CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-998/S-010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

Drug Substance Patent

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

Patent #	Owner	Title	Expiration
5,466,823	G.D. Searle & Co.	Substituted Pyrazolyl Benzenesulfonamides	Nov. 30, 2013

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

Drug Product (Composition) Patent

The following U.S. Patent contains claims directed to formulations/dosage forms of the drug substance, celecoxib, which is the subject of the present application:

Patent #	Owner	Title	Expiration
5,563,165	G.D. Searle & Co.	Substituted Pyrazolyl Benzenesulfonamides for the Treatment of Inflammation	Nov. 30, 2013

The undersigned declares that the above patent covers the formulations and/or compositions of the drug substance, celecoxib. This drug product is the subject of this application for which approval is being sought.

Drug Product (Method of use) Patent

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

Patent #	Owner	Title	Expiration
5,760,068	G.D. Searle & Co.	Substituted Pyrazolyl Benzenesulfonamides for the Treatment of Inflammation	Jun. 2, 2015

The undersigned declares that the above patent covers the methods of using the drug substance, celecoxib. This drug product is the subject of this application for which approval is being sought.

Patent Owner

The undersigned certifies that the above listed patents are assigned to G.D. Searle & Co., who is also the NDA applicant.

EXCLUSIVITY SUMMARY for NDA # 20-998 SUPPL # 010
Trade Name Celebrex™ Generic Name celecoxib
Applicant Name G.D. Searle & Co. HFD-550
Approval Date 17-October-01

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/__/NO /__X_/

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

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

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

   YES /_X__/ NO /___/

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

   _____

   _____

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

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

_____

_____

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

YES /___/ NO /_X_/

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

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

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

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

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

YES /___/ NO /_X_/

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

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

1. Single active ingredient product.

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

YES /_X_/ NO /_/

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

NDA # **20-998** **celecoxib**

NDA # **21-156** **celecoxib**

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 /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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

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

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

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

YES /_X__/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the

investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES /__X/ NO /___/

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

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

YES /___/ NO /__X_/

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

YES /___/ NO /_X__/

If yes, explain: _____

_____

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

YES /___/NO /_**X**__/

If yes, explain: _____

_____

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

Investigation #1, Study # **N49-99-02-129**

Investigation #2, Study # **N49-99-02-130**

Investigation #3, Study # **N49-97-02-070**

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

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

Investigation #1 YES /___/ NO /_**X**__/

Investigation #2 YES /___/ NO /_**X**__/

Investigation #3 YES /___/ NO /__X__/

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

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

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

Investigation #1 YES /___/ NO /__X__/

Investigation #2 YES /___/ NO /__X__/

Investigation #3 YES /___/ NO /__X__/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #1, Study # **N49-99-02-129**

Investigation #2, Study # **N49-99-02-130**

Investigation #3, Study # **N49-97-02-070**

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 # **48,395** YES /_X_/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # **48,395** YES /_X_/	NO /___/ Explain: _____
	_____
	_____

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

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____

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

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

Barbara Gould ***October 18, 2001***
Signature of Preparer Date
Title: ***Project Manager***

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD-550/Division File

HFD-550/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

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020998
Trade Name: CELEBREX
Generic Name: CELECOXIB
Supplement Number. 010 **Supplement Type:** SE1
Dosage Form:
Regulatory Action: OP **Action Date:** 12/19/00
COMIS Indication: FOR THE ACUTE OR CHRONIC USE IN THE TREATMENT OF THE SIGNS AND SYMPTOMS OF OSTEOARTHRITIS AND RHEUMATOID ARTHIRITIS AND FOR THE MANAGEMENT OF PAIN

Indication #1: Management of actue pain in adults
Treatment of primary dysmenorrhea
Label Adequacy: Other - see comments
Formulation Needed: Other
Comments (if any) 18-Oct-01 Celebrex was granted waiver per request submitted on April 12, 2001.

Lower Range	Upper Range	Status	Date
0 years	16 years	Waived	
10/16/01			

Comments:

This page was last edited on 10/18/01

Signature

18-Oct-01
Date

DEBARMENT STATEMENT

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

SEARLE

December 18, 2000

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Jonca Bull, M.D.
Director
Division of Anti-inflammatory, Analgesic
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, MD 20850

Celebrex® (celecoxib)
NDA 20,998
Supplemental NDA

Dear Dr. Bull,
Pursuant to 21CFR 314.70, we are submitting a Supplemental New Drug Application for Celebrex.

This application seeks approval for the following indications:

1. The management of acute pain in adults

2. For the treatment of primary dysmenorrhea

This application consists of 17 studies:

Post-oral surgery: 5 studies (4 of which have previously been reviewed as part of NDA 20,998 and are re-submitted here for ease of reference).

Post-surgical pain: 9 studies (3 of which have previously been reviewed as part of NDA 20,998 and are re-submitted here for ease of reference).

Musculo-skeletal pain: 1 study

Primary dysmenorrhea: 2 studies

The studies in primary dysmenorrhea are submitted to support both of the indications listed above.

In submitting the draft proposed labeling you will note that there have been two prior supplements S-008 (submitted 4/15/00) and S-009 (submitted 6/12/00). Approval of S-008 was received December 1, 2000, S-009 is still pending. The draft label included herein comprises these prior supplements as well as the proposed changes with respect to this supplement.

The entire submission is presented in Electronic form, with all portions except for items 11 and 12 also available in paper.

The submission will be presented on two CD-ROM discs, comprising less than one gigabyte in total storage requirements.

The submission is virus free, checked using McAfee ViruScan version 4.0.3 using Virus Definitions 4.0.4109 from 12/1/2000.

The following gives a hierarchical representation of this dossier and includes the folder names for the electronic submission:

Item(s)	Comments	Paper Volume Location	Electronic Submission Folder Name
1: Index and cover letter	Paper and Electronic	1	(main folder)
2: Labeling	Paper and Electronic	1	Labeling
3: Summary	Paper and Electronic	2	Summary
4: Chemistry, Manufacturing and Control	Paper and Electronic	2	\cmc\cacatex.pdf
5: Nonclinical Pharmacology and Toxicology	(not applicable)	None	-
6: Human Pharmacokinetics and Bioavailability	(not applicable)	None	-
7: Clinical Microbiology	(not applicable)	None	-
8: Clinical Data Section	Paper and Electronic	3-44	Clinstat
9: Safety Update Report	Paper and Electronic	1	Update
10: Statistical Section	Paper and Electronic (Copy of Item 8)	3-44	Clinstat
11: Case Report Tabulations	Electronic	-	CRT
12: Case Report Forms	Electronic	-	CRF
13: Patent Information	Paper and Electronic	1	other\patent.pdf
14: Patent Certification	(not applicable)	None	-
15: Establishment Description	(not applicable)	None	-
16: Debarment Certification	Paper and Electronic	1	other\debar.pdf
17: Field Copy Certification	(not applicable)	None	-
18: User Fee Cover Sheet	Paper and Electronic	1	other\userfee.pdf
19; Other	Paper and Electronic	1	Other

The overall index to this supplement is provided Volume 1. In addition, Items 3 and 8 each have their own indices appearing in Volumes 2 and 3, respectively. Each paper

volume contains its own detailed table of contents. Volume numbers for this supplement are assigned consecutively beginning with 1 and ending with 44. The pagination is by volume, page numbers are located in the lower right hand corner of each page. The summary documents contained in Items 3 and 8 are annotated to the volume and first page of the referenced document. These annotatations appear in the reference section of the summary documents.

The product label for this supplement is provided as follows;

1. A line-formatted document, which contains the proposed product label including the data from this supplement, the changes submitted 12-June-2000 in S-009 and also the changes submitted 25-April-2000 in S-008 which was approved on 1-December-2000. A diskette with the MS-Word version of this document is located within a marked envelope in Volume 1.

2. A side-by-side document of S-008, S-009 and the additional changes proposed in this supplement. The changes for this supplement are annotated to the report and summary volume locations contained in this supplement.

3. A photocopy of the printed version of the approved product label dated 23-December-2000; the recently approved changes (12/01/00) for S-008 and S-009 shown in bold type on the right hand column. The label changes to this supplement are shown in italics on the right hand column.

Under the pediatric rule 21 CRF 314.55 (c) we request a waiver from the requirement to conduct pediatric studies in pain and dysmenorrhea as described in CFR 314.55 (a).

A check for the supplemental NDA userfee in the amount of $142,870.00 was received at 8:41 am on Monday, December 11, 2000 by Mellon Bank (FDA 360909) and signed for by ———.

Should you have any questions regarding the content of the SNDA, please contact the undersigned at (847)-982-8155 or (84)-982-8090 (fax)

Sincerely,

Winifred M Begley

Winifred M. Begley
Senior Director
Regulatory Affairs
phone (847) 982-8155
fax (847) 982-8090

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
G. D. Searle & Co.	12/18/2000
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(847) 982-8155	(847) 982-8090

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
4901 Searle Parkway
Skokie, IL 60077

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 20-998**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
celecoxib	Celebrex™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide	SC-58635

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsule	100 and 200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
For the management of acute pain and primary dysmenorrhea

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☒ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 44

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONI

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 48,395 (SC-58635) IND 53,734 (SC-65872 in Migraine) NDA 21-294 (Parecoxib Sodium for Injection)
IND 52,153 (SC-65872) IND 52,613 (SC-69124A)

This application contains the following items: *(Check all that apply)*

X	1.	Inde
X	2.	Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
X	3.	Summary (21 CFR 314.50 (c))
	4.	Chemistry section
		A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
		B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
		C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8.	Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
X	9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12.	Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14.	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15.	Establishment description (21 CFR Part 600, if applicable)
X	16.	Debarment certification (FD&C Act 306 (k)(1))
	17.	Field copy certification (21 CFR 314.5 (k) (3))
X	18.	User Fee Cover Sheet (Form FDA 3397)
X	19.	OTHER (Specify) Pre S/NDA Meeting Minutes

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Winifred M Begley	Winifred M. Begley, Senior Director, Worldwide Regulatory Affairs	12/18/2000

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
4901 Searle Parkway Skokie, IL 60077	(847) 982-8155

Public reporting burden for this collection of information is estimated to average 40 hours 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:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

MEMORANDUM OF TELECON

DATE: September 26, 2001

APPLICATION NUMBER: NDA 20-998/S-010

BETWEEN:

Name:	Mark Fletcher, MD	Kenneth Verburg, PHD
	Mona Wahba, MD	Frank Musat
	Lori Shafner, PHD	Neil Wolf
	Steve Geis, MD, PHD	Wnifred Begley
	Andrew Brugger, MD	Eva Essig
	David Jordan, PHD	James Barras
	Representing: Pfizer & Pharmacia	

AND

Name:	Larry Goldkind, MD	Deputy Division Director
	Joel Schiffenbauer, MD	Medical Reviewer
	Barbara Gould	Project Manager
	Division of Anti-Inflammatory, An gesic, & Ophthalmic Drug Products, HFD-550	

SUBJECT: To discuss the wording for the dosing/dosing interval for celebrex acute pain and dysmenorrhea indications

A teleconference was requested by the Division to discuss the wording for the dosing/dosing interval to be used in the label for the acute pain and dysmenorrhea indications for celebrex. The Pharmacia was asked to propose language for the label based on twice a day dosing derived from the time to rescue medication. In terms of dosing it appears that the 200 or 400 mg doses would be appropriate recommended dose. In the post operative orthopedic studies 40-70% of patient required rescue medication with a median range of 3-8 hours. In the second set of oral surgery studies 60% of patients required rescue medication with a median range of 9 hours and with dysmenorrhea 12 hours was the median range for time to rescue medication.

It was proposed that the initial dose would be a 400 mg loading dose to cover both dysmenorrhea and other pain models with b.i.d. dosing as needed. In terms of clinical the sponsor was asked to add a discussion on ———————and time to rescue under the Clinical Trial section of the label.

Pharmacia agreed to provide a revised label for review early in the week of October 1st. A teleconference will be schedule to discuss the revised label.

Barbara Gould 01-October-01
Barbara Gould Date
Project Manager

Larry Goldkind, MD 01-October-01
Larry Goldkind, MD Date
Deputy Division Director

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/s/

Barbara Gould
10/1/01 07:53:28 AM
CSO

Electronic copy approved 28-Sep-01

Lawrence Goldkind
10/1/01 08:49:58 AM
MEDICAL OFFICER

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 CABG 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

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/s/

Barbara Gould
9/26/01 12:27:01 PM
CSO

Electronic copy approved 26-Sep-01

Lawrence Goldkind
9/29/01 01:35:54 PM
MEDICAL OFFICER

TELECON MINUTES

DATE: July 9, 2001

PARTICIPANTS: Dr. Schiffenbauer and Ms. Walling/FDA and Drs. Essig, Cui, Brugger, Shu, Pritza, and Medich/Searle

SUBJECT: NDA 20-998/S-010/ Celebrex

The call was placed in response to a July 3, 2001 letter from the sponsor requesting a clarification of FDA fax June 26, 2001.

Regarding the scheduling of assessments of pain relief after the first does of study medication;

Dr. Schiffenbauer stated that since the sponsor did not assess pain relief and intensity at 24 hours following the first dose, they should submit what they have (maximum pain intensity) at day2 (bedtime) along with duration between first dose and bed time on day2.

The sponsor should provide the data on the maximum pain intensity on all patients and breakdown the frequency and time of mild, moderate and severe pain for studies 129 and 130.

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/s/

Mary Jane Walling
8/3/01 08:48:25 AM
CSO

Joel Schiffenbauer
8/3/01 02:23:26 PM
MEDICAL OFFICER

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Eva Essig, Ph.D.	**From:** Yoon Kong, Pharm. D.
Fax: (847) 982-8090	**Fax:** 301-827-2531
Phone: (847) 982-8980	**Phone:** 301-827-2090
Pages: 2 (including cover page)	**Date:** June 26, 2001
Re: NDA 20-998/S-010	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

● Comments:

Dear Eva,

In order to facilitate review of this supplemental application, please provide the following information as soon as it can be made available.

For both studies 129 and 130:

1) Analysis using the modified ITT population (to include those patients who took study medication) for cycle 1 only, to include all primary and secondary endpoints.

2) Modified ITT population (to include those patients who took study medication who completed any cycle for all cycles combined using the cross over design.*

***Please note:** The analyses in 2 should include data for SPID8, 12; TOTPAR8, 12; time to rescue medication; and data at 12 and 24 hours for PID, PR, PRID (12 and 24 hour data should be for those individuals not requiring rescue medication at 12 hours). Include pairwise p values for all analyses described above as well as the pairwise p-values for the original analyses for the endpoints above.

In addition, please utilize the following methods of imputation and subsequently, provide the information generated.

Method of imputation:

1. If only one observation (one cycle) is available: for each individual patient impute this to other cycles.

2. If data is available from 2 cycles: for each individual patient if placebo is missing, impute results from celecoxib for the placebo; if celecoxib is missing impute data from placebo; if naproxen is missing, then impute data from placebo.

Please do not hesitate to call me if you have any further questions or need clarification concerning this fax.

Thank you.

Yoon Kong, Pharm.D.

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/s/

Yoon Kong
6/26/01 01:47:42 PM
CSO

Already reviewed and oked hard copy, please review and sign in DFS. Th
ank you.

Joel Schiffenbauer
6/26/01 02:00:56 PM
MEDICAL OFFICER

MEETING MINUTES

MEETING DATE: September 13, 2000 **TIME:** 11 a.m.-12 noon **LOCATION:** CORP S300

IND#: 48,395 **Meeting Request Submission Date:** July 11, 2000
Briefing Document Submission Date: July 21, 2000
Additional preparation documents: August 4, 2000 (individual study tables from 3 European pain trials)
August 8, 2000 (draft table of contents)

DRUG: Celebrex® (celecoxib capsules) Capsules, 100 mg and 200 mg

SPONSOR/APPLICANT: G.D. Searle

TYPE of MEETING: pre-NDA

FDA PARTICIPANTS:

Robert Delap, M.D., Ph.D.	Office Director, Office of Drug Evaluation V
Jonca Bull, M.D.	Acting Division Director, DAAODP
James Witter, Ph.D.,M.D.	Medical Officer Reviewer
Lawrence Goldkind, M.D.	Medical Team Leader, Anti-inflammatory
Kent Johnson, M.D.	Medical Officer
Robert Osterberg, R.Ph., Ph.D.	Acting Pharmacology/Toxicology Team Leader
Laura Lu, Ph.D.	Statistics Reviewer
Yoon Kong, Pharm.D.	Project Manager

INDUSTRY PARTICIPANTS:

Searle

Winifred Begley	Senior Director, Regulatory Affairs
Dr. A. Brugger	Senior Director, Clinical Research
O. Coughlin	Senior Project Director, Project Management
Dr. S. Geis	Vice-President ,Clinical Research
J. Gyzen	Director Electronic Submissions
M. Novak	Assistant Director, Clinical Research
J. Oidtman	Senior Director, Global Regulatory Operations
Dr. N. Ridge	Associate Director, Clinical Research
Dr. Y.F. Yang	Senior Statistician
Dr. W. Zhao	Director, Clinical Statistics

Pfizer

S. Cristo	Associate Director, Drug Regulatory Affairs
Dr. W. Frost	Senior Associate Director Therapeutic Area Leader
Dr. L. Loose	Director, Clinical Development
Dr. M. Wahba	Senior Associate Director, Clinical Development

MEETING OBJECTIVES: To discuss sponsor's questions to Agency submitted in meeting package dated July 21, 2000, with respect to expanding indications for Celebrex for management of acute pain, treatment of primary dysmenorrhea, and relief of the signs and symptoms of

QUESTIONS for DISCUSSION:

Proposed Organization and Content of Celecoxib sNDA ISE

1. **Is the overall organizational plan of the ISE satisfactory?**

   FDA indicated that it appears to be reasonable.

2. **In presenting the data for the management of acute pain and treatment of primary dysmenorrhea, we plan to resubmit the pain studies summarized in the original celecoxib NDA as well as include pain studies completed subsequent to the original NDA submission. Is that acceptable?**

   FDA indicated that it appears acceptable to submit and stated that the adequacy of the data will be a review issue.

3. **In presenting efficacy results for the management of acute pain and treatment of primary dysmenorrhea, the following efficacy measurements will be discussed in the text of the report:**

- **Time specific PID (categorical), PR and PRID**
- **SPID and TOTPAR**
- **Time and percent of patients with onset of analgesia**
- **Time and percent of patients who took rescue medication**
- **PPR and PPID (categorical)**

The primary efficacy analysis will utilize the LOCF method of imputing missing values. Analyses utilizing the BOCF and WOCF methods of imputation will also be provided. Is this acceptable?

Following points made by the FDA:

- Generally, favors the ITT with LOCF (given primacy in analyses) analyses. Sponsor agreed with this approach.
- Considers the BOCF and WOCF as meaningful secondary analyses. Sponsor stated that these types of analyses would be contained in the appendices of the application.
- Pre-planned statistical analyses should be identified for each study. Any modifications/adjustments made, should be described, and the impact of such changes (e.g., need for statistical adjustments) should be described.
- Data presented in the ISE is an efficient way to look at all studies. Any important analyses and amendment to the initial design should be noted in the ISE.
- Consistency of results and endpoints across studies will be important.

Additional FDA Comments:

1) FDA asked whether the primary endpoints that sponsor selected would be the same for all studies. Sponsor informed FDA that this would be the case, except for the primary dysmenorrhea studies.

2) FDA asked if sponsor is planning to reformulate drug product. In study 139, there was an alcohol suspension formulation. The sponsor informed FDA that the current sNDA will only include the celecoxib capsule formulation, but they will follow up with this in more detail.

4. **The following efficacy measures for the management of acute pain and treatment of primary dysmenorrhea will also be included in the appendices of the ISE:**

- **Time and percent of patients with onset of perceptible pain relief**
- **Time and percent of patients with meaningful pain relief**

Is this acceptable?

FDA indicated that this appears to be acceptable.

5. **Analyses of pooled results for the management of acute pain and treatment of primary dysmenorrhea will be conducted to assess the following subgroups:**

- **Gender**
- **Ethnic origin**
- **Age**

Is this acceptable?

➢ This is generally acceptable, however, the sponsor would need to provide additional data to support appropriateness of pooling of results across different studies.

FDA asked sponsor to confirm why they would want to pool data from individual studies, in addition to analyzing each individual study. Sponsor noted that they would include their justification for pooling data within the ISE. According to sponsor, pooling would provide better estimation of subgroup effects. The sponsor stated that studies 085 and 086 are similar in study design and population and there is no interaction in terms of efficacy and demographics, hence, pooling of data is valid in this case. Also, sponsor explained further that they would assess the data from the dental and post-operative studies separately.

At this juncture in the meeting, sponsor presented slides (slides #16 and #17- see attachments).

Sponsor asked whether they could pool data by similar study design using the same population. FDA stated that sponsor could pool very similar studies for subgroup and safety analyses. However, primary analyses cannot be pooled.

➢ Expressed concern with sponsor using results of pooled data to support a labeling claim.

➢ It would be problematic if sponsor finds analysis of primary endpoints not to be successful, and then would turn to the subgroup analysis as primary vs. supportive. Sponsor assured FDA that they did not intend to claim the subgroup analysis in terms of pooled data, but would probably use this as supportive evidence.

➢ Sponsor should provide a justification for pooling data and define how this data varies from primary study results.

- Sponsor should be attentive to gender analysis in analgesia (e.g., differences in gender in pain studies). Sponsor indicated that they believe that have data that differs across models, studies and groups.

[

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Proposed Organization and Content of Celecoxib sNDA ISS

1. **Is the overall organizational plan of the ISS satisfactory?**

   FDA stated that this appears to be acceptable.

2. **In presenting the safety data, we plan to resubmit the pain studies summarized in the original celecoxib NDA as well as include pain studies completed subsequent to the original NDA submission. Is that acceptable?**

   FDA stated that this appears to be acceptable.

3. **In discussing the safety data we plan to pool data from similar studies grouped as follows:**
   - **Post-oral surgery studies**
   - **Post-gynecological and post-orthopedic surgery studies**
   - **Primary dysmenorrhea studies**

   The following European studies do not lend themselves to pooling and will be discussed individually:

   - **European post-surgical pain study**
   - **European narcotic-sparing post surgical pain study**
   - **European low back pain study**

   Is this acceptable?

   FDA stated that this appears to be acceptable.

4. **Analyses will be conducted in the following subgroups:**
   - **Gender**
   - **Ethnic origin**
   - **Age**

   Is this acceptable?

   FDA stated that this appears to be acceptable.

Labeling

1. **We (Searle) are seeking approval for the management of acute pain, the treatment of primary dysmenorrhea and the treatment of ————————**

2. **In the adverse event section we plan to discuss adverse events encountered in the studies of primary dysmenorrhea in a separate section. This section would be similar to the FAP adverse event section. A draft of the language is: [**

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With respect to labeling, FDA indicated that we would need to view the data before labeling would be established for the use of Celebrex for various indications. These issues are primarily review issues.

FDA also pointed out that we would examine carefully the data presented and tries to determine the most appropriate means of conveying this information via the labeling of the drug product.

As mentioned earlier in this discussion, FDA would like to discuss such issues in an EOP2 meeting in the near future for sponsor's drug development plan for the ———————— indication that sponsor is seeking.

Sponsor gave a slide presentation with the remaining time left in the meeting (see attachments).

ACTION ITEMS:

1. Sponsor will provide slides that were presented in the meeting.

2. FDA will provide the ———— article on ———————— to sponsor.

Yoon Kong, Pharm.D.
Project Manager

Concur:
Jonca Bull, M.D.
Acting Division Director, DAAODP

Attachments: Sponsor's slide presentation (NDA 20-998/S-009, serial number 596).

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