CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 017697-S014

Trade Name: KINEVAC

Generic Name: Sincalide

Sponsor: BRACCO

Approval Date: 11/27/2002

Indications:

- stimulate gallbladder contraction, as may be assessed by various methods of diagnostic imaging, or to obtain by duodenal aspiration a sample of concentrated bile for analysis of cholesterol, bile salts, phospholipids, and crystals;

- stimulate pancreatic secretion (especially in conjunction with secretin) prior to obtaining a duodenal aspirate for analysis of enzyme activity, composition, and cytology;

- accelerate the transit of a barium meal through the small bowel, thereby decreasing the time and extent of radiation associated with fluoroscopy and x-ray examination of the intestinal tract.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S014

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S014

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-697/S-012, S-013, S-014, S-015

Bracco Diagnostics
Attention: Melanie Benson, M.S., R.A.C.
Director, US Regulatory Affairs
P.O. Box 5225
Princeton, New Jersey 08543-5225

Dear Ms. Benson:

Please refer to your supplemental new drug applications dated August 28, 2002, received August 30, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kinevac® (sincalide) for Injection 5 mcg/vial.

We acknowledge receipt of your submissions dated October 3, October 21, October 23, November 1, November 4, November 8, and November 20, 2002.

These supplemental new drug applications provide for the following:

1. Supplement-012 provides for the change in the manufacturing site for the drug product.

2. Supplement-013 provides for the change in the formulation for the drug product.

3. Supplement-014 provides for the change in the packaging for the drug product.

4. Supplement-015 provides for the change in the testing for the drug product.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the submitted labeling text.

The final printed labeling (FPL) must be identical to the labeling package insert, vial label, and shipper label submitted August 28, October 3, and as amended on November 4, 2002.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 10 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 17-697/S-012, S-013, S-014, S-015." Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submissions dated November 8, 2002 and November 20, 2002.

These commitments are listed below:

1. To set specifications for impurities at the conclusion of the two-year stability study. The proposed specifications will be submitted as a prior approval supplement by March 2005.

2. To test the three validation batches (initial timepoint) and the three stability batches (18-month timepoint) by both (b)(4)---------- to provide comparative data. The results of these comparative studies will---------- in January 2003 as a prior approval supplement.

3. To work with (b)(4)-------to reduce (or eliminate) the (b)(4)----------. The status and results will be reported in Annual Reports (July), with the final results being reported in the July 2004 Annual Report.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Although, not approvability issues, we have the following comment and recommendation.

In the draft labeling, you have removed the periods after the N and J in N.J. to read as NJ except in the draft shipper label. For consistency, consider making this editorial change throughout the labeling.

If you have any questions, call Betsy Scroggs, Pharm. D., Consumer Safety Officer, at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice

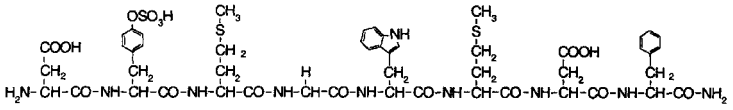
11/27/02 03:08:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S014

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #2	1. Organization: HFD-180	2. NDA Number: 17-697
3. Name and Address of Applicant (City & State): Bracco Diagnostics P.O. Box 5225 Princeton, NJ		4. AF Number: 5.Supplement(s)
6. Name of Drug: Kinevac® for injection	7. Nonproprietary Name: sincalide	Numbers / Dates SCM-012 August 28, 2002 SCF-013 August 28, 2002 SCP-014 August 28, 2002 SCS-015 August 28, 2002
8. Supplement Provides for: Change in formulation, manufacturing site and process, test methods		9. Amendments and Other (Reports, etc.) Dates: SCM-012 BC November 8, 2002 BC, C November 20, 2002 SCF-013 BC November 8, 2002 BC, C November 20, 2002 SCP-014 BC November 8, 2002 BC, C November 20, 2002 SCS-015 BC November 8, 2002 BC, C November 20, 2002
10. Pharmacological Category: gallbladder contraction stimulator for diagnostic testing	11. How Dispensed: R_X √ OTC ___	12. Related IND/NDA/DMF(s):
13.Dosage Form: parenteral	14. Potency: 5 µg/vial	
15. Chemical Name and Structure: cholecystokinin octapeptide Asp-Tyr(SO3H)-Met-Gly-Trp-Met-Asp-Phe-NH2 		16. Records and Reports: Current _____ Yes _____ No Reviewed _____ Yes _____ No
17. Comments: See Review Notes cc: NDA 17-697 HFD-180/Div File HFD-180/BScroggs HFD-180/MKowblansky HFD-180/ LZhou		
18. Conclusions and Recommendations: This supplement should be approved with the		
19. Reviewer		
Name: Marie Kowblansky, Ph.D.	Signature:	Date Completed: 11/20/02

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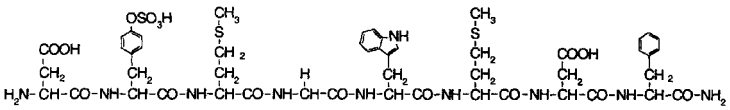
/s/

Marie Kowblansky
11/20/02 06:01:54 PM
CHEMIST

Liang Zhou
11/21/02 01:14:37 PM
CHEMIST

CHEMIST'S REVIEW #2	1. Organization: HFD-180	2. NDA Number: 17-697
3. Name and Address of Applicant (City & State): Bracco Diagnostics P.O. Box 5225 Princeton, NJ		4. AF Number: 5.Supplement(s)
6. Name of Drug: Kinevac® for injection	7. Nonproprietary Name: sincalide	Numbers / Dates SCM-012 August 28, 2002 SCF-013 August 28, 2002 SCP-014 August 28, 2002 SCS-015 August 28, 2002
8. Supplement Provides for: Change in formulation, manufacturing site and process, test methods		9. Amendments and Other (Reports, etc.) Dates: SCM-012 BC November 8, 2002 SCF-013 BC November 8, 2002 SCP-014 BC November 8, 2002 SCS-015 BC November 8, 2002
10. Pharmacological Category: gallbladder contraction stimulator for diagnostic testing	11. How Dispensed: R_X √ OTC ___	12. Related IND/NDA/DMF(s):
13.Dosage Form: parenteral	14. Potency: 5 µg/vial	
15. Chemical Name and Structure: cholecystokinin octapeptide Asp-Tyr(SO3H)-Met-Gly-Trp-Met-Asp-Phe-NH2 		16. Records and Reports: Current _____ Yes _____ No Reviewed _____ Yes _____ No

17. Comments: See Review Notes

cc: NDA 17-697
HFD-180/Div File
HFD-180/BScroggs
HFD-180/MKowblansky
HFD-180/ LZhou

18. Conclusions and Recommendations:

This supplement is approvable (with an 18-month expiration for the product) pending resolution of the issue cited in the Draft Deficiency letter (at the end of the review).

19. Reviewer

Name: Marie Kowblansky, Ph.D.	Signature:	Date Completed: 11/15/02

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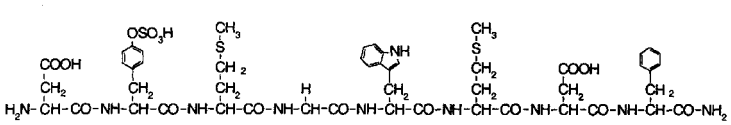
/s/

Marie Kowblansky
11/19/02 01:17:30 PM
CHEMIST

Liang Zhou
11/19/02 01:44:16 PM
CHEMIST

CHEMIST'S REVIEW #1	1. Organization: HFD-180	2. NDA Number: 17-697
3. Name and Address of Applicant (City & State): Bracco Diagnostics P.O. Box 5225 Princeton, NJ		4. AF Number: 5.Supplement(s)
6. Name of Drug: Kinevac® for injection	7. Nonproprietary Name: sincalide	Numbers / Dates SCM-012 August 28, 2002 SCF-013 August 28, 2002 SCP-014 August 28, 2002 SCS-015 August 28, 2002
8. Supplement Provides for: Change in formulation, manufacturing site and process, test methods		9. Amendments and Other (Reports, etc.) Dates: October 21, 2002
10. Pharmacological Category: gallbladder contraction stimulator for diagnostic testing	11. How Dispensed: R_X √ OTC ___	12. Related IND/NDA/DMF(s):
13.Dosage Form: parenteral	14. Potency: 5 µg/vial	
15. Chemical Name and Structure: cholecystokinin octapeptide Asp-Tyr(SO3H)-Met-Gly-Trp-Met-Asp-Phe-NH2 		16. Records and Reports: Current _____ Yes _____ No Reviewed _____ Yes _____ No

17. Comments: See Review Notes

cc: NDA 17-697/SCM012
HFD-180/Div File
HFD-180/BScroggs
HFD-180/MKowblansky
HFD-180/ LZhou

18. Conclusions and Recommendations:

This supplement is approvable (with an 18-month expiration for the product) pending resolution of the issues cited in the Draft Deficiency letter (located at the end of the review) and completion of the Medical, Pharm/Tox, and Biopharm reviews.

19. Reviewer

Name: Marie Kowblansky, Ph.D.	Signature:	Date Completed: 10/16/02

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/s/

Marie Kowblansky
10/28/02 01:06:31 PM
CHEMIST

Liang Zhou
10/28/02 01:26:16 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S014

OTHER REVIEW(S)

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 17-697/S-012, S-013, S-014, S-015

Name of Drug: Kinevac® (sincalide) for Injection 5 mcg/vial

Sponsor: Bracco Diagnostics Inc.

Materials Reviewed

Submission Date	Receipt Date
August 28, 2002	August 30, 2002
October 3, 2002	October 4, 2002
October 21, 2002 facsimile	October 21, 2002
October 21, 2002 (hardcopy submission for document received via facsimile on October 21, 2002)	October 22, 2002
October 23, 2002 facsimile	October 23, 2002
October 23, 2002 (hardcopy submission for document received via facsimile on October 23, 2002)	October 29, 2002
November 1, 2002 facsimile	November 1, 2002
November 4, 2002 facsimile	November 4, 2002
November 4, 2002 (hardcopy submission for documents received via facsimile on November 1 and November 4, 2002.	November 7, 2002
November 8, 2002 facsimile	November 8, 2002

Background and Summary Description: NDA 17-697 is approved for use in stimulation of gallbladder contraction and pancreatic secretion and/or intestinal motility for diagnostic purposes.

Kinevac® was approved on July 21, 1976 for E. R. Squibb and Sons, Inc. Bracco Diagnostics Inc acquired Kinevac® in 1994. E. R. Squibb and Sons, Inc. continued to manufacture the product for Bracco Diagnostics Inc. Bracco Diagnostics Inc notified the Agency that the firm had lost its drug substance manufacturer and drug product manufacturer as of June 30, 2001 thus creating a drug shortage of Kinevac®. On September 21, 2001 the Agency determined that Kinevac® was a medically necessary product.

Supplement -011, submitted on January 21, 2002 provides for a new drug substance manufacturer. The Division approved S-011 on October 29, 2002.

Supplement -012, submitted on August 28, 2002, provides for a change in manufacturing site, formulation, packaging, and testing of the drug product. An expedited review was requested by the firm and granted by the Division.

To delineate all of the proposed changes in the supplement, the Division administratively split S-012 into four supplements as follows:

1. Supplement-012 provides for the change in the manufacturing site for the drug product.

2. Supplement-013 provides for the change in the formulation for the drug product.

3. Supplement-014 provides for the change in the packaging for the drug product.

4. Supplement-015 provides for the change in the testing for the drug product.

On October 3, 2002, the firm submitted three enlarged copies of the proposed shipper label identical to that provided in the original August 28, 2002 submission in response to request by the Division.

On October 11, 2002, the Division issued a Chemistry Information Request letter. On October 21 and October 23, 2002, the firm submitted, by facsimile, draft amendments in response to the Division's October 11, 2002 Information Request letter.

On October 30, 2002, the Division issued a Chemistry Discipline Review letter (DR). The firm responded on November 1, 2002 by facsimile. This facsimile contained, as a follow-up from the October 30, 2002 DR, questions to be addressed in the teleconference that was scheduled for November 4, 2002.

Prior to the scheduled November 4, 2002 teleconference, the firm submitted by facsimile, additional proposed labeling revisions.

Following the November 4, 2002 teleconference, the firm submitted by facsimile, additional proposed labeling revisions.

This supplement has also been reviewed by the following disciplines:
Clinical (see Medical Officer review dated November 1, 2002)
Pharmacology (see Pharmacology review dated November 1, 2002)
Chemistry (See Chemistry review dated October 28, 2002)
Microbiology (see Microbiology review dated October 21, 2002)
Biopharmaceutics (See Biopharmaceutics review dated November 6, 2002)

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Betsy Scroggs
11/21/02 02:42:31 PM
CSO

Joyce Korvick
11/22/02 10:29:47 AM
MEDICAL OFFICER
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM OF TELECON

DATE: November 4, 2002

APPLICATION NUMBER: NDA 17-697/SCM-012, SCF-013, SCP-014, SCS-015

BETWEEN:

Name:
Larry Callan (Senior Director, Regulatory Affairs)
Richard Hunt (Associate Director, Regulatory Affairs)
Melanie Benson (Director, US Regulatory Affairs)

Phone: (609) 514-2262

Representing: Bracco Diagnostics Inc.

AND

Name:
Liang Zhou (Chemistry Team Leader)
Marie Kowblansky (Chemistry Reviewer)
Alice Kacuba (Regulatory Health Project Manager)
Betsy Scroggs (Consumer Safety Officer)

Representing: Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: To discuss how to deal with (b) (4) impurities in the new drug formulation.

BACKGROUND: NDA 17-697 is approved for use in stimulation of gallbladder contraction and pancreatic secretion and/or intestinal motility for diagnostic purposes.

Kinevac® was approved on July 21, 1976 for E. R. Squibb and Sons, Inc. Bracco Diagnostics Inc acquired Kinevac® in 1994. E. R. Squibb and Sons, Inc. continued to manufacture the product for Bracco Diagnostics Inc. Bracco Diagnostics Inc notified the Agency that the firm had lost its drug substance manufacturer and drug product manufacturer as of June 30, 2001 thus creating a drug shortage of Kinevac®. On September 21, 2001 the Agency determined that Kinevac® was a medically necessary product.

Supplement -011, submitted on January 21, 2002 provided for a new drug substance manufacturer and was approved October 29, 2002.

Supplement -012, submitted on August 28, 2002, provides for a change in manufacturing site, formulation, packaging, and testing of the drug product. An expedited review was requested by the firm and granted by the Division.

To delineate all of the proposed changes in the supplement, the Division administratively split S-012 into four supplements as follows:

1. Supplement-012 provides for the change in the manufacturing site for the drug product.

2. Supplement-013 provides for the change in the formulation for the drug product.

3. Supplement-014 provides for the change in the packaging for the drug product.

4. Supplement-015 provides for the change in the testing for the drug product.

SUMMARY OF TODAY'S CALL:
The reason for today's telephone conversation is to discuss and answer questions faxed by the firm on November 1, 2002 in response to the Division's October 30, 2002 Discipline Review (DR) letter.

The firm's questions related to the DR letter deficiencies numbers 1, 3, and 8 are below:

1. We have provided information on the source of the (b) (4) impurities in our October 23 submission. Do you need additional information? If yes, can you be more specific in your request?

3. (b) (4)
We understand that the FDA is requesting us to conduct additional (b) (4) . We need to determine for which batches of Kinevac we need to perform the (b) (4) In our October 23 response we indicated we would test the initial three validation batches using the (b) (4) .
We could also test the three stability batches which are now at the 18-months timepoint. Will this satisfy the Agency for the additional (b) (4) ?

8. Based on you comment, we plan to eliminate the (b) (4) Does the Agency have any comments on our plan?

Outcome: Following a lengthy discussion, the firm agreed to the following pending discussion with their upper management and would send the submission within one week.

1. To set specifications for impurities at the conclusion of the two-year stability study. The proposed specifications will be submitted as a prior approval supplement by March 2005.

2. To test the three validation batches (initial timepoint) and the three stability batches (18-month timepoint) by [redacted](b) (4), to provide comparative data. The results of these comparative studies will be provided to FDA in January 2003 as a prior approval supplement.

3. Ben Venue proposes to immediately initiate a project to investigate possible paths of product exposure and evaluate production and/or engineering controls that may provide improved control of, and perhaps minimize the concentration of, these [redacted](b) (4) Because of the extensive validation work that may be involved, it is possible that it could take up to a year or more to complete this project. The status and results of this project would be reported in Annual Report (July).

Respectfully submitted,

Betsy Scroggs

cc:
Archival NDA 17-697
HFD 180 Division Files
HFD 180 L. Zhou/ M. Kowblansky
Drafted by: BHS/ November 22, 2002
Initialed by:A. Kacuba/November 22, 2002
Final:B. Scroggs/ November 25, 2002
Filename:C:\Documents and Settings\scroggsb\My Documents\NDA 17-697 Kinevac\Supp012\MEMORANDUM OF TELECON 1104.doc

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/s/

Betsy Scroggs
11/25/02 10:20:55 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 19, 2002

To: Melanie Benson	**From:** Alice Kacuba, RN, MSN, RAC Regulatory Health Project Manager
Company: Bracco Diagnostics	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (609) 514-2539	**Fax number:** (301) 827-1305
Phone number: (908) 240-1989	**Phone number:** 301-827-1602

Subject: Post approval commitment for NDA 17-697/S-012, S-013, S-014, S-015.

Total no. of pages including cover: ___

Comments: Attached is a request regarding the above supplements.

Document to be mailed: ❑ YES ☑ NO

In order to complete our action for S-012, S-013, S-014, S-015, we request a written commitment from you:

Please delete the specifications for [redacted] (b) (4) from the drug product specifications. Instead, provide a post-approval commitment that Bracco will work with Ben Venue to eliminate or minimize these contaminants.

Please include a timeframe with your commitment.

Please submit your response as soon as possible as an amendment to NDA 17-697/S-012, S-013, S-014, S-015.

A fax response is acceptable, providing that it includes a signed 1571 form and the fax is followed by a hardcopy submission.

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/s/

Alice Kacuba
11/19/02 02:30:46 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-697/S-012, S-013, S-014, S-015

DISCIPLINE REVIEW LETTER

Bracco Diagnostics
Attention: Melanie Benson, M.S., R.A.C.
Director, US Regulatory Affairs
P.O. Box 5225
Princeton, New Jersey 08543-5225

Dear Ms. Benson:

Please refer to your August 28, 2002 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kinevac® (sincalide) for Injection, 5mcg/vial.

We also refer to your submission dated October 3, October 21, and October 23, 2002.

Our review of the Chemistry, Manufacturing, and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Please identify the source of [redacted] (b) (4) impurities.

2. Please report the levels of the identified [redacted] (b) (4) impurities individually in samples on stability testing, as well as [redacted] (b) (4) impurities. This should be in addition to the total [redacted] (b) (4) impurities which you have reported. In terms of setting specifications for these impurities, either of the following options will be acceptable:

   a) report the individual impurities as "information only" for the first three post approval batches on stability testing and commit to set specifications for these impurities at the conclusion of the stability studies as a prior approval supplement.

   b) set specifications for each of the identified impurities now, based on the stability data that have already been submitted, and make changes as necessary as a prior approval supplement.

   When the individual impurities are reported, please also submit representative mass spectra for each of the [redacted] (b) (4) impurities that have been identified.

3. Since the [redacted] (b) (4) will need to be included in the proposed specifications. To allow

[redacted], we will need to evaluate the correlation between the results from [redacted] for samples on stability testing. Data for the three batches currently on stability testing should be sufficient for this purpose. A prior approval supplement will need to be submitted to accomplish this. [redacted] data for each of the batches at release and at the proposed expiry date of 18 months should be sufficient to support the request. (This approach is being suggested as an alternative to the [redacted] on post approval batches, suggested in our facsimile information request communication of October 11, 2002.) In the meantime, we recommend that you contact the [redacted].

4. [redacted]

5. The [redacted] limit should be lowered to reflect levels observed in your batch test data.

6. The Stability Protocol should be amended to include sterility testing at expiry.

7. The submitted stability data support an eight hour storage time for product reconstituted with water. [redacted] The label should be revised to only recommend storage conditions that can be supported by data.

8. Please be aware that it is not a requirement to set specifications for excipients in the finished product, unless there is a specific reason to do so.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your total application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Please note that we have administratively split your suplemental NDA into 4 separate supplements.

1. S-012 provides for the change in the manufacturing site for the drug product.
2. S-013 provides for the change in formulation for the drug product.
3. S-014 provides for the change in packaging for the drug product.
4. S-015 provides for the change in the testing for the drug product.

Any response to this Discipline Review Letter should reference all 4 supplements.

If you have any questions, call Betsy Scroggs, Pharm.D., Consumer Safety Officer, at 301-827-1250.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou

10/30/02 03:01:18 PM