CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-341

ADMINISTRATIVE DOCUMENTS

PATENT STATEMENT UNDER 21 USC 355(b)(1)

Drug Substance Patent

The following U.S. Patent contains claims directed to the drug substance valdecoxib, which is the subject of the present application:

Patent No.	Owner	Title	Expiration
5,633,272	G.D. Searle & Co.	Substituted Isoxazoles for the Treatment of Inflammation	Feb. 13, 2015

The undersigned declares that the above patent covers the drug substance valdecoxib, which is the subject of this application for which approval is being sought.

Drug Product (Composition) Patent

Drug Product (Method of Use) Patent

In the opinion and to the best knowledge of the undersigned, there are no patents other than the Drug Substance Patent (above) that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

James M. Warner
Associate Attorney

Claimed Product Exclusivity Under 21 USC 355(c)(3)(D)(ii)

The Applicant, G.D. Searle & Co., is claiming exclusivity under 21 CFR §314.108(b)(2) for the drug containing the active moiety, valdecoxib, which is the subject of the present application.

21 CFR §314.50(i)(3) Assertion

To the best of the Applicant's knowledge or belief, a drug containing valdecoxib as the active moiety, which is the subject of the present application, has not previously been approved under section 505(b) of the Act.

James M. Warner

James M. Warner
Associate Attorney

EXCLUSIVITY SUMMARY for NDA # 21-341 SUPPL # _____

Trade Name Bextra_____ Generic Name valdecoxib

Applicant Name Searle/Pharmacia HFD- 550
Approval Date November 16,2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_x__/ NO /___/

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

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

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

      YES /_x__/ NO /___/

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

      _____

      _____

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

      _____

      _____

d) Did the applicant request exclusivity?

YES /_x__/no/___/

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

5 years

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

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /__x/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /x__/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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 /x___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

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

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

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

_____

_____

Investigation #2

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

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

Signature of Preparer

Date 11/16/01

Title: Chief Project Manager

_____

Signature of Office or Division Director

_____

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Attached (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study See Attached (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

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

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Gunnar Casserstedt	Vice President, R&D Finance
FIRM/ORGANIZATION: G.D. Searle & Co.	
SIGNATURE	DATE: Nov. 30, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3455 (3/99)

Printable Pediatric Page

Welcome to the Pediatric Page Printed Page. To produce your pediatric page, simply print this page (this paragraph will not print). However, most versions of Internet Explorer will print a header on each page (i.e., the name of the web site, etc.) To eliminate these when printing the Pediatric Page, go to 'File', then 'Page Setup', and clear the 'Header' and 'Footer' Boxes. (Cut and paste to a document [or write down] the contents of these boxes first if you want to restore the headers and footers afterwards.)

PEDIATRIC PAGE

NDA Number:	021341	**Trade Name:**	TBD (VALDECOXIB)5/10/20/40MG TABLETS
Supplement Number:	000	**Generic Name:**	VALDECOXIB
Stamp date:	1/16/01	**Action Date:**	1/16/01
Supplement Type:	N		
COMIS Indication:	PREVENTION AND TREATMENT OF ACUTE PAIN IN ADULTS/TREATMENT OF PRIMARY DYSMENORRRHEA/RELIEF OF THE SIGNS AND SYMPTOMS OFOSTEOARTHRITIS AND ADULTS RHEUMATOID ARTHritis		

Indication #1: The signs and symptoms of osteoarthritis The signs and symptoms of adult rheumatoid arthritis dymenorrhea - Date Entered: 11/15/01

Status: A full waiver was granted for this Indication.

Reason for This Waiver: Other- see comments

Comments: Bextra was granted a waiver per request submitted on submission of the NDA

This page was printed on 11/15/01

/S/ _____ 11/15/01

Signature Date

DEBARMENT STATEMENT

Pursuant to section 306 (k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant did not and will not employ or otherwise use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)] in connection with this application.

Richard Shubart 2/14/01
Richard Shubart
Senior Director
Global R&D Quality Assurance

RECORD OF A TELECON

DATE: Oct. 2, 2001/3:00 pm

PARTICIPANTS: Dr. Bull and Ms. Walling/FDA and Dr. R. Spivey/Searle

SUBJECT: [redacted]
21-341/valdecoxib

Dr. Spivey called to follow-up on the concern that the FDA may have regarding the safety data for [redacted] from the [redacted] study and how this might impact valdecoxib, especially in the setting of acute pain.

Dr. Bull replied that the [redacted] population is different from the OA/RA and the route of administration is different for the drugs. We have a level of concern for the oral use for acute pain. The concern was made known to Searle by Dr. Goldkind to keep the communication channel open during the review and make our views know sooner rather than later.

Dr. Bull indicated that we would be having some discussion with them in the next couple of weeks to help understand appropriate settings for the use of valdecoxib in the presence of "the noise around COX-2s".

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 24, 2001

APPLICATION NUMBER: NDA 20-998 Celebrex and NDA 21-341 Valdecoxib

BETWEEN:

Name: Eva Essig
Peter East
Representing: Pharmacia

AND

Name: Larry Goldkind, MD Deputy Division Director
Joel Schiffenbauer, MD Medical Reviewer
Division of Anti-Inflammatory, Analgesic, & Ophthalmic Drug Products, HFD-550

SUBJECT: Feedback on the status of the acute pain sNDA for Celebrex and Valdecoxib NDA.

Drs Goldkind and Schiffenbauer returned a call from the regulatory affairs office from Pharmacia. Eva Essig and Peter East requested feedback on the status of the acute pain sNDA for Celebrex as well as the Valdecoxib NDA. Joel Schiffenbauer and Larry Goldkind spoke briefly informing Eva Essig that at this point, Celebrex appeared approvable for acute pain but that we anticipated making some changes to the proposed label and beginning negotiations within several days of receiving an electronic copy of the current approved label for Celebrex.

Dr. Goldkind informed Peter East that at this time Valdecoxib appeared approvable for the OA and RA indications at 10 mg but that the safety concerns identified in the —— study represented issues that may prevent approval for the acute pain indication.

Eva and Peter expressed appreciation for the feedback and the call ended cordially.

Larry Goldkind, MD Date
Deputy Division Director

Food and Drug Administration
Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products, HFD-550

From: Sharon A. Schmidt
Direct Line: 301-827-2536
Div. Phone: 301-827-2090
FAX: 301-827-2531

DATE: June 6, 2001

TO: **Name** Peter East
Company Searle
City Skokie **State** Illnois
Phone 847-982-8606

FAX 847-982-8152

Number of Pages (Including Cover Page) __2___

Additional Message:
Re: NDA 21-341

Follows is a request from the Statistical reviewer Laura Lu Hong.

Sharon A. Schmidt
Project Manager

Corrected fax

NDA 21-341
REQUEST from the Statistical Reviewer June 6, 2001

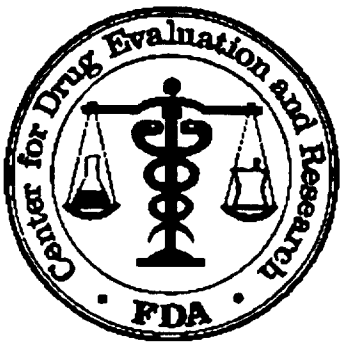
1). Please provide MS word document for the final study report of the following studies:

[redacted] studies: 058, 059, 064, 080, 93-014
[redacted] studies: 010, 011, 032, 033, 052, 072
Primary dysmenorrhea studies: 065, 066
[redacted] nalgesia studies: 024, 037, 93-022
[redacted] nalgesia studies: 038, 051, 93-035
Osteoarthritis studies: 049, 053
Rheumatoid arthritis studies: 060, 061
GI studies: 047, 048, 803

2). Please provide a by-patient data set (SAS transport) for each of the studies listed in 1). Each data set should include patient number, treatment code, center codes (pooled and un-pooled), patient demographics and baseline characteristics, patient disposition (time to withdrawal (study duration) and type of withdrawal), primary and secondary efficacy (safety for GI studies) variables (time to event should be included for survival type of analysis). Please provide detailed label for each variable in the data sets.

3). Please provide Kaplan-Meier Estimators (plots) to drop-out rates due to lack of efficacy and adverse events for each of the studies listed 1) in MS word.

4). If significant center by treatment interaction ($p<0.1$) is found in primary results of a study, please provide the center code (un-pooled) of the centers with negative results (active treatment worse than placebo).



Food and Drug Administration
Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products, HFD-550

From: Sharon A. Schmidt
Direct Line: 301-827-2536
Div. Phone: 301-827-2090
FAX: 301-827-2531

DATE: April 18, 2001

TO: **Name** Peter East
Company Searle
City Skokie **State** Illnois
Phone 847-982-8606

FAX 847-982-8152

Number of Pages (Including Cover Page) __1____

Additional Message:
Re: NDA 21-341

Follows is a request from the PK reviewer, Veneeta Tandon:

Please provide individual subjects plasma and urine concentration data and individual subject PK parameters along with individual subject demographics and treatment groups for the replicate design BE studies. These study numbers are N91-97-02-009 and N91-99-02-050. Please provide the data electronically in excel format. The data for only study N91-99-02-056 has been provided earlier. Also provide the same for Study N91-00-02-078, as this has not been provided earlier.

Sharon A. Schmidt
Project Manager

Food and Drug Administration
Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products, HFD-550

From: Sharon A. Schmidt
Direct Line: 301-827-2536
Div. Phone: 301-827-2090
FAX: 301-827-2531

DATE: April 6, 2001

TO: **Name** Peter East
Company Searle
City Skokie **State** Illnois
Phone 847-982-8606

FAX 847-982-8152

Number of Pages (Including Cover Page) __8____

Additional Message:
Re: NDA [redacted] 21-341

Follows is a request from the Pk reviewer, Veneeta Tando.
We need this ASAP. Thanks

/S/

Sharon A. Schmidt
Project Manager

Re: Warfarin Drug Interaction Study (013 and 075):

Study 013: Please explain the discrepancy between the plasma concentration time profile for warfarin on page 83-84 of volume 1.122 and that of the PK parameters and plasma concentration data provided on pages 51, 236-244. The figure shows that the plasma concentrations are higher in the warfarin+paracoxib treatment group, yet the data and PK parameters show a decrease in the exposure. The figure provided in the summary volume shows an opposite trend than that of the study report in Vol 1.122 (plasma concentration lower in the parecoxib+warfarin group). In the label, the last sentence says that there was a slight increase in the plasma concentration of R-warfarin, not S-warfarin. The raw data as reviewed indicates an increase in plasma concentration of both R and S-warfarin. Please explain these differences and an explanation of why one is right and the other wrong. All data in the Appendix indicates a decrease in concentration, except the individual subjects raw data as provided in the excel spreadsheet to the reviewer. Some pages of the NDA submission are attached for reference. Please provide explanations and reanalysis of the data as needed. All information should be provided electronically to the reviewer.

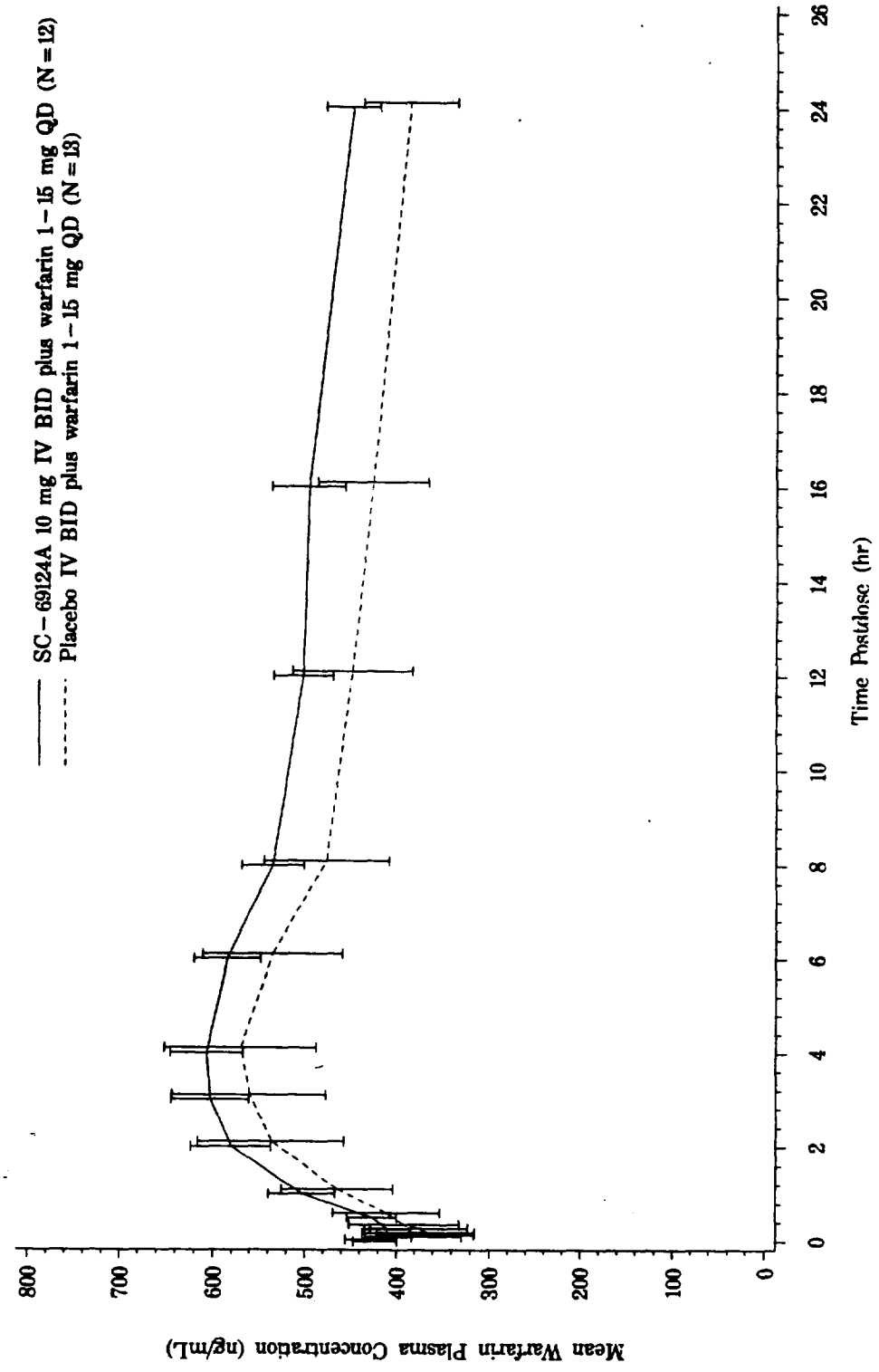
The decrease in the LSM ratios in this study is opposite to that of Study 075. Please explain this difference as well.

Study 075: Please provide a Figure of INR values (not PT) over time (Day -10 through Day 8) as provided for Study 013 in the PK summary, figure F27, page 200.

APPEARS THIS WAY
ON ORIGINAL

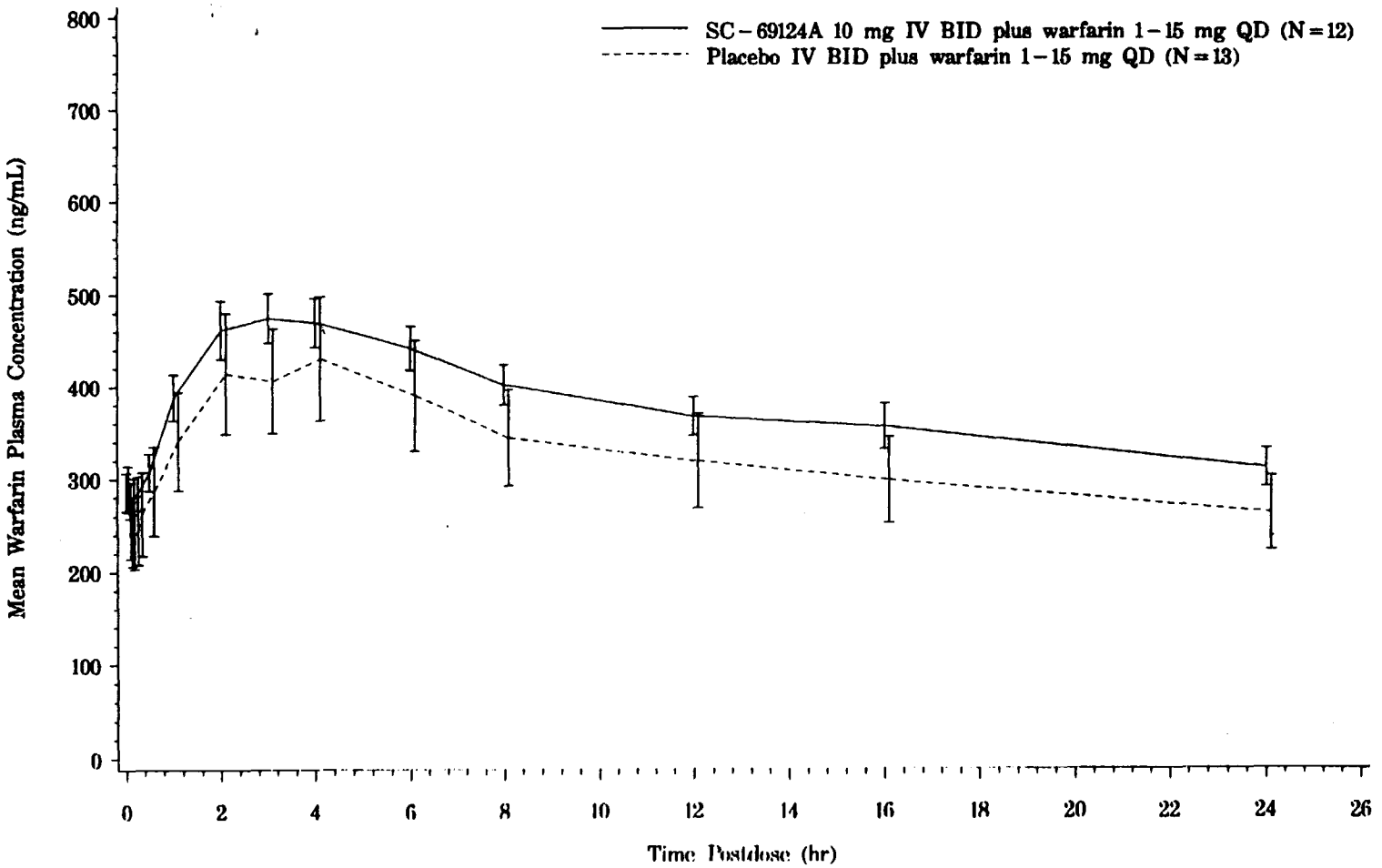
SC-69124A IV WARFARIN INTERACTION PK STUDY
N93-97-02-013

Figure 2.2.1
Mean (+/- SEM) Warfarin Plasma Concentration (ng/mL) 0-24 Hours Postdose on Day 7 by Treatment Group: R-Enantiomer



SC-69124A IV WARFARIN INTERACTION PK STUDY
N93-97-02-013

Figure 2.2.2
Mean (+/- SEM) Warfarin Plasma Concentration (ng/mL) 0-24 Hours Postdose on Day 7 by Treatment Group: S-Enantiomer



SC-69124A IV WARFARIN INTERACTION PK STUDY
N93-97-02-013

APPENDIX 2.2.2
S-ENANTIOMER DOSE ADJUSTED WARFARIN PLASMA CONCENTRATION (ng/mL) SUMMARY

ALL RANDOMIZED SUBJECTS

DAY 7	SC-69124A 10 MG IV BID PLUS WARFARIN 1-15 MG QD (N=12)	PLACEBO IV BID PLUS WARFARIN 1-15 MG QD (N=13)
PREDOSE (-15 MIN)		
N	12	13
MEAN	72.39	75.47
STD DEV	34.086	29.357
MEDIAN	64.10	74.67
RANGE		
2 MIN POSTDOSE		
N	11	13
MEAN	69.14	72.45
STD DEV	33.580	27.246
MEDIAN	60.60	63.00
RANGE		
5 MIN POSTDOSE		
N	12	13
MEAN	69.77	71.49
STD DEV	31.693	26.134
MEDIAN	63.60	66.33
RANGE		
10 MIN POSTDOSE		
N	12	13
MEAN	70.94	73.62
STD DEV	32.214	28.246
MEDIAN	64.80	64.67
RANGE		
15 MIN POSTDOSE		
N	12	13
MEAN	71.42	80.02
STD DEV	30.807	44.078
MEDIAN	64.20	64.00
RANGE		

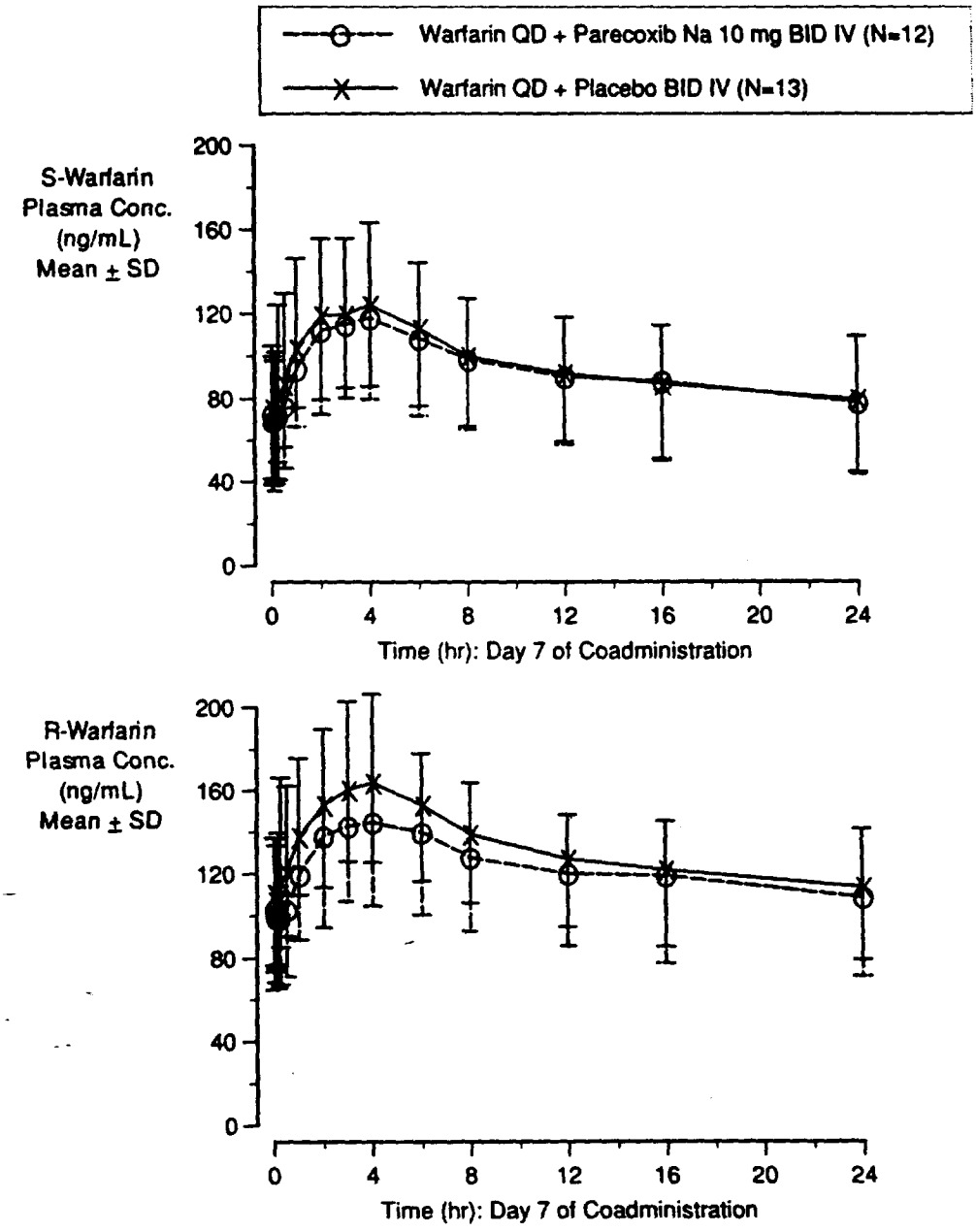
SC-69124A IV WARFARIN INTERACTION PK STUDY
N93-97-02-013

APPENDIX 2.2.1
R-ENANTIOMER DOSE ADJUSTED WARFARIN PLASMA CONCENTRATION (ng/mL) SUMMARY

ALL RANDOMIZED SUBJECTS

DAY 7		SC-69124A 10 MG IV BID PLUS WARFARIN 1-15 MG QD (N=12)	PLACEBO IV BID PLUS WARFARIN 1-15 MG QD (N=13)
PREDOSE (-15 MIN)			
	N	12	13
	MEAN	102.98	110.71
	STD DEV	34.646	26.586
	MEDIAN	90.35	101.25
	RANGE		
2 MIN POSTDOSE			
	N	11	13
	MEAN	100.90	106.93
	STD DEV	36.198	30.148
	MEDIAN	91.33	98.80
	RANGE		
5 MIN POSTDOSE			
	N	12	13
	MEAN	98.99	106.65
	STD DEV	33.510	26.904
	MEDIAN	87.79	101.40
	RANGE		
10 MIN POSTDOSE			
	N	12	13
	MEAN	99.79	109.41
	STD DEV	34.267	30.340
	MEDIAN	88.63	99.60
	RANGE		
15 MIN POSTDOSE			
	N	12	13
	MEAN	99.06	116.00
	STD DEV	31.960	50.026
	MEDIAN	89.28	101.00
	RANGE		

Figure F26. **Mean (SD) Dose Adjusted Plasma Concentrations of S-Warfarin (Upper Panel) and R-Warfarin (Lower Panel) in Healthy Subjects Following Coadministration of Racemic Warfarin QD With Parecoxib Sodium 10 mg BID IV or Placebo.**



Reference: Report No. N93-99-16-013. (49)

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Food and Drug Administration
Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products, HFD-550

From: Sharon A. Schmidt
Direct Line: 301-827-2536
Div. Phone; 301-827-2090
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DATE: April 5, 2001

TO: **Name** Peter East
Company Searle
City Skokie **State** Illnois
Phone 847-982-8606

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Number of Pages (Including Cover Page) __1____

Additional Message:
Re: NDA 21-341

Peter,

It is indicated in vol 6.15b(now vol 1.139) page 8 that a Diskette containing data sets for the PK/PD analysis and NONMEN control files will be provided separately. These are not included in the submission. Please provide the diskette for the PK-PD analysis as well as the population analysis. If already provided, please indicate its location

Sharon A. Schmidt
Project Manager

Food and Drug Administration
Division of Anti-Inflammatory, Analgesics and Ophthalmic Drug Products, HFD-550

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Number of Pages (Including Cover Page) __2____

Additional Message:
Re: NDA 21-341

Follows is a request from the PK reviewer, Veneeta Tandon:

1. Please electronically provide individual subject INR values at the various days (days -10 through Day 7) in an excel spreadsheet format with 'Days' as columns and 'subject IDs' as rows for Study 075. Also include subject demographics on a separate sheet.

2. Re: Drug-drug Interaction Studies: The long-term storage stability data for a lot of drugs were not reported in the assay validation report as they were ongoing at the time the report was made. Please provide an update on the long-term storage stability data for such drugs (eg. Glyburide, ketoconazole, methotrexate, dextromethorphan or any others that were not reported).

Sharon A. Schmidt
Project Manager