CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20998/S007

ADMINISTRATIVE DOCUMENTS

PROJECT MANAGER REVIEW OF LABELING

The 12-23-99 draft package insert for NDA 21-156 for Celebrex was reviewed and compared with the approved label text found on the CDER shared drive.

In CLINICAL PHARMACOLOGY, Mechanism of Action, "In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors." was added as the last sentence.

In CLINICAL PHARMACOLOGY, Pharmacokinetics, *Absorption*, the first paragraph was changed to:

> Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional to 200 mg BID; at higher doses there are less than proportional increases in Cmax and AUC (see Food Effects). Absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before day 5.

In CLINICAL PHARMACOLOGY, Pharmacokinetics, *Food Effects*, "Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in Cmax and AUC which is thought to be due to the low solubility of the drug in aqueous media." was added. CELEBREX capsules can be administered without regard to the timing of meals." was deleted. The following sentence was also added, "CELEBREX, at doses up to 200 mg BID can be administered without regard to timing of meals. Higher doses (400 mg BID) should be administered with food." The complete section reads as follows:

> When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. Coadministration of CELEBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC. CELEBREX, at doses up to 200 mg BID can be administered without regard to timing of meals. Higher doses (400 mg BID) should be administered with food.

In CLINICAL PHARMACOLOGY, Pharmacokinetics, Hepatic Insufficiency, the second sentence was changed to the following.

> Therefore, the daily recommended dose of CELEBREX capsules should be reduced by approximately 50%, in patients with moderate (Child-Pugh Class II) hepatic impairment.

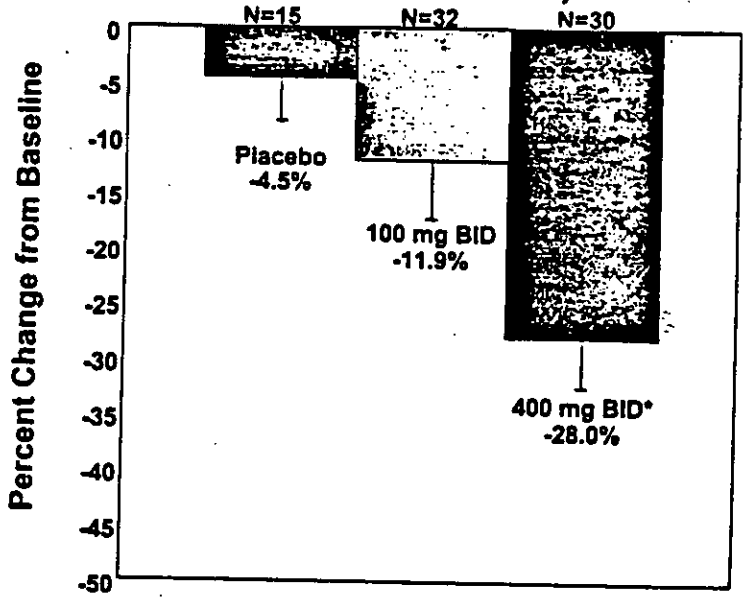
In CLINICAL STUDIES, The following subheading, table and text were added.

Familial Adenomatous Polyposis (FAP): CELEBREX was evaluated to reduce the number of adenomatous colorectal polyps. A randomized double-blind placebo-controlled study was

conducted in 83 patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype.

One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for CELEBREX 400 mg BID, 12% for CELEBREX 100 mg BID and 5% for placebo. The reduction in polyps observed with CELEBREX 400 mg BID was statistically superior to placebo at the six-month timepoint (p=0.003). (See Figure 1.)

Figure 1
Percent Change from Baseline in Number of Colorectal Polyps (FAP Patients)



* p=0.003 versus placebo

CORRESPONDING TABLE AND FIGURE NUMBERS WERE APPROPRIATELY CHANGED IN HEADINGS AND TEXT.

In INDICATIONS AND USAGE, the following was added as the third paragraph.

3) To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance , surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients . It is also not known whether the effects of CELEBREX treatment will persist after CELEBREX is discontinued. The efficacy and safety of CELEBREX treatment in patients with FAP beyond six months has not been studied (See CLINICAL STUDIES, WARNINGS and PRECAUTIONS sections).

In WARNINGS, Anaphylactoid Reactions, " Anaphylactoid reactions were not reported in patients receiving CELEBREX in clinical trials. However," was deleted. The second sentence was changed to "As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX." The following sentence was added. "In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX." The section now reads:

> **Anaphylactoid Reactions**
> As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS - Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

In WARNINGS, the following heading and text were added, all in bold face.

> **Familial Adenomatous Polyposis (FAP): Treatment with CELEBREX in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of CELEBREX. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.**

In PRECAUTIONS, Hepatic Effects, "including CELEBREX . (See ADVERSE REACTIONS – post-marketing experience.)" was added to the following sentence "Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX. (See ADVERSE REACTIONS – post-marketing experience.)"

In PRECAUTIONS, Information for Patients, the following paragraph was added.

> Patients with familial adenomatous polyposis (FAP) should be informed that CELEBREX has not been shown to reduce colo-rectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP-related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving CELEBREX.

PRECAUTIONS, Drug Interactions, *Warfarin*, was modified to the following.

> ***Warfarin:*** Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anti-coagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

In ADVERSE REACTIONS, "arthritis" was added to "Adverse events from controlled arthritis trials:" heading.

In ADVERSE REACTIONS, "From Controlled Arthritis Trials" was added to the Table heading: Adverse Events Occurring in ≥2% Of Celebrex Patients From Controlled Arthritis Trials

In ADVERSE REACTIONS, the "rarely" heading now reads:

Other serious adverse reactions which occur rarely (estimated <0.1%), regardless of causality: The following serious adverse events have occurred rarely in patients, taking CELEBREX. Cases reported only in the post-marketing experience are indicated in italics.

The following changes were made to the "rarely" section.

In **Cardiovascular:** *vasculitis* was added.

In **Gastrointestinal:** was deleted.

The following was added.

Liver and biliary system: Cholelithiasis, *hepatitis, jaundice, liver failure*

In **Hemic and lymphatic:** "*agranulocytosis, aplastic anemia, pancytopeni, leukopenia*" were added.

The following was added
Metabolic: *Hypoglycemia..*

In **Nervous system:** "suicide" was added.

In **Renal:** *interstitial nephritis* was added

The following was added.
Skin: *Erythema multiforme, exfoliative dermatitis, Stevens-Johnsons Syndrome, toxic epidermal necrolysis*

In **General:** "*anaphylactoid reaction, angioedema*" was added.

In ADVERSE REACTIONS, the following paragraph was added.

> **Adverse events from the controlled trial in familial adenomatous polyposis:** The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg BID, and two at 400 mg BID) who had prior intestinal surgery.

In DOSAGE AND ADMINISTRATION, "For osteoarthritis and rheumatoid arthritis," was added to the beginning of the first sentence. "For osteoarthritis and rheumatoid arthritis, the lowest dose of CELEBREX should be sought for each patient." The following sentence was also added, " These doses can be given without regard to timing of meals."

In DOSAGE AND ADMINISTRATION, the following heading and text were added.

> **Familial adenomatous polyposis (FAP):** Usual medical care for FAP patients should be continued while on CELEBREX. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg (2 X 200 mg capsules) twice per day to be taken with food.

In DOSAGE AND ADMINISTRATION, the following heading and text were added.

> **Hepatic Insufficiency:** The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class II) should be reduced by approximately 50% (see CLINICAL PHARMACOLOGY – Special Populations).

/S/

12/22/99

Paul F. Zimmerman, Project Manager/date

cc:
Orig NDA 21-156
Div File
HFD-150/PZimmerman
HFD-150/JChiao

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)

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

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
G. D. Searle & Co.	December 17, 1999
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(847) 982-7670	(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 21-156

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

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

CODE NAME (*If any*)
SC-58635

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
capsules	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
For the reduction and regression of adenomatous colorectal polyps in Familial Adenomatous Polyposis patients.

JCATION 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
Amended patent statement

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

NUMBER OF VOLUMES SUBMITTED THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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	IND
ND	IND
INC	IND
IND	NDA 20-998 (Celebrex - celecoxib)

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

	1.	Index
	2.	Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	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))
	8.	Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12.	Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	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)
	16.	Debarment certification (FD&C Act 306 (k)(1))
	17.	Field copy certification (21 CFR 314.5 (k) (3))
	18.	User Fee Cover Sheet (Form FDA 3397)
	19.	OTHER (Specify): Amended patent statement

TIFICATION

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
Anita Piergiovanni	Anita Piergiovanni, M.Sc. Director, Worldwide Regulatory Affairs	12/17/1999

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
4901 Searle Parkway Skokie, IL 60077	(847) 982-7670

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
'ndependence Avenue, S.W.
ington, DC 20201

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PATENT STATMENT 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 and the related supplemental 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 and the related supplemental 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 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 and the related supplemental application:

Patent #	Owner	Title	Expiration
5,760,068	G.D. Searle & Co.	Substituted Pyrazolyl Benzenesulfonamides for the Treatment of Inflammation	Jun. 2, 2015
5,972,986	G.D. Searle & Co.	Method of Using Cyclooxygenase-2 Inhibitors in the Treatment and Prevention of Neoplasia	Oct. 14, 2017

The undersigned declares that the above patents cover methods of using the drug substance, celecoxib, including for the treatment of adenomatous polyps and prevention of colorectal cancer, 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/SNDA applicant.

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

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Patent Owner

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

Anita Piergiovanni

Anita Piergiovanni, MSc
Director of Worldwide Regulatory Affairs
14 Apr 1999

CLAIMED PRODUCT EXCLUSIVITY UNDER 21 USC 355(c)(3)(D)(iii)

The Applicant, G.D. Searle & Co., is claiming exclusivity under 21 CFR §314.108(b)(5) for the celecoxib drug product, which is the subject of the present application.

New Clinical Investigations:

The undersigned certifies that to the best of applicant's knowledge that each of the clinical investigations included in the present application meets the definition of "new clinical investigation" set forth in §314.108(a).

Essential to Approval:

The undersigned certifies that the Applicant has thoroughly searched the scientific literature and, to the best of applicant's knowledge, there are no published studies or publicly available reports of clinical investigation regarding indications of FAP for a celecoxib drug product. The clinical studies contained in this application were essential to approval of the celecoxib drug product.

Conducted or Sponsored by:

The undersigned certifies that the Applicant was not the sponsor named in the Form FDA-1571 for an investigational new drug application (IND), under which the new clinical investigations which are essential to approval were conducted. However, substantial support was provided. A certified statement is provided attesting that the Applicant provided 50% or more of the cost of the study.

Anita Piergiovanni

Anita Piergiovanni, M.D.
Director of Worldwide Regulatory Affairs

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21156	**Trade Name:**	CELEBREX (CELECOXIB) 200MG CAPSULES
Supplement Number:		**Generic Name:**	CELECOXIB
Supplement Type:		**Dosage Form:**	
Regulatory Action:	PN	**Proposed Indication:**	reduction and regression of adenomatous colorectal polyps in Familial Adenomatous Polyposis patients

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Pediatric waiver granted October 7, 1999.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, PAUL ZIMMERMAN

Signature

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.

ONCOLOGY DIVISION MEETING MINUTES

MEETING DATE: February 26, 1998 TIME: 1:00 - 3:00 pm LOCATION: Conf. E, rm 4023

IND/NDA: IND
DRUG: Celecoxib
SPONSOR: NCI-DCP-Chemoprevention Branch and G. D. Searle Pharmaceuticals, Inc.

TYPE of MEETING: 1. Advice on trial design and drug development

PROPOSED INDICATION:

1. Celecoxib is indicated for the regression and prevention of colorectal adenomatous polyps which may lead to the development of colon cancer in patients with Familial Adenomatous Polyposis.

2. Celecoxib is indicated for the regression and prevention of colorectal adenomatous polyps which may lead to the development of colon cancer.

Meeting Request Submission Date:	12.19.97
Briefing Document Submission Date:	12.19.97
Additional Submission Dates:	none

FDA PARTICIPANTS:
Robert J. DeLap, Oncology Division Director
Julie Beitz, Medical Team Leader
Karen Johnson, Medical Reviewer
Wendy Schmidt, Pharm-Tox Reviewer
John R. Senior, G.I. Medical Reviewer, DGCDP/HFD-180
Tony Koutsoukos, Biometrics Team Leader
Ning Li, Biometrics Reviewer
Linda McCollum, CSO 4.28.98

INDUSTRY PARTICIPANTS:
Thomas Darling, Searle, Project Management
Louis Godio, Searle, Statistics
Gary Gordon, Searle, Clinical Research-Oncology
Richard Hubbard, Searle, Clinical Research-Arthritis
Anita Piergiovanni, Searle, Regulatory Affairs
Karen Seibert, Searle, Pharm-Tox
Jeff Sherman, Searle, Clinical Research-Oncology
Bernard Levin, M.D. Anderson Cancer Center
Gary Kelloff, NCI-DCP-Chemoprevention Branch Chief
Ernie Hawk, NCI-DCP-Chemoprevention Branch Reviewer
Caroline Sigman, CCS Assoc., Regulatory Affairs

MEETING OBJECTIVE:

1. To come to an understanding regarding the design of the proposed studies for celecoxib.
2. To discuss the use of surrogate endpoints in the design of the studies.

QUESTIONS for DISCUSSION, FDA RESPONSE and DECISIONS REACHED:

Pre-clinical

1. The studies performed relevant to prevention of colon cancer (in addition to the other pre-clinical work) support the proposed Phase 2-3 and Phase 3 clinical studies in sporadic Adenomatous polyps (SAP).

a. Determination of efficacy will be based on human clinical data.

b. No additional pre-clinical studies are required for the adenomatous polyp indications.

c. Regarding validation of biomarkers, human data is fundamental to demonstrate utility of biomarkers. At this point in time, biomarkers are neither necessary nor sufficient for approval.

Clinical

2. Further to the publication by G. Kelloff et al., (National Cancer Institute: Chemoprevention Branch and FDA participation), "Approaches to the development and marketing approval of drugs that prevent cancer"; Volume 4, 1-10, January/February 1995), please confirm that FDA continues to consider adenomatous polyps as pre-malignant lesions of colon cancer amenable to prevention intervention.

a. FDA considers adenomatous polyps to be neoplastic lesions that may progress to colon cancer and are amenable to a chemopreventive intervention.

b. Depending on the results from clinical trials, a chemopreventive intervention may be identified that prevents or resolves adenomatous colon polyps. Patients receiving the chemopreventive intervention should be followed to assess the incidence of colon cancer in the treated population. It might be possible to demonstrate alternative clinical benefits, such as a reduced need for surgeries or increased retention of the rectal segment.

c. FDA agrees that it may be possible to file an NDA based on effects on adenomatous polyps as a surrogate endpoint.

d. A registry would be helpful for identifying longer term benefits or drawbacks associated with the surrogate endpoint and treatment.

3. The clinical endpoints (parameters) being evaluated in the ongoing FAP studies and the proposed SAP studies are appropriate.

FDA internal meeting comment:

Study 001: A clinically significant reduction in the number of polyps is helpful but may not be sufficient because the overall results in the entire colorectal remnant need to be consistent. Study 001 is exploratory in nature (heterogeneous population, endpoints of uncertain clinical significance). Once this trial is completed, a multicenter trial will be needed, based on a well-defined patient population and evaluation of results using clinically relevant endpoints. A process needs to be defined whereby adequate numbers of patients are enrolled on study so that results for a duration of use in excess of 6 months can be obtained.

Sponsor meeting comments:

a. FAP population is small, studies are difficult to complete, 001 is substantially larger than other published studies.

b. The company can provide additional data that may be reassuring regarding the study population (e.g., study probably includes few if any patients with attenuated form of FAP, and, relatively few patients who have not had surgery have been enrolled.)

Action Items:

1. Company will develop a detailed plan for the statistical analysis including a carefully defined primary analysis; plus information regarding demographic characteristics of patients enrolled.

2. FDA will review this statistical plan and there will be follow-up communication regarding study 001 and possibility of using it as a definitive study.

Study 003: Modulation of COX-2 expression in HNPCC carriers/patients is inadequate for accelerated approval of celecoxib for the prevention of adenomatous polyps.

a. Searle considers Study 003 a supportive study only and accepts this conclusion.

Study 005: As a polyp prevention endpoint, the prevention of subsequent polyps in patients with a cleared colon is acceptable. Based on the literature descriptions (e.g. those describing the Polyp Prevention Trial, PPT, and the Colorectal Adenoma Prevention Trial, CAPS), the period of follow-up may need to be longer than 12 months or the sample size larger to show a difference in polyp incidence. Whether or not patients are treated with study medication for more than one year, consideration should be given to a follow-up period that extends beyond one year, consistent with standard practice for monitoring after the diagnosis of a sporadic polyp. A protocol should be submitted, which among other information provides the rationale for an endpoint chosen to demonstrate clinically significant polyp reduction.

a. FDA needs to review the protocol for Study 005; but it is possible that a one year study with positive results could be adequate for an NDA filing. Longer term data will be of interest and will probably be required.

Study 007: The endpoint is not acceptable for approval. The regression of a single, small, sporadic, unbiopsied, polypoid lesion in the colon is inadequate for use as clinical evidence of a celecoxib effect.

a. Please submit a protocol for Study 007 which describes how this study will protect the patients studied, considering the departure from standard practice that it represents.

4. **The FAP trial supports a submission for this proposed indication: "Celecoxib is indicated for the regression and prevention of colorectal adenomatous polyps which may lead to the development of colon cancer in patients with FAP."**

a. The results from Trial 001 may support the proposed indication; however, a second study may be needed for approval. See question 3.

b. A plan is needed for long term follow-up of the patient population in trial 001, with attention to data collection concerning the incidence of colorectal carcinoma, and the occurrence of further ablative therapy. See question 3.

c. The exact indication will follow review of the data.

5. The FAP regression and prevention trial, the SAP regression trial and the SAP prevention trial support a submission for this proposed indication: "Celecoxib is indicated for regression and prevention of colorectal adenomatous polyps which may lead to the development of colon cancer."

a. Approval for a SAP indication will rely mainly on the results from Study 005.

b. Studies of, and labeling for regression in SAP are problematic.

c. Depending on the results, data from a FAP study (001) may support an indication in SAP.

d. For the present, proposed indications should be specific to the patient population that has provided the pivotal clinical data.

Administrative

6. Prevention of adenomatous polyps is a surrogate endpoint for colon cancer and 21 CRF Subpart H - Accelerated Approval of New Drugs for Serious Life Threatening Illnesses applies to regression and prevention of adenomatous polyps which may lead to the development of colon cancer.

a. A demonstration of the prevention (or possibly the delay in progression) of adenomatous colorectal polyps is potentially acceptable for accelerated approval for FAP.

b. For conversion to regular approval, reduction in the incidence of colorectal cancer or other clinical benefits would be considered (See Question 2).

c. If clinical benefits can be demonstrated with follow-up of the first study (001) then it may be possible to fulfill the requirements for conversion to full approval, otherwise a second study will be necessary to demonstrate other potential benefits that might allow conversion to full approval.

d. "Making the case" cannot be based only on epidemiology; it must be based on data from these (FAP) patients.

e. SAP patients may possibly be used to support a FAP indication.

f. Regarding accelerated approval for SAP, this must be based on follow-up data.

7. Given the small number of patients affected and the unmet medical need, is there a mechanism whereby Searle could file a separate NDA for Familial Adenomatous Polyposis (FAP) before the approval of an NDA for the same drug Celecoxib for arthritis? If so, can the NDA for FAP include information on Celecoxib, other than that specific to FAP, by cross-reference to Celecoxib in the initial NDA for Arthritis?

- See answer to question 4.
- An NDA for the use of celecoxib in the treatment of FAP could be filed in advance of an NDA for another potential celecoxib indication. Safety data from clinical trials for indications other than polyp prevention/regression might be pertinent, especially for a duration of use of 6 months or longer.
- This question will be addressed closer to the time of submission.

UNRESOLVED ISSUES or ISSUES REQUIRING FURTHER DISCUSSION:

ACTION ITEMS:

1. Company will develop a detailed plan for the statistical analysis including a carefully defined primary analysis; plus information regarding demographic characteristics of patients enrolled.

2. FDA will review this statistical plan and there will be follow-up communication regarding study 001 and possibility of using it as a fefinitive study.

The meeting was concluded at 3:30 p.m. There were no unresolved issues or discussion points.

/S/ 4.13.98
Project Manager

Concurrence: /S/ 4/29/98
Meeting Chair

ATTACHMENTS: None

Div.

TELECON MINUTES

TELECON DATE: November 23, 1998 **TIME:** 3:30pm **LOCATION:** room 2064 (B)

Drug Name: celecoxib **IND:** **Type of meeting:** EoP2

Sponsor: NCI/DCP and Searle **Preparation package:** submissions sn 014 /October 1 and sn 019/November 18, 1998

FDA attendees, titles and offices:
Robert Justice, M.D., Acting Division Director
Julie Beitz, M.D., Medical Team Leader
Donna Griebel, M.D., Medical Officer
Gang Chen, Ph.D., Statistical Team Leader
Paul Zimmerman, R.Ph., Project Manager

Sponsor:
Gary Kelloff, M.D., Branch Chief, NCI-Chemoprevention Branch
Ernie Hawk, M.D., M.Ph., Chemoprevention, NCI
Caroline Sigman, Ph.D., Regulatory Consultant, CCS, Inc.
Jeffery Sherman, M.D., Clinical Research Oncology, Searle
Gary Gordon, M.D., Clinical Research Oncology, Searle
Louis Godio, Ph.D., Statistics, Searle
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle
Thomas Darling, Ph.D., Project Management, Searle
Michael Ostrander, Ph.D., Regulatory Affairs, Pfizer
Jose Barrueco, Ph.D., Clinical, Pfizer
Benard Levine, M.D., MDAnderson, Searle consultant

Meeting Objective(s):
The purpose of this telecon was to obtain agreement on the suitability of the revised FAP trial statistical plan, and obtain agreement that the FAP trial is considered a pivotal study in support of the proposed FAP revised claims of 1) prevention of colorectal adenomatous polyps which may lead to the development of colon cancer, and 2) regression and prevention of colorectal adenomatous polyps which may lead to the development of colon cancer in patients with familial adenomatous polyposis (FAP) and/or 3) regression and prevention of duodenal adenomatous polyps which may lead to the development of duodenal cancer in patients with familial adenomatous polyposis (FAP).

Discussion:
After reviewing the information (serial numbers 014 and 019) submitted by the sponsor, the FDA provided the sponsor (November 20, 1998 fax) with seven requests to be addressed during the telecon. The requests and responses are listed below.

Question 1:
Please explain why it has become necessary to change the original statistical analysis plan from a primary endpoint of change in number of polyps, to adding a co-primary endpoint of change in a very specific aspect of the duodenal disease.

Sponsor response:
- The high percentage (58%) of duodenal polyps in these patients is an opportunity to assess effects of the drug. Percent of the area involved is thought to be more quantitative than other duodenal endpoints. From the beginning of the study, this proposed endpoint had been stated to be a secondary endpoint.

Question 2:
Are "plaque-like" duodenal polyps a newly recognized entity associated with FAP, and are there references to demonstrate that they are associated with a different prognosis?

Sponsor response:
- The "plaque-like" duodenal polyps are not a new entity associated with FAP, and there is no evidence that they have a different prognosis.

Question 3:
It appears that the duodenal ampulla analysis is a new part of the statistical analysis plan. If this is true, what has prompted this change?

Sponsor response:
- A large proportion of patients had enlargement of the ampulla at baseline. Abnormalities in that area are common and important.

Question 4:
Please explain the reason for the alteration in the wording of the primary endpoint from "number of polyps" to "number of colorectal polyps".

Sponsor response:
- The alteration is an attempt to be more specific in identifying each count (colorectal vs. duodenal).

Question 5:
The recent amendments to the protocol appear to alter the statistical analysis plan from comparing all 3 arms on the trial to comparing only the high dose to placebo in the primary analysis. If that is true, please justify the change.

Sponsor response:

- We expect to see efficacy in the high dose arm and therefore do not want to compare high dose vs low dose. We will compare high dose vs placebo and low dose vs placebo.

FDA statistical comment:
The Sponsor will need to adjust for multiple endpoints and for multiple comparisons between arms.

Question 6:
Please explain why the follow-up period after the last dose on therapy has been shortened.

Sponsor response:

- This enlarges the window for the follow-up phone call only (post 6 month endoscopy phone call).

Question 7:
Please provide literature references regarding the statement in the meeting package that upper gi (duodenal) cancer has overtaken large bowel cancer as cause of death in FAP patients.

Sponsor response:

- Wallace, M. and Phillips R., Upper gastrointestinal disease in patients with familial adenomatous polyposis. British Journal of Surgery. 85: 742-750, 1998 was provided.

In addition, the following statistical comments were provided to the sponsor.

FDA statistical comment:
We are always concerned when there are changes in endpoints of analyses this late in a study. Has the blind been broken or the treatments unblinded because of toxicity, etc.?

Sponsor response:

- The blind has not been broken or the treatments unblinded because of toxicity, etc.

FDA statistical comment:
If addition of a co-primary endpoint was based on the data analyzed, results of such analysis should be considered as exploratory and a confirmatory study is necessary.

FDA statistical comment:
ITT population should include all patients as randomized.

Sponsor response:

- The Sponsor will do both ITT and evaluable analyses.

FDA statistical comment:
The proposed plan for exclusion of missing data may not be appropriate.

FDA statistical comment:
If any conclusion will be made based on secondary endpoints, significance level should be adjusted for the number of secondary endpoints.

Action Items:

The sponsor plans to freeze the database on December 4, 1998 and the blind will be broken December 8, 1998.

The sponsor plans to provide a revised statistical plan or letter addressing the FDA questions, comments, etc. before December 8, 1998.

The issue concerning the "pivotal" status of this trial may be discussed at the pre-NDA meeting. The sponsor plans to request this pre-NDA meeting in early January 1999.

/S/ 11/30/98
Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: /S/ 11/30/98
Donna Griebel, M.D., Medical Officer/date

cc:
Original IND
Div File
HFD-150/PZimmerman

TELECON MINUTES

DNF 15

TELECON MINUTES

TELECON DATE: December 8, 1998 **TIME:** 2:30pm **LOCATION:** room 2064 (B)

Drug Name: celecoxib **IND:** **Type of meeting:** Statisistics/EoP2

Sponsor: NCI/DCP and Searle **Preparation package:** fax dated December 7, 1998 + SN 019 + SN 014

FDA attendees, titles and offices:
Julie Beitz, M.D., Acting Deputy Director
Gang Chen, Ph.D., Statistical Team Leader
Paul Zimmerman, R.Ph., Project Manager

Sponsor:
Gary Kelloff, M.D., Branch Chief, NCI-Chemoprevention Branch
Ernie Hawk, M.D., M.Ph., Chemoprevention, NCI
Caroline Sigman, Ph.D., Regulatory Consultant, CCS, Inc.
Jeffery Sherman, M.D., Clinical Research Oncology, Searle
Gary Gordon, M.D., Clinical Research Oncology, Searle
Louis Godio, Ph.D., Statistics, Searle
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle
Thomas Darling, Ph.D., Project Management, Searle
Michael Ostrander, Ph.D., Regulatory Affairs, Pfizer
Jose Barrueco, Ph.D., Clinical, Pfizer

Meeting Objective(s):
The purpose of this telecon was to discuss the December 7, 1998 revised FAP trial statistical plan.

Discussion:

NCI/DCP and Searle provided the FDA with the following (items 1-5) concerning the Statistical Analysis Plan for the Celecoxib Familial Adenomatous Polyposis Study, Protocol IQ4-96-02-001 to describe changes in the statistical analysis plan based on their understanding of the Nov 23, 1998 FDA, NCI/DCP and Searle teleconference.

1. There will be one primary endpoint: percent change from baseline for colorectal polyps. The key statistical treatment comparisons will be high-dose vs. Placebo and low-dose vs. Placebo, each comparison at type 1 error of 0.05.

2. There will be one secondary endpoint: percent change in area of duodenal plaque-like polyps. The key statistical treatment comparisons will be high-dose vs. Placebo and low-dose vs. Placebo, each comparison at type 1 error of 0.05. No conclusions will he based on the endpoint unless the primary endpoint attains statistical significance.

3. All other variables listed in the Aug. 18, 1998 version of the analysis plan will be tertiary variables.

4. The Intent-to-treat analysis will include all randomized patients.

5. Missing data will be handled as follows:

-relative to the primary endpoint, there are five discontinued patients with no data beyond baseline. For these five, all % changes from baseline scores for the primary endpoint will be defined as 0%. This will ensure that all five will be included in the intent-to-treat analysis per the Agency's recommendation Nov 23.

-relative to the secondary endpoint, there are two patients with no duodenal plaque at baseline and some duodenal plaque at end of study. Since the % change from baseline for these patients can't be determined, the baseline value be defined as 1 % for both these patients . This will result in both being included in the secondary endpoint analysis.

Concerning item 1 above the FDA stated since two comparisons (high dose vs. Placebo and low dose vs. Placebo) will be performed and the conclusion may be only based on results of one of the two comparisons, if 0.05 is used as significance level for each comparison, the overall type error will be inflated. FDA always requires adjustment for such multiple comparisons. However, the sponsor may allocate the α in an unequal manner, i.e., assign more α to one comparison which the sponsor believes more important (e.g., 0.04 and 0.01). The total α level should be controlled at the 0.05 level.

The sponsor noted that they will apply 0.04 to the high dose and 0.01 to the low dose.

Concerning item 2 above the FDA stated that it is acceptable to use "percentage change in area of duodenal plaque-like polyps" as a secondary endpoint. However, α level should also be adjusted for the two comparisons (see comment 1).

Concerning item 3 above the FDA stated that the sponsor needs to clarify whether any claims will be made based on those tertiary variables. Usually, the efficacy conclusion will be based on evaluation of the primary endpoint and results of secondary endpoint analyses will be considered for labeling. Those tertiary variables the sponsor wishes to consider including in labeling in the future should be treated as secondary endpoints and adjustment for multiple endpoints is necessary.

The sponsor noted that they intend to make no claims on the tertiary endpoints.

Concerning item 4 above the FDA stated that the ITT analysis plan is acceptable.

1 IV.

MEETING MINUTES

MEETING DATE: March 29, 1999 **TIME:** 1PM **LOCATION:** room 6002 (G)

DRUG NAME: celecoxib **IND:** **TYPE OF MEETING:** pre-NDA

SPONSOR: NCI/DCP and Searle **Preparation package:** dated March 1, 1999

FDA Attendees, titles and offices:
Robert Temple, M.D., Director, ODE1
James Krook, M.D., ODAC
Representative (premeeting)
Robert Justice, M.D., Acting Division Director
Julie Bietz, M.D., Acting Deputy Director
Donna Griebel, M.D., Medical Officer
Gang Chen, Ph.D., Statistical Team Leader
Clara Chu, Ph.D., Statistical Reviewer
John Senior, M.D., Medical Officer, DGCDP
JoAnn Minor, Public Health Specialist, OSHI
Paul Zimmerman, R.Ph., Project Manager

Sponsor, titles and offices:
Gary Kelloff, M.D., Branch Chief, NCI-Chemoprevention Branch
Ernie Hawk, M.D., M.Ph., Chemoprevention, NCI
Caroline Sigman, Ph.D., Regulatory Consultant, CCS Inc.
Jeffery Sherman, M.D., Executive Dir., Clinical Research Oncology, Searle
Gary Gordon, M.D.,Ph.D., Clinical Research Oncology, Searle
James Lefkowith, M.D., Clinical Research Arthritis
Louis Godio, Ph.D., Director, Statistics, Searle
Karen Seibert, Ph.D., Pharmacology, Searle
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle
Leland Loose, Ph.D., Clinical Research, Pfizer
Jose Barrueco, Ph.D., Clinical, Pfizer
Wayne Frost, Regulatory Affairs, Pfizer
Bernard Levin, M.D., Consultant, MDAnderson CC

Meeting Objective(s):
To discuss the format of the application including: The general content of the application; presentation of patient demographics; format and approach to the summary of the primary efficacy data, including tables and text (percent change from baseline for colorectal polyps); and the format and approach to the summary of the safety data, including tables, specific findings, and comparison with data from arthritis patients.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question #1:
Is the general organizational plan of the sNDA as defined in the table of contents acceptable?

FDA response:
Yes.

Question #2:
Is the general organizational plan of the clinical study report and data presentations acceptable? Are there any additional breakdowns of interest to the agency?

Concerning item 5 above the FDA stated that the plan for missing data is acceptable.

Regarding the pivotal status of this study, the FDA stated that it is acceptable to submit this single study for NDA filing.

Action Items:

The sponsor stated that the blind will not be broken until a written response concerning the SAP is provided by FDA.

The sponsor plans to provide the SAP revisions to FDA by fax within the next few days. The SAP revisions and full SAP will also be submitted to the IND.

The FDA plans to provide a written response regarding the revised SAP and the single study filing within a few days of receipt of the revised SAP.

/S/ 12/10/98
Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: /S/ 12/10/98
Julie Beitz, M.D., Acting Deputy Director/date

cc:
Original IND
Div File
HFD-150/PZimmerman
/ GClen

TELECON MINUTES

FDA response:
The current plan appears acceptable, except for the following:

- PK data should be submitted for review.
- Individual patient data listings will need to be provided, and the methodology for obtaining and independently confirming these data must be clearly presented in the application.
- The data regarding interval development of new polyps, the number of polyps that were removed/biopsied on study, and the presence of areas of confluence should be presented.
- We will need to verify your polyp counts and all other endpoints. Please submit your finalized methodology for performing your assessment including counts and measurements. Please submit photos, videos, and case report forms on all patients.

Additional analyses of interest may become evident as the review progresses. Will the primary data be made available electronically to facilitate the review process? The preferred format is SAS transport files. An annotated case report form is requested with the submission of the electronic data set.

The sponsor noted that the sponsor will provide both PC SAS data sets and SAS transport files. Both annotated CRFs and processed data set will be provided.

Question #3:
Is the proposed outline of the content and format of the comparison of safety data on celecoxib from FAP study vs. the arthritis studies' patient populations acceptable to the agency? Are there any additional breakdowns of interest to the agency?

FDA response:

- The current plan appears acceptable.
- You should consider how to analyze the adverse experience to account for the difference in treatment duration between polyp patients and arthritis patients.

Question #4:
Since the study was conducted prior to February 1999 and was conducted by the NCI under its IND, our understanding is that only form 3454 is required to be submitted by Searle. Please confirm.

FDA response:
We will refer this question to Linda Carter.

FDA comments:
Based on this package, an sNDA would be acceptable for filing however, we have the following concerns that should be addressed in the sNDA.

- Sample size
- Lack of clarity in defining and assessing endpoints
- Short treatment duration
- Dose finding is limited
- No data for long term dosing at the proposed dose
- Adequacy of polyp reduction as a surrogate endpoint for clinical benefit, e.g., reduction of the risk of colon cancer, reduction in the need for colectomy, etc.
- The proposed package insert should reflect the data, i.e., the reduction in the number of existing polyps compared to placebo. The data do not appear to support a claim for prevention of polyps much less cancer.
- Assuming this is recommended for approval, what are your plans for your post-marketing study to confirm clinical benefit in FAP?
- Do you have plans for evaluating safety and efficacy beyond 6 months?

The meeting was concluded at 2:15PM.

/S/ 3/31/99
Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: /S/ 3/31/99
Donna Griebel, M.D., Medical Officer/date

cc:
Original IND
HFD-150/Div File

MEETING MINUTES

TELECON MINUTES

TELECON DATE: April 26, 1999 **TIME:** 2:00pm. **LOCATION:** room 2064 (B)

Drug Name: celecoxib **IND:** **Type of meeting:** preNDA issues

Sponsor: NCI/DCP and Searle **Preparation package:** submission dated April 12, 1999

FDA attendees, titles and offices:
Donna Griebel, M.D., Medical Officer, DODP
John Senior, M.D., Medical Officer, GDCDP
Randy Levin, M.D., Medical Officer, DNDP
Paul Zimmerman, R.Ph., Project Manager

Sponsor:
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle

Meeting Objective(s):
The purpose of this impromptu telecon was to clarify and discuss the sponsor's proposal for submission of video tapes, photographs, and CRFs regarding the NDA for FAP.

Discussion:

The sponsor proposed to submit 4 to 6 video cassettes per patient (83 patients) for FDA review. They would be packaged about 20 videos per box in about 15 to 20 boxes. The Division noted that the duodenal videos were not being requested at this time and that only the videos used to obtain the sponsor's primary endpoint (colorectal polyp counts) results should be submitted. The videos must be provided in NDA jackets and only one copy need be submitted. The sponsor noted that only one or two videos would fit into one NDA jacket. Ms. Piergiovanni proposed to contact the sponsor's medical personnel to identify which videos were used to obtain their results and to advise the Division of her findings. Ms. Piergiovanni also suggested that the Agency and sponsor could meet to review the sponsor's method of assessment if this would be helpful .

The sponsor noted that they plan to submit super VHS copies of the original videos and that digital reproduction had not been possible for the videos produced in the UK. The Division noted that the copies need to be of sufficient quality for the Agency to duplicate the sponsor's results. Lesser quality copies may be disadvantageous to the sponsor if the Agency is unable to duplicate their efficacy results..

The sponsor proposed to submit sleeved photographs tabbed per patient in NDA jackets. The Division proposed that the sponsor consider providing the photographs digitally. If the sponsor chose to pursue the digital format, the Division suggested that they first provide examples of the photographs and digital reproductions of those photographs for the Division to evaluate, to assure that they are of comparable quality for review.

The proposal for submission of CRFs on CD-ROM (consistent with FDA requirements) is acceptable.

/S/ 4/27/99
Paul Zimmerman, Project Manager/date
Minutes preparer

/S/ 4/27/99
Concurrence:
Donna Griebel, M.D., Medical Officer/date

cc:
Original IND
Div File
HFD-150/PZimmerman
HFD-150/DGriebel
HFD-150/JBeitz
HFD-180/JSenior

TELECON MINUTES

MEETING MINUTES

MEETING DATE: October 27, 1999 **TIME:** 12PM **LOCATION:** room 6041 (I)

DRUG NAME: Celebrex **NDA:** 21-156 **SPONSOR:** NCI/DCP and Searle

TYPE OF MEETING: 1) Phase 4 study and 2) proposed pivotal trial

Preparation package: meeting request dated September 1, 1999
meeting package dated September 27 and October 8, 1999

FDA Attendees, titles and offices:
Robert Temple, M.D., Director, ODE1
Rachel Behrman, M.D., Deputy Office Director
James Krook, M.D., ODAC representative
Richard Pazdur, M.D., Division Director
Robert Justice, M.D., Deputy Division Director
Julie Bietz, M.D., Medical Group Leader
Judy Chiao, M.D., Medical Officer
Rebecca Wood, Ph.D., Chemistry Team Leader
Sung Kim, Ph.D., Chemistry Reviewer
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
John Duan, Ph.D., Biopharmaceutics Reviewer
Wendy Schmidt, Ph.D., Pharmacology Reviewer
Paul Andrews, Ph.D., Pharmacology Team Leader
Gang Chen, Ph.D., Statistical Team Leader
John Lawrence, Ph.D., Statistical Reviewer
John Senior, M.D., Medical Officer, DGCDP
Patty Delaney, Public Health Specialist, OSHI,
Paul Zimmerman, R.Ph., Project Manager
(FDA attendees are bolded)

Sponsor, titles and offices:
Gary Kelloff, M.D., Branch Chief, NCI-Chemoprevention Branch
Ernie Hawk, M.D., M.Ph., Chemoprevention, NCI
Caroline Sigman, Ph.D., Regulatory Consultant,CCS,Inc.
Jeffery Sherman, M.D., Executive Director, Clinical Research Oncology, Searle
Gary Gordon, M.D., Ph.D., Clinical Research Oncology, Searle
Louis Godio, Ph.D., Director, Statistics, Searle
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle
Olivia Coughlin, MSA, Project Management, Searle
Marcia Canto, M.D., Director, Therapeutic Endoscopy and Endoscopic Ultrasonography, Johns Hopkins Hospital
Michael Ostrander, Ph.D., Regulatory Affairs, Pfizer
Jose Barrueco, Ph.D., Clinical, Pfizer
Bernard Levin, M.D., Scientific Consultant, MD Anderson Cancer Center
Richard Spivey, Pharm D., Ph.D., V.P. Searle Worldwide Regulatory Affairs
Monica Bertagnolli, M.D., SAP Principal Invesigator, Cornell
Jamie Masferrer, Ph.D., Searle Discovery

Meeting Objective(s):
To discuss the proposed Sporadic Adenomatous Polyposis (SAP) study as the follow-up trial for traditional approval of NDA 21-156 for FAP and as the pivotal trial for an sNDA for the prevention of colorectal adenomatous polyps which may lead to the development of colon cancer.
To discuss the proposed clinical trial as the sole pivotal study for Barrett's Dysplasia

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question 1.
Are the clinical endpoints (parameters) being evaluated in the proposed Spontaneous Adenomatous Polyposis (SAP) study appropriate and is the trial design acceptable?

FDA response:
The endpoints are acceptable for consideration of accelerated approval but not for traditional approval presently. Efficacy endpoints in Phase IV studies to convert Celebrex accelerated approval to traditional approval must demonstrate the clinical benefits associated with a reduction of adenomatous polyps, e.g., a reduction in the incidence of colorectal cancer. This will require long term follow-up. An additional 300 patients will be required to insure an adequate power of 80%.

Question 2.
Is the sole proposed SAP study pivotal and supportive of a submission for the following proposed indication? "Celebrex is indicated for the prevention of colorectal adenomatous polyps which may lead to the development of colon cancer."

FDA response:
One study may suffice for accelerated or traditional approval if the results are dramatic. Note that for traditional approval, the endpoints your propose are not acceptable presently. However, this will be discussed at ODAC.

Question 3.
Is the proposed SAP prevention trial acceptable as a follow-up trial for the full approval on NDA 21-156 for Celebrex in FAP.

FDA response:
This point will be discussed at ODAC. For traditional approval of Celebrex in FAP a clinical benefit must be demonstrated in FAP.

We have reservations regarding whether the demonstration of clinical benefit in the SAP population will suffice to support conversion of the FAP claim to full approval. This concept (not the protocol) will be discussed at ODAC.

Question 4.
Are the clinical endpoints (parameters) being evaluated in the proposed Barrett's dysplasia study appropriate and is the trial design acceptable?

FDA response:
Please provide further clarification on the primary endpoint and patient population. The change in the % of biopsies exhibiting any dysplasia, or different degrees of dysplasia may not be a reliable endpoint because of difficulties in measuring changes in the esophageal surface and sampling errors. An acceptable and clinically meaningful endpoint would be a reduction in the incidence of esophageal cancer.

It is not known at the present time whether Celebrex will cause regression of esophageal dysplasia or not. Patients with high grade dysplasia may be candidates for the trial if they are inappropriate

candidates for esophagectomy or refuse esophagectomy. You should stratify by high grade vs. low grade and standardize other Barrett's therapy, e.g., anti-reflux therapy.

A follow-up telecon will be arranged for the Barrett's esophagus issues

Question 5.
Is the sole proposed Barrett's dysplasia study pivotal and supportive of a submission for the following proposed indication? "Celebrex is indicated for the regression and prevention of Barrett's dysplasia which may lead to the development of esophageal cancer in patients with Barrett's dysplasia."

FDA response:
To be discussed in the follow-up telecon for Barrett's esophagus issues. See answer to question 4.

FDA comments:

Clinical Pharmacology and Biopharmaceutics Comments:

1. Sparse sampling to compare the exposures in different populations is recommended.

2. It is noted that several molecular markers will be studied. This effort is highly appreciated. The data should be used to attempt to establish pharmacokinetic/pharmacodynamic relationships. Therefore, collection of pharmacokinetic data is recommended.

Action Item:

The sponsor will provide a full draft protocol on Barrett's dysplasia and propose a follow-up telecon.

The meeting was concluded at 1:40PM.

/S/ 11/8/99
Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: /S/ 11/8/99
Judy Chiao, M.D., Medical Officer/date

Attachments: Sponsor's overheads

cc:
Original IND
HFD-150/Div File
MEETING MINUTES

TELECON MINUTES

DATE: November 2, 1999 **NDA:** 21-156 **DRUG:** celebrex

BETWEEN: Dr. Gang Chen, Dr. John Lawrence, Mr. Paul Zimmerman,, FDA

AND: Ms. Anita Piergiovanni, Dr. Robert Ryan, Dr. Louis Godio

TELEPHONE NUMBER: (847)-982-7670

The applicant requested clarification regarding the statistical comment (see below) provided as the FDA response (last sentence) to the applicants' Question 1 from our October 27, 1999 meeting.

> ***Are the clinical endpoints (parameters) being evaluated in the proposed Spontaneous Adenomatous Polyposis (SAP) study appropriate and is the trial design acceptable?***
> FDA response:
> The endpoints are acceptable for consideration of accelerated approval but not for traditional approval presently. Efficacy endpoints in Phase IV studies to convert Celebrex accelerated approval to traditional approval must demonstrate the clinical benefits associated with a reduction of adenomatous polyps, e.g., a reduction in the incidence of colorectal cancer. This will require long term follow-up. An additional 300 patients will be required to insure an adequate power of 80%.

The conference call focused on the power of the proposed SAP study. In this trial, there are two different doses of the treatment drug and two different time points when the doses will be compared to the placebo. Hence, there are different interpretations of what the applicant will consider a successful trial. The applicant clarified that, for the purposes of calculating the power, a success is counted if at least one dose beats the placebo at the final analysis. With this clarification, the agency agreed that 650 patients per arm is sufficient.

On a related issue, there was a discussion about the expected treatment effect. The applicant assumed that the proportion of patients in the treatment arms who have polyps after 3 years will be 35% less than the corresponding proportion in the placebo arm. The proposed sample size is adequate to detect this size treatment effect with high probability. However, if the true treatment effect is not this large, the study may lack power to detect the treatment effect. This risk is exacerbated by spending a proportion of the overall Type I error (alpha) at the one-year interim analysis. The applicant is aware of these risks and has determined that the design as specified in the protocol is the best design to meet their goals.

/S/ 11/4/99
Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: /S/ 11/4/99
Gang Chen, Ph.D., Statistical Team Leader/date

cc:
Orig. NDA
Division File
HFD-150/PZimmerman/JLawrence/GChen

TELECON MINUTES

DATE: November 29, 1999 **NDA:** 21-156 **DRUG:** celebrex

ROOM: 2064 **TIME:** 4PM

BETWEEN:
Rachel Behrman, M.D., Deputy Office Director
Richard Pazdur, M.D., Division Director
Robert Justice, M.D., Deputy Division Director
Julie Bietz, M.D., Medical Group Leader
Judy Chiao, M.D., Medical Officer
Gang Chen, Ph.D., Statistical Team Leader
Mark Avigan, M.D., Medical Officer, DGCDP
Paul Zimmerman, R.Ph., Project Manager
(FDA attendees are bolded)

AND:
Gary Kelloff, M.D., Branch Chief, NCI- Chemoprevention Branch
Jeffery Sherman, M.D., Executive Director, Clinical Research Oncology, Searle
Gary Gordon, M.D., Ph.D., Clinical Research Oncology, earle
Louis Godio, Ph.D., Director, Statistics, Searle
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle
Michael Ostrander, Ph.D., Regulatory Affairs, Pfizer
Jose Barrueco, Ph.D., Clinical, Pfizer
Richard Spivey, Pharm D., Ph.D., V.P. Searle Worldwide Regulatory Affairs

TELEPHONE NUMBER: (847)-982-7670

The purpose of the telecon was to discuss the applicants proposed FAP (follow-up) trial. A follow-up trial is needed for traditional approval and must be in place before an accelerated approval NDA can be approved. The proposed follow-up trial was submitted in the November 18, 1999 submission.

The FDA noted that the proposed single arm study is unacceptable for the follow-up trial because there is no control arm, the proposed primary analysis using COX model is exploratory in nature, and the proposed clinical events are not equal in their significance. There was discussion about each of the above points. The FDA noted that a blinded study with sufficient power is needed and suggested that time to FAP related surgery (with guidelines for surgery) should be the primary endpoint. Necessary FAP disease related surgery, progression to FAP related cancer, and FAP disease related death may be secondary endpoints. The study would need to have long term follow-up (5 years) for cancer in both arms. The FDA suggested the use of a log rank test.

The applicant will send a revised proposal within the next few days.

It was suggested that the applicant should describe the detailed draft protocol outline of the proposed follow-up trial at the ODAC. FDA would then ask ODAC about the adequacy of the proposed trial.

There was also discussion about the MDAnderson prints as described in our request dated November 23, 1999 which follows.

FDA review of the still photographs so far has revealed the following problems:

1. The still photographs from MD Anderson Cancer Center are NOT photographs but are prints from a color printer and are of inferior quality when compared to photographs from St. Mark's.
2. Multiple color prints were submitted for one tattoo or anatomically marked area and it was often not possible to determine which ones were used to derive the colorectal polyp count in the primary efficacy dataset. In addition, with multiple color prints on one page, it was not possible to construct "cloverleaf" pictures for adequate polyp counting as was possible for St. Mark's.
3. These color prints are small and lack in details, making it nearly impossible to identify the tattoo center or the anatomical markers in many of the prints.
4. Some color prints showed that dyes were sprayed on the rectal or colonic segments. It was not possible to identify tattoos in these prints, making polyp counting more difficult.

The applicant inquired which of the MDAnderson prints we were referring to. The FDA noted that all of the MDAnderson prints were problematic.

The applicant noted that the original photographs are at MDAnderson and MDAnderson is not willing to release the photos for FDA review. The applicant has also not independently confirmed the polyp counts in the NDA. There was discussion about sending an FDA representative to MDAnderson to review the photographs. The question(s) remains open.

/S/ 12/16/99
Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: /S/ 12-15-99
Judy Chiao, M.D./Medical Officer/date

cc:
Orig. NDA
Division File
HFD-150/PZimmerman/JChiao

TELECON MINUTES

DATE: December 1, 1999 **NDA:** 21-156 **DRUG:** celebrex

ROOM: 2002 **TIME:** 1PM

BETWEEN:
Rachel Behrman, M.D., Deputy Office Director
Richard Pazdur, M.D., Division Director
Robert Justice, M.D., Deputy Division Director
Julie Bietz, M.D., Medical Group Leader
Judy Chiao, M.D., Medical Officer
Paul Zimmerman, R.Ph., Project Manager
(FDA attendees are bolded)

AND:
Gary Kelloff, M.D., Branch Chief, NCI- Chemoprevention Branch
Ernie Hawk, M.D., M.Ph., Chemoprevention, NCI
Jeffery Sherman, M.D., Executive Director, Clinical Research Oncology, Searle
Gary Gordon, M.D., Ph.D., Clinical Research Oncology, Searle
Gideon Steinbach, MD, PhD, MD Anderson Cancer Center
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle
Michael Ostrander, Ph.D., Regulatory Affairs, Pfizer
Caroline Sigman, Ph.D., Regulatory Consultant, CCS Inc.

TELEPHONE NUMBER: (800)-309-6535

The purpose of the telecon concerned the prints regarding the MDAnderson patients.

As noted in the November 29, 1999 telecon, the prints concerning the MDAnderson patients provided in the application are problematic and are not adequate. The FDA noted that these photographs need to be provided in Rockville for review by the Division. It is not an option for an FDA representative to go to MDAnderson for this purpose. The FDA also noted that photographs are needed for all of the MDAnderson patients.

The Applicant noted that they will expedite getting the photographs to the Division and will provide a representative to help the Division with questions regarding the photographs.

/S/ 12/16/99
Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: /S/ 12-15-99
Judy Chiao, M.D./Medical Officer/date

cc:
Orig. NDA
Division File
HFD-150/PZimmerman/JChiao

TELECON MINUTES

DATE: December 6, 1999 **NDA:** 21-156 **DRUG:** celebrex

ROOM: 2064 **TIME:** 12:15PM

BETWEEN:
Richard Pazdur, M.D., Division Director
Robert Justice, M.D., Deputy Division Director
Julie Bietz, M.D., Medical Group Leader
Judy Chiao, M.D., Medical Officer
Gang Chen, Ph.D., Statistical Team Leader
John Lawrence, Ph.D., Statistical reviewer
Mark Avigan, M.D., Medical Officer, DGCDP
Paul Zimmerman, R.Ph., Project Manager

AND:
Jeffery Sherman, M.D., Executive Director, Clinical Research Oncology, Searle
Gary Gordon, M.D., Ph.D., Clinical Research Oncology, earle
Louis Godio, Ph.D., Director, Statistics, Searle
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle
Jose Barrueco, Ph.D., Clinical, Pfizer
Ernie Hawk, M.D., M.Ph., Chemoprevention, NCI
Caroline Sigman, Ph.D., Regulatory Consultant, CCS, Inc.
Jeffery Kent, M.D., Searle, Clinical
David Jordan, Ph.D., Statistics, Searle
Robert Ryan, consultant, Searle.
Monica Bertagnolli, M.D., SAP Principal Investigator, Cornell

TELEPHONE NUMBER: (800)-309-6535

The purpose of the telecon was to follow up on our November 29, 1999 discussion concerning the applicant's proposed Phase 4 FAP study. A follow-up trial is needed for traditional approval and must be in place before an accelerated approval NDA can be approved. On December 3, 1999, the applicant provided three revised FAP protocol outline proposals for FDA consideration.

Discussion:

The FDA noted that, of the 3 submitted proposals, the applicant should consider pursuing protocols 2 (in adolescence) and 3 (second surgery). There was discussion concerning the criteria for FAP related surgery.

The Agency asked if the applicant agreed to present proposals 2 and 3 to ODAC. Searle preferred (and it was agreed) to present proposal 2 noting that proposal 3 required a large sample size and proposal 1 had unresolved endpoint issues.

The Agency noted that the protocol needs to be specific about risk/benefit concerning what effect the delay of surgery will have.

The applicant plans to revise proposal 2 and provide it to FDA this week. It was left open whether FDA would respond to the applicant before ODAC.

/S/ 12/16/99
Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: /S/ 12-15-99
Judy Chiao, M.D., Medical Officer/date

cc:
Orig. NDA
Division File
HFD-150/PZimmerman/JChiao

TELECON MINUTES

DATE: December 21 and 22, 1999 **NDA:** 21-156 **DRUG:** celebrex

ROOM: 2064 **TIME:** 1PM

BETWEEN:
Robert Temple, M.D., Director, Office of Drug Evaluation I
Rachel E. Behrman, M.D., Deputy Office Director
Richard Pazdur, M.D., Division Director
Robert Justice, M.D., Deputy Division Director
Julie Bietz, M.D., Medical Group ~~Leader~~
Judy Chiao, M.D., Medical Officer
Mark Avigan, M.D., Medical Officer, DGCDP
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
Jean Ah Choi, DDMAC
Tracey Acker, DDMAC
Karen Midthun, M.D., Division Director, DAAODP
John Hyde, M.D., Medical Team leader, DAAODP
James Witter, M.D., Medical Officer, DAAODP
Anthony Zeccola, Project Manager, DAAODP
Renan Bonnel, R.Ph, DDREI
Paul Zimmerman, R.Ph., Project Manager
all of the above did not attend both meetings.

AND:
Anita Piergiovanni, M.Sc., Regulatory Affairs, Searle
Richard Spivey, Pharm D., Ph.D., V.P. Searle Worldwide
Regulatory Affairs
Et al.

TELEPHONE NUMBER: (800)-309-6535

The purpose of the telecon was to finalize the labeling and Phase 4 commitments.

Discussion:

/S/ 12/23/99
Paul Zimmerman, Project Manager/date
Minutes preparer
cc:
Orig. NDA
Division File
HFD-150/PZimmerman/JChiao