ORIGINAL

NDA [illegible] AMENDMENT

BM

SEARLE

October 28, 1998

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

Robert DeLap, M.D., Ph.D., Acting 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

Re: NDA 20-998
Celebrex™

Dear Dr. DeLap,

In response to a request from Dr. Witter faxed on Oct 22, 1998 please find enclosed the Kaplan-Meier plots for time-to-withdrawal by AE and treatment failure at the final dose level. Also enclosed are the patient disposition tables categorized similarly. They were generated for OA and RA separately.

In general, withdrawal rates due to treatment failure were higher in the group with the higher final dose than in lower dose group. However, the withdrawal rate pattern reversed for withdrawals due to adverse events. This means the higher the final dose, the lower the withdrawal rate would be. This phenomenon may be explained by a dose escalation decision that only patients who were non-responders in efficacy and had good tolerability could be dose escalated.

The results therefore should be interpreted with caution due the possible dose escalation selection bias.

Please direct any comments or questions concerning this submission to the undersigned.

Sincerely,

Winifred M Begley

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

Enclosures
WMB/tb

NEW CORRESP
NC

SEARLE

ORIGINAL

NC

October 28, 1998

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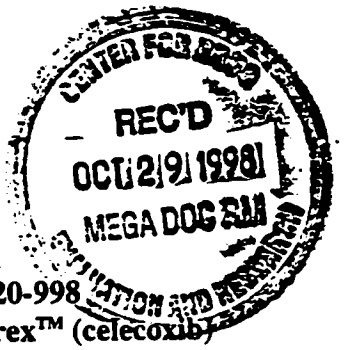

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Enclosed please find the minutes for the telecon with FDA statisticians concerning a re-presentation of the safety data. If there are any misunderstandings on what FDA are looking for in the re-presentation of the data please let me know.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

ORIGINAL

SEARLE

October 28, 1998 NDA CTD AMENDMENT

BS

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Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

In response to a fax request Oct 23, 1998 from the FDA statisticians requesting a re-presentation of the safety data, and as a follow-up to the telecon discussing this fax on Oct 26, 1998, we have enclosed the information requested. In order to orient you to the layout we have provided the following key to the tables:

Tables designated 1.A.1, 1.A.2, 1.B.1, 1.B.2

1. refers to serious AEs

A. refers to short term <12 weeks data

B. refers to >/= 12 weeks data

1 includes counts

2 includes p-value

Tables 2.A.1, 2.A.2, 2.B.1, 2.B.2

2. refers to withdrawals

A. refers to short term <12 weeks data

B. refers to >/= 12 weeks data

1 includes counts

2 includes p-value

Appendix 1A, 1B, 2A and 2B include patient identities for the above tables.

Appendix 3 is a listing of significant GI adverse events which are not captured on the above tables as they are from a separate database.

Appendix 4 is a listing of all the preferred terms we have used and a notation if a term other than the preferred term was used.

Please call if you have questions regarding this submission.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

SEARLE

ORIGINAL

NEW CORRESP NC

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-

October 26, 1998

Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

In response to a request from Sue Lee on 20-Oct-1998, enclosed is one desk copy of volumes 1.74 and 1.144-1.149 from the original NDA application of 29-Jun-1998. These volumes contain the following:

Volume 1.74 - Human In Vitro reports (beginning with page 226)

Volumes 1.144-1.149 - platelet study reports: document numbers: N49-97-16-009, N49-97-16-026, N49-97-16-032, N49-98-06-065.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl
QRS#108

Desk Copy: Sue Lee (7 volumes)

SEARLE

ORIGINAL

October 30, 1998

NDA ORIG AMENDMENT
BB

SEARLE
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Robert DeLap, M.D., Ph.D., Acting Director
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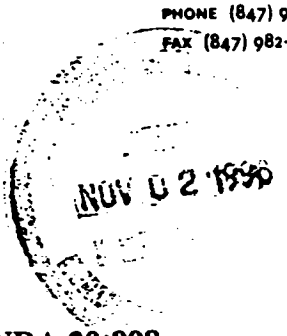
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850



RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Enclosed is our response to the request from Dr. S. Lee (PK reviewer) concerning the apparent volume of distribution and effective half life of celecoxib and the information on genotyping requested Oct 26, 1998. The information is contained in the document:

Summary of volume of distribution at steady state (Vss/F) and effective half life of celecoxib in healthy adult subjects, document number N49-98-07-827, dated 29 October 1998.

Please contact me if you have further questions.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl
QRS #129

Enc.

SEARLE

ORIGINAL

NDA ORIG AMENDMENT

October 30, 1998

BC

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Robert DeLap. M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

In response to a request from the reviewing Chemist please find enclosed our mock labels for the bottles, cartons and unit dose packs for Celebrex 100mg and 200mg capsules.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

SEARLE

ORIGINAL

November 2, 1998

NDA ORIG AMENDMENT
BM

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4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7[illegible]
FAX (847) 982-[illegible]

Robert DeLap, M.D., Ph.D.
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA 20-998
Celebrex™

Dear Dr. DeLap:

In reference to a faxed request from Dr. Witter on October 22, 1998 as well as our October 28, 1998 written response, please find enclosed a diskette containing the Kaplan-Meier plots for time-to-withdrawal by AE and treatment failure at the final dose level and the similarly categorized patient disposition tables, in an electronic format, per a request by Dr. Witter on November 2, 1998.

The Kaplan-Meier plots (Fig 1-4) are in MSWord format, while the patient disposition tables are in Ascii format (please note that the tables can be viewed clearly in Microsoft's Notepad).

Please direct any comments or questions concerning the submission to the undersigned.

Sincerely,

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

Desk Copy: Dr. Witter

Enclosure

SEARLE

ORIGINAL

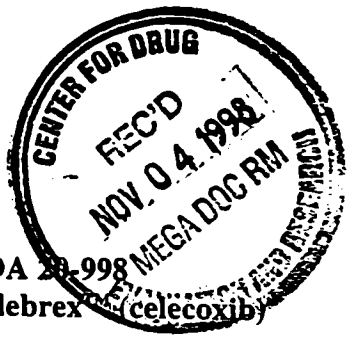
NDA ORIG AMENDMENT

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4700

November 3, 1998

BM

Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850



RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

In response to a request from Dr. Throckmorton of 2-Nov-1998, enclosed please find the following:

- List of Patients who withdrew due to renal adverse events: long-term open label trial -024

Sincerely,

for Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl
QRS#139

Enc.

Desk Copy: Dr. Throckmorton/Division of Cardio-Renal

SEARLE

ORIGINAL

November 4, 1998

NDA ORIG AMENDMENT

BC

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PHONE (847) 982-7000
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Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Reference is made to Searle's pending New Drug Application, NDA 20-998, for Celebrex™ (celecoxib). Reference is also made to FDA requests for additional information as specified in a facsimile entitled, "EA Review #2, NDA 20-998; Deficiency List," dated October 18, 1998.

In response to FDA queries, Searle encloses the following information:

Document:	"Response to Environmental Assessment Queries"
Document Number:	3103-CEL-ZA-02
Dated:	4 Nov 1998

Document:	"Environmental Assessment"
Document Number:	2742-CEL-EA-02
Dated:	2 Nov 1998

If you have additional questions or comments please contact me directly.

Kind regards,

Roger Nosal
Director,
Regulatory Affairs - Chemistry, Manufacturing & Controls
(847) 982-7250
(847) 982-8961 Fax

RN/pl

Enc.

SEARLE

ORIGINAL

NDA ORIG AMENDMENT

November 5, 1998

BB

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4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (8[illegible]
FAX (8[illegible]

Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

In response to a request of 4-Nov-1998 please find enclosed the following report as referenced in the mouse diet admix carcinogenicity study (study SA 4452/ P30S4452):

Spontaneous neoplastic lesions in the Crl:CD-1BR mouse.

Sincerely,

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

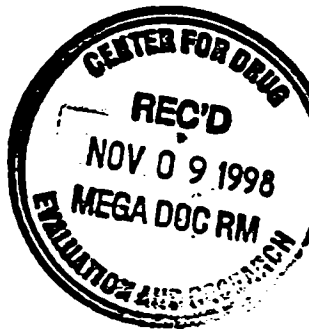
Desk Copy: Dr. Josie Yang

SEARLE ORIGINAL

November 6, 1998

NEW CORRESP
NC

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701



Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Enclosed are 25 copies of the Briefing Document for Celebrex™ Capsules. An additional 30 copies of the briefing document were forwarded to FDA Advisors and Consultants Staff on 5-Nov-1998 under separate cover.

Sincerely,

for Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

SEARLE

ORIGINAL

NDA DRUG AMENDMENT

SU

November 6, 1998

SEARLE
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FAX (847) 98

Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
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Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Enclosed is the electronic 120 Day Safety Update for Celebrex, dated 5-Nov-1998. The paper copy was submitted to the NDA on 28-Oct-1998.

Sincerely,

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

NDA ORIG AMENDMENT ORIGINAL

SEARLE

SU

November 10, 1998

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4901 SEARLE PARKWAY
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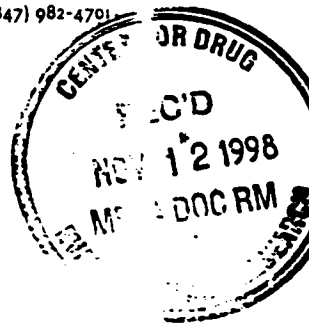

Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

As follow up to our 6-Nov-1998 submission of the electronic 120 Safety Update for Celebrex, enclosed is an additional CD along with a copy of installation instructions.

Please forward this information and CD to Ken Edmunds for installation on the network.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

NDA ORIG AMENDMENT ORIGINAL

SEARLE

November 11, 1998

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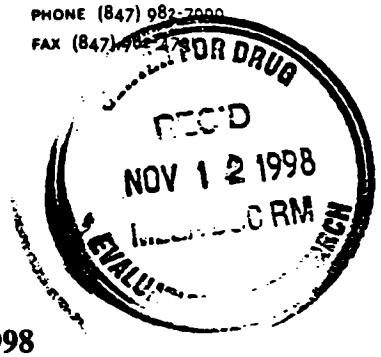

Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

With reference to a request from Dr. Sue Lee please find enclosed the following:

1. SC-58635 PK parameters at steady state which includes AUC (0-12 hours), also included is a separate listing with just AUC (0-12 hours) is included.

2. A diskette: 1. Study N49-96-02-015 including AUC (0-12hours)
2. SAS codes (Proc VARCOMP)

3. SAS program codes of intra and inter subject variability variability (PROC VARCOMP) for BE studies 018 and 044. Log-transformed data of AUV and Cmax were used to acheive better normality. Please note that the estimates were read from the last run of the parameter estimation iterations. To calculate the corresponding %CV of AUC and Cmax in the original scale, the formula of square root of the variance obtained from the log-transformed data was used.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl
QRS#143

Enc.

NDA ORIG AMENDMENT 3M ORIGINAL

SEARLE

November 11, 1998

SEARLE
4901 SEARLE PARKWAY
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Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

In reference to a fax provided by Ms. Lutwak October 7, 1998 which contained a draft review of the renal/cardiac safety consultation, in Section 2.5.1 page 4: Dr. Throckmorton incorrectly states that we conclude that celecoxib does not produce RPN because this injury was not seen at lower doses.

He apparently may not have seen our report: Re-evaluation of histologic sections of the kidney of rats, dogs and mouse from preclinical safety studies with celecoxib (SC-58635) by the expert pathologists and should be directed to that document (P3098002, dated 5 March 1998) in the preclinical section of the NDA (section 5D in the electronic submission) before he finalizes his review document.

Thank you for your attention to this matter.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

Desk Copy: Dr. Throckmorton/Division of Cardio-Renal

NDA ORIG AMENDMENT

SEARLE

ORIGINAL

November 12, 1998

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
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FAX (847) 982-4701

Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Dr. Throckmorton called Nov 12, 1998 to clarify our letter sent Nov 11, 1998 concerning RPN. I agreed to discuss this further with our toxicologist. Below addresses our previous concern which was as follows:

The FDA review document states:

Per the sponsor, later studies using lower-doses of celecoxib did not demonstrate any histologic evidence of renal toxicity. The sponsor then concluded that the "absence of renal papillary necrosis in chronic rodent studies" suggested that celecoxib "is different from NSAIDs".

Our concern was that with the two sentences juxtaposed as above, we felt a reader might conclude that we based our conclusion only on lower doses whereas in fact we did a review of both lower and higher doses and found no evidence of RPN (see preclinical study P3098002).

We trust this clarifies what we meant to convey in our previous correspondence.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

Desk Copy: Dr. Throckmorton/Division of Cardio-Renal

NDA ORIG AMENDMENT BM ORIGINAL

SEARLE

SEARLE
4901 SEARLE PARKWAY
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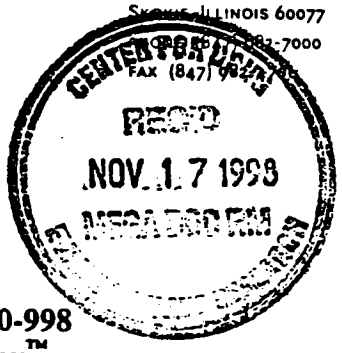

November 16, 1998

Robert DeLap, M.D., Ph.D., Acting 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

Re: NDA 20-998
Celebrex™

Dear Dr. DeLap,

Enclosed please find a copy of our minutes of the telecon of October 30, 1998 concerning a discussion of the renal aspects of celecoxib. We would appreciate a copy of your minutes as soon as they are available.

Sincerely,

Winifred M. Begley

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

Enclosures
WMB/anb

SEARLE ORIGINAL

NEW CORRESP

NC

November 19, 1998

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4901 SEARLE PARKWAY
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Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

With reference to the FDA Advisory Briefing document and the upcoming Advisory Committee meeting on December 1, 1998 we would like to refer Dr. Yang to a submission we have made recently which should address her concerns as written in the Briefing Document conclusions:

Lesions with slight-mild chronic multifocal perivascular/periventricular lymphocytic infiltrate identified in a 4-week dog study: please refer to our submission of October 23, 1998.

We realize that Dr. Yang's document is still draft and that our responses may not have yet been incorporated, however we disagree with the conclusions made as currently written and wish to alert you of this.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

SEARLE ORIGINAL

November 19, 1998

NDA ORIG AMENDMENT

BB

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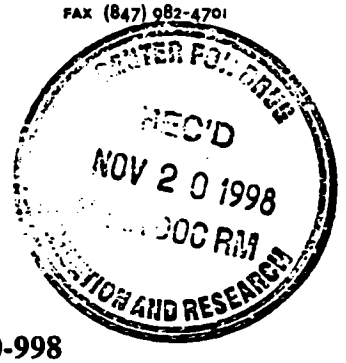

Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Enclosed are corrected pages to summary report entitled "Clinical pharmacokinetic profile of celecoxib: summary report of all data and overall conclusions", document number N49-98-07-810. Also attached is a rationale for these corrections. As this document was included in both Sections 6 (volume 1.81) and 8 (volume 1.131) of the initial NDA, we have included 2 copies of the correction pages, paginated as within the initial application.

Sincerely,

Winifred M Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

SEARLE

ORIGINAL

November 23, 1998

NDA DRUG AMENDMENT

BB

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Robert DeLap, M.D., Ph.D., Acting Director
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Office of Drug Evaluation V
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Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Enclosed are corrected pages to summary report entitled "Celecoxib: Summary of Clinical Pharmacokinetics", document number N49-98-07-806. Also attached is a rationale for these corrections. This document is located in volume 1.2 of the initial application. The corrected pages have been paginated to reflect the initial application.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

WMB/pl

Enc.

SEARLE ORIGINAL

NEW CORRESP
NC

November 23, 1998

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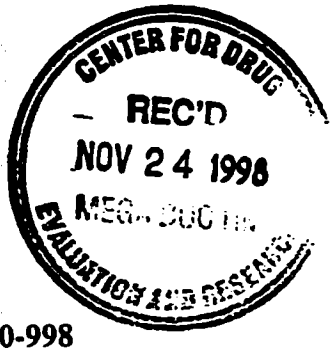

Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Enclosed are our minutes from the telecons held with FDA on Nov 13 and 16, 1998 concerning preparations for the Advisory Committee on December 1. Please send your minutes when they are available.

Sincerely,

Winifred M Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
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NC ORIGINAL

SEARLE

December 3, 1998

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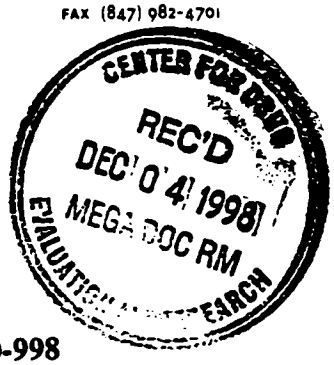

Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Please find enclosed a copy of our minutes of the telecon with FDA on November 24, 1998 on the pain indication. Please send a copy of your minutes when available.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
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SEARLE ORIGINAL

December 8, 1998

NDA ORIG AMENDMENT
BM

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Robert DeLap, M.D., Ph.D., Acting Director
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and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

In response to a request from Dr. L. Goldkind for upper GI events complications data, enclosed please find events as they appear in the original NDA (Volumes 2-7 of this submission) and those that appear in the 120-day safety update (volumes 9-11 of this submission).

Cases include some or all of the following:

- GI events summaries
- GI event narratives by Kendle (CRO)
- GI event narratives by Searle
- Diagnostic Tests:
  - Upper endoscopies
  - Colonoscopies
  - Abdominal films
  - Other miscellaneous
- Surgical Reports
- Pathology Reports
- Discharge Summaries
- Miscellaneous Notes
  - cc:mail
  - CRF pages, etc.

There may appear to be duplicates in some cases. This is because updates were sent to the committee to provide additional information.

GI Event Summaries reviewed by the GI Committee and signed are provided separately. These summaries are contained in Volumes 1 & 8 of this submission.

A listing of cases adjudicated for the NDA (cutoff 11/21/97) is contained in the archival copy only. A listing of cases adjudicated in the 120-day update (11/21/97-7/24/98) is contained only in the archival copy. Dr. Goldkind has been supplied with a blinded copy of the cases.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
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Enc.

Review Copy: Dr. L. Goldkind/Division of GI & Coagulation

NDA ORIG AMENDMENT

ORIGINAL

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December 9, 1998

Robert DeLap, M.D., Ph.D., Acting 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, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Reference is made to Searle's pending New Drug Application, NDA 20-998, for Celebrex™ (celecoxib). Reference is also made to FDA requests for additional information as specified in a facsimile entitled, "Deficiencies and Information Requests for NDA 20-998;" dated November 24, 1998 and in a facsimile entitled "Deficiencies;" dated December 7, 1998.

In response to FDA queries, Searle encloses the following information:

Document Title:	"Response to FDA Chemistry, Manufacturing and Control Queries"
Document No:	3189-CEL-ZA-01
Document Date:	8 Dec 1998

If you have additional questions or comments please contact me directly.

Kind regards,

Roger Nosal
Director,
Regulatory Affairs - Chemistry, Manufacturing & Controls
(847) 982-7250
(847) 982-8961 fax

NDA ORIG AMENDMENT

ORIGINAL

SEARLE

December 10, 1998

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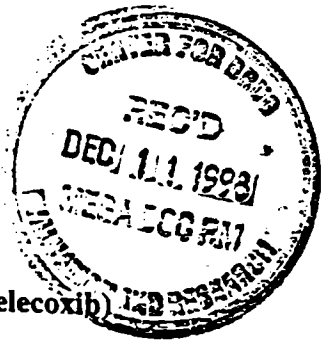

Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Reference is made to Searle's pending New Drug Application, NDA 20-998, for Celebrex™ (celecoxib). Reference is also made to Searle's response to FDA requests for additional information (as specified in a facsimile entitled, "Deficiencies and Information Requests for NDA 20-998;" dated November 24, 1998 and in a facsimile entitled "Deficiencies;" dated December 7, 1998) as provided in the following submission:

Submission Date:	9 December 1998
Document Title:	"Response to FDA Chemistry, Manufacturing and Control Queries"
Document No:	3189-CEL-ZA-01
Document Date:	8 Dec 1998

In a subsequent teleconference, FDA Reviewing Chemist, Dr. Vispi Bhavnagri, proposed a change to the aforementioned submission for which Searle agreed to provide an additional amendment to the drug product stability commitment.

In addition to Searle's commitment to place one annually marketed production lot of each dosage strength of celecoxib capsules packaged in the largest and smallest count for each package container/closure system on stability, Searle agrees to place a second, single annual marketed production lot of each dosage strength of celecoxib capsules packaged in the least protective container/closure system on stability annually at an interval approximately six months staggered from the other annual lot.

A copy of the amended stability commitment is provided in the following document enclosure:

Document Title:	Stability Commitment for Celecoxib Capsules
Document No.:	98-015-1B
Document Date:	10 Dec 1998

Replaces document no. 98-015-1A submitted in "Response to FDA Chemistry, Manufacturing and Control Queries," Document No: 3189-CEL-ZA-01, dated 8 Dec 1998 and document no. 98-015-1 submitted in the original new drug application.

FDA and Searle agreed to reevaluate the need for this additional annual stability commitment when sufficient data becomes available.

If you have additional questions or comments please contact me directly.

Kind regards,

Roger Nosal
Director
Regulatory Affairs - Chemistry, Manufacturing & Controls
(847) 982-7250
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Enc.

SEARLE

DUPLICATE

December 10, 1998

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Robert DeLap, M.D., Ph.D., Acting Director
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Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap:

Please find enclosed responses to questions raised by Dr. S. Lee in a fax received December 7, 1998.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs
(847) 982-8155
(847) 982-8090 Fax

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Enc:

BL ORIGINAL

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December 18, 1998

Robert DeLap, M.D., Ph.D., Acting 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

Re: NDA 20-998
Celebrex™

Dear Dr. DeLap,

Enclosed please find a side-by side copy of Searle and FDA label proposals in a table format for Celebrex. Also included are 2 pages to support the calculations for the section on hepatic impairment which we believe are incorrect in the FDA version of the label.

In addition, per the discussion with Dr. Bashaw yesterday, the paroxetine protocol, N49-98-02-116 was submitted to the IND on 3 Nov 1998, SN:369. Preliminary data from this study are supplied in the attached document, dated December 18, 1998.

Also included are responses or comments made by the FDA biopharm reviewer of celecoxib NDA 20-998, dated December 14, 1998.

Sincerely,

Winifred M. Begley

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

Enclosures
WMB/anb

BL

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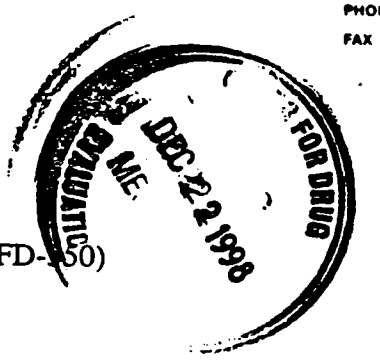
December 21, 1998



Ms. Vickey Lutwak
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-150)
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 20-998
Celebrex™

Dear Vickey,

Enclosed please find the text version of the Searle proposal of the Celebrex label as was faxed to you December 18, 1998.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director
Regulatory Affairs
(847) 982-8155
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