CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 017697-S012

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-S012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S012

APPROVAL LETTER

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-S012

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE **October 31, 2002:**

TO: Division File

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader (GI Drugs)
Division of Gastrointestinal Drug Products
HFD-180

SUBJECT: **NDA 17-697/SCM-012, Kinevac® for Injection**
Submission of August 28, 2002
Sponsor: Bracco Diagnostics, Princeton, NJ

Kinevac® (Sincalide for injection, USP) is a cholecystopancreatic-gastrointestinal hormone synthetically-prepared C-terminal octapeptide of cholecystokinin (CCK-8). CCK has many biological effects. It stimulates pancreatic enzyme secretion, causes gallbladder contraction, relaxes the sphincter of Oddi, enhances release/output of other hormones and has an effect on food intake.The precise indications for which the drug has been approved are 1) To stimulate gallbladder contraction; 2) To stimulate pancreatic secretion, and 3) To accelerate the transit of barium meal through the small bowel, thereby decreasing the time and extent of radiation associated with fluoroscopy and X-ray examination of the GI tract.The most important clinical use is as a diagnostic test for gallbladder contraction, for which, there are no drugs that can be used instead of CCK. Since its introduction in 1976 both manufacturing and analytical issues have been discussed between FDA and the sponsor at the time of the meeting or interaction. With the termination of contractual obligations with Bristol-Myers Squibb and the ensuing technology transfer of the product to a new manufacturing site, Ben Venue Laboratories, Inc. (Bedford, OH), Bracco (the current sponsor of the Kinevac NDA) used this opportunity to address various outstanding FDA issues. The standard method for (b) (4)

In essence, the current sponsor has reformulated the product, identified a new manufacturing site, (b) (4) Bracco seeks to eliminate the (b) (4) for the product .Because Kinevac® is currently on FDA's Drug Shortages List and there is no alternative drug that can be used as a diagnostic tool for gallbladder contraction, this supplemental application is being assessed under Expedited Review. Reviews from the following disciplines are expected: Chemistry, Biopharmaceuticals, Pharmacology/Toxicology , Microbiology and Medical. In the present secondary review, reviews from each one of these

disciplines are considered. A recommendation for regulatory action is formulated on the basis of input from this multidisciplinary approach

1. CHEMISTRY.

The reviewer, Dr. Marie Kowblansky, has concluded that the submission is **approvable** (with an 18-month expiration for the product) pending resolution of the issues (1. through 8.) cited in the Draft Deficiency Letter , located on pages 9 and 10 of her review (date completed October 16, 2002).

2. MICROBIOLOGY

The product Quality Microbiology Review, dated October 21, 2002 was carried out by Paul Stinavage. The application is recommended for **approval** on the basis of sterility assurance. The reviewer notes that Ben Venue Labs has upgraded its facility where the product is manufactured. (b) (4) Additional items have been properly installed or relocated. All of this is acceptable.

3. PHARMACOLOGY/TOXICOLOGY

According to the reviewer, Dr. Sushanta Chakder, from a preclinical standpoint, the supplemental application is **approvable** (Review date October 31, 2002). The reviewer notes a study comparing the gallbladder contractile effects of the 3 batches of Kinevac new formulation to the old formulation (control) after I.V. administration to guinea pigs. No differences in the gallbladder contractile effect were seen between different batches of the new vs the old formulation. In another acute toxicity study in mice , there was no difference s in the toxicology profiles between the new and old formulations . The reviewer notes further that to improve the stability of the new formulation, the sponsor has added several additional ingredients. In his opinion, the new ingredients, at the proposed concentrations, do not appear to pose any risk to the recipients. In conclusion, no apparent differences in the pharmacology and toxicology parameters were observed between the marketed, old formulation and the newly proposed formulation of Kinevac.

4. BIOPHARMACEUTICS

There is no Biopharm review available because a review is not needed. From interactions with Dr. Suresh Doddapaneni, Bioparm Team Leader, we conclude that, because the product is being administered intravenously, at the recommended dose and mode of administration as the old products, the product is 100% bioavailable . There are no scientific reasons to propose that the ingredients added to improve the stability of the drug in the new formulation might result in significant changes in the pharmacokinetic profile of the drug. Thus, from the Biopharm viewpoint, the submission is **approvable.**

5. MEDICAL

There are neither efficacy nor safety concerns with the new formulation.. The pharmacology data show no differences in gallbladder contractile effects between 3 batches of the new Kinevac formulation and the old, when these formulations are administered intravenously to guinea pigs. This is the standard bioassay to test CCK activity. The sponsor has adequately justified the

choice of formulation components. Since they are all compendial, these formulation components are acceptable.

[redacted]

a) They are part of the normal diet.
b) They are administered parenterally (I.V.) as a usual component of TPN (Total Parenteral Nutrition) in patients that cannot ingest nutrients orally because of gut insufficiency. An example of TPN, [redacted]
c) In the newly proposed Kinevac® formulation are presents at concentrations (see above) that are far less than the [redacted]
d) Each 5ug Kinevac® vial contains [redacted] Based on the calculations carried out by Dr.Chakder, the Pharm/Tox reviewer, these represent [redacted] of the daily doses, respectively, being injected as TPN therapy.

It is therefore concluded that the amounts of [redacted] present in the newly proposed Kinevac® formulation would not pose any safety risks to patients. In addition, Kinevac is used as a diagnostic test for one time only, although in practice, when the desired gallbladder contraction is not obtained with one injection, a second dose of the diagnostic test is administered. There is no reason to propose that 2 consecutive doses of the formulation would be of concern, from the safety viewpoint.

RECOMMENDATION FOR REGULATORY ACTION

The new formulation of Kinevac, under supplement # SCM-012 to NDA 17-697 represents a significant improvement over the old formulation. The new formulation is more stable, so that the [redacted] of the active ingredient sincalide in the currently approved formulation has been eliminated. [redacted]. The formulation is expected to perform as efficiently as the old and the ingredients added such as [redacted] and other components do not represent a safety concern. Thus, the newly proposed Kinevac® formulation should be approved, pending resolution of the CMC deficiencies listed on pages 9 and 10 of Dr. M. Kowblansky's review.

cc: HFD-180 File/RJustice/JKorvick/HGallo-Torres/
LZhou/MKowblansky/JChoudary/SChakder/Pcooney/PStinavage/SDoddapaneni/BScroggs

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/s/

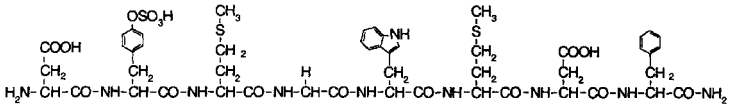
Hugo Gallo Torres
11/1/02 07:21:54 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S012

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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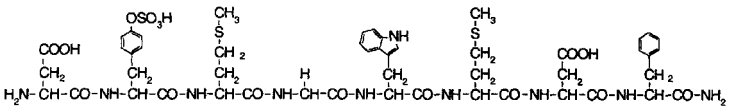
/s/

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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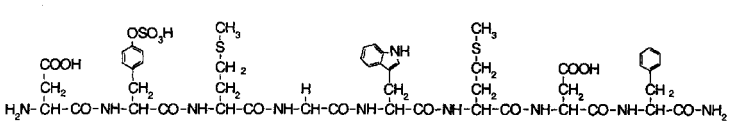
/s/

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
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CHEMIST

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S012

PHARMACOLOGY REVIEW(S)

PHARMACOLOGIST'S REVIEW OF NDA 17-697
(Supplement # SCM – 012 Dated August 28, 2002)

Sponsor and Address: Bracco Diagnostics Inc.
Princeton, NJ 08543
Reviewer: Sushanta Chakder, Ph. D.
Pharmacologist, HFD-180
Date of Submission: August 28, 2002
Date of HFD-180 Receipt: August 30, 2002
Date of Review: October 31, 2002
Drug: Kinevac (Sincalide) for Injection
Category: Cholecystopancreatic-gastrointestinal hormone
Proposed Marketing Indication: Diagnostic to stimulate gallbladder contraction and pancreatic secretion and/or intestinal mobility.

Dose: Intravenous - 0.02 μg/kg to 0.12 μg/kg.
Intramuscular- 0.1 μg/kg

SUBMISSION CONTENTS:

Kinevac (Sincalide) for Injection is currently approved in the US for its use (1) to stimulate gall bladder contraction, (2) to stimulate pancreatic secretion, and (3) to accelerate the transit of 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. The drug is on short supply because the manufacturer of the drug substance and product, BMSqiubb, stopped manufacturing Kinevac due to closure of their manufacturing facility. To improve the stability of the active drug, the sponsor, Bracco Diagnostics Inc. has reformulated Kinevac. The revised Kinevac formulation will be manufactured in Ben Venue Laboratories (BVL), Bedford, OH. The compositions of the old formulation and the new formulation are as follows:

In the present supplemental application, the sponsor has submitted full reports of the following preclinical studies:
1. Pharmacology study to evaluate the responsiveness of guinea pig gallbladder to Kinevac following intravenous injection,
2. Acute toxicity study of Kinevac in mice by the intravenous route.

PHARMACOLOGY:

Evaluation of Guinea Pig's Gallbladder Responsiveness *in situ* Following Intravenous Injection of Kinevac®. Comparison Between Batches 197559, 207146 and 243032 (Study # RF-01-0091).

Methods: The study was conducted to compare the gallbladder contracting effects of the new formulation of Kinevac with that of the old formulation in a guinea pig model. Three batches of the new formulation were compared with a control batch of the old formulation in their ability to contract the gallbladder. Kinevac was administered intravenously at doses of 0.0078, 0.0156, 0.0312 and 0.0624 µg/kg. The maximum tension developed after administration of a dose was measured in grams.

Results: All three batches of the new Kinevac formulation (batch nos. 197559, 207146 and 243032) caused contractions of the guinea pig gall bladder in a dose-dependent manner. The control article (batch # OB28194) also produced similar contractions and no differences in the contraction were observed between different batches.

The gallbladder tensions in grams after administration of different doses of the three batches of the new formulation and the control batch of Kinevac is summarized in the Table below.

Table: Effect of different doses of Kinevac on guinea pig gall bladder (grams of tension; mean ± S.D)

Batch #	**0.0078 µg/kg**	**0.0156 µg/kg**	**0.0312 µg/kg**	**0.0624 µg/kg**
197559	0.67 ± 0.10	1.05 ± 0.26	1.45 ± 0.29	2.17 ± 0.33
207146	0.67 ± 0.12	1.03 ± 0.28	1.52 ± 0.22	2.22 ± 0.32
243032	0.62 ± 0.26	1.08 ± 0.22	1.57 ± 0.23	2.33 ± 0.20
OB28194 (Control)	0.63 ± 0.16	1.05 ± 0.31	1.38 ± 0.25	2.22 ± 0.18

In summary, the gallbladder contractile effects of the three batches of Kenevac new formulation were compared with the old formulation (control) after IV administration in guinea pigs. No differences in the gallbladder contractile effect were observed between different batches of the new formulation and the old formulation.

TOXICOLOGY:

Study Title: Acute Toxicity of Kinevac after Intravenous Administration to Mice.

Key study findings: In the single-dose IV acute toxicity study in mice, 1.0, 12.5 and 25 µg/kg doses of the new formulation and 25 µg/kg of the old formulation were administered to different groups of animals. There were no deaths of animals in any group. Treatment-related clinical signs, such as dypsnea and hypoactivity, were observed in animals receiving the 25 µg/kg dose of both formulations.

The clinical signs lasted for up to 30 minutes in animals receiving the new formulation, and for up to 4 hours in animals receiving the old formulation. Thus, no difference in the toxicity profiles was observed between animals receiving the new and the old formulation.

Study no: CdS149.

Conducting Laboratory (and location if not sponsor): Bracco Imaging S.p.A, Via E. Folli, 50 20134 Milan, Italy
Dates of study initiation & completion: May 10, 2001 & October 04, 2001.

GLP compliance: Yes

QA Report Yes (X) No ( )

Drug, Lot #, radiolabel (if applicable), and % purity: Kinevac new formulation, Batch no. 197559; Kinevac old formulation, Batch no. 57117021 (Control # OB28194).

Formulation/vehicle: Lyophilized Kinevac (Sincalide) formulations were dissolved in sterile water for injection (1 µg/ml) before IV administration to the animals.

Methods:
Dosing:

Species/strain: CRL : CD-1 (ICR) BR IGS mice.
#/sex/group or time point: 12 animals/sex/group
Age: Males- 9-weeks old, Females- 6 weeks old
Weight: males – 26.0g – 30.2g, females – 22.5g – 26.1g.
Doses in administered units: 1.0, 12.5 and 25 µg/kg doses of the new formulation, and the 25 µg/kg dose of the old formulation was used.
Route, form, volume, and infusion rate: The drug was administered via tail vein at a rate of 1 ml/min (administration volume 5 ml/kg) using a Harvard infusion pump.

Observations and times:

Clinical signs: The animals were observed before dosing, immediately after dosing, and 5 min, 30 min, 1, 2, 4 and 6 hours after dosing. During the observation period, the animals were observed twice a day.
Body weights: Body weights were recorded on Days –3, 0 (dosing day), 2, 7 and 13.
Hematology: Blood samples for hematological examinations were collected before sacrifice on Days 3 and 15 after dosing.
Gross pathology: Half of the animals were sacrificed on Day 3 and the rest of the animals were sacrificed on Day 15 by cardiac puncture under anesthesia. All animals were subjected to macroscopic examination. The following organs were collected for histopathology examinations: kidney, liver, lungs, gall bladder and intestine.

Results:

Mortality: There was no mortality in any group.

Clinical signs:

Animals receiving 1.0 and 12.5 μg/kg doses of the **new formulation** showed no clinical signs related to treatment with Kinevac. All males and 1 female (of 12) receiving the 25 μg/kg dose showed signs of dyspnea immediately after dosing, and hypoactivity was observed 5 minutes after dosing. The clinical signs disappeared within 30 minutes after dosing.

Only one dose of the old formulation (25 μg/kg) was used in the study. All males and 4 females receiving the drug had dyspnea immediately after dosing and lasted for up to 1 hr after dosing. Hypoactivity was observed in all males and few females that lasted for 30 minutes to 4 hours.

Body weights: No changes in the body weights were observed in any group.

Hematology: No treatment-related changes in the hematological parameters were observed in any group.

Gross pathology: No treatment related changes were observed in any group.

Histopathology: Histopathological examinations of the kidneys, liver, lung, gall bladder and intestine, conducted on Days 3 and 15, did not show any treatment-related changes in any group.

In summary, in the acute toxicity study was conducted in mice with the new formulation of Kinevac after IV administration of 1.0, 12.5 and 25 μg/kg doses and compared with the 25 μg/kg dose of the old formulation. There were no deaths in any group; so the minimal lethal dose was not known. Treatment related clinical signs such as dyspnea and hypoactivity were observed in animals receiving the 25 μg/kg dose of both the old and the new formulation. The clinical signs were observed within 5 minutes of dosing, and lasted for up to 30 minutes in animals receiving the new formulation and for up to 4 hours in animals receiving the old formulation of Kinevac. No treatment-related gross or histopathological changes were observed in any groups of mice sacrificed on Days 3 and 15. Thus, there were no differences in the toxicology profiles between the new and the old formulation in the acute toxicity study in mice. The earliest time at which the gross and histopathological examinations were conducted was 48 hours after dosing. Histopathological examinations were conducted only of limited tissues and no blood chemistry determinations were done in this acute toxicity study.

SUMMARY AND CONCLUSION:

Sincalide is a cholecystokinin C-terminal octapeptide and it evokes a variety of biological responses, including smooth muscle contraction of the gallbladder and small intestine, relaxation of the choledochoduodenal junction, protein secretion by the pancreas and acid secretion by the stomach. It is more potent than cholecystokinin on a weight or molar basis. Sincalide (Kinevac) for Injection is currently approved in the US as a diagnostic agent to stimulate gall bladder contraction, to stimulate pancreatic secretion, and to accelerate the transit of barium meal through the small bowel. The recommended doses for gall bladder contraction ranges from 0.02 to 0.12 μg/kg i.v., or 0.10 μg/kg i.m. For stimulation of parcreatic secretion, the recommended i.v. dose is 0.02 μg/kg, and for acceleration of transit of barium meal through the small bowel, the recommended i.v. doses range from 0.04 to 0.12 μg/kg. The drug is on short supply because the manufacturer of the drug substance and product, BMSqiubb, stopped manufacturing Kinevac due to closure of their manufacturing facility. The sponsor

of the NDA (17-697), Bracco Diagnostics Inc., has reformulated Kinevac and has submitted a supplement to the NDA. The revised Kinevac formulation will be manufactured in Ben Venue Laboratories (BVL), Bedford, OH. The sponsor has conducted two preclinical studies with the new formulation: (a) a pharmacology study to evaluate the responsiveness of guinea pig gallbladder following intravenous Injection and (b) an acute toxicity study of Kinevac in mice by the intravenous route.

In the proposed new formulation, the sponsor has added several additional ingredients to improve the stability of the active drug (sincalide) (b) (4)

[redacted]

.

The gallbladder contracting effects of three batches of the new Kinevac formulation was compared with that of the old formulation and no differences in the gallbladder contractile effects were observed between different batches of the new formulation and the old formulation, when administered intravenously to guinea pigs.

In the single dose acute IV toxicity study in mice, groups of animals received 1.0, 12.5 and 25 µg/kg doses of Kinevac. In addition, for comparison, another group of animals received a 25 µg/kg of the old formulation of the drug. Half of the animals were sacrificed on Day 3 and the rest of the animals were sacrificed on Day 15 after the dosing. There was no mortality in any group, so, the minimal lethal dose is not known. Treatment related clinical signs such as dyspnea and hypoactivity were observed in animals receiving the 25 µg/kg dose of both the old and the new formulation. The clinical signs were observed within 5 minutes of dosing, and lasted for up to 30 minutes in animals receiving the new formulation, and for up to 4 hours in animals receiving the old formulation of Kinevac. No treatment-related gross or histopathological changes were observed in any groups of mice sacrificed on Days 3 and 15. However, the sponsor conducted histopathological examinations of only limited number of tissues.

Sincalide (Kinevac) for Injection is currently approved in the US as a diagnostic agent to stimulate gall bladder contraction, to stimulate pancreatic secretion, and to accelerate the transit of

barium meal through the small bowel. The sponsor of the NDA (17-697), Bracco Diagnostics Inc., has reformulated Kinevac and has submitted a supplemental NDA application to manufacture Kinevac in a new facility (Ben Venue Laboratories, Bedford, OH). To improve the stability of the new formulation, the sponsor has added several additional ingredients. The new ingredients, at the proposed concentrations, do not appear to pose any risk to the recipients. The new formulation of Kinevac was equipotent to the old formulation in causing guinea pig gall bladder contractions, and had similar toxicity profiles in the acute toxicity study in mice. Thus, no apparent differences in the pharmacology and toxicology parameters were observed between the marketed, old formulation and the new formulation of Kinevac.

RECOMMENDATION:

From a preclinical standpoint, the supplemental application is approvable.

_____ _____

Sushanta Chakder, Ph.D. Date
Pharmacologist, HFD-180

COMMENTS

_____ _____

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

cc:
NDA 17-697
HFD- 180
HFD- 181/CSO
HFD- 180/Dr. Chakder
HFD- 180/Dr. Choudary
HFD-180/Dr. Zhou
HFD-180/Dr. Kawblansky

R/D Init.: J. Choudary 10/31/02

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/s/

Sushanta Chakder
11/1/02 08:32:53 AM
PHARMACOLOGIST

Jasti Choudary
11/1/02 08:40:55 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S012

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

Consult Review for HFD-180

09 October 2002

NDA: 17-697/SCM-012

Name of Drug: Kinevac® (sincalide) for Injection

Review Number: 1

Submission Date: 28 August 2002

Applicant: Bracco Diagnostics, Inc.

Name of Reviewer: Paul Stinavage

Recommendation on Approvability – The application is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **NDA:** 17-697/SCM-012

2. **REVIEW NUMBER:** 1

3. **REVIEW DATE:** 08 October 2002

4. **TYPE OF SUPPLEMENT:** Prior Approval

5. **SUPPLEMENT PROVIDES FOR:** Product manufacture in Ben Venue Laboratories' facility in Bedford, OH.

6. **APPLICANT/SPONSOR:** Bracco Diagnostics, Inc.
107 College Road East
Princeton, New Jersey 08540
Name: Bracco Diagnostics, Inc.
Representative: Richard Hunt, Ph.D.
Telephone: (609)514-2439

7. **MANUFACTURING SITE:** Ben Venue Laboratories, Bedford, OH

8. **DRUG PRODUCT NAME:**
Proprietary: Kinevac® for Injection
Non-proprietary: sincalide
Drug Priority Classification: Expedited – Drug Shortage

9. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Intravenous

10. **METHOD(S) OF STERILIZATION:** (b) (4)

11. **PHARMACOLOGICAL CATEGORY:** Lyophilized

B. 1. **DOCUMENT/LETTER DATE:** 28 August 2002
2. **RECEIPT DATE:** 29 August 2002
3. **CONSULT DATE:** 13 September 2002
4. **DATE OF AMENDMENTS:** (none)
5. **ASSIGNED FOR REVIEW:** 27 September 2002
6. **SUPPORTING/RELATED DOCUMENTS:** (b) (4)

C. **REMARKS:** Ben Venue Labs has upgraded its facility where the product is manufactured. (b) (4)


(b) (4)

Executive Summary

I. Recommendations

A. Recommendation on Approvability – The application is recommended for approval on the basis of sterility assurance.

B. Recommendation on Phase 4 Commitments and/or Agreements, if Approvable

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology

The submission seeks approval for product manufacture in Ben Venue's upgraded South Facility.

B. Brief Description of Microbiology Deficiencies

Not Applicable

C. Assessment of Risk Due to Microbiology Deficiencies-

Very low risk of patient injury due to distribution of contaminated product.

III. Administrative

A. Reviewer's Signature _____

B. **Endorsement Block**

Paul Stinavage/09 October 2002
P.H. Cooney/

C. **CC Block:**

Original NDA 17-697
HFD-180/Division File/NDA 17-697/A. Kacuba/B. Scroggs

n17697s12.doc

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/s/

Paul Stinavage
10/21/02 05:30:56 AM
MICROBIOLOGIST
Product manufacture in Ben Venue's upgraded facility.

Peter Cooney
10/21/02 11:24:28 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMORANDUM

DATE:	11/05/02
FROM:	Suresh Doddapaneni, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader.
TO:	File of NDA 17-697 (Kinevac® (sincalide) for Injection)
SUBJECT:	Reformulation (Supplement SCM-012; submission dated 08/28/02)

In order to maintain the stability of sincalide in both bulk solution and final lyophiized product, the reformulated product now contains: (b) (4) [redacted] In addition, the following changes were also made: (b) (4) [redacted] and to use Ben Vue Laboratories as an alternate drug product manufacturer.

Clinical review (dated 11/01/02) addressed the safety aspects of the newly added inactive ingredients and the implications of eliminating the (b) (4) [redacted]. Pending resolution of CMC issues, the clinical review recommended approval of the changes.

During its use, this product is administered intravenously, and from the viewpoint of Clinical Pharmacology and Biopharmaceutics, the formulation and manufacturing site changes are not expected to affect the *in vivo* bioavailability of sincalide.

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/s/

Suresh Doddapaneni
11/6/02 08:12:41 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 017697-S012

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)

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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-S012

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

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/s/

Hugo Gallo Torres
10/31/02 08:53:18 PM
MEDICAL OFFICER

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

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 10, 2002

To: Melanie Benson	**From:** Betsy Scroggs
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:** 301-827-1250

Subject: NDA 17-697/ S-012

Total no. of pages including cover: 3

Comments: This is an information request regarding supplement 012.

Document to be mailed: ❑ YES ☑ NO

Dear Ms. Bensen:

We refer to supplement 012 submitted August 28, 2002 for which an expedited review was requested and granted. The chemist has identified additional information that is needed for the review of this supplement.

1. Please identify the source of [redacted] impurities.

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

a) For the first three post approval batches on stability testing, report the individual impurities as "information only". Commit to a post-approval commitment, in writing (and include appropriate timelines) to set specifications for these impurities at the conclusion of the stability studies, and submit this information as a prior approval supplement in the future.

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

3. Please report the results of [redacted] for the three batches of the finished drug product for which [redacted] have been reported. Since the [redacted]

4. For the first three post approval batches we request a post-approval commitment in writing from you (include appropriate timelines) that in addition to conducting the [redacted] at release, you will also conduct it as part of the stability program, at least at expiry.

Please submit your written response, as an amendment to S-012 as soon as possible so that the Expedited Review can be completed. Please be advised that there may be additional information requests as the review proceeds.

Sincerely,

Betsy Scroggs, Pharm. D. Consumer Safety Officer,
Division of Gastrointestinal and Coagulation Drug Products, HFD 180 Center for Drug Evaluation and Research, Food and Drug Administration
Tel: (301) 827-1250 Fax: (301) 827-1305

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/s/

Betsy Scroggs
10/11/02 11:30:30 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Peter Cooney, HFD-805, Parklawn Building, Room 18B-08			FROM: Alice Kacuba, Regulatory Health Project Manager for Betsy Scroggs, HFD-180	
DATE Sept 13, 2002	IND NO.	NDA NO. 17-697	TYPE OF DOCUMENT S-012	DATE OF DOCUMENT August 28, 2002
NAME OF DRUG Kinevac	PRIORITY CONSIDERATION Expedited Review granted		CLASSIFICATION OF DRUG GI diagnostic	DESIRED COMPLETION DATE November 1, 2002

NAME OF FIRM: Bracco

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- XXX OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS: Bracco has submitted a cmc supplement that provides for a change n manufacture, formulation, and testing for Kinevac. CMC has asked for a micro consult of this submission. CMC has granted the firm's request for an expedited review. We are asking that all reviews be completed by Nov 1, 2002.

3 volumes will be sent to you.

The CMC reviewer is Marie Kowblansky 7-7466.
The CSO is Betsy Scroggs 7-1250.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Alice Kacuba
9/13/02 09:47:48 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-697/S-012

PRIOR APPROVAL SUPPLEMENT

Bracco Diagnostics Inc.
Attention: Richard J. Hunt, Ph.D.
Associate Director, Regulatory Affairs
P.O. Box 5225
Princeton, NJ 08543

Dear Dr. Hunt:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Kinevac (sincalide) for Injection

NDA Number: 17-697

Supplement Number: S-012

Date of Supplement: August 28, 2002

Date of Receipt: August 30, 2002

This supplement proposes the following change: a change in the manufacturing site, formulation, and testing for Kinevac.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 29, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 30, 2002.

We note that your submission requested an expedited review under MAPP 5310.5. This request has been granted.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm.D.
Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Alice Kacuba
9/11/02 12:56:56 PM
Signed for Betsy Scroggs