization Action Plan (RiskMAP) to minimize risk would be normally associated. We also note that the immediate release product, marketed for approximately 30 years, has not to date required risk management tools beyond standard product labeling. If the sponsor or the Review Division identifies a safety concern and determines that a RiskMAP is warranted, please refer to the guidance documents Development and Use of Risk Minimization Action Plans:

<http://www.fda.gov/cder/guidance/6358fn1.htm> and

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:

<http://www.fda.gov/cder/guidance/6359OCC.htm> .

Should the review division want ODS to review a future RiskMAP submission please send a consult to ODS and notify the ODS-IO Project Manager, Mary Dempsey, at 301-827-3213.

Claudia B. Karwoski, Pharm.D.,
Office of Drug Safety, HFD-400

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

/s/

Mary Dempsey
3/24/05 03:52:16 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
3/25/05 09:57:44 AM
DRUG SAFETY OFFICE REVIEWER

45-DAY MEETING
Fileability Checklist
NDA 21-744
— CLINICAL —

Based on your initial overview of the NDA submission:	Yes	No	N/A
1. On its face, is the clinical section of the NDA organized in a manner to allow a substantive review to begin? (See 21 CFR §314.50(d)(5).)	X	<input type="checkbox"/>	<input type="checkbox"/>
2. Is the clinical section of the NDA indexed and paginated in a manner to allow a substantive review to begin? (See 21 CFR §314.50.)	X	<input type="checkbox"/>	<input type="checkbox"/>
3. On its face, is the clinical section of the NDA legible so that a substantive review can begin?	X	<input type="checkbox"/>	<input type="checkbox"/>
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X	<input type="checkbox"/>	<input type="checkbox"/>
5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	X	<input type="checkbox"/>	<input type="checkbox"/>
6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X	<input type="checkbox"/>	<input type="checkbox"/>
7. Are all data sets for pivotal efficacy studies complete for all indications requested?	X	<input type="checkbox"/>	<input type="checkbox"/>
8. Do all pivotal efficacy studies appear to be adequate and well controlled within current FDA (see 21 CFR §314.126) and divisional/office policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X	<input type="checkbox"/>	<input type="checkbox"/>
9. Has the applicant submitted case report tabulations (CRT; line listings and patient profiles) in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in a format agreed to previously by the Division? If the CRTs were submitted electronically, are they consistent with CDER's Guidance for Industry – Archiving Submissions for Electronic Format — NDAs?	X	<input type="checkbox"/>	<input type="checkbox"/>
10. Has the applicant submitted a rationale for assuming the applicability of foreign data (disease specific) to the US population?	<input type="checkbox"/>	<input type="checkbox"/>	X

Based on your initial overview of the NDA submission: Yes No N/A

11. Has the applicant submitted all additional required case report forms (CRF) (beyond deaths and dropouts) previously requested by the Division? X

12. If CRFs were submitted electronically, are they consistent with CDER's Guidance for Industry - Archiving Submissions for Electronic Format — NDAs? X

13. Has the applicant presented safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? X

14. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? X

15. Has the applicant submitted draft labeling consistent with 21 CFR §201.56 and §201.57, current divisional/office policies, and the design of the development package? X

16. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? X

17. From a clinical perspective, is this NDA fileable? If "no", please state why it is not. (Use additional sheet of paper if needed.) Yes

18. If certain claims are not fileable, please state which claims they are and why they are not fileable. (Use additional sheet of paper if needed.) _____

Clinical Reviewer (sign & date)

Medical Team Leader (sign & date)

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

/s/

Joette Meyer
9/8/04 10:38:26 AM
MEDICAL OFFICER

Eileen Navarro
9/10/04 04:03:36 PM
MEDICAL OFFICER



SEP 7 2004

Food and Drug Administration
Rockville MD 20857

Bret Berner, Ph.D.
Vice President, Product Development
Depomed, Inc.
1360 O'Brien Drive
Menlo Park, CA 94025-1436

**RE: Depomed, Inc., Small Business Waiver Request 2004.040 for NDA 21-744,
Proquin XR (Ciprofloxacin HCl Extended Release Tablets)**

Dear Dr. Berner:

This responds to your May 11, 2004, letter requesting a waiver of the human drug application fee for new drug application (NDA) 21-744 for Proquin XR (ciprofloxacin HCl) extended release tablets under the small business waiver provision, section 736(d)(1)(D)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2004.040). For the reasons described below, the Food and Drug Administration (FDA) grants Depomed, Inc.'s (Depomed's), request for a small business waiver of its application fee for NDA 21-744 for Proquin XR.

According to your waiver request, Depomed is a small business with _____ employees. You stated Depomed does not have any affiliates. You noted Depomed does not have a prescription drug product introduced or delivered for introduction into interstate commerce, and you do not expect to introduce a prescription drug product within the next 12 months. You anticipated submission of NDA 21-744 within 90 days of your waiver request.

Under section 736(d)(3)(B) of the Act,² a waiver of the application fee is granted to a small business for the first human drug application that a small business or its affiliate³ submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant Depomed's request for a small business waiver for NDA 21-744 for Proquin XR is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated July 9, 2004, that Depomed has fewer than 500

¹ 21 U.S.C. 379h(d)(1)(D) (previously 21 U.S.C. 379h(d)(1)(E) until amended by the Prescription Drug User Fee Amendments of 2002).

² 21 U.S.C. 379h(d)(3)(B).

³ "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

Depomed, Inc.
Waiver Request # 2004.040
Page 2

employees, including the employees of its affiliate; Depomed Development, Ltd. Second, according to FDA records, the marketing application for Proquin XR is the first human drug application, within the meaning of the Act, to be submitted to FDA by Depomed or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 21-744 for Proquin XR is granted.

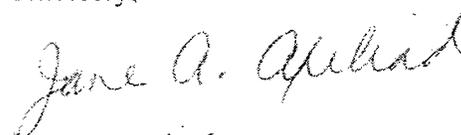
If FDA refuses to file the application or Depomed withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Depomed should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for Depomed's NDA 21-744. FDA records show that Depomed's application was submitted on July 19, 2004, and FDA was notified of the \$573,500 payment for the application on July 20, 2004. You should receive a refund of \$573,500. If you do not receive this refund within 30 days of the date of this letter, please contact Pothen (Sunny) Joseph, OFM, at 301-827-5086.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman, Michael Jones, or Tawni Schwemer at 301-594-2041.

Sincerely,



Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

Depomed, Inc.
Waiver Request # 2004.040
Page 3

BCC:
HFD-5 M. Jones
HFD-5 B. Friedman
HFD-5 Chronological File
HFD-5 Depomed, Inc. waiver file
HFM-110 C. Vincent/R. Eastep
HFA-103 S. Farran (RECORD ON PAYMENT AND ARREARS LIST)
HFA-120 P. Joseph, S. Butler (Refund to Process)
HF-20 F. Claunts
HFD-590 Y. Yu
HFV-3 T. Forfa
HFV-100 D. Newkirk

Drafted: B. Friedman 7/30/04
Reviewed: M. Jones 8/2/04
Edited: F. Purdie 8/30/04
Reviewed J. Axelrad

August 30, 2004

P:\waiver\Pending\Depomed\2004.040\04A0511v3.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

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

Depomed, Inc
1360 O'Brien Drive
Menlo Park, CA 94025

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-744

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.)

2. TELEPHONE NUMBER (Include Area Code)

(650) 462-5900

3. PRODUCT NAME
ProquinTM

6. USER FEE I.D. NUMBER
4804

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, 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 SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

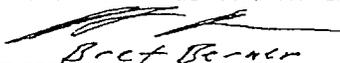
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE
Vice President
Product Development

DATE
7/17/2004



IND 62,386

Depomed, Inc.
Attention: Ms. Patricia Taylor
Director, Regulatory Affairs
1360 O'Brien Drive
Menlo Park, CA 94025

Ms. Taylor:

Please refer to the meeting between representatives of your firm and FDA on February 5, 2004. The purpose of the meeting was to discuss your planned NDA submission for Ciprofloxacin GR.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Yon Yu, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director, Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

MEETING DATE: February 5, 2004
TIME: 3:30-4:30 pm
APPLICATIONS: IND 62,386
DRUG: Ciprofloxacin GR (Gastric Retentive)
SPONSOR: Depomed, Inc.
TYPE OF MEETING: Pre-NDA
FORMAT: Face-to-Face
BRIEFING DOCUMENT SUBMISSION DATE: January 2, 2004

FDA PARTICIPANTS:

Renata Albrecht, M.D.,	Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP)
Steve Gitterman, M.D.	Deputy Director, DSPIDP
David Roeder, M.S.	Associate Director of Regulatory Affairs
Joette Meyer, Pharm D.	Clinical Reviewer
Norman Schmuff, Ph.D.	Chemistry Team Leader
Ramesh Sood, Ph.D.	Chemistry Reviewer
Stephen G. Hundley, Ph.D., DABT	Pharmacology & Toxicology Reviewer/Acting Team Leader
Shukal Bala, Ph.D.	Microbiology Team Leader
Peter A. Dionne, M.S.	Microbiology Reviewer
Philip Colangelo, Pharm D., Ph.D.	Clinical Pharmacology & Biopharmaceutics Team Leader
Gerlie De Los Reyes, Ph.D.	Clinical Pharmacology & Biopharmaceutics Reviewer
Ruthanna Davi, Ph.D.	Mathematical Statistician/Biomedical Reviewer
Yon Yu, Pharm D.	Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Bret Berner, Ph.D.	Vice President, Product Development
William Callahan, B.S.	Director, Operations
_____	Biostatistics Consultant, _____
Joyce Chinn, B.S., MBA	Project Manager
Verne Cowles, Ph. D.	Director, GI Physiology
_____	Clinical Consultant
Daniel Dye, M.S.	Vice President, Quality Systems
_____	Biopharmaceutics Consultant, _____
_____	Medical Consultant
Edward Hou, Ph. D.	Sr. Director, Formulations and Pharmacokinetics
_____	CMC Consultant, _____
_____	Microbiology Consultant _____
_____	Regulatory Consultant
_____	_____
Patricia Taylor, B.S.	Director, Regulatory Affairs
Hayley Welton, B.S.	Regulatory Associate

BACKGROUND:

This meeting is being held as a result of Depomed's request for a face-to-face Pre-NDA meeting to discuss their NDA submission plans for Ciprofloxacin GR. Depomed had originally planned to submit a 505(b)(2) NDA for Ciprofloxacin GR. However, post-EOP II meeting, on August 16, 2002, the sponsor submitted a letter requesting the Division's comments on their decision to submit a 505(b)(1) NDA for Ciprofloxacin GR for the treatment of uncomplicated urinary tract infection. On January 27, 2003, the Division discussed with Depomed via teleconference the requirements for a 505(b)(1) NDA and informed the sponsor of additional studies necessary for their application to be considered under a 505(b)(1) approval. In preparation for the Pre-NDA meeting, Depomed has provided synopses of completed Phase II and Phase III studies along with a list of questions in a Briefing Package, submitted on January 2, 2004, seeking the Division's comments on the information to be included in the planned NDA submission. The sponsor proposes to cite literature to support some of the statements in the proposed draft labeling for Ciprofloxacin GR. Depomed is of the position that some literature studies may be referred to in support of a 505(b)(1) NDA.

MEETING SUMMARY:

It was stated at the onset of the meeting that the Division's review of Depomed's planned NDA submission for Ciprofloxacin GR as outlined in the Briefing Package found it to not meet the criteria for a 505(b)(1) application. The Division stated that a discussion on the classification of the sponsor's planned NDA submission (i.e. 505(b)(1) vs. 505(b)(2)) will require the participants of the Agency's legal counsel. Therefore, it was recommended that the regulatory discussion of 505(b)(1) vs. 505(b)(2) will be tabled for another time. It was agreed that the meeting will focus on the scientific discussion of the drug product. After an induction of all the attendees, Depomed provided a presentation on Ciprofloxacin GR describing its mechanism of action, PK profile, adverse events as well as a brief summary of Phase III study. Following the presentation, the sponsor facilitated the discussion by requesting the Division's response to their questions listed in the Briefing Package. The Division's responses are summarized below.

QUESTIONS FOR DISCUSSION WITH THE AGENCY'S RESPONSES:

(The sponsor's questions are reproduced in italicized type below in the order they were asked during the meeting.)

Format of the Hybrid CTD

- 1. Depomed intends to file a Ciprofloxacin NDA in the CTS format. The proposed table of contents is provided in Appendix 1; does the Division concur that this layout is acceptable?*

Yes, the proposed format is acceptable.

- 2. The source database and analysis files used for each of the 2 clinical study reports will be submitted electronically as SAS transport files under ICH E3 section 16.4 "Individual Patient Data Listings" of each individual study report within module 5.3.5 for "Reports of Efficacy and Safety Studies". Therefore, please concur that the hard copy or electronic copy of the Individual Patient Data Listings (so called "patient profile") will not be required for inclusion in this NDA submission.*

Yes, we concur.

Microbiology

- 3. The proposed labeling for the microbiology subsection will be based upon the data obtained from the clinical trials and medical literature. Depomed has provided a draft package insert for the proposed application. Does the Division concur that the layout of the Microbiology section is acceptable for approval of the 505(b)(1) NDA application?*

A 505(b)(1) NDA relies exclusively on studies that you conducted, that were conducted for you, or for which you have the right of reference. Therefore, any information required for the labeling in the microbiology subsection must come from studies you have conducted or were conducted for you or for which you have right of reference. To include organisms in the *in vitro* activity listing (list #2) in the labeling, you will need to conduct 2 separate studies (2 different laboratories) that show MIC 90 values for each species below susceptibility breakpoints. Usually at least 100 isolates of each species must be tested. You may need to

establish breakpoints on your own data if you can not refer to other studies. This would require more than 100 isolates. Since NCCLS documents are public you may be able to reference these documents to establish breakpoints.

The sponsor asked if multi-center study is acceptable.

We recommend 2 separate studies (i.e. 2 different laboratories). However, if you choose to do a multi-center study, it must be a well established reputable center.

Clinical

- 4. The clinical program is comprised of one Phase II Study and one Phase III Study. In addition, safety data from 7 pharmacokinetic studies will be included in the clinical safety summary. The Phase II (81-0005) and Phase III (81-0015) studies were conducted to determine safety and efficacy of Ciprofloxacin GR for the treatment of uncomplicated urinary tract infections (UTI) in adult females. Both studies were randomized, double-blind, parallel-group studies that compared Ciprofloxacin GR to immediate release (IR) ciprofloxacin (CIPRO). Does the Division concur that these studies meet the requirements for a 505(b)(1) NDA filing?*

One Phase III study with supportive Phase II study is acceptable.

- 5. Approximately 294 patients were included in the efficacy population and 544 patients were included in the safety population in the overall clinical program with treatment with 500 mg Ciprofloxacin GR once daily for 3 days. Is this extent of exposure adequate to support this 505(b)(1) filing?*

Yes.

Biostatistics

- 6. The efficacy results generated from 2 clinical studies, Phase II Study 81-0005 and Phase III study 81-0015 will be presented individually for each study in section 2.7.3.2 Summary of Results from Individual Studies. This section will include tables for the primary and secondary efficacy parameters. Tables included will be the same format as those in the study reports. Is this acceptable?*

Yes.

- 7. The efficacy data from these 2 individual studies will not be pooled for data analysis. Visual integration of key efficacy data will be 2.7.3.3. We will compare and analyze results across studies by presenting results from these 2 studies within the same table as side-by-side columns with no statistical comparisons being made across studies. Is this acceptable?*

Yes, we find it acceptable.

- 8. Are there any additional analyses of efficacy data required for this NDA submission?*

Not at this time. However, we may request additional analyses during the NDA review.

The sponsor then inquired about the adequacy of the use of a per-protocol analysis group in the primary efficacy analysis.

It is Division policy to consider the results of the modified intent-to-treat group (i.e., including all patients enrolled who had documented baseline infection) of at least as much importance as that of the per-protocol group. Subjects in the modified intent-to-treat group with missing efficacy evaluations should be considered failures for this analysis. The sponsor is not obligated to include this modified intent-to-treat analysis for submission of the NDA; however, the Division would like to inform the sponsor that this analysis will be conducted and considered in the Division's evaluation of the study.

9. *The baseline demographics, termination and adverse event data collected for patients from 2 clinical studies (81-005 and 81-0015) will be pooled for the integrated safety data presentations. Is this acceptable? Are there any other safety parameters for which data must be pooled across these studies*

Pooling the safety data is acceptable.

10. *Adverse events will be summarized by the type of treatments patients received (Ciprofloxacin GR and Ciprofloxacin IR). A two-sided Fisher's Exact test will be performed for the comparison of the adverse event rates. Is this acceptable?*

Yes, it is acceptable.

11. *The safety results generated from PK Studies (81-0024, 81-0025, 81-0026, 81-0027, 81-0028, and 81-0029) will be presented and discussed individually. The safety data collected for normal volunteers from these PK studies will not be pooled for data analyses. No statistical comparison will be made across studies. Is this acceptable?*

Yes, this is acceptable.

Pharmacology/Toxicology

12. *Additional non-clinical pharmacology data and information were summarized from the literature without relying on the innovator's SBA or labeling as proposed in the draft package insert submitted to the Division on April 29, 2003 (Serial 016). Does the Division agree that the non-clinical Pharmacology/Toxicology information is adequate for the NDA filing as outlined in the meeting information?*

The preliminary review of the pre-clinical studies submitted to date finds the studies to be appropriate. However, full review is reserved. For the series of reproductive toxicology studies that have been completed, please submit the studies that have been audited. For a 505(b) (1) approval, the information to be included in the labeling will be restricted to the information that is provided from your own studies.

Clinical Pharmacology and Biopharmaceutics

13. *Does the Division agree that the ongoing studies under IND 62,386 fulfill the human pharmacokinetics and bioavailability requirements for the NDA filing?*

No, not for a 505(b)(1) NDA consideration.

14. *The bioavailability and Cmax of Ciprofloxacin GR fasted are reduced to approximately 35 to 40% of that when administered after a meal (Study 81-0024). This supports labeling of administration with dinner or the substantial meal of the day. The results of this food-effect study and its incorporation into the design of the Phase II and Phase III clinical studies are sufficient to support this labeling. Does the Division concur?*

This is a review issue.

15. *Does the Division concur that this study supports this labeling?*

This is a review issue.

16. *A minor interaction between antacids and Ciprofloxacin GR (Study 81-0028) has been observed to define a window of — prior to administration and — after administration. Does the Division concur that this study adequately supports this labeling?*

This is a review issue

17. *The PK package as discussed at the End of Phase II meeting and the 505(b)(1) teleconference with reference to referred PK articles in journals is intended to be the complete PK package to support the labeling for*

Ciprofloxacin GR. Depomed is utilizing this approach based on the understanding that the other 505(b)(1) NDA applications for approved novel dosage forms may have utilized only PK literature references to define the labeling for the basic pharmacokinetics and ADME of their products. Does the Division concur with this approach?

No, the requisite for a 505(b)(1) NDA consideration is that the applications relies exclusively on studies that you conducted, that were conducted for you, or for which you have the right of reference.

18. As agreed at the EOP II meeting, the In-Vivo/In-Vitro Correlation (IVIVC) study in the fed state (since there is incomplete absorption in the fasted state) of a slow-releasing, fast-releasing and standard dosage form in comparison to oral immediate release Ciprofloxacin is intended to support BE waiver and specifications for dissolution. Does the Division concur with the design of this study and its adequacy to support a BE waiver and dissolution specifications?

The synopsis of the preliminary analysis of the study appears to be acceptable. However, a full review of the study is required to determine its adequacy in supporting a BE waiver and dissolution specifications.

Chemistry

19. Depomed has provided the proposed drug substance specifications for related substances for commercial product. Are these acceptable? If not, what further requirements will the Division seek?

Please categorize impurities into specific groups as per ICH Q3A Guidance. The division also recommends that the impurity acceptance criteria should be included in the drug substance specification as the provided drug substance specification did not include the impurities.

20. Depomed has provided a provisional specification for _____ for initial commercial product and a strategy for development of a _____ specification for ongoing routine commercial manufacture. Is this acceptable?

Please include your current acceptance criterion for _____ in your provisional specification. For the proposed final specification, please include values for _____

21. Pivotal stability studies are going for _____ count _____ bottles. Depomed is proposing to commercialize a package that may have a different fill count but will not have a fill volume that falls below the minimum fill volume (36%) represented by the _____ count package currently on stability. The proposed commercial pack will be of the same material as that currently used. Based on this approach, there would be no requirement for additional stability studies provided there are no significant changes observe under long-term storage conditions with the current studies. Does the Division agree with this proposal?

The first 3 lots of the commercial batch packaged in marketed packaging should be placed on the accelerated and room temperature stability studies.

22. Does the Division concur with the acceptability of the proposed stability plan to support the proposed shelf life and change of packaging site for the _____

The sponsor's proposal of providing stability data for _____ packaged at the previous site is not acceptable. The stability data for a total of three primary batches stored at room temperature and under accelerated temperature conditions should be provided as per ICH Q1A (R2). One batch from the previous packaging site with two batches from the new site is acceptable for filing provided that the two packaging operations and the stability data are found to be comparable.

ADDITIONAL COMMENTS:

The Division acknowledged the receipt of the outline of the labeling comprehension study plan submitted by Depomed via fax on January 29, 2004 and stated that the Division looks forward to receiving the full study report.

Questions regarding the definition of common knowledge and prior scientific knowledge and how they relate to 505(b)ness of a NDA were raised. It was agreed that for a further discussion on the issue of literature support for a 505(b)(1) NDA, Depomed will first provide the Agency with their position statement that delineates and supports their opinion.

Yon Yu, Pharm D.
Regulatory Project Manager
DSPIDP

Date
{See appended electronic signature page}

Renata Albrecht, M.D.
Director, DSPIDP

Date
{See appended electronic signature page}

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

/s/

Renata Albrecht
3/5/04 06:44:52 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-744

Depomed, Inc.
Attention: Bret Berner, Ph. D.
Vice President, Product development
1360 O'Brien Drive
Menlo Park, CA 94025-1436

Dear Dr. Berner:

Please refer to your July 18, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ProquinTM (Ciprofloxacin HCl extended-release) Tablets, 500 mg.

We also refer to your submission dated August 18, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on September 17, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office Drug Evaluation IV
Office New Drugs

**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
9/15/04 01:47:47 PM

CONSULTATION RESPONSE

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

DATE RECEIVED:

May 11, 2004

DESIRED COMPLETION DATE:

July 11, 2004

ODS CONSULT #: 04-0147

TO:

Renata Albrecht, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products
HFD-590

THROUGH:

Susan Peacock, M.S.
Project Manager, Division of Special Pathogen and Immunologic Drug Products
HFD-590

PRODUCT NAME:

Proquin XR (Primary Name)
——— (Alternate Name)
(Ciprofloxacin Extended-release Tablets) 500 mg

NDA SPONSOR: Depomed, Inc.

NDA#: 21-744

SAFETY EVALUATOR: Charlie Hoppes, R.Ph., M.P.H.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name ——— DMETS has no objections to the proprietary name Proquin, but does not recommend its use with the "XR" suffix. The "XR" modifier for this product implies that an immediate-release formulation is available, is unnecessary, and may cause confusion as described in Section II. of this review.
2. DMETS recommends implementation of the labeling revisions outlined in Section III. of this review to minimize potential errors with the use of this product. DMETS recommends that container labels and carton labeling be forwarded for review and comment when they become available.
3. DDMAC finds the proprietary names Proquin XR and ——— acceptable from a promotional perspective.
4. We recommend consulting Guirag Poochikian, Acting Chair, CDER Labeling and Nomenclature Committee for the proper designation of the established name.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 30, 2004

NDA# 21-744

NAME OF DRUG: Proquin XR (Primary name) and _____ (Alternate name)
(Ciprofloxacin Extended-release Tablets) 500 mg

NDA HOLDER: Depomed, Inc.

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 proprietary names, Proquin XR and _____, regarding potential name confusion with other proprietary or established drug names. The container labels, carton and package insert labeling and patient information was provided for review and comment.

A study to support the proposed proprietary names conducted by _____, was submitted by the sponsor. Although the sponsor was initially interested in _____, this modifier has since been withdrawn from consideration in favor of the modifier "XR".

PRODUCT INFORMATION

Proquin XR (or _____ is a fluoroquinolone antibiotic and an extended-release formulation of ciprofloxacin hydrochloride. Proquin XR is indicated solely for uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains designated microorganisms. The usual dosage is once daily following the main meal of the day for three days. Proquin XR will be available in 500 mg extended-release tablets. Package sizes have not yet been specified by the sponsor.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which

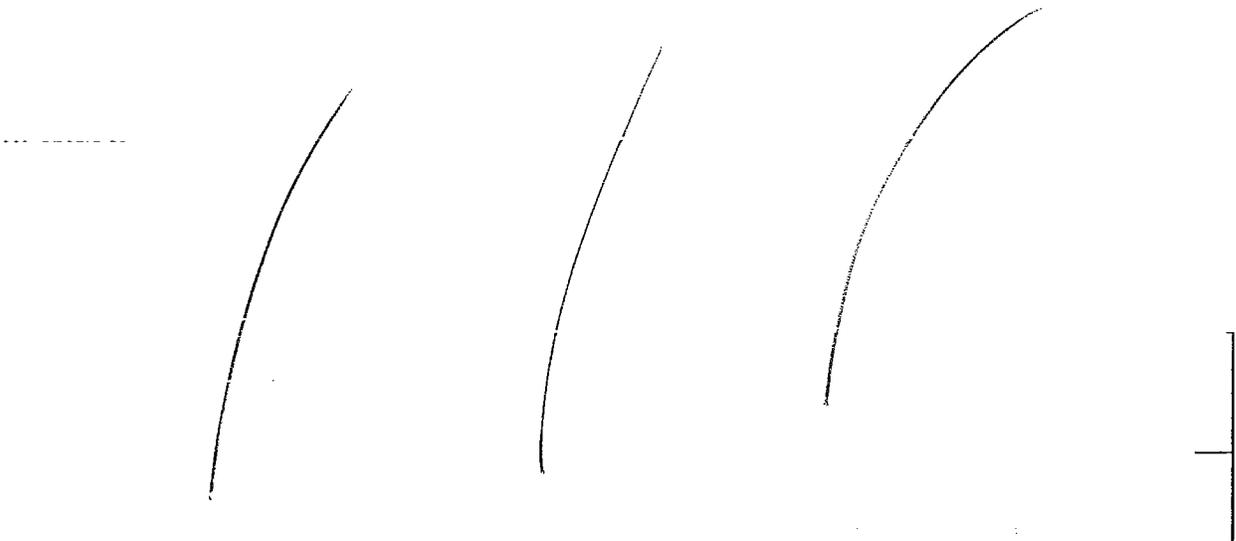
¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Proquin XR	Ciprofloxacin Hydrochloride Extended-Release Tablets, 500 mg 10,000 Units/mL, and 20,000 Units/mL	Take one tablet once daily following the main meal of the day for three days.	
Profen II	Dextromethorphan Hydrobromide, Guaifenesin, Pseudoephedrine Hydrochloride Tablets, 30 mg/800 mg/45 mg	Take one to one and one half tablets every 12 hours up to three tablets daily.	SA/LA
Propine	Dipivefrin Hydrochloride Ophthalmic Solution USP, 0.1%	One drop in the affected eye or eyes every 12 hours.	LA
Proleukin	Aldesleukin for Injection, Each vial contains 22 X 10 ⁶ International Units of Aldesleukin	600,000 IU/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute IV infusion for a maximum of 14 doses. Following 9 days of rest, the schedule is repeated for another 14 doses, for a maximum of 28 doses per course, as tolerated.	SA
ProCream Plus***	Progesterone Cream	Apply as directed.	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike). ***Discovered after Prescription Studies for Proquin XR Completed.			

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel



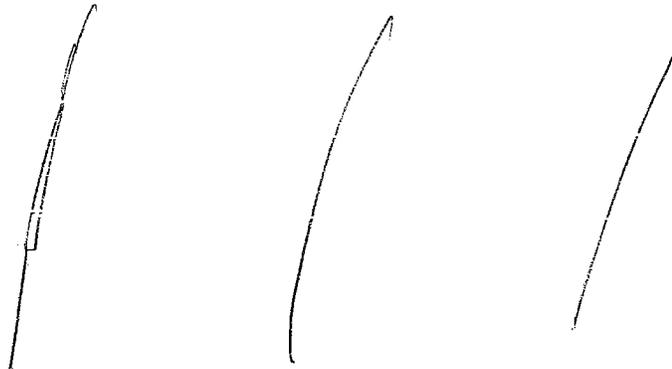
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. No additional names of concern were identified in POCA that were not discussed in EPD.

C. PRESCRIPTION ANALYSIS STUDIES

I. Methodology:

Six separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Proquin XR and _____ with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each study employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and prescriptions for Proquin XR and _____ respectively (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.



Proquin XR Study

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p><i>Proquin XR</i> <i>Sig 1 po qd x 3 days</i> <i># 3</i></p>	<p>Proquin XR Sig: One p.o. q.d. times three days Number 3</p>
<p>Inpatient RX:</p> <p>Proquin XR Sig 1 po qd x 3 days #3</p>	

2. Results:

Respondents of the verbal prescription study for Proquin XR interpreted the proposed name as Prograne XR, Procream XR, and Procrin XR, names which sound and look similar to currently marketed products, Beta-Prograne, Procream Plus, and Procrin, respectively. None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

1. Sound-alike and Look-alike Confusion with Proquin XR

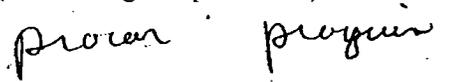
In reviewing the proprietary name Proquin XR, the primary concerns related to look-alike and sound-alike confusion with Preven, Procan, Procrit, Profen II, Propine, Proleukin, and Procream Plus. Proleukin was not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Proquin XR in addition to numerous differentiating product characteristics such as the product strength, indication for use, route of administration, administration setting, dosing regimen, and dosage formulation.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process for the proposed name, Proquin XR. Amongst responses received in the DMETS study were, "Pograne XR", "Procream XR", and "Procrin XR", which sound and look similar to the currently marketed products, Beta-Prograne, Procream Plus, and Procin, respectively. The majority of misinterpretations were misspelled/phonetic variations of the proposed names, Proquin XR. The suffix "XR" was omitted from the response of two study participants from the Proquin XR prescription studies.

- a. Preven was identified as a name that sounds similar to Proquin XR when spoken. Preven is levonorgestrel and ethinyl estradiol tablets. Preven is indicated for the prevention of pregnancy following unprotected intercourse or a known suspected contraceptive failure. The usual recommended adult dose is two tablets as soon as possible within 72 hours after unprotected intercourse and two tablets 12 hours later. Preven may sound similar to Proquin XR, especially if the suffix "XR" is omitted. Since Proquin XR is not available as an immediate-release product known as Proquin, it is more likely that a prescription for this product may be written without the "XR" modifier. Both names begin with the "Pr" sound and end with the short vowel "e" vs. "i" followed by "n". However, the middle of the names, "ev" vs. "oqu" may serve to distinguish the name pair phonetically. The products also have similarities, including dosage form (tablets) and route of administration (oral). There is concern that since both of these drug products has one specific indication, strength, and administration course, an order phoned in for "a course of

Preven” could be misinterpreted as “a course of Proquin”, or vice versa. Despite sound-alike properties and some similar product characteristics, Preven and Proquin XR have differences which may distinguish them including dosing regimen (two tablets now then two tablets 12 hours later vs. one tablet every day for three days), indications of use (prevention of pregnancy vs. treatment of urinary tract infection), number of tablets dispensed and different middle sounds of the name, which will decrease the risk of a medication error.

- b. Procan and Procan SR may sound and look similar to Proquin XR. Procan is procainamide hydrochloride, available in immediate-release or extended-release (SR) tablets. Procan and Procan SR are indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that are judged to be life-threatening. Although Procan and Procan SR have been discontinued from the marketplace, there may still be brand recognition for these products, reference to Procan remains in the literature and the world-wide web, and many generic procainamide products currently exist. The products also have similarities, including dosage form (tablets), route of administration (oral), and strength (500 mg). Procan may sound like Proquin XR, especially if the suffix “XR” is omitted. Also, the “XR” suffix proposed for Proquin may sound similar to the “SR” suffix of Procan SR. The name pair differs in the middle of each name, “ca” vs. “qui”. Even so, the “c” sound may also sound like “qu”, and both vowels which follow are short vowels with the potential for confusion. The names may also look alike, although the down stroke of the letter “q” in Proquin may serve to differentiate the names orthographically (see writing sample below).

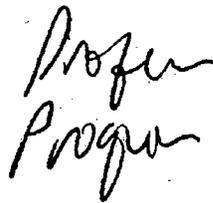
A handwritten sample comparing the words 'Procan' and 'Proquin'. The word 'Procan' is written in a cursive script, and 'Proquin' is written in a similar cursive script. A vertical line is drawn between the two words to separate them for comparison.

Despite sound-alike and look-alike properties, Procan/Procan SR and Proquin XR have differences which may distinguish them including dosing regimens (every 6 or every 12 hours vs. every day), and indications for use (for arrhythmias vs. treatment of urinary tract infection), respectively. Overall, the product differences between Procan SR and Proquin XR and the fact that the Procan products are no longer available in the marketplace will minimize the potential for error.

- c. Procrit was identified as a name that sounds similar to Proquin XR when spoken. In fact, one participant of the study submitted by the sponsor in support of the proposed proprietary name stated that “...there was a minor chance that Proquin might be confused with Procrit...”. Procrit is epoetin alfa for injection. Procrit is indicated for the treatment of anemia related to certain disease conditions, e.g., chronic renal failure, HIV positive conditions, chemotherapy anemias, etc. Procrit may sound like Proquin XR, especially if the suffix “XR” omitted. The name pair owes phonetic similarities to the shared letters, “Pro”, and “i”. Although the “c” in Procrit may sound like the “qu” in Proquin XR, the “t” vs. “n” ending may serve to distinguish them phonetically. Product differences between Procrit and Proquin XR include, route of administration (intravenous or subcutaneous vs. oral), dosage form (injection vs. tablet), strengths (2,000 Units/mL, 3,000 Units/mL,

4,000 Units/mL, 10,000 Units/2 mL, 10,000 Units/mL, and 20,000 Units/mL vs. 500 mg), and dosing regimen (50 to 100 units per kilogram of body weight intravenously or subcutaneously three times a week vs. one tablet daily for three days), respectively. Also, the patient information which accompanies Procrit may serve to prevent its administration in the event of product confusion. These differences will minimize the potential for error.

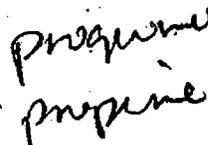
- d. Profen II may sound and look similar to Proquin XR. Profen II is Dextromethorphan Hydrobromide, Guaifenesin, and Pseudoephedrine Hydrochloride Tablets, a decongestant/expectorant combination available by prescription only. Profen II may sound like Proquin XR, especially if the suffixes "II" and "XR" are omitted. In fact the root names differ phonetically only in the middle "f" sound in Profen vs. the "qu" sound in Proquin. The names may also look-alike when scripted (see writing sample below).



The image shows two lines of handwritten text. The top line is "Profen" and the bottom line is "Proquin". Both are written in a cursive, slanted script. The letters "P", "r", "o", and "n" are shared between the two words, making them look similar when written quickly.

Besides sound-alike and look-alike properties, the products have other similarities, including dosage form (tablets), and route of administration (oral). Despite these similarities, Profen II and Proquin XR have differences which may distinguish them including dosing regimens (every 12 hours vs. every day), and indications for use (as a decongestant/expectorant vs. treatment of urinary tract infection), respectively. These differences will minimize the potential for error.

- e. Propine was identified as a name that looks similar to Proquin XR when written. Propine is Dipivefrin Hydrochloride Ophthalmic Solution, indicated as initial therapy for the control of intraocular pressure in chronic open-angle glaucoma. Orthographic similarities between Proquin XR and Propine may be attributed to the shared letters, "Pro" and "in" and to the similarities between the letter "q" and "p" (see writing sample below).



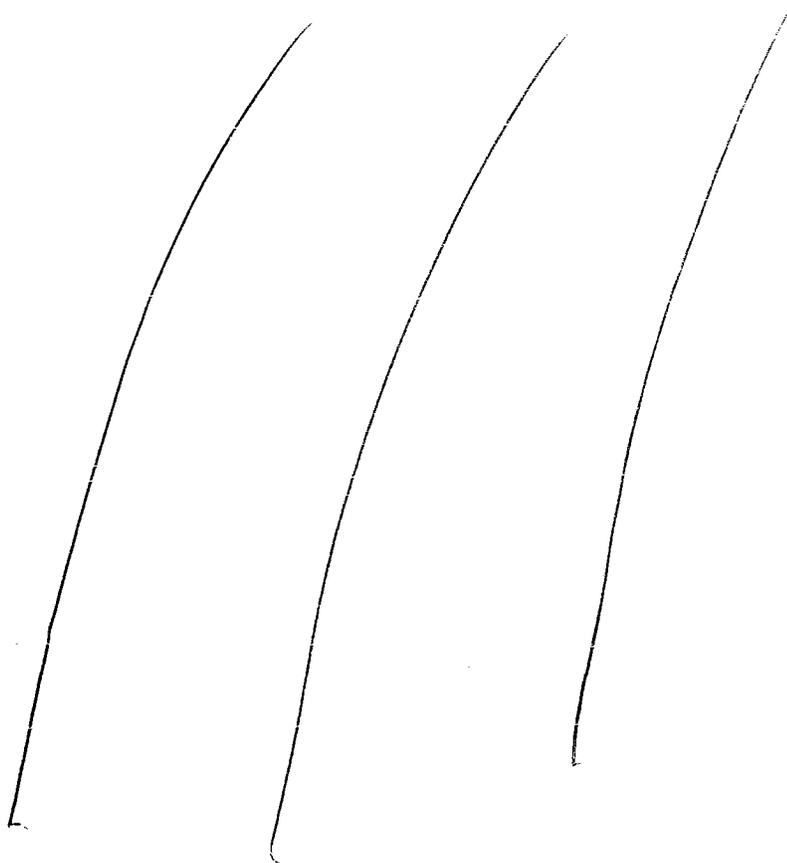
The image shows two lines of handwritten text. The top line is "Proquin" and the bottom line is "Propine". Both are written in a cursive, slanted script. The letters "P", "r", "o", "i", and "n" are shared between the two words, making them look similar when written quickly.

Although the names share orthographic similarities, there are many product differences between Propine and Proquin XR including, route of administration (ophthalmic vs. oral), dosage form (solution vs. tablet), strengths (0.1% vs. 500 mg), and dosing regimen (one drop in the affected eye or eyes every

12 hours vs. one tablet daily for three days), respectively. These differences will minimize the potential for error.

- f. Procream Plus was identified as a name that sounds similar to Proquin XR when spoken. Procream Plus is an over-the-counter (OTC) topical preparation for alleviating estrogen dominance in women suffering from menopausal symptoms. Procream Plus may sound like Proquin XR, especially if the suffixes "Plus" and "XR" omitted. Orthographic similarities in the root names may be attributed to identical first syllables and similarities in the second syllable of each name including sound-alike, "c" vs. "qu" and "m" vs. "n". The "r" sound in "Procream" may serve to distinguish the names phonetically. Although the names share phonetic similarities, there are product differences between Procream Plus and Proquin XR including, route of administration (topical vs. oral), dosage form (cream vs. tablet), and prescriptive status (OTC vs. by prescription only), respectively. These differences will minimize the potential for error.

2. Sound-alike Confusion with 



⁶ 2003 Drug Topics Redbook. Medical Economics. Thomson Healthcare.

⁷ Web Reference: http://destinationrx.com/default_firstvisit.asp

⁸ Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com



3. Comments Regarding the Modifier "XR"

DMETS does not recommend use of the modifier "XR" in nomenclature for this product. The "XR" modifier for this product implies that an immediate-release formulation is available. To DMETS' knowledge, there is no immediate release or other extended-release product currently in development. DMETS believes that use of a modifier with the proposed proprietary names is unnecessary, especially since the fact that this is an extended release product is already reflected in the established name. In the prescription studies conducted by DMETS, the "XR" modifier was disregarded by some of the study participants and postmarketing experience indicates that omission of the modifier occurs in the marketplace⁹. This will likely occur frequently because the modifier is not necessary to identify the correct product for dispensing. Additionally, this modifier may be confused, especially since there is no currently existing product to which it serves to differentiate. A situation is described by the Institute of Safe Medication Practices¹⁰, where "XR" was interpreted as "X 2" and the patient received two doses of immediate release tablets instead of a single extended-release tablet (see sample at the top of page 11).

⁹ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

¹⁰ ISMP Medication Safety Alert! Safety Briefs. October 3, 1996. Vol. 1, Issue 21.

Dilacor XR

In the case of Proquin XR, although there is no immediate release tablet, it is conceivable that where "XR" is misinterpreted as "X 2" the patient may receive two doses of the extended release product.

E. INDEPENDENT NAME ANALYSIS

A study of the proposed proprietary names, "Proquin & _____", was conducted by _____ a contract research organization (CRO), on behalf of the sponsor, Depomed, Inc. _____ recommendation "...would be for Proquin XR as the brand name." The study was conducted with four pharmacist participants. The study findings along with DMETS' responses appear below.

1. Pronunciation

Pharmacists were asked how pronounceable the names were on a scale of 1-3.

- 1- being easy to pronounce
- 2- being some difficult to pronounce
- 3- being extremely difficult to pronounce

- *No pronunciation problems surfaced. All pharmacists rated both names a 1.*

DMETS Response

DMETS acknowledges the opinion of the four pharmacists regarding pronunciation.

2. Characteristics & Product Class Associations

Following the pronunciation phase, pharmacists were then asked what characteristics the names suggested. What drug class(es) they associated the names with, and what conditions/diseases they thought drugs with these names would be indicated for. Additionally, they were asked to comment on _____ XR modifiers.

- *All pharmacists assumed both names indicated antibiotics in the fluoroquinolone class, but did not find that the names suggested any particular characteristic.*
- *3 of 4 thought XR stood for "extended release"*
- *1 of 4 did not know what XR stood for but thought it "sounded better"*
- *All preferred the XR modifier, mostly because they "knew what it meant"*
- *None of the pharmacists knew (or guessed) what _____ meant*

DMETS Response

DMETS does not believe that "quin" will be associated with the fluoroquinolone class in every instance, especially since there are

non-fluoroquinolone drug products with the “quin” root in the name. In addition, DMETS acknowledges that not all pharmacists know the meaning of the modifier, “XR”. A more extensive discussion of the use of “XR” with the product name appears in Section D.3. of this review. DMETS acknowledges comments regarding the modifier — and also acknowledges that the sponsor is not pursuing — as part of the proprietary name of either product at this time.

3. Negative Connotations

Pharmacists were asked if either names had any negative connotations or communicated anything inappropriate.

- *All pharmacists responded that there were no significant negative or inappropriate connotations for either name. The following are a few specific comments of interest.*

- / / / / / / /
- / / / / / / /

DMETS Response

DMETS acknowledges comments regarding the / / / / / / /

4. Appropriateness to Concept

Pharmacists were read a drug concept statement, and asked to rate the names on a scale of 1-5 (with 1 being not at all appropriate and 5 being completely appropriate).

- *3 of 4 rated both names 5, being completely appropriate*
- *Only 1 rated Proquin a 3 and — this pharmacist could not provide a coherent reason for his rating*

DMETS Response

The drug concept statement was not provided for DMETS’ review. DMETS considers inclusion of this information as necessary to impart any meaning to the information provided.

5. Existing Name Associations

Pharmacists were then asked if either of the names sounds like an existing drug and if there was a likelihood of confusion.

- / / / / / / /
- *Another pharmacist suggested that there was a minor chance that Proquin might be confused with Procrit (for anemia)*

- *When pressed, none of the pharmacists believed that the names presented potential for confusion that would make them unacceptable as final names*

DMETS Response

[Handwritten signatures]

DMETS agrees with the pharmacist that believes that there is a chance that Proquin might be confused with Procrit but considers the risk of dispensing the wrong medication to be low based on product differences between Procrit and Proquin XR. The association between these two names is explored further in Section D.I. of this review.

6. **Handwritability**

Pharmacists were asked if the names would be easily legible considering most doctors' handwriting.

- *[Handwritten signature]*
- *[Handwritten signature]*

- *One pharmacist said Proquin might be confused with Procrit (for anemia)*
- *Again, when pressed, none of the pharmacists believed that the names presented a potential for confusion that would make them unacceptable as final names*

DMETS Response

[Handwritten signatures]

DMETS Concluding Comments

From a medication safety perspective, DMETS' overall impression is that the study conducted for the sponsor by _____, lacks appropriate content, design, rigor, power, and adequate controls. Regarding study content, DMETS believes that in many respects the study misses the objective of attempting to ascertain the potential for safe use of this drug product in the marketplace. When reviewing the acceptability of a proposed proprietary name, DMETS is particularly interested in the potential for medication errors as a result of the introduction of that name into the marketplace. While _____ solicited opinions in areas such as ease of pronunciation, name connotations, and appropriateness of name to concept, other important medication safety areas went largely unexplored. For example, even when one of the four pharmacists surveyed identified Procrit

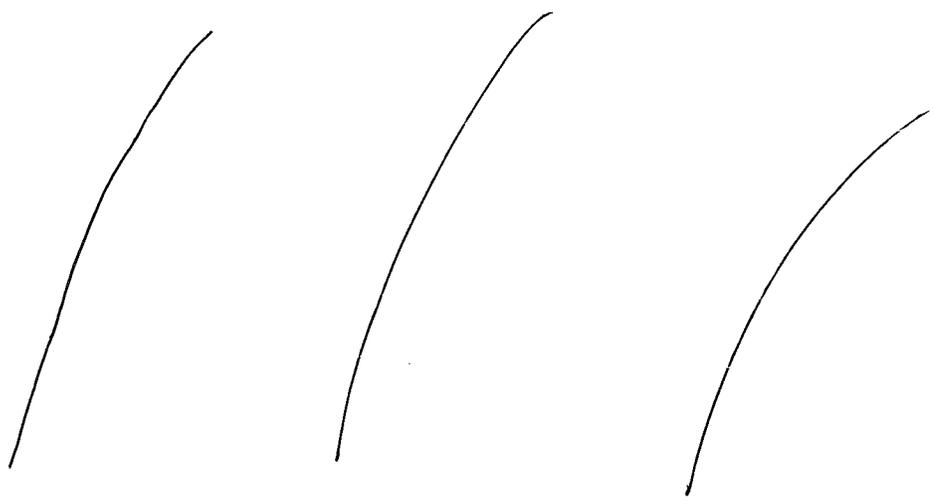
as a product having potential for confusion with Proquin. _____, did not analyze this risk further.

The study design, although not fully described by the CRO seems to have been nothing more than to ask four pharmacists a series of questions. DMETS did not have the benefit of reviewing either the questions or the answers given by the pharmacists since this information was not provided. It was DMETS impression that these questions were not rigorous in nature and did not explore potential for medication errors with introduction of the proposed names. No attempt was made by the CRO through study design to introduce the possibility for the study participants to misinterpret the proposed names. Also, since only four pharmacists participated in the study, very little useful information was gathered. Although DMETS could not adequately evaluate the methods employed by the CRO (not provided), it appears that no attempt was made to use appropriate controls. DMETS was left to wonder whether the pharmacists surveyed were even allowed to make anonymous responses. The statement, "*When pressed, none of the pharmacists believed that the names presented a potential for confusion that would make them unacceptable as final names.*", conjures the image that some type of pressure or follow up questioning was necessary to elicit this conclusion. Additionally, although _____ specifically recommends the name, "Proquin XR", no such recommendation was made for the name _____.

**APPEARS THIS WAY
ON ORIGINAL**

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name _____ DMETS has no objections to the proprietary name Proquin, but does not recommend its use with the "XR" suffix. In reviewing the proprietary name _____



B. Comments Regarding the Modifier "XR"

DMETS does not recommend use of the modifier "XR" in nomenclature for this product. The "XR" modifier for this product implies that an immediate-release formulation is available. To DMETS' knowledge, there is no immediate release or other extended-release product currently in development. DMETS believes that use of a modifier with the proposed proprietary names is unnecessary, especially since the fact that this is an extended release product is already reflected in the established name. In the prescription studies conducted by DMETS, the "XR" modifier was disregarded by some of the study participants and postmarketing experience indicates that omission of the modifier occurs in the marketplace¹¹. This will likely occur frequently because the modifier is not necessary to identify the correct product for dispensing. This modifier may be confused, especially since there is no currently existing product to which it serves to differentiate. A situation is described by the Institute of Safe Medication Practices¹², where "XR" was interpreted as "X 2" and the patient received two doses of immediate release tablets instead of a single extended-release tablet (see sample below).

Dilacor X2

¹¹ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

¹² ISMP Medication Safety Alert! Safety Briefs. October 3, 1996. Vol. 1, Issue 21.

In the case of Proquin XR, although there is no immediate release tablet, it is conceivable that where "XR" is misinterpreted as "X 2" the patient may receive two doses of the extended release product.

C. Labeling Comments

Additionally, DMETS reviewed the container labels, carton and package insert labeling and patient information from a safety perspective. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENT

We note that you have designated the established name of your product as, "ciprofloxacin hydrochloride extended-release tablets". We do not believe that this is the correct nomenclature since dosing of this product is based on the active moiety. We have recommended that the Division consult Guirag Poochikian, Acting Chair, CDER Labeling and Nomenclature Committee for the proper designation of the established name.

2. CONTAINER LABELS (/ , 50's. ✓

- a. See GENERAL COMMENT above.
- b. Revise to relocate the expression of net quantity to appear at the top of the principal display panel. The "Artwork #" may appear elsewhere on the label.
- c. Revise to remove the expression of strength, 500 mg, from the parenthetical statement containing the established name. The expression of strength should appear with prominence beneath the established name on the principal display panel.
- d. Revise the "Description" statement appearing on the side panel to indicate that 500 mg of ciprofloxacin is present as ciprofloxacin hydrochloride.

3. CARTON LABELING (—————

See GENERAL COMMENT and comments under CONTAINER LABELS above.

4. INSERT LABELING (revised July 9, 2004)

a. DESCRIPTION

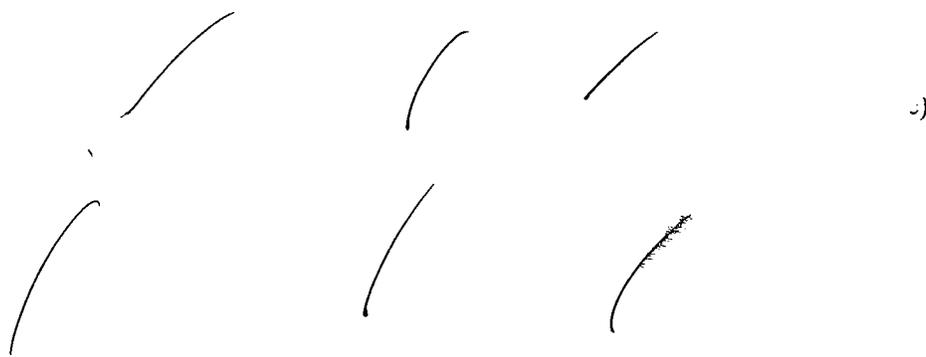
Information appearing in the last paragraph and elsewhere in this section describes clinical pharmacology and actions of the drug in humans and should be relocated to the CLINICAL PHARMACOLOGY section.

b. HOW SUPPLIED

Include the established name of the drug in this section. We refer you to the first comment under the DESCRIPTION section above.

5. PATIENT INFORMATION

- a. We recommend that the Division of Surveillance, Research & Communication Support be consulted to review patient comprehension aspects of the patient information.



**APPEARS THIS WAY
ON ORIGINAL**

IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary name _____ DMETS has no objections to the proprietary name Proquin, but does not recommend its use with the "XR" suffix. The "XR" modifier for this product implies that an immediate-release formulation is available, is unnecessary, and may cause confusion as described in Section II. of this review.
- B. DMETS recommends implementation of the label and labeling revisions outlined in Section III. of this review that might lead to safer use of the product. DMETS recommends that container labels and carton labeling be forwarded for review and comment when they become available. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary names Proquin XR and _____ acceptable from a promotional perspective.
- D. We recommend consulting Guirag Poochikian, Acting Chair, CDER Labeling and Nomenclature Committee for the proper designation of the established name.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

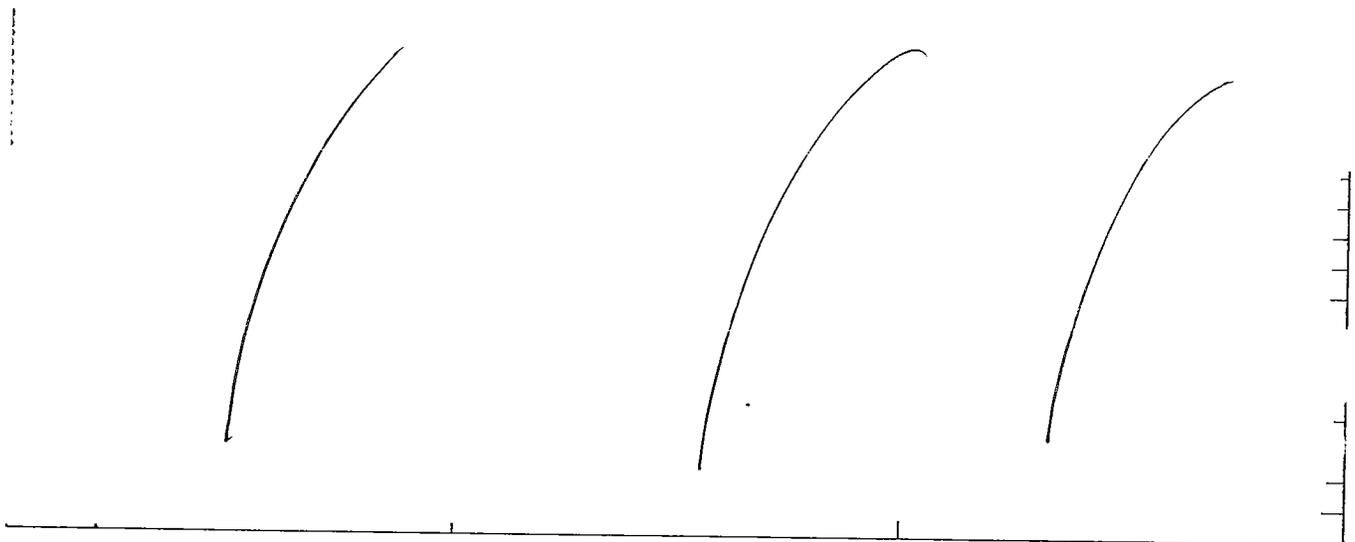
Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

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

Appendix A. Prescription Studies for Proquin XR and

Verbal	Proquin XR	
	Inpatient	Outpatient
Proquin XR	Proquin XR	Proquin XR
Proquin XR	Proquin XR	Proquin XR
Proquin XR	Proquin XR	Proquin XR
Proquin XR	Proquin XR	Proquin VR
Prograne XR	Proquin	Proquire VR
Proquin XR	Proquin XR	Proquin XR
Proquin XR	Proquin XR	Proquire XR
Proquin XR	Proquin XR	Proquin XR
Procream XR	Proquin XR	Proquire
Progran XR	Proquin XR	Proquin XR
Proquin XR	Proquin XR	Proquire XR
Progran XR	Proquin XR	Proquin XR
Procran XR	Proquis XR	Proquin XR
Proquine XR		Proquin TR
Procrin XR		
Proquine XR		



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/s/

Charles Hoppes
9/8/04 03:27:40 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/8/04 04:27:33 PM
DRUG SAFETY OFFICE REVIEWER



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

FACSIMILE TRANSMITTAL SHEET

DATE: February 28, 2003

To: Bret Berner	From: Jouhayna Saliba
Company: DepoMed Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax number: 650-462-9993	Fax number: 301-827-2475
Phone number: 650-462-5900	Phone number: 301-827-2127
Subject: Clinical pharmacology studies	

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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DATE: February 28, 2003

TO: Bret Berner, Ph.D.
Vice President Product Development

ADDRESS: 1360 O'Brien Drive
Menlo Park, CA 94025-1436

FROM: Jouhayna Saliba, Pharm.D.
Regulatory Project Manager

IND: 62,386

SUBJECT: Clinical pharmacology studies

Please refer to the teleconference held on January 27, 2003 where we discussed your decision to submit a 505 b(1) application instead of a 505 b(2). During the teleconference we told you that we would get back to you with regard to the clinical pharmacology studies needed for a 505 b(1) submission. Below is a list of these studies in addition to the already agreed upon studies at the 'End of Phase II' meeting held on July 1, 2002.

1. In vitro metabolism studies to evaluate the induction/inhibition/substrate potential of Ciprofloxacin GR using human liver microsomes for inhibition studies and substrate evaluation and human liver hepatocytes for induction studies.
2. Plasma protein binding studies.
3. Mass balance study to identify routes of elimination and metabolites.
4. Based on results obtained from the in vitro metabolism and the mass balance studies, Phase I in vivo drug interaction studies in healthy volunteers may be required.
 - Please refer to the Clinical Pharmacology Guidance regarding conduct of in vitro metabolism and in vivo drug interaction studies (www.fda.gov/cder/guidance/index.htm).
5. A pharmacodynamic interaction study between warfarin and ciprofloxacin GR is also necessary.
6. A PK study to establish dose-proportionality.
7. Pivotal bioequivalence study of the 'To-be-marketed' formulation vs. clinical formulation.
8. Based on results obtained from the in vitro metabolism and mass balance studies, PK studies may be necessary in the following patient populations:
 - Renal Impairment

- Hepatic Impairment.

Please refer to the Clinical Pharmacology Guidance documents regarding conduct of renal and hepatic impairment studies (www.fda.gov/cder/guidance/index.htm).

9. The pharmacokinetics of Ciprofloxacin GR needs to be characterized as a function of age (elderly vs. young), gender (male vs. female) and race in an adequate number of subjects in each category.

If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2127.

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/s/

Jouhayna Saliba
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CSO



MEMORANDUM OF MEETING

DATE: July 1, 2002

MEETING TYPE: End of Phase II meeting

IND: 62,386

DRUG: Ciprofloxacin GR

DEPOMED ATTENDEES:

Bret Berner, Ph.D., VP Product Development
— , Biostatistics Consultant
— Clinical Consultant
Verne Cowles, Ph.D., Director GI Physiology
— Regulatory consultant
— Clinical Consultant
Lynne Rowe, Project Leader and Senior Clinical Research Associate
— Regulatory consultant
— PK consultant
— Regulatory Consultant

FDA ATTENDEES:

Renata Albrecht, M.D., Acting Division Director
Rigoberto Roca, M.D., Medical Team Leader
Eileen Navarro, M.D., Medical Reviewer
Joette Meyer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Kofi Kumi, Ph.D., Clinical Pharmacology and Biopharmaceutics Acting Team Leader
Karen Higgins, Sc.D., Statistical Team Leader
Ruthanna Davi, M.S., Statistical Reviewer
Stephen Hundley, Ph.D., Pharm-Tox Reviewer
Norman Schmuff, Ph.D., Chemistry Team Leader
Dorota Matecka, Ph.D., Chemistry Reviewer
Robert Shibuya, M.D., DSI
David Roeder, M.S., Assistant Director, Regulatory Affairs
Ellen Frank, R.Ph., Chief, Project Management Staff
Kristen Miller, Pharm.D., Project Manager
Andrei Nabawski, Pharmacy intern
Jouhayna Saliba, Pharm.D., Project Manager

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

Discussion Item (1)

DepoMed is considering performing an In Vitro/In Vivo Correlations (IVIVC) study to avoid potential bioequivalence studies in the future. If an IVIVC is performed, our recommendation is to administer the drug in the fed mode, preferably with the standard OGD breakfast (Egg McMuffin). The guidance document, "extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations," states, "IVIVCs are usually developed in the fasted state. When a drug is not tolerated in the fasted state, studies may be conducted in the fed state." Ciprofloxacin GR is to be administered with food, is likely to be considerably less bioavailable in the fasted state, and in the fasted state may lead to delivery to the colon and poor tolerability. The fed state would be selected for this IVIVC. Is this proposal for the IVIVC study appropriate? If the design is not acceptable, what changes do you propose?

Yes, it is acceptable to perform the IVIVC study in the fed state following a standard high-fat breakfast.

In general, the IVIVC relationship should be demonstrated with two or more formulations with different release rates to result in corresponding differences in absorption profiles. The reference product may not be used as one of the formulations. Exceptions to this approach (i.e., use of only one test formulation) may be considered if in vitro dissolution is found to be independent of the dissolution test conditions (e.g., medium, agitation, pH). To determine if dissolution is independent of pH, it is recommended that the applicant investigate at least two other types of media (of different pHs), in addition to 0.1 N HCl, and other rotation speeds (or consider other apparatus, i.e., paddle at 50 rpm). Also, as described in the guidance document Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, the applicant should submit data verifying the internal predictability of the IVIVC model and conduct external validation of the correlation, using another set of data in the IVIVC equation to predict in-vivo performance.

Discussion Item (2)

Is the proposed PK package (without the inclusion of the PK study on postural effects or the PK study on the effect of antacids on pharmacokinetics as discussed in section 6.0) sufficient to support the 505 (b)(2) submission? If not what changes or additions do you propose?

Because Ciprofloxacin GR is not a floating tablet, the Sponsor does not have to conduct a postural study.

The Division suggested that the current omeprazole study design be changed where 40 mg of omeprazole is given as 3 days pretreatment followed by Ciprofloxacin GR on the 4th day.

The Division requested that the Sponsor conduct an interaction study with antacids. The Sponsor should propose the timing of Ciprofloxacin GR dosing in relation to the antacid, based on the known pharmacokinetics of Ciprofloxacin GR.

The Division requested 2 additional media with respect to the Sponsor's dissolution method.

Discussion Item (3)

Are results from the 28-day toxicology study in dogs (Section 8.0) sufficient to support 505(b)(2) filing for ciprofloxacin GR tablets? If not, what changes or additions do you propose?

The 28-day toxicology study is sufficient to support a 505(b)(2) NDA.

Discussion Item (4)

In your comments of March 20, 2002, the list of exclusions is stated to limit the generalizability of the efficacy of the study. These exclusion criteria largely follow the draft guidance, "Uncomplicated Urinary Tract Infections – Developing Antimicrobial Drugs for Treatment" (Anti-/2567 dft.wpd). Could you please elaborate on your suggested changes in the exclusion criteria and their consequences for approval or labeling?

The phase III study will be the intended population, which will effect the labeling. The Sponsor will also propose modified exclusion criteria (including criteria #4, 5) that reflects the intended population and the labeled indication.

Discussion Item (5)

In this same correspondence, it is recommended that females of childbearing potential use 2 methods of active birth control for the duration of the study. This is not currently used in practice with the immediate release form of ciprofloxacin, and this requirement could be sufficiently prohibitive to prevent the enrollment of women of childbearing potential. We believe the generalizability and the more realistic use conditions are the predominant considerations, and the inclusion criteria require only a single form of birth control. Does the Agency concur with this decision? If not, how would you propose to implement this without adversely affecting the study?

The Division is in agreement with the current protocol, "acceptable methods of birth control include abstinence, oral contraceptives, condom and foam, IUD, vaginal spermicidal suppository, progestin implant or injection, or sterilization of partner."

The requirement for 2 barrier methods of birth control is standard. However, abstinence and one other active form of contraception is adequate.

Discussion Item (6)

In the draft guidance, "Uncomplicated Urinary Tract Infections – Developing Antimicrobial Drugs for Treatment" (Anti-/2567dft.wpd), refers to superinfections (during therapy) and new infections (after completion of therapy, as bacterial infections resulting from an uropathogen different from the original one. Since the Test-of-Cure Visit is after completion of therapy, there can never be a superinfection detected, and we removed this from the protocol. Does the Agency concur?

Consistent with the standards of medical care, patients who clinically deteriorate or have persistent symptoms will be evaluated at an unplanned visit and superinfections and new infections will thus be identified.

Discussion Item (7)

We would like assistance on the interpretation of "clinical failure" in the aforementioned draft guidance. Does it include any patient that is not a clinical cure or does it include only those patients that still have both signs and symptoms of UTI or took another antibiotic for UTI? One shows lack of complete success and the other absence of therapeutic improvement. Which interpretation does the Division prefer?

Uncomplicated UTI is a microbiologically driven indication, and clinical outcome is secondary. Nevertheless, the Sponsor will propose criteria for evaluation of patients with persistence of one or more clinical signs or symptoms. The concern is that some symptoms of UTI may persist despite overall successful outcome. The Division does not agree with the addition of an outcome of "improvement".

Discussion Item (8)

A single double-blind, controlled safety and efficacy study in female UTI patients is proposed for the submission of a 505(b)(2) NDA. The patient exposure will be up to 720 patients for 3 days. The reference product for the 505(B)2 NDA filing will be Cipro®. Does the Division view this as a complete NDA package for review and approval?

The Sponsor will consider the Agency's proposal for a label comprehension study and an efficacy study in complicated UTI and will propose alternatives for patient and provider education before the pre-NDA meeting.

Discussion Item (9)

Does the Division accept the statistical analysis and proposed criteria of non-inferiority in efficacy and safety of the ciprofloxacin GR tablets to the ciprofloxacin IR tablets?

The Sponsor's phase 3 protocol specifies that the primary analysis group will include all randomized patients who met the enrollment criteria for positive urine microbiology and uropathogen susceptibility and who completed 3 days of dosing with study medication. FDA's position is that an Intent-to-Treat Analysis group (including all patients randomized who had a positive pre-treatment culture) should be the primary analysis group but we do look for consistency of efficacy results with a efficacy-evaluable group such as is described in the Sponsor's protocol.

The Sponsor plans to conduct an interim analysis after enrollment of 100 patients. The objective of the interim analysis is to calculate the overall microbiological eradication rate in order to validate the assumptions used for the original sample size calculation for the study. Interim analysis results will not be presented by treatment group and the blind will remain unbroken. Since no comparisons between treatment groups are being made at this interim analysis and the

Ciprofloxacin GR
IND 62,386

blind is not being broken, we are in agreement with the Sponsor that no adjustment of the significance level for the final treatment comparison is necessary.

Discussion Item (10)

In light of the recent article by Bent et al (2002)¹, should new vaginal discharge be added as an exclusion criteria to the Phase III Protocol?

The Sponsor has the option of revising the exclusionary criteria to exclude women with vaginal discharge. This criteria has been found to increase the sensitivity of patient symptoms in uncomplicated UTI, thereby eliminating the need to routinely perform urinalyses and urine cultures. The Division points out that the criteria for inclusion into the study do require the microbiologic establishment of a UTI, rendering this issue irrelevant.

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

Conference Chair (or designated signatory): _____ Date: _____
Renata Albrecht, M.D., Acting Division Director

Attachment/Handouts: Overhead slides

B

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 20, 2002

To: Bret Brener	From: Jouhayna Saliba
Company: DepoMed Inc.	Division of Division of Special Pathogen and Immunologic Drug Products
Fax number: 650-462-9993	Fax number: 301-827-2475
Phone number: 650-462-5900	Phone number: 301-827-2127
Subject: Comments to submission of IND 62,386	

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES NO

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DATE: March 20, 2002

TO: Bret Berner, Ph.D.
Vice President Product Development

ADDRESS: 1360 O'Brien Drive
Menlo Park , CA 94025-1436

FROM: Jouhayna Saliba, Pharm.D.
Regulatory Project Manager

IND: 62,386

SUBJECT: Comments and recommendations regarding IND 62,386

Please refer to your Investigational New Drug Application (IND) submitted under section 505(I) of the Federal Food, Drug, and Cosmetic Act for Ciprofloxacin GR.

We completed our 30-day, safety review of your application, and as discussed with you in a telephone conversation on September 27, 2001, concluded that you may proceed with your proposed clinical investigation.

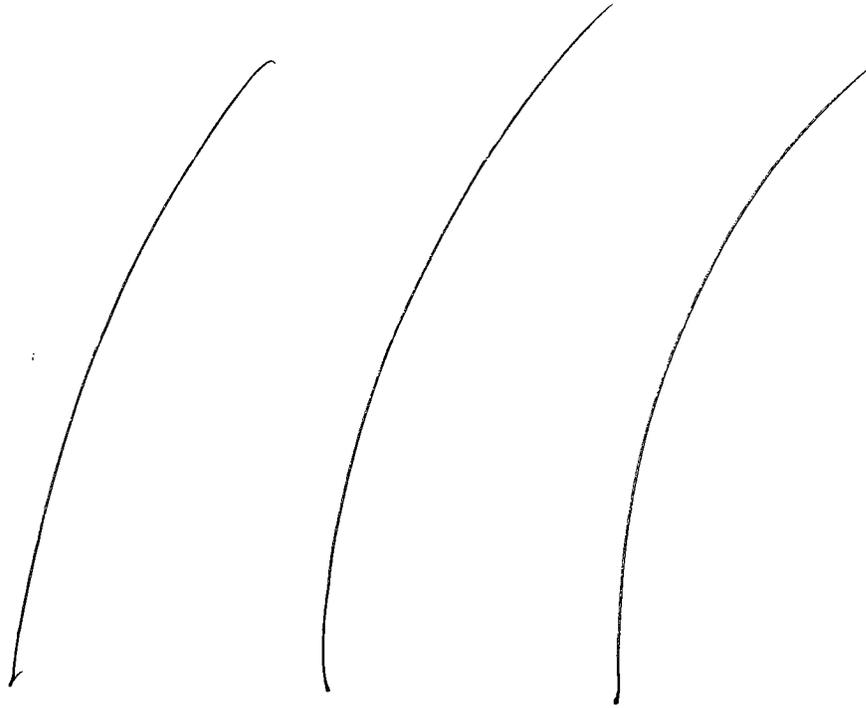
We have the following comments and recommendations intended to aid you in your drug development process. Some of these were relayed to you in the letter dated August 10, 2001. Please note that the following are not clinical hold issues.

1. Thank you for submitting the individual plasma concentration-time profiles and urinary excretion rate-time profiles of ciprofloxacin, as well as individual plasma and urine pharmacokinetic parameters for the study "Comparison of Ciprofloxacin Pharmacokinetics from a Single Dose Administration of Gastric Retentive (GR) Tablets Versus Immediate Release (IR) Tablets in Healthy Volunteers". When available, we will also be interested in reviewing the complete study report
2. The following comments were conveyed in a fax dated August 13, 2001 and are being sent as a reminder. These comments should be kept in mind as your drug development plan proceeds.
 - a. In order to fully characterize the pharmacokinetic similarities and differences between immediate and sustained release ciprofloxacin, please include the following assessments in the study reports of your completed and proposed pharmacokinetic studies:
 - C_{min}
 - AUC/MIC (for the least susceptible urinary pathogen)
 - C_{max} /MIC (for the least susceptible urinary pathogen)
 - Time above the MIC (for the least susceptible urinary pathogen)
 - Complete urinary excretion rate-time profiles

- b. Please perform a drug interaction study with a drug known to increase stomach pH (i.e., a proton pump inhibitor). Urinary excretion data should be collected in addition to plasma data.
 - c. Please perform a drug interaction study with a clinically relevant dose of antacids to identify an appropriate dosing window. Urinary excretion data should be collected in addition to plasma data.
 - d. Please consider performing a study of the effect of posture on the pharmacokinetics of the GR tablet.
 - e. Please begin to give consideration to the development of a dissolution method.
3. This comment pertains to the inclusion criteria in the Phase II study protocol: Females of childbearing potential must use two medically acceptable methods of birth control throughout the study.
 4. This comment pertains to the exclusion criteria in the Phase II study protocol as it impacts the proposed Phase III study "This extensive list of exclusions would be acceptable in a Phase II study, but would limit generalizability of the efficacy in a phase III study."
 5. Please provide an informed consent document that includes the following:
 - a. The patients' consent by way of a signature
 - b. A statement that the information has been reviewed with the patient
 - c. A statement that the patient understands the information provided.
 6. The following comment pertains to the investigator's brochure:
 - a. There is a failure to clearly distinguish when data presented refers to the approved ciprofloxacin formulation and when the data refers to ciprofloxacin GR. Please revise the document to emphasize this distinction.
 - b. The mechanism of the GR tablet is dependent on absorption in the upper gastrointestinal tract, and may make it susceptible to interactions not seen with ciprofloxacin IR. The investigator's brochure should incorporate a discussion on the possible risks of the GR formulation, relative to the following:
 - The unanticipated risks attributable to the excipient
 - The anticipated risk of treating an unrecognized complicated UTI or pyelonephritis when the drug's efficacy has not been demonstrated for these clinical situations
 - The unanticipated risks of as yet unstudied drug-food interactions
 - c. A discussion of the studies that are needed to show that the ciprofloxacin GR product approximates the kinetics, efficacy and safety of ciprofloxacin IR also needs to be

incorporated for fair balance.

- d. Please address the 40% difference in C_{max} between ciprofloxacin GR and ciprofloxacin IR and how this difference may affect the efficacy of the study drug.



If you have any questions please contact Jouhayna Saliba, Project Manager at 301-827-2127.

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/s/

Jouhayna Saliba
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