CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20937

CORRESPONDENCE

MALLINCKRODT

November 24, 1999

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 Phone: 314.654.2000 www.mallinckrodt.com

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Medical Imaging and
Radiopharmaceutical Drug Products, HFD-160
Document Control Room 18B-06
5600 Fishers Lane
Rockville, Maryland 20857

Ref: NDA 20-937/ OptiMARK® (gadoversetamide injection)
Safety Update Report

Dear Sir or Madam:

As specified in 21 CFR 314.50(d)(5)(vi)(b), Mallinckrodt Inc. is hereby submitting a safety update report for OptiMARK (gadoversetamide injection).

There has been no new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

The pediatric pharmacokinetic study in normal subjects (Study 552) which was referenced in the June 7, 1999 resubmission of NDA 20-937 has been terminated. The data for this study are in the process of being summarized. There were no adverse events reported in this study.

On May 13, 1999 a new protocol, "A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Safety and Dose-Related Efficacy of OptiMARK® Compared with Magnevist® in Identifying Lesions in the Body by MRI," was provided to the Agency under IND . This is an on-going clinical study; therefore, the database is not locked and no statistical analysis has begun. Anecdotal evidence from monitor visits indicate no adverse events have occurred other than those which have been described in the draft package insert which was included in our NDA 20-937 submission. On November 5, 1999 a Serious Adverse Event for this study was reported to the Agency. This event occurred for a patient who had been dosed with the comparator drug. At approximately 64 hours post dose with the comparator drug, the patient exhibited symptoms of abdominal pain, dizziness, diarrhea and hypotension. She was admitted to the hospital for further observation and evaluation. The investigator deemed the event

not related to the drug which had been administered, but rather to the underlying disease for which surgery had been scheduled. A copy of the IND Safety Report is attached.

Please add this information to NDA 20-937.

Sincerely,

Mary E. Hamilton
Manager, Regulatory Affairs
Telephone (314) 654-3272
Telefax (314) 654-3344

Attachment: IND

cc: James Moore, R.Ph., M.A., Project Manager

MALLINCKRODT

Mallinckrodt Inc. 675 McDonnell Boulevard PO Box 5840 St. Louis MO 63134 Phone: 314.654.2000 www.mallinckrodt.com

November 5, 1999

Food and Drug Administration
Center for Drug Evaluation & Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products, HFD #160
ATTN: Document Control Room, 18B-06
5600 Fishers Lane
Rockville, Maryland 20857

Ref: IND Injection (gadoversetamide injection)

Dear Sir or Madam:

Please amend IND with this report of a serious adverse event. Details are provided in the attached Safety Report.

Sincerely,

Mary E. Hamilton
Manager, Regulatory Affairs
Telephone (314) 654-3272

cc: James Moore, Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Mallinckrodt Inc.

2. DATE OF SUBMISSION
November 5, 1999

3. ADDRESS *(Number, Street, City, State and Zip Code)*
675 McDonnell Blvd.
St. Louis, MO 63042

4. TELEPHONE NUMBER *(Include Area Code)*
(314) 654-2000

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
OptiMARK™ (gadoversetamide, MP-1177/10 Injection

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Contrast Enhanced Imaging for identifying lesions of the body by MRI.

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. *IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) ould be numbered "Serial Number: 001." Subsequent submissions should be mbered consecutively in the order in which they are submitted.*

SERIAL NUMBER
1 4 4

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☒ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DOR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

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

1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Adeoye Olukotun, M.D.
Vice President, Medical and Regulatory Affairs

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Adeoye Olukotun, M.D.
Vice President, Medical and Regulatory Affairs

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Mary E. Hamilton	Mary E. Hamilton	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Mallinckrodt Inc. 675 McDonnell Blvd. St. Louis, MO 63042	(314) 654-3272 (314) 654-3344	11/5/99

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Please DO NOT RETURN this application to this address.

84

MALLINCKRODT

Improving Healthcare and Chemistry

ORIGINAL

11.1

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone. 314.654.2000

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ FINAL ☐ [illegible]
CSO INITIALS 8/4/98 DATE

There are no safety issues raised
A E Jones
12/28/98

CENTER FOR DRUG
REC'D
JUL 31 1998
HFD-160
EVALUATION AND RESEARCH

July 29, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
5600 Fishers Lane
Rockville, MD 20857

ATTN: Patricia Y. Love, M.D., M.B.A.

RE: **Safety Update Report**
NDA 20-937/OptiMARK® (gadoversetamide injection)
NDA 20-975/OptiMARK Pharmacy Bulk Package
NDA 20-976/OptiMARK in Plastic Syringe

Dear Dr. Love:

As specified in 21 CFR 314.50(d)(5)(vi)(b), Mallinckrodt Inc. is hereby submitting a safety update report for OptiMARK (gadoversetamide injection).

There has been no new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling. ✓

The only domestic clinical study in process is the pediatric pharmacokinetic study in normal subjects (Study 552). The protocol was submitted to the Agency on June 5, 1998 as Amendment 135 to IND To date, there have been no adverse events reported in this study.

Amendment 082 to IND provided the protocols for six Phase 3 clinical studies to be conducted in Japan. These studies are incomplete; however, once these data are available, this information will be provided to the Agency.

Please add this report to NDAs 20-937 (OptiMARK original submission), NDA 20-975 (OptiMARK Pharmacy Bulk Package) and NDA 20-976 (OptiMARK in Plastic Syringe).

Sincerely,

Mary E. Hamilton

Mary E. Hamilton
Manager, Regulatory Affairs

cc: Kim Colangelo, CSO

MALLINCKRODT

Improving Healthcare and Chemistry

ORIGINAL

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.L. ☐ MEMO
CSO INITIALS 8/4/98 DATE

CENTER FOR DRUG
REC'D
JUL 31 1998
HFD-160
EVALUATION AND RESEARCH

July 29, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical
Drug Products, HFD-160
5600 Fishers Lane
Rockville, MD 20857

ATTN: Patricia Y. Love, M.D., M.B.A.

RE: **Safety Update Report**
NDA 20-937/OptiMARK® (gadoversetamide injection)
NDA 20-975/OptiMARK Pharmacy Bulk Package
NDA 20-976/OptiMARK in Plastic Syringe

Dear Dr. Love:

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Please add this report to NDAs 20-937 (OptiMARK original submission), NDA 20-975 (OptiMARK Pharmacy Bulk Package) and NDA 20-976 (OptiMARK in Plastic Syringe).

Sincerely,

Mary E. Hamilton
Manager, Regulatory Affairs

cc: Kim Colangelo, CSO

DEPARTMENT OF HE. H & HUMAN SERVICES — ublic Health Service

D F.

Food and Drug Administration
Rockville MD 20857

JUN 22 1999

NDA 20-937, 20-975, 20-976

Mallinckdrodt, Inc.
P.O. Box 5840
St. Louis, Mo 63134

Attention: Mary Hamilton
Manager, Regulatory Affairs

Dear Ms. Hamilton:

We acknowledge receipt on June 8, 1999 of your June 7, 1999 resubmission to your new drug applications (NDAs 20-937, 20-975, 20-976) for Optimark (gadoversetamide) Injection.

This resubmission contains additional INFORMATION ON ASSESSMENT OF CARDIAC SAFETY, CLINICAL PHARMACOLOGY, STATISTICAL INFORMATION, AND INFORMATION ON CMC, METHODS VALIDATION, and DRAFT LABELING submitted in response to our December 23, 1998 action letter.

We consider this a class 2 resubmission in response to our action letter. Therefore, the user fee goal date is December 8, 1999.

If you have any questions, contact James Moore, R.Ph., M.A., Project Manager, at (301) 827-7510.

Sincerely,

/S/ 6/22/99

Robert K. Leedham, Jr.
Chief, Project Management Staff
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Colangelo

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-937

MAR 10 1998

Mallinckrodt Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Attention: James E. Keller
Director, Regulatory Affairs

Dear Mr. Keller:

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

Name of Drug Product: OptiMARK™ (gadoversetamide injection, glass vial container)

Therapeutic Classification: Standard

Date of Application: February 28, 1998

Date of Receipt: March 2, 1998

Our Reference Number: 20-937

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 May 1, 1998, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact me at (301) 443-3500.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

Kim Colangelo
Consumer Safety Officer
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

HFD-160 Colangelo

SEP 28 1998

NDA 20-937

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis, MO 63134

Attention: Mary E. Hamilton
Manager, Regulatory Affairs

Dear Ms. Hamilton:

Please refer to your pending March 2, 1998, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OptiMARK (gadoversetamide) Injection.

We also refer to the conversation between yourself and Ms. Kim Colangelo, Consumer Safety Officer, on September 11, 1998, and your submission dated September 23, 1998.

We are reviewing the Clinical section(s) of your submission and have the following comments and information requests.

To clarify the information submitted on September 23, 1998, the following is needed:

1. The basis of certification for the principal investigator or internist who interpreted the EKGs.
2. Clarification whether the EKGs were interpreted manually or by an automated system.
3. A breakdown of the number of EKGs read by each of the three medically qualified individuals (i.e., principal investigator, internist, and cardiologist) for each study.
4. Further breakdown of the number and timing of EKGs collected in the 0 to 2 hour period after dosing (e.g., how many were collected at 15 minutes, at 30 minutes, etc.) where applicable.

We would appreciate your prompt written response so we can continue our evaluation of your NDA. While this information is requested for all studies used to assess the safety of OptiMARK, to ensure timeliness, the information for the Phase 1 studies should be submitted first.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the 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 are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Ms. Colangelo or Mr. James Moore at (301) 443-3500.

Sincerely,

/S/ 9/25/98

Robert K. Leedham, Jr.
Chief, Project Management Staff
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

HFD-160/Calongele

NDA 20-937

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis, MO 63134

Attention: Mary E. Hamilton,
Manager, Regulatory Affairs

Dear Ms. Hamilton:

Please refer to your pending March 2, 1998, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OptiMARK (gadoversetamide) Injection.

We are reviewing the Clinical section of your submission and have the following comments and information requests:

1. A table containing information regarding the extent of agreement between the site investigator and the blinded readers for both the final diagnosis and number of lesions is needed for the pivotal trials (#488 and #525) for the CNS indication. If appropriate, this information should be provided for the pivotal trials for the Liver indication. These tables should be similar in format to the agreement table provided in Volume 2.54, p. 12.2769.

2. Data on the final diagnosis is not presented for all patients. For example, the data for patients A-001-(age)-(sex) through A-006-(age)-(sex) is provided in some of the efficacy tables (e.g., "Technical Satisfaction of Image and Disease Type per Blinded Reader", Volume 2.54, p. 12.2562), but data is not provided for these patients in other efficacy tables (e.g., "Technical Satisfaction of Image and Disease Type per Site Investigator", Volume 2.54, p. 12.2662). The omitted data, or an explanation which includes identification of each randomized patient for whom data for all outcome variables is not available, should be provided for each case.

3. Clarification is needed regarding how conspicuity and border delineation scores were assigned for patients with no imaged lesions.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the 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 are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Kim Colangelo at (301) 443-3500.

Sincerely,

/S/ 9/21/98

Robert. K. Leedham, Jr.
Chief, Project Management Staff
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MALLINCKRODT

Improving Healthcare and Chemistry

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654 2000

April 13, 1998

James Moore
Center for Drug Evaluation & Research
Division of Medical Imaging & Radiopharmaceutical Products, HFD #160
5600 Fishers Lane
Rockville, MD 20857

Ref: NDA 20-937/OptiMARK™ Injection (gadoversetamide injection)
Teleconference on April 10, 1998
Analysis and presentation of clinical laboratory data

Dear Mr. Moore,

As described in the fax provided to you on Friday, April 10, 1998, three examples of clinical laboratory data are attached for consideration by the statistical and clinical review team.

Mallinckrodt would also like to request a follow-up telephone conference call (at your earliest convenience) to determine whether the sample data provided adequately address the FDA concerns and needs for analysis of the laboratory data.

Following that teleconference discussion, Mallinckrodt will provide all data in the Integrated Summary of Safety (ISS) report with the agreed to method for analysis and presentation of the laboratory data.

Sincerely,

Laura C. Navarre for

Robert G. Wolfangel,
Associate Director of Regulatory Affairs

RGW

cc:
Ms. Ruth Davi, Biometrics
Ms. Kim Colangelo, CSO

MALLINCKRODT

Improving Healthcare and Chemistry

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.895.2000

March 24, 1998

Kim Colangelo, C.S.O.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical
Drug Products, HFD-160
5600 Fishers Lane
Rockville, MD 20857

RE: **Request For Categorical Exclusion for Environmental Assessment**
NDA 20-937/OptiMARK™ (gadoversetamide injection)
NDA 20-975/OptiMARK Pharmacy Bulk Package
NDA 20-976/OptiMARK in Plastic Syringe

Dear Ms. Colangelo:

Please reference our telephone conversation on March 18, 1998 regarding the possibility that OptiMARK may qualify for a request for Categorical Exclusion from the requirement for an environmental assessment. Per the final rule published in the Federal Register on July 29, 1997 and effective August 28, 1997 for 21 CFR § 25.31(b), Mallinckrodt Inc., hereby, requests a Categorical Exclusion for OptiMARK™ (gadoversetamide injection). Information supporting this request is provided on the following pages in the "Statement of Categorical Exclusion From the Requirement for an Environmental Assessment."

In October of 1997, an Environmental Assessment was provided in the pre-submission for NDA 20-937. This information was provided in Volume 1.13, pages 13.001 through 13.012. Mallinckrodt Inc., respectfully, requests FDA to withdraw the Environmental Assessment and replace it with the request for Categorical Exclusion.

Since NDA 20-975/OptiMARK Pharmacy Bulk Package and NDA 20-976/OptiMARK in Plastic Syringe reference the Environmental Assessment provided in NDA 20-937, this request is applicable to these NDAs as well.

Thank you for your assistance in this matter.

Sincerely,

Mary E. Hamilton
Manager, Regulatory Affairs

OptiMARK™ (gadoversetamide injection)

STATEMENT OF CATEGORICAL EXCLUSION FROM THE REQUIREMENT FOR AN ENVIRONMENTAL ASSESSMENT

Date: March 23, 1998

Submitted By: Mallinckrodt Inc.
675 McDonnell Blvd.
P.O. Box 5840
St. Louis, MO 63134

Proposed Action:

Mallinckrodt has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for OptiMARK™ in 10, 15, 20 and 30 mL plastic syringes; 10, and 20 mL glass vials and 50 mL glass bottles.

Claim of Exclusion:

FDA regulations, at 21CFR25.31, state:

Sec. 25.31 Human drugs and biologics.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

(b) Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

(c) .....

The expected use of gadoversetamide in the fifth year of production is 9925 Kg. At this rate of production the maximum Expected Introduction Concentration (EIC) from all sources could be no greater than:

$$EIC = A \times B \times C \times D \ *$$

Where: A = Kg/yr production
B = 1/liters per day entering POTW's
C = 1 year/365 days
D = 10^6 mg/kg

* - Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, Center for Drug Evaluation and Research (CDER), November, 1995.

OptiMARK™ STATEMENT OF CATEGORICAL EXCLUSION FROM THE REQUIREMENT FOR AN ENVIRONMENTAL ASSESSMENT - (Continued)

Therefore, the maximum EIC will be:

$$EIC = 9925 \times 1/1.115 \times 10^{11} \times 1/365 \times 10^{6} \text{ ppm}$$

$$EIC = 2.44 \times 10^{-4} \text{ ppm}$$

$$EIC = 0.24 \text{ ppb}$$

Since this concentration is below 1 ppb, Mallinckrodt asserts that the proposed action should qualify for a categorical exclusion from the requirement for an environmental assessment for the approvals of NDA 20-937, NDA 20-975, and NDA 20-976 under 21 CFR § 25.31(b).

Certification:

I certify that the information provided is true, accurate and complete to the best of my knowledge and that no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

James B. Coyne
Environmental Program Manager