CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20937

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

2.1

Food and Drug Administration
Rockville MD 20857

DEC 23 1998

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

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

Attention: Mary Hamilton
Manager, Regulatory Affairs

Dear Ms. Hamilton:

Please refer to your new drug applications (NDAs 20-937, 20-975, 20-976) dated February 28, 1998, received March 3, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OptiMark™ (gadoversetamide) Injection. NDA 20-937 provides for the drug product in a glass syringe; NDA 20-975 provides for the drug product in a pharmacy bulk pack, and NDA 20-976 provides for the drug product in a plastic syringe.

We acknowledge receipt of your submissions dated March 1, 11, 14, 16, 23, and 24; April 3, 4, 8, 13 and 24; May 14, 22, 27, and 29; July 9 and 29; September 11, 15, 23, and 30; October 9, 23, and 30; November 3, and 12, 1998.

We also acknowledge receipt of your submission dated August 28, 1998. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter. Please be advised that the issues identified in the Warning Letter of July 2, 1998 issued by FDA's Atlanta District Office must be satisfactorily resolved and the preapproval inspection of OptiMark™ must be acceptable before OptiMark™ can be approved.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

I. CHEMISTRY, MANUFACTURING and CONTROLS

A. Drug Product.

We also acknowledge receipt of your submission dated November 20, 1998. This provides a proposed approach to be used to characterize This submission has not been reviewed in the current review cycle. We are glad to discuss your submission or other approaches to develop the supporting documentation necessary to address the deficiencies cited in this letter.

2. The application lacks a sufficient description of, and clarity on, the process of vials during the packaging process of the drug product.

3. The application lacks a consistent specification for the determination of pH for OptiMark™.

   The specifications for the release and expiry stability for the drug product should be identical. Instead of defining two different pH specifications, one for release and one for expiry, please incorporate the tighter specification required at the time of release into the in-process controls and tests.

B. Drug Substance

1. The application lacks data supporting the roles of versetamide or calcium versetamide as stabilizers.

2. The application lacks clarity on the isolation of versetamide.

3. The application lacks data that characterize complexes using assays.

4. The application lacks appropriate data on the temperature at which relaxivity data were obtained.

   Please provide the experimental temperature at which the relaxivity measurements were obtained.

C. Methods Validation:

The submission lacks a sufficiently self contained Methods Validation Section.

In its current form, the Methods Validation section contains numerous references to corresponding volumes in the NDA. As such, full details are available only by cross referencing to other volumes. The Methods Validation section should be a comprehensive, sequentially arranged section. It should include all specifications, methods, reagents, details for the preparation of standard solution, validation procedures, raw data, data analysis results (graphical and tabular), and suitability results for versetamide, gadoversetamide, and OptiMark™.

To resolve this deficiency, please submit a revised comprehensive Methods Validation section when the NDA is resubmitted. This section should be updated to reflect your responses to the CMC deficiencies cited in other sections of this letter.

D. Deficiency in NDA 20-976 Only

E. Deficiencies of NDA 20-975 Only

II. CLINICAL

A. The submission lacks sufficient analyses of the electrocardiographic safety database.

The format of the data presentation for the collected electrocardiograms (ECGs) does not allow for a comprehensive assessment of interval changes. Also, it is not clear if the ECG interpretations are derived from computer generated ECG intervals or from manual evaluations. Additionally, we note that the ECG upper and lower limits used in your analysis are more generous than those typically quoted in textbooks of cardiology. Upon review of the cardiac safety database, a number of patients were identified with changes in PR, QRS, QT, or QTc intervals; in heart rate; or arrhythmias. Also, at least two patients are reported as having QT prolongation.

Please submit a reanalysis of all ECGs obtained during the development of OptiMark™. This analysis should use more standard ECG interval ranges of normal. The mean, median and range of each interval should be reported. The method of QT correction should be specified. Also, for all patients who have abnormal ECGs, please submit details of their ECGs and any associated arrhythmias.

Please be advised that the has the potential to affect electrophysiologic responses. Depending on the chemistry data and the ECG data analysis, additional studies might be needed in humans and animal models.

B. For NDA 20-976 Only

The application lacks sufficient clarity to justify the safe use of the 50 mL pharmacy bulk pack.

The drug delivery systems as described in NDA 20-937 and NDA 20-975 have various sizes of glass and plastic syringes. These drug delivery systems appear to be consistent with the intended uses of OptiMark™ as represented in these NDAs.

However, a rationale or justification supporting the approval for a pharmacy bulk pack as a drug delivery system was not submitted. The safety database showed that the dose and average volume of drug product administered in the Phase 3 studies were 0.1 mmol/kg and 15 mL, respectively. The maximum volume of 35 mL was injected as a manual bolus. The pharmacy bulk pack contains 50 mL without a preservative. Thus, the container closure should be penetrated only once. This suggests that the maximum volume administrated to a single patient could be 50 mL.

At present the literature indicates that such volumes are used in
in repeat doses for CNS imaging, and in drug delivery via
To date, FDA has not approved magnetic resonance imaging products for
The submissions do not contain sufficient data for the safe and effective use of OptiMark™ in doses up to 50 mL, with

Please provide an explanation to justify use of the 50 mL pharmacy bulk pack.

The following comments are not the basis for non-approval; however, these issues should be resolved with the resubmission.

I. STATISTICAL METHODOLOGY

We have completed an analysis of the data using a Wilcoxon test to compare the results of OptiMark™ enhanced MRI to results of imaging with non-enhanced MRI. This appears to more appropriately represent the benefits of OptiMark™. Although labeling will not be addressed at this time, it appears that this analysis along with the number of patients whose OptiMark™ images are better, the same, or worse than non-enhanced images might be more appropriate for labeling. We request that you perform these analyses to confirm our results. A separate discussion can be arranged for this purpose.

II. CLINICAL PHARMACOKINETICS - PHARMACOKINETICS

Upon review of the modeling method used to calculate the pharmacokinetic parameters, it appears that the method does not provide the best data fit. We completed an analysis using
Please perform these analyses to confirm our results. Again, a separate discussion can be arranged for this purpose.

Please be advised that labeling will not be addressed until OptiMark™ is otherwise approvable.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

Sincerely yours,

/S/

12/23/98

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20937	**Trade Name:**	OPTIMARK(GADOVERSETAMIDE INJ) 0.5 MMOL/M
Supplement Number:		**Generic Name:**	GADOVERSETAMIDE INJECTION
Supplement Type:		**Dosage Form:**	Injectable; Injection
Regulatory Action:	NA	**Proposed Indication:**	Indicated for use with MRI in adults to provide contrast enhancement of intracrainal lesions, spianl lesions and associated tissues and hepatic lesions with abnormal vascularity

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? ~~YES~~ NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
____Children (25 Months-12 years)
____Adolescents (13-16 Years)
_X_Other Age Groups (listed): adults only

Label Status	INADEQUATE Labeling for ALL PEDIATRIC ages
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. ~~Applicant NOT WILLING to do them~~
Study Status	Protocols are under discussion. Comment attached

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

COMMENTS:
December 18, 1998 This application does not contain information on pediatric studies. The product is only indicated for adults patients.

Pediatric Studies ongoing and planned for supplemental submission

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER. JAMES MOORE

/S/ 11-29-98

Signature Date

ADMINISTRATIVE REVIEW OF NDA (review pkg)
OFFICE OF DRUG EVALUATION III

NDA: 20-937, 20-975, 20-976
Drug: Optimark (gadoversetamide) Injection [provided in glass syringe (20-937), in pharmacy bulk pack (20-975), and in plastic syringe (20-976)]
Classification: 1 S
Sponsor: Mallinckrodt, Inc.
Project Manager/CSO: James Moore

Reviewer: Bronwyn Collier, ADRA ODE III
Review Date: December 14, 1998

Review Cycle 1

Date Submitted: February 28, 1997
Date Received: March 2, 1998
Original Goal Date: March 2, 1998
Extended Goal Date: not applicable
Proposed Action: not approvable

Review

Although this application is part of the FY 98 cohort, the division has planned the review time line for a 10 month review and action.

Letter:

1. The letter prioritizes the deficiencies in three levels- critical, non-critical, and items that are not the basis for the non-approvable action but must, nevertheless, be answered with the resubmission. Since all of the cited deficiencies must be addressed prior to approval, all will be of equal importance for the applicant to answer in the resubmission. In addition, the review clock for the resubmission will not be activated until all the deficiencies are addressed, regardless of priority. Thus, the prioritization seems artificial.
2. Minor editorial corrections indicated on draft letter.

Labeling: Not addressed for NA action.
Patent Information: Provided.
Exclusivity Checklist:
Debarment Certification: Provided.
Pediatric Page: None provided.
Review Elements:

Div Dir Memo: A draft memo was provided recommending a not approvable action based primarily on chemistry deficiencies.
Group Leader Memo: Recommendation for approvable action.
Clinical: Multiple medical reviewers-reviews complete.
Stats (Clinical): Completed.

Biopharm: Complete.
Pharm/tox: Complete.
Chem: Complete.
EA: Categorical exclusion granted.
Stats (Stability): Included in chemist's review (12/4/98).
Micro: Complete
Safety Update: A safety update was submitted7/29/98. Review of the submission could not be located in the review package.
DSI: Audits complete–sites found acceptable.
Nomenclature: Trademark review requested 7/20/98. The chemist's review ((12/4/98) indicates that the trademark was found acceptable. However, the documentation of the review has not been included in the review package.
EER: Recommendation to withhold approval.
Advisory Committee: none
Advertising Materials: Not addressed for not approvable action.

Conclusions/comments

1. Recommend that prioritization of deficiencies in the letter be removed.

2. The trademark review needs to be added to the package.

3. Review of the safety update needs to be documented.

4. A pediatric page needs to be completed.

/S/
/ 12/14/98

BC/12/14/98/C:\mydocuments\nda\20937r1.doc

MEMORANDUM

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

DATE: December 7, 1999

FROM: Florence Houn MD MPH FACP /S/

SUBJECT: Office Director Memo

TO: NDA 20-937 OptiMARK

Mallinckrodt's NDA for OptiMARK (gadoversetamide injection) is approved for use with magnetic resonance imaging (MRI) in patients with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues as well as in patients who are highly suspect for liver structural abnormalities identified on computed tomography. There are several issues that were discussed with the division pertaining to the safety and effectiveness of OptiMARK. These issues are documented in this memo: the drug's indications, electrocardiographic changes requiring precautions, and the need for further phase 4 studies to characterize potential risk of QTc prolongation.

Indications

The first indication is worded in the manner that is consistent with the other approved MRI CNS imaging contrast agents. This indication is not consistent in format as recommended in the Center's current Draft Guidance for Industry: Developing Medical Imaging Drugs or Biologics. However, once the guidance is finalized, the division will be assisting sponsors in developing indications that are consistent with this guidance.

The liver imaging indication is a first time indication for this class of products. The indication was amended to include the basis for how suspicion for liver abnormalities was derived. Patients in the clinical trials were those that had an abnormal CT scan. The effectiveness in this population was demonstrated. There is no data on how well this drug would perform in a different population, such as patients with abnormal liver function tests.

Electrocardiographic Changes in the Precautions Section

There were patients who received OptiMARK and had QTc prolongation. However, there was no difference in percentage of these patients compared to a small placebo group. The studies were not designed and conducted to definitively determine the drug effects on QTc. There were no pre-clinical investigations on appropriate *in vitro* and *in vivo* systems. A wide range of doses need to be tested. Monitoring was not consistently performed. The reviews note that each of the 175 frequently monitored patients who received drug or placebo had some type of QTc prolongation, suggesting methodologic issues with the assessment.

The acute cardiotoxic effects of gadolinium-based contrast agents have been reviewed by Dr. Ramesh Raman through an on-line literature search. He has also discussed the issue of cardio-toxicity with members of the cardio-renal division and has used their written documents on evaluation of QTc. He has also documented his approach to evaluating OptiMARK's QTc issues. There is some suggestion in *in vitro and in vivo* studies that gadolinium is a stretch-activated channel blocker and it may have action via the calcium channel or Na+ - Ca+2 exchange. A search of the post-marketing data bases in the Office

of Post-market Drug Risk Assessment (OPDRA) for any gadolinium associated ventricular arrhythmias revealed one case. However, this single case of Torsades de Pointes was in a Cisapride user, a drug with known associations with prolongation of the QTc, Torsades, ventricular arrhythmias, and death.

Phase 4 Agreements

The company has agreed to conduct preclinical and clinical studies to define the effects of their product, if any, on QTc. Labeling may be amended based on these findings. We have set due dates for protocol submission and completion of studies.

Decision

Given the QTc effects similar to placebo, lack of dose response in three OptiMARK dose groups, the drug being indicated for single-dose studies, it being administered in an observed setting (during Cmax), and a new indication for the drug class for the detection of structural liver abnormalities (often times a serious finding), this drug is approved with labeling that advises precautions concerning the potential for QTc prolongation and general advice to minimize such risk. Because the potential for QTc prolongation needs further work up, phase 4 agreements have been made. Other gadolinium agents have this similar potential and the division will be approaching them to conduct work ups for their drug-specific effects on QTc, if any. Depending upon the results of these studies, there may be need for further discussions within the Center (through the Medical Policy Coordinating Committee) or with an advisory committee. OPDRA has been informed of safety issues surrounding this product to monitor post-market events.

Memorandum

Date: 6 December 1999

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Patricia Y. Love, M.D., Dir., HFD-160
Nakissa Sadrieh, Ph.D., TL Pharm./Tox., HFD-160

Subject: NDAs 20-937, 20-975, 20-976
OPTIMARK® Injection, Gadoversetamide injection (contrast agent)
Review of Pharm./Tox. Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 20-937, written by John Melograna, M.S.
2. NDA 20-937, 20-975 and 20-976 Approval Package, with Draft Product Labeling (dated 29 November 1999, 2:17 P.M.).

II. Comments and Recommendations

1. A review of the action package for NDAs 20-973, 20-975 and 20-976 OPTIMARK® Injection, suggests that the product has been adequately evaluated in multiple non-clinical acute and repeat-dose safety studies up to 1 month duration for approval of the requested indication (single dose intravenous administration as a contrast enhancing agent prior to Magnetic Resonance Imaging of CNS/spinal cord vascular abnormalities or the liver).

2. As indicated in the pharmacology review for OPTIMARK® Injection, further evaluation of the potential for adverse cardiovascular effects (QVC and arrhythmogenic effects) following the intravenous administration of gadoversetamide appear warranted and are recommended for inclusion in Phase 4 commitments made with the drug sponsor. Further non-clinical safety evaluations may include (but may not necessarily be limited to): drug effects on cardiac membrane ion channels/ion flux; drug formulation effects on extracellular and/or intracellular concentrations of divalent cations; and, the evaluation of drug effects on cardiovascular function at higher multiples of human exposure.

3. Proposed Product Label –

III. Summary

A review of the action package for NDAs 20-973, 20-975 and 20-976 (OPTIMARK® Injection) suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval of the requested indication. The proposed product label, with revision as suggested in the preceding section, adequately reflects the non-clinical safety data for this product. Recommendations for possible additional safety evaluations (cardiovascular safety) to be included as Phase 4 commitments are presented in the preceding section of this document.

MEMORANDUM

TO: Patricia Love, Director, HFD-160
Nakissa Sadrieh, PharmTox Team Leader, HFD-160

F ROM: John Melograna, Toxicology Reviewer, HFD-160

CC: James Moore, CSO, HFD-160
Florence Houn, Director, Office of Drug Evaluation III

DATE: 12-07-1999

RE: NDAs 20-937, 20-975, 20-976 Response to Optimark Labeling Recommendations in memorandum of 12-06-1999 from David Morse to Florence Houn

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These are Dr. Morse's comments about the PharmTox sections of the labeling (#3 in his attached memorandum) and responses from the reviewer:

•Reference to the brand name for gadoversetamide (i.e., OPTIMARK®) should be eliminated from the discussion of all non-clinical safety studies in the product label, unless those studies were specifically conducted with the 'to be' marketed drug formulation. All discussions of non-clinical studies conducted with other than the clinical drug formulation should make reference to the generic compound name of 'gadoversetamide.' (See the Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy and Nursing Mothers sections of the proposed product label.)

Reviewer comment: References to gadoversetamide and Optimark are already correct. They do not need to be changed.

•It is recommended that all interspecies dose comparisons included in the product label be based on pharmacokinetic parameters (i.e., AUC, Cmax or other relevant parameter) unless there is clear scientific justification for the use of another scaling method (i.e., allometric scaling or nominal dose), or there is insufficient pharmacokinetic data to allow for interspecies dose comparisons.

Reviewer comment: As in humans, the available PK data in animals demonstrate that the volume of distribution of gadoversetamide is the extracellular fluid volume. The sole route of elimination is renal. These data justify body surface area scaling. Scaling by body surface area is consistent with Division policy and with the labels for other approved gadolinium contrast agents. AUC and Cmax are usually not submitted for

this class of drugs; initial drug exposure in animals is the same as in humans for iv administered drugs. Changes are not needed.

•It is recommended that the reference to gadoversetamide tissue distribution in pregnant and lactating rats, which is included in the "Clinical Pharmacology" section of the proposed product label (see page 2, paragraph 3 'Distribution'), be moved to the Nursing Mothers or Pregnancy sections of the product label.

Reviewer comment: No opinion.

In accordance with Pharm./Tox. Policy regarding the description of genotoxicity study findings, all references to the dose(s) at which individual assays demonstrated positive mutagenic or clastogenic effects with the test compound should be removed from the proposed product label. The product label should provide information only as regards which assays revealed positive or negative effects and under what test conditions (i.e., in vitro or in vivo, and with or without the addition of a metabolic activation factor).

Reviewer comment: Agree. The last sentence in the first paragraph of the Carcinogenesis.... section should be changed to read:

> **The in vitro CHO chromosome aberration assay without metabolic activation was positive.**

•It is recommended that paragraphs 2-4 under 'Carcinogenesis, Mutagenesis and Impairment of Fertility' (pages 8-9) be condensed and presented in a single paragraph, as each of these paragraphs describes related testicular/spermatogenic effects of repeat-dose gadoversetamide exposure.

Reviewer comment: Paragraph 2 describes the results of a fertility study; Paragraph 3 describes the results of a separate 28-day study in which different measures were included; Paragraph 4 describes the results of a single dose study which did not produce effects on the male reproductive system. To clarify the type of study, the beginning of the first sentence in Paragraph 2 can be changed to:

> **Optimark administered to rats in a fertility study.....**

Additional comment: Reference to the species was inadvertently omitted from Paragraph 3 of the last version. This was a rat study. Please identify as such, for example:

> **In a separate 28-day repeat dose study in rats, ...**

•It is recommended that in paragraphs 1 and 2 under "Pregnancy Category," reference to the body surface area adjusted multiplicity of human exposure (i.e.,

animal versus human exposure) be presented in parentheses to be consistent with other non-clinical studies sections of the proposed product label.

Reviewer comment: Multiples of the human dose in the Pregnancy section are already included in parentheses except for one intended instance: The second mention of 0.5 mmole/kg is not followed by the multiple because the first mention is already followed by a multiple. Changes are not needed.

•If the data are available, consideration should be given to the inclusion of information on breast milk drug concentration and potential neo-natal drug exposure in woman administered OPTIMARK® during lactation.

Reviewer comment: Data are not available to describe human breast milk concentration following iv administration or to describe Gd uptake from the GI tract following oral dosing via breast milk. Changes not possible.

•It is recommended that all interspecies dose comparisons included in the product label be "rounded" to no more than one significant digit beyond the decimal point.

Reviewer comment: All dose comparisons are already rounded to no more that one significant figure. Changes not needed.

Attachment:

Memorandum

Date: 6 December 1999

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Patricia Y. Love, M.D., Dir., HFD-160
Nakissa Sadrieh, Ph.D., TL Pharm./Tox , HFD-160

Subject: NDAs 20-937, 20-975, 20-976
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2. As indicated in the pharmacology review for OPTIMARK® Injection, further evaluation of the potential for adverse cardiovascular effects (QVC and ___ arrhythmogenic effects) following the intravenous administration of gadoversetamide appear warranted and are recommended for inclusion in Phase 4 commitments made with the drug sponsor. Further non-clinical safety evaluations may include (but may not necessarily be limited to): drug effects on cardiac membrane ion channels/ion flux; drug formulation effects on extracellular and/or intracellular concentrations of divalent cations; and, the evaluation of drug effects on cardiovascular function at higher multiples of human exposure.

3. Proposed Product Label –

4. If the data are available, consideration should be given to the inclusion of information on breast milk drug concentration and potential neo-natal drug exposure in woman administered OPTIMARK® during lactation.

5. It is recommended that all interspecies dose comparisons included in the product label be "rounded" to no more than one significant digit beyond the decimal point.

III. Summary

A review of the action package for NDAs 20-973, 20-975 and 20-976 (OPTIMARK® Injection) suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval of the requested indication. The proposed product label, with revision as suggested in the preceding section, adequately reflects the non-clinical safety data for this product. Recommendations for possible additional safety evaluations (cardiovascular safety) to be included as Phase 4 commitments are presented in the preceding section of this document.

Memorandum to the File

Subject: Optimark-45 day Filing Meeting for Resubmission

Date: July 14, 1999

FDA Attendees:

Patricia Love, M.D., M.B.A, Division Director, HFD-160
Sally Loewke, M.D., Team Leader, Clinical, HFD-160
Ramesh Raman, M.D., Clinical Reviewer, HFD-160
Eldon Leutzinger, Ph.D., DNDCII, HFD-820
David Place, Ph.D., DNDCII, HFD-820
Ruthann Davi, M.S., Biometrics Reviewer, HFD-715
James Moore, R.Ph., M.A., Project Manager, HFD-160
Alfredo Sancho, Ph.D., Clinical Pharmacology Reviewer, HFD-870

A 45-day filing meeting was held on July 14, 1999 at 3:00pm to discuss whether the resubmission of June 8, 1999 from Mallinckrodt should be filed. Each discipline was asked if the information submitted answered the questions in the not-approvable letter of December 23, 1998. Each discipline responded that the questions asked in the December 23, 1998 letter had been addressed appropriately. The application was then considered filed.

/S/
James Moore
Project Manager, HFD-160

cc: Original NDA 20-937, 20-975, 20976
NDA Division File 20-937, 20-975, 20-976
HFD-160/moore
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Minutes of the Telephone Conference between Mallinckrodt and the Division of Medical Imaging and Radiopharmaceutical Drug Products October 25, 1999 regarding Optimark 20-937

Mallinckrodt Attendees:

Don Beussink, Director Pharmaceutical Science Resource Center
Russ Chong, Research Associate
Lynn DeLearie, Quality Assurance Manager
Mary Hamilton, Manager, Regulatory Affairs
James Keller, Vice President, Regulatory Affairs
Ed Porter, Senior Regulatory Affairs Associate
Dave White, Senior Research Chemist
Robert Wolfangel, Ph.D., Director Regulatory Affairs
Peri Periasamy, Director, Research and Development

FDA Attendees:

Eldon Leutzinger, Ph.D., Chemistry Team Leader, DNDCII, HFD-820
David Place, Ph.D., Chemistry Reviewer, DNDCII, HFD-820
Robert K. Leedham, Jr., Associate Director, HFD-160
James Moore, Project Manager, HFD-160

The telephone conference was requested by the division. FDA requested that in process controls be provided for calcium versetamide during the manufacture of Optimark and that the methods validation also be provided. Mallinckrodt stated that information on in-process controls for calcium versetamide would be sent to FDA by October 29, 1999. According to FDA, the quantification of the calcium versetamide in the product was acceptable, but the qualification was not. FDA stated that [redacted] would be a good method for the qualification of this ingredient. Mallinckrodt said that the methods validation information would be sent to FDA by the end of the year.

The minutes were prepared by James Moore, project manager.

/S/

James Moore
Project Manager, HFD-160

cc: Original NDA 20-937, 20-975, 20-976
Division File NDA 20-937, 20-975, 20-976
HFD-160/Moore
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Minutes of the Telephone Conference between the Division of Medical Imaging and Radiopharmaceutical Drug Products and Mallinckrodt February 17, 1999 regarding Optimark (NDA 20-937)

Mallinckrodt Attendees:

James Keller, Vice President, Regulatory Affairs
Robert Wolfangel, Director Regulatory Affairs
Don Beussink, Director, Pharmaceutical Science Resource Center
Steve Woulfe, Director, Chemistry Resource Center
Lynn Delearie, Validation Associate
Hwaing Lin, Senior Research Pharmacist
Russ Chong, Research Associate
Dave White, Senior Research Chemist
Peri Periasamy, Director MR Contrast Media and Research and Development
Todd Huettemann, Regulatory Affairs Associate
Ed Porter, Senior Regulatory Affairs Associate
Mary Hamilton, Manager Regulatory Affairs

FDA Attendees:

Eldon Leutzinger, Ph.D., Team Leader Chemistry, DNDCII, HFD-820
David Place Ph.D., Reviewer; Chemistry, DNDCII, HFD-820
Robert K. Leedham, Jr., M.S. Associate Director, HFD-160
James Moore, RPh., M.A., Project Manager, HFD-160

Mallinckrodt requested this telephone conference to clarify points in the not approvable letter. It was decided that the points in the not approvable letter would be discussed individually.

Point 1- Calcium Versetamide Identity and Purity

The applicant agreed to obtain additional information and characterize multiple batches. FDA emphasized that the procedure should be reproducible.

Point 2- Modification of Labeling to reflect contribution of calcium versetamide to product

The sponsor agree to the requested change in labeling.

Point 3- Actual chemical composition of calcium versetamide in Optimark

The sponsor agreed to provide the actual quantity of this ingredient in the product.

Point 4- Label calcium versetamide as key excipient

The sponsor agreed to this labeling change.

Point 5- In process Controls

The sponsor agreed to provide in process controls for calcium versetamide.

Point 6-Methods validation

The sponsor agreed to provide required methods validation for this product.

Point 7-Format of Chemistry Section of NDA

The sponsor agreed to reformat the chemistry section of the NDA so that sections would match the new data being submitted, but also pointed to sections in the NDA where some of the requested info was found. The sponsor agreed to provide required SOPs.

Point 8- Stopper for product

The applicant agree to provide data on the stopper because of the potential for extractables to leave the stopper and enter the product.

The minutes were prepared by James Moore, project manager.

/S/

James Moore
Project Manager, HFD-160

cc: Original NDA 20-937, 20-975, 20-976
NDA Division File 20-937, 20-975, 20-976
HFD-160/moore
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Minutes of the Telephone Conference between Mallinckrodt and the Division of Medical Imaging and Radiopharmaceutical Drug Products regarding Optimark (NDA 20-937) February 9, 1999

Mallinckrodt Attendees:

Gary Stevens, Ph.D., Director of Biostatistics and Scientific Data
Rita Kristy, Senior Statistician
James Baker, Ph.D., Manager of Pharmacokinetics
James Keller, Vice President of Regulatory Affairs
Adeoye Olukotum, Vice President of Medical and Regulatory Affairs
Mary Hamilton, Manager, Regulatory Affairs

FDA Attendees:

Ramesh Raman, M.D., Clinical Reviewer, HFD-160
Alfred Eric Jones, M.D., Clinical Team Leader, HFD-160
Robert K. Leedham, Jr., Supervisory Project Manager, HFD-160
James Moore, Project Manager, HFD-160

This telephone conference was held at the request of Mallinckrodt to discuss EKG safety issues contained in the not approvable letter of December 23, 1998. Though FDA considered the letter very clear and requested specific information from the applicant, the applicant still wanted to speak with FDA to further clarify those requests. Prior to the telephone conference a document was faxed to the applicant that outlined a suggested format for reporting EKG safety data.

The applicant asked for clarification on the reporting of changes in intervals for the EKG parameters. That information was provided for each interval and Mallinckrodt stated that the requests were very clear after the telephone conference. Additionally, Mallinckrodt said the requested EKG safety data would be provided. Mallinckrodt did ask when is it was appropriate to use Bassett's formula and the response was for the QTc. Mallinckrodt said they would send samples tables for FDA review to insure that Mallinckrodt was proceeding as the division had requested in reanalysis of the EKG safety data.

The minutes were prepared by project officer, James Moore.

/S/

James Moore
Project Manager, HFD-160

cc: Original NDA 20-937, 20-975, 20-976
NDA Division File 20-937, 20-975, 20-976
c:\data\wpfiles\optimine.299
HFD-160\moore

Minutes of T-Con with Mallinckrodt regarding Optimark (N20-937) Chemistry Issues
November 12, 1998 10:30am, Room 18B39, Parklawn

FDA Attendees:

Robert K. Leedham, Jr., Supervisory Project Manager, HFD-160
James Moore, Project Manager, HFD-160
David Place, Ph.D., Chemistry Reviewer, DNDCIII, HFD-820
Mary Zakhem, Pharmacy Student, Howard University College of Pharmacy

Mallinckrodt Attendees:

Donald Beussink, Pharm.D., Director of Pharmaceutical Science
Russell Chong, Research Associate
David White, Ph.D., Senior Research Associate
Robert Wolfangel, Ph.D., Director of Regulatory Affairs
Edward Porter, Senior Regulatory Affairs Associate
Mary Hamilton, Manager Regulatory Affairs
Todd Huettemann, Regulatory Affairs Associate
Hwaing Lin, Ph.D., Senior Research Pharmacist

Introduction

The meeting began with introductions of FDA personnel and the representatives of Mallinckrodt attending the conference. Dr. Place made introductory remarks and began the discussion of the five points outlined in the fax previously sent to the Applicant.

According to Dr.Place, there was a disconnect between the contents of the vial and the labeling as presented in the application. According to Dr. Place, Calcium Versetamide is cited as a stabilizer in the application, but neither the qualities exhibited nor the data presented support this designation. Calcium Versetamide is 10% of the finished dosage form. It is necessary to further characterize calcium versetamide, verify its assay, and ascertain its stability. After these introductory remarks each point from the faxed document was discussed.

Point 1) Characterization, Manufacture of calcium versetamide.

FDA: Regarding analytical methods for characterizing calcium versetamide neither method is good for characterization of this ingredient. A more rugged method must be developed to characterize the ingredient.

Applicant: We have tried numerous methods to characterize the calcium versetamide and thus far have been unable to characterize the ingredient fully.

FDA: The characterization of this ingredient is indeed a challenge, but it has been done.

Applicant: Can you share with us how others have performed analysis on this ingredient.

FDA: Because such information is trade secret regrettably that information cannot be shared with you.

Applicant: We agree to begin working on the characterization of this component of our product.

Point 2) Change of Label to reflect True Composition.

Applicant: Mallinckrodt agreed to change the label for the product.

Points 3-5)

Applicant: Mallinckrodt agreed to address the presence of the calcium versetamide in the product, to the manufacture of a reference standard, to identify the calcium versetamide in the labeling as a key excipient and will no longer be called a stabilizer. In addition the sponsor agreed to change its manufacturing method to include the assay of calcium versetamide in the manufacturing process and validation of regulatory methods.

Mallinckrodt will submit a proposal to Dr. David Place for his review prior to implementing the new procedures and the collection of required data.

The minutes were prepared by CAPT James Moore, project manager.

/S/

James Moore, R.Ph.,M.A.
Project Manager, HFD-160

Dec. file

INDUSTRY MEETING MINUTES

DATE: June 29, 1995
TIME: 10:00am
DRUG: MP-1177 Injection, IND
SPONSOR: Mallinckrodt, Inc.
PURPOSE: Discussion of Phase 3 Clinical Development

FDA ATTENDEES:

Patricia Y. Love, M.D., M.B.A., Division Director, HFD-160
Alfred E. Jones, M.D., Supv. Medical Officer, HFD-160
Joseph Pierro, M.D., Rev. Medical Officer, HFD-160
Hsien Ju, M.D., Rev. Medical Officer, HFD-160
John Melograna, Ph.D., Rev. Toxicologist, HFD-160
Michael Welch, Ph.D., Biomedical Statistician, HFD-713
Roy Blay, Ph.D., Consumer Safety Officer, HFD-160
Amy Chapman, Consumer Safety Officer Tech., HFD-160

SPONSOR ATTENDEES:

Kris Piper, Director, Regulatory Affairs
Edward Aten, M.D., Consultant
Larry Kvols, M.D., Director, Clinical Research
Jeffrey Brown, Consultant, Washington University
Kathleen Madsen, Ph.D., Senior Biostatistician
Gudrun Gaida-Schmidt, M.D., Global Clinical Project Leader
Russell Bryant, Market Development Manager
Peri Periasamy, Ph.D., Assistant Director MRCM Development

Mallinckrodt Medical submitted their proposed plan for Phase 3 on April 11, 1995. FDA review of this submission resulted in numerous questions prompting Mallinckrodt to request a meeting with FDA to reach agreement on Phase 3 studies.

The meeting began with a presentation by the sponsor providing the results of the Phase 2 studies and an overview of the Phase 3 clinical plan. The sponsor summarized the results of the Phase 2 studies as being safe at all dose levels with no serious adverse events. The sponsor wished to come to agreement on the numbers of patients and the types of studies needed to support the proposed dose range.

- The sponsor was asked if they planned using labeling different from other similar products. The sponsor replied that they would like to provide dose ranging information in the labeling, otherwise the labeling would be similar. The sponsor felt that the physician should have the flexibility of choosing which dosage would be best for the patient; the package insert would provide guidance regarding dose selection. FDA stated that the sponsor would need appropriate trials with adequate numbers of patients to support such guidance, particularly regarding the marketing and promotion of the agent.

- FDA indicated that there were policy questions remaining regarding the use of additive doses (e.g., 0.1 mmol/kg followed by 0.2 mmol/kg) or only high doses (e.g., 0.3 mmol/kg) and asked if the sponsor intended to address the issue of single doses as compared to additive dosing in the labeling.

- The sponsor is comparing MP-1177 to Magnevist to demonstrate equivalence in safety and sensitivity. The sponsor should determine the optimal dose for comparison; for determination of efficacy, a dose equivalent to current Magnevist dosing should be used.

- FDA noted that patient numbers became increasingly small when considered per subgroup per indication. FDA cautioned that the numbers of patients must be statistically significant and that sufficient 72 hour data must be collected. These sample sizes would be particularly critical in pivotal studies. There could be imbalance in the numbers of patients per indication. The sponsor was asked how they planned to deal with any imbalances in patient numbers.

- FDA requested additional information on the CNS indication. Current information suggested trends but was not confirmatory.

- The sponsor said that it would integrate its 72 hour follow-ups; however, the inclusion of additional patients would be prohibitively expensive and difficult. The sponsor noted that 48 hour data would be available. The sponsor requested guidance on numbers of patients to be included in the studies.

- FDA said that there was concern over laboratory values at 24 hours. Renal function should be evaluated at 48 and 72 hours post-administration. FDA noted that current studies would not allow for guidance to practitioners if the numbers of patients studied do not support the findings.

- FDA suggested the use of a decision tree for guidance that would consider the language that would be used in the labeling.

- FDA requested that all doses be analyzed across indications and that this analysis be submitted. This analysis should consider the sample sizes for the various indications.

- FDA suggested the following as its best recommendations:

  - The inclusion of adequate 72 hour data
  - The use of statistically adequate sample sizes
  - Inclusion of 72 hour (or as close as possible) data on renally impaired patients.

- FDA noted that pharmacology/toxicology issues such as half-lives and metabolites could affect subsequent discussions and recommendations.

- FDA indicated its concern over renal vacuolization and the need for more descriptive, statistically significant information.

- The sponsor asked how many patients should be included per dose group. FDA said that the types of adverse reactions should be considered in determining numbers of patients, particularly since the incidence of adverse reactions increased with increasing dosage. FDA expressed concern with high risk patients such as those with compromised liver and renal function.

- The sponsor should not seek to use disclaimers as currently used in other products since these firms are addressing problematic areas in Phase 4 studies. Pharmacokinetic profiles in renally impaired patients would be needed to determine dose adjustments.

- The sponsor indicated that MP-1177 would be compared to Magnevist in Phase 3 trials. The trials are powered such to detect a 20% difference in adverse events. Efficacy data would also be collected. FDA cautioned that the study would need to be set up properly to demonstrate equivalence or superiority.

- The sponsor suggested the possibility of developing an indication for single dosing only.

- The sponsor asked if trend information could be included in the labeling. FDA responded saying that the inclusion of such information would be dependent on the numbers of patients safety and efficacy questions, etc.

- FDA requested information on creatinine, drug excretion, vital signs, and oximetry at 72 hours post-administration. The sponsor replied that it was not possible for some investigators to collect data at certain time points.

- FDA requested information on the use of the agent in the pediatric population, especially dose adjustments in neonates. Sufficient numbers of patients should also be enrolled in the 2-12 year old age bracket. FDA suggested the enrollment of approximately 100 pediatric patients. FDA expressed concern over pharmacokinetic profiles in the pediatric population.

- FDA indicated that the proposed studies (sent by facsimile) concerning the use of a comparator appeared satisfactory.

- The sponsor indicated that Japanese Phase 2 studies are beginning. FDA noted that approval can be based on foreign data. The sponsor said it would summarize data from ongoing studies.

Summary issues:

- Appropriate trials with adequate numbers of patients should be submitted to support guidance in the labelling.

- Numbers of patients must be statistically significant and sufficient 72 hour data must be collected.

- Pharmacokinetic profiles in renally impaired patients are needed to determine dose adjustments.

- Information on the use of the agent in the pediatric population should be submitted.

cc:
IND [redacted]
HFD-160/Div. File
HFD-160/Pierro/Ju/Melograna
HFD-161/Blay
HFD-713/Welch
Acknowledge: Jones/August 29, 1995/Pierro/July 31, 1995/Ju/July 31, 1995/
Love/August 17, 1995
F/T by: mlo/8-22-95

CLARIFIED

Division of Medical Imaging and Radiopharmaceutical Drug Products
Clinical and Statistical Pre-NDA Meeting Minutes

IND:
DRUG: OptiMARK
SPONSOR: Mallinckrodt, Inc.
DATE: December 3, 1997

MALLINCKRODT, INC.

James E. Keller, Director, Regulatory Affairs
Gary Stevens, Ph.D., Director of Biostatistics and Data Management
Peri Periasmy, Ph.D., Project Manager
Michele Yelmene, Manager of Medical Writing
Rita Kristy, Senior Statistician
Mary Hamilton, Manager, Regulatory Affairs

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

Patricia Love, M.D., M.B.A., Division Director
A. Eric Jones, M.D., Medical Team Leader
Joseph Zolman, M.D., Ph.D., Medical Reviewer
Ramesh Raman, M.D., Medical Reviewer
Young-Moon Choi, Ph.D., Biopharmaceutics Reviewer
Michael Welch, Ph.D., Statistical Team Leader/Reviewer
Kim Colangelo, Consumer Safety Officer

BACKGROUND

A meeting package was received from Mallinckrodt on November 12, 1997, which included summary information on the intended content and format of the NDA. Mallinckrodt's objectives for this meeting are to discuss the format and presentation of the data in the submission.

Mallinckrodt has already pre-submitted the Chemistry, Manufacturing, and Controls, Microbiology, and Pharmacology/Toxicology sections of the NDA. The full NDA is anticipated for submission in February, 1998. Mallinckrodt did not request a Clinical/Statistical pre-NDA meeting. The Division noted that their comments can only address format since data are not presented.

The section headings in the minutes reflect the sections of the meeting package.

PROPOSED INDICATION AND ADMINISTRATION

The final wording of the indication and administration in the labeling will be based upon the NDA data review.

In order for labeling to support a diagnostic claim, technical features need to be identified in Phase 2 and confirmed in the Phase 3 pivotal trials. "Diagnostic confidence" is a very subjective endpoint. Based on assumptions from the information provided, it appears that a more general indication might be attainable. Mallinckrodt indicated that they are currently looking for equivalent labeling with Magnevist. The Division also noted that Mallinckrodt has not studied OptiMARK for all of the indications that are labeled other approved gadolinium drugs. It is possible that statements regarding indications within the product class (gadolinium agents) which were not studied with OptiMARK may need to be included in the label.

DESCRIPTION OF CLINICAL PROGRAM AND STUDIES

Clarification regarding the labeling and marketing intentions for pediatric patients was requested by the Division. Mallinckrodt reported that a study is ongoing, and will be completed prior to the first action taken on the application. The Division stated that all information (studies for proposed labeling) must be submitted at the time of filing. Mallinckrodt stated their intention to submit the information as a pediatric efficacy supplement after OptiMARK has been approved by FDA; labeling for the pediatric population will not be included in the first application. The Division agreed to this approach.

The Division requested that when the data supporting OptiMARK use in pediatric patients are submitted, that it be stratified by age groups (e.g., neonate to 1 year, 1 to 2 years, and so forth). Mallinckrodt stated that enrollment had been stratified by age groups.

INTEGRATED SUMMARIES

The Division inquired about the planned pooled efficacy assessment for the liver and CNS trials. Mallinckrodt stated that this was done because the primary efficacy endpoints were identical, therefore they wanted to compare the efficacy data and look for differences between the two indications, in order to present a global picture. The Division's stated that its primary efficacy assessment will be based upon the data analysis for the two indications independently and in reference to the two independent studies for each indication.

Mallinckrodt also plans to report data pooled for safety and efficacy by demographic subgroups, as well as for renally and hepatically impaired patients. The Division stated that safety data should be pooled with the appropriate subgroups.

ELECTRONIC SUBMISSION PLAN AND IMAGE DATABASE SUBMISSION

Statistical SAS data sets can be provided by Mallinckrodt on either diskette or CD. Primary and secondary efficacy data for the pivotal studies were requested separate from the entire clinical data set. All clinical data (safety and efficacy) data will be available in electronic form.

Mallinckrodt proposed supplying both hardware and software needed to view the imaging database. The Division is in the process of procuring both the hardware and software Mallinckrodt is intending to use and supply, therefore, all items may not be needed. Due to space logistics, the Division may only request certain components of the systems. The Division will know which, if any, of the components will be needed closer to the time of submission.

The Division reminded Mallinckrodt that all electronic forms of data should be submitted with the application, and must be functional in order for the NDA to be filed. The Division suggested the possibility of piloting the system with some of the images from Phase 2 to allow the reviewers to become familiar with the system. A conference call between the Division's and Mallinckrodt's Information Technology personnel will be scheduled by Ms. Colangelo and Ms. Hamilton.

OUTLINE OF DATA PRESENTATION

(Roman Numerals represent corresponding section heading in meeting package.)

III. Demographics

The Division requested that age, gender, racial, and appropriate subgroups be included in the demographics section for the entire NDA. Also, the number of patients should be subdivided down to the number of image sets for blinded interpretation (intent to treat and per protocol).

V. Adverse Events

The Division requested information from any patient follow-up available beyond 72 hours of patients who had serious adverse events (SAE) or died. Mallinckrodt reported that narratives will be provided, along with the case report forms (CRF) for all patients with SAE or patient deaths. The Division requested that these reports be specifically included in the index.

V.A. Overall Patient adverse Event Distribution by Treatment Group and Body System and COSTART Term. Number of Patients with an Adverse Event

Adverse events from Phase 1 studies should be pooled for unique timepoints. Volunteers and patients should be separated for data analysis.

V.G. Adverse Event Summary for All Patients in the Phase 3 Pivotal Studies by Severity. Number of Patients with an Adverse Event

All adverse events at the 0.1 mmol/kg dose should be reported, not just for the Pivotal Phase 3 trials but for all phases of development, based on severity and indication (e.g., the pooled data and all Phase 1, 2, and 3 data).

VI. Laboratory Parameters and VII. Vital Sign Parameters

The Division recommends looking for a dose related effect on the laboratory and vital sign parameters, specifically in parameters expected to be affected by gadolinium agents (e.g., hemoglobin, copper, zinc and iron parameters). Mallinckrodt reported that the data will be standardized, and both the standardized and raw data will be reported. The Division requested definition of all cut points be included.

Mallinckrodt indicated that reports will include 20, 40, 60 and 80 percent changes in parameters, as appropriate. The Division noted that for some laboratory parameters, these cuts might not be justified. If not, then the appropriate number should be used. Sub-grouping for the geriatric population (less than 40 years, 40 to 65 years, and over 65 years old) will be included. The Division requested two-by-two tables for related parameter pairs (e.g., hematocrit and hemoglobin, bilirubin and alkaline phosphatase). Adverse event tables should report the total number and percent of patients with an adverse event. In addition, the tables should include the number and percent of patients with an adverse event for each body system. Finally, the number and percent of patients that meet the cut off should be reported in the tables.

ATTACHMENT 2; SHELL TABLES FOR INTEGRATED SUMMARY OF SAFETY

The individual study reports will have the same table format as the Integrated Summary tables, as appropriate. The Division requested that the location of the clinical protocol, blinded reader protocol, and the CRF for the blinded and unblinded readers be clearly indicated. Mallinckrodt stated they will be following ICH guidelines for formatting their application.

Mallinckrodt stated that anyone dosed but not imaged, or producing a poor quality image, was included in the intent to treat analysis, and received the lowest possible score. Mallinckrodt will provide summary tables and text in each study report and the integrated summaries stating the reason each patient was enrolled in the pivotal studies. The Division requested that a safety assessment by disease state be provided if available.

I. Timing of Safety Parameters by Study

Mallinckrodt will provide the number of patients that had clinical laboratory parameters assessed at each timepoint for each study.

II. Study Enrollment Tables

The Division requested that patients who were not considered evaluable be listed with the reasons they were not considered evaluable (e.g., incomplete image set, technically inadequate images), at what point in the protocol this decision was made, and who determined they were not evaluable. Mallinckrodt reported that all images considered technically inadequate by unblinded readers were given to the blinded readers, who also qualified the images as technically adequate or inadequate. The number of subjects exposed will be equal to the number of subjects evaluable for safety.

III. Demographics

The Division requested that "Race" be expanded to include Asians and/or Hispanics, if the numbers were sufficient. Mallinckrodt stated that they have added an Asian subgroup (not shown in the submission), and could add Hispanics as well.

Mallinckrodt reported that the patients receiving multiple doses of OptiMARK can be identified. The database provided will indicate the patients receiving multiple doses as well as the sequence of the doses. In addition, the applicable individual study reports will group patients by dose sequence. The Division requested that a column be added to all demographic tables which includes the numbers of all patients that received any dose.

IV. Dosing

The Division requested that a column be added to all dosing tables which includes the numbers of all patients that received any dose.

V. Adverse Event Tables

The Division requested that a single column be added for all patients that had an adverse event, as well as including a row for each body system as a whole. Mallinckrodt agreed to do this.

Mallinckrodt reported that patients with two adverse events which fell into the same COSTART term (i.e., chest pain and angina) were counted as the worse event. The Division stated that this was acceptable.

In addition, the Division requested that terms for the same or similar disorders (that might be in different body systems) be reported together in a special table.

V.I. Laboratory Parameter Tables

The Division requested that Mallinckrodt report laboratory parameters for patients receiving 0.1 mmol/kg OptiMARK across all studies.

VIII. Electrocardiogram Parameters

Mallinckrodt stated that all electrocardiogram parameters obtained will be reported, not only at 24 hours as shown in the table shell.

ATTACHMENT 3; SHELL TABLES FOR INTEGRATED SUMMARY OF EFFICACY

The Division requested that the image acquisition protocol and training material be provided. The Division will need text with the specification of the models. The models used are complex and the interpretation could be problematic, therefore adequate discussion is needed.

Tables should reflect sample sizes for primary comparisons. For categorical outcomes, Mallinckrodt may choose to dichotomize and apply a matched-pairs analysis using a McNemar statistic.

ATTACHMENT 4; SAMPLE (TABLE OF CONTENTS) TOC FOR A CLINICAL STUDY REPORT

Mallinckrodt will present both clinically and statistically significant changes. Clinically significant changes were reviewed for statistical significance, and statistically significant changes were reviewed for clinical significance. The clinical relevance will be commented on in the report. Extreme values seen in shift tables and scatter plots will be discussed as well.

ADDITIONAL DISCUSSION

Pharmacokinetic Review Requests

The Division requested the following:

- concentration vs. time data and pharmacokinetic (PK) parameters,
- individual subject data (Mallinckrodt stated that these are available as Microsoft Excel Spreadsheets),
- scatter plots,
- sample calculations of PK parameters,
- analytical assay validations, including quality controls and standard curves,
- demographic and dosing tables (Mallinckrodt stated that these are available as Microsoft Excel Spreadsheets),
- data handling (according to protocols).

Mallinckrodt stated that the PK reports were not a separate section, but an appendix to the clinical section. The Division requested an extra volume with the PK reports.

FOLLOW-UP

A conference call will be scheduled between the Division's and Mallinckrodt's Information Technology personnel will be scheduled by Ms. Colangelo and Ms. Hamilton to facilitate the submission of electronic data.

Division of Medical Imaging and Radiopharmaceutical Drug Products
Meeting Minutes

NDA: 20-937
DRUG: OptiMARK
SPONSOR: Mallinckrodt, Inc.
DATE: April 8, 1998

Mallinckrodt Inc.

Robert Wolfangel, Ph.D., Regulatory Affairs
Gary Stevens, Ph.D., Director of Biostatistics and Data Management
Rita Kristy, Senior Statistician
Mary Hamilton, Manager, Regulatory Affairs
Peri Periasmy, Ph.D., Project Manager

Division of Medical Imaging and Radiopharmaceutical Drug Products

Patricia Love, M.D., M.B.A., Division Director
A. Eric Jones, M.D., Medical Team Leader
Padma Rao, M.D., Medical Reviewer
Ramesh Raman, M.D., Medical Reviewer
Ruthanna Davi, Ph.D., Statistical Reviewer
Kim Colangelo, B.S., Consumer Safety Officer

5/15/98

BACKGROUND

This conference call was requested by Mallinckrodt to clarify a request for information from the Division for data tables of the actual laboratory values instead of normalized or transformed values.

DATA TRANSFORMATION

The transformation of the data was done based on Mallinckrodt's concerns regarding the different laboratory ranges, which varied in Phase 3 from Phase 2, not with the data itself. The transformation was done in an effort to consolidate the data across the trials. The transformation calculates the percent change from baseline, and does not affect the lab range table, p value, or shift tables. The Division stated that clinical interpretation is based on the actual lab values, not solely on the percent change from baseline. The Division requested documentation verifying that the formula used to transform the data reproducibly predicts the range and degree of normal or abnormality, which validates the correlation of the transformed data to "real world" values, and shows how the interpretations can be made. In addition, the Division requested the non-transformed data set with the appropriate mean tables.

FOLLOW-UP

Mallinckrodt will provide mean change tables for raw data values for the Integrated Summary of Safety by May 1, 1998, the filing date for the NDA. Mean change tables for the study reports will be provided at a later date.

Rough draft: Colangelo May 15, 1998
Concurrence/Revisions:

cc: Original NDA 20-937
HFD-160/Division File
HFD-160/Raman/Rao/Colangelo
HFD-720/Davi

Division of Medical Imaging and Radiopharmaceutical Drug Products
Meeting Minutes

NDA: 20-937
DRUG: OptiMARK
SPONSOR: Mallinckrodt Inc.
DATE: April 15, 1998

Mallinckrodt Inc.
Robert Wolfangel, Ph.D., Regulatory Affairs

Division of Medical Imaging and Radiopharmaceutical Drug Products
Padma Rao, M.D., Medical Reviewer
Ruthanna Davi, M.S., Statistical Reviewer
Kim Colangelo, B.S., Consumer Safety Officer

BACKGROUND

The Division called Mallinckrodt to discuss the sample tables sent via facsimile on April 13, 1998 (attached).

1. The Division requested that tables as presented in samples 2 and 3 be submitted, and that the minimum and maximum values be added to the table. Mallinckrodt agreed to submit the tables as requested. The Division requested clarification that sample table 3 used gender specific reference ranges. Mallinckrodt indicated that the parameters reported will be the same for both sets of tables.

2. The Division requested clinical justification (e.g., a clinical journal article or other documentation) explaining the rationale for the transformation chosen (i.e., documentation substantiating the "proportional relationship" among laboratories).

3. The Division requested a means to correlate the abnormal lab values and patient number. Mallinckrodt proposed submitting a list of patients. This topic may need further discussion in a conference call. Mallinckrodt will generate a sample table for comment. The Division requested that the parameters be grouped sensibly in a clinically relevant manner.

4. The Division requested that shift tables be submitted as originally proposed (i.e., scatter plots are needed for actual lab values).

5. The electronic SAS data sets are not functional. The error messages will be sent to Mallinckrodt via facsimile.

6. The Division noted that the spreadsheets state they are used to convert transformed data to approximate "real" values for baseline values only. The Division asked if there was some reason these spreadsheets were not applicable to any transformed value. Mallinckrodt stated that they should be applicable to post-dose values as well.

ACTION ITEMS

Mallinckrodt will:

- Submit tables as presented in samples 2 and 3, with maximum and minimum values included.
- Provide clinical justification explaining why this transformation of the data is appropriate and clinically valid.
- Verify if the sample 3 tables use gender specific reference ranges.
- Generate sample tables correlating abnormal lab values and patient numbers.

The Division will:

- Send a copy of the SAS data set error messages to Mallinckrodt via facsimile.

ATTACHMENT

Drafted: Colangelo, 05.15.98
Concurrence/Revisions: Rao, 05.18.98; Davi, 05.19.98
Final: Colangelo, 05.20.98

/S/ 05/20/98

cc: Original NDA 20-937
HFD-160/Division File
HFD-160/Jones/Rao/Raman/Colangelo
HFD-720/Davi

SAMPLE TABLE FORMAT

- In order to facilitate and expedite the clinical review of the NDA for OptiMARK™, we request that the following data available from different portions of the NDA be consolidated into a single table so that these may be considered together
- Please provide this information for all Pivotal Phase 3 Studies (i.e., Studies # 488, 490, 525, & 526)
- Please provide the information in electronic format if possible, in addition to a paper copy for archival.

Patient ID #	Drug Given	Dose Date	Medical & Surgical* History	Indication^ for Qualifying Exam	Final Diagnosis	Basis for Final Diagnosis@	Adverse Events, Abnormal Labs, Etc. as Flagged#
Site Pt # Age Sex	OptiMARK or Magnevist	date and time drug admin- istered	[e.g., from Appendix 16.2.4-5 of Study # 490] * specify tissue diagnosis/es and date (prior to Study, if any)	[e.g., from Appendix 16.2.4-4 of Study # 490] ^ specify pre-Study working diagnosis (suspected disease for which high degree of clinical suspicion existed at enrollment)	[e.g., from Appendix 16.2.6-17 of Study # 490]	[e.g., from Appendix 16.2.6-20 of Study # 490] @ specify tissue diagnosis/es and date (after Study, if any)	# include timing in relation to drug administration

HFD-160/Colangelo

MEMORANDUM OF TELECON

DATE: August 31, 1998

APPLICATION NUMBER: NDA 20-937, NDA 20-975, NDA 20-976; OptiMARK

BETWEEN:

Name: Mary Hamilton, Manager, Regulatory Affairs
Phone: 314-654-3272
Representing: Mallinckrodt, Inc.

AND

Name: Kim Colangelo
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Conference Call and Information Request

I contacted Ms. Hamilton regarding the following:

1. I inquired of the availability of representatives of Mallinckrodt, Inc. to discuss questions regarding the Blind Read Methodology with our Clinical and Statistical review teams. I proposed holding the call on Thursday, September 3, from 4:15 - 5:00 PM EDT. Ms. Hamilton stated that this time would be acceptable. She agreed to inform me of the telephone number for the call if it was different than originally provided.

2. I requested a summary table listing the name of each laboratory used to analyze clinical blood samples, the applicable study numbers, and the reference range of each measurement. Ms. Hamilton stated Mallinckrodt would provide this information, and she would contact me once she knew of an estimated time of submission of this information.

3. I inquired about the facility in North Carolina, which received a warning letter from the Division of Manufacturing Product Quality. I asked Ms. Hamilton if Mallinckrodt felt that this letter impacted one, two, or all three products currently under review. She stated that all three products were impacted. She stated that a response was sent to the Field Office on Friday, August 28, 1998. She agreed to send a courtesy copy of the letter to me via facsimile, hopefully today. Ms. Hamilton stated that a request for follow-up inspection was planned for mid-September.

/S/

Kim Colangelo
Consumer Safety Officer

HFD-160/Colangelo

MEMORANDUM OF TELECON

DATE: August 28, 1998

APPLICATION NUMBER: NDA 20-937; OptiMARK

BETWEEN:

Name: Mary Hamilton,
Phone: 314-654-3272
Representing: Mallinckrodt Inc.

AND

Name: Kim Colangelo
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Conference Call Scheduled for September 3, and Clinical Requests for Clarification

I had contacted Ms. Hamilton on August 27, 1998, to request clarification on the following issues. Her response follows each question.

Were the reference ranges used to determine abnormal laboratory values based on the reference text by Henry? No, the reference ranges used to determine abnormal laboratory values were the reference ranges of each laboratory which analyzed the samples. If a determination of abnormal laboratory values based on the reference by Henry is desired, Ms. Hamilton believed it could be provided within a week.

Is there a listing of abnormal laboratory values including the value, the patient number, for each study conducted? Ms. Hamilton provided an example for Study 488. The listing is in the appendix, Table 16.2.8-2 lists the abnormal hematology values, and Table 16.2.8-4 lists the abnormal clinical laboratory values. The listing includes the patient number. Ms. Hamilton believed that the listings were located similarly for each study.

Ms. Hamilton provided a phone number (314-654-3434) for the conference call scheduled for September 3 at 3:15 PM EDT. *[Note: This call will be rescheduled due to a Division conflict.]*

Ms. Hamilton inquired whether Dr. Joe Pierro would be able to participate in the conference call due to his former employment within this Division. I informed Ms. Hamilton that since Dr. Pierro was actually the Medical Reviewer for OptiMARK during his tenure here, that it would not be appropriate for him to represent Mallinckrodt to the Division in matters involving OptiMARK.

/S/

Kim Colangelo
Consumer Safety Officer

HFD-160/Colangelo

MEMORANDUM OF TELECON

DATE: September 2, 1998

APPLICATION NUMBER: NDA 20-937; OptiMARK

BETWEEN:

Name: Mary Hamilton, Manager, Regulatory Affairs
Phone: 314-654-3272
Representing: Mallinckrodt, Inc.

AND

Name: Kim Colangelo
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Comments regarding Facsimile from Sponsor dated September 1, 1998 (attached)

I contacted Ms. Hamilton regarding the facsimile sent September 1, 1998, in response to our request for a summary of laboratory reference ranges used for the analysis of clinical blood samples. The facsimile contained an example of the proposed table format and content for one of the pivotal trials, and requested feedback from Dr. Raman, Reviewing Clinician. The following comments were conveyed to Ms. Hamilton:

1. The laboratory parameters measured should be grouped according to their clinical relevance (i.e., hematology, serum chemistry, and urinalysis as grouped in the protocol).

2. It was noted that each parameter could have more than one unit of measurement, depending on the laboratory used (e.g., bilirubin is listed in mg/dL for the US and Canadian sites, and in µmol/L for the European site). I inquired if the data listings and analysis tables prepared contained a standardized set of units (e.g., the European data was converted to the North American units). Accepting that the case report forms (CRF) would most likely be in "site specific" units, if the data listings and analysis tables are based on a standardized set of units, I requested that the reference range table also utilize a standardized set of units. Ms Hamilton stated that she would investigate how the data listings and analysis tables were prepared, and would modify the reference range table accordingly.

I reminded Ms. Hamilton that the reference range table should encompass all studies, not just the pivotal trials, included in the Integrated Summary of Safety. This would include the Japanese studies as well as the studies for MRA and breast imaging indications.

/S/

Kim Colangelo
Consumer Safety Officer

HFD-160/Colangelo

MEMORANDUM OF TELECON

DATE: September 11, 1998

APPLICATION NUMBER: NDA 20-937; OptiMARK

BETWEEN:

Name: Mary Hamilton, Manager, Regulatory Affairs
Phone: 314-654-3272
Representing: Mallinckrodt, Inc.

AND

Name: Kim Colangelo
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Information Requests

Ms. Hamilton called to inform me that responses to the Clinical and Statistical Review Teams questions regarding the Blinded Read Methodology for the pivotal studies had been forwarded via facsimile, and that hard copies (including attachments) would be sent via Federal Express. She also stated that work was continuing on the electronic database (requested May 21, 1998), and on the tables summarizing the reference ranges used in the safety studies (requested August 28, 1998).

I asked Ms. Hamilton for information on the "medically qualified personnel" who read the EKGs in all of the studies included in the safety analysis; specifically I requested the name, title, and specialty of each individual who read the EKGs. Ms. Hamilton stated she would investigate this and contact me as soon as she had the information.

/S/
Kim Colangelo
Consumer Safety Officer

cc: Original NDA 20-937
HFD-160/Div. File
HFD-160/Colangelo/Raman/Jones/Yaes
HFD-720/Davi

TELECON

Section 14 Patent Certification

Mallinckrodt Inc. certifies the patents: 5130120, 5137711 and 5508388 are beneficially owned by Mallinckrodt Inc., by assignment from the inventors of record.

Wendell Ray Guffey
Patent Attorney

Section 13 Patent and Exclusivity Information

Patent Information:

Mallinckrodt Inc. maintains the following three patents pertaining to **OptiMARK™ (gadoversetamide injection)**, which is the subject of this application.

Patent Number: 5130120
Date of Expiration: July 14, 2009
Patent Type: Drug Substance, Drug Product and Method of Use
Patent Owner: Mallinckrodt Medical, Inc.

Patent Number: 5137711
Date of Expiration: July 14, 2009
Patent Type: Drug Substance, Drug Product and Method of Use
Patent Owner: Mallinckrodt Medical, Inc.

Patent Number: 5508388
Date of Expiration: April 16, 2013
Patent Type: Process
Patent Owner: Mallinckrodt Medical, Inc.

The undersigned declares that Patent Nos. 5130120 and 5137711 claim the composition and/or method of use of OptiMARK™ (gadoversetamide injection). This product is the subject of this application for which approval is being sought: NDA 20-937.

/

Wendell Ray Guffey
Patent Attorney

Section 13 Patent and Exclusivity Information (continued)

Claimed Exclusivity:

Mallinckrodt Inc. hereby requests, under 21CFR§314.108(b)(2), an EXCLUSIVITY PERIOD of **5 years** for OptiMARK™ (gadoversetamide injection) after NDA 20-937 is approved. To the best of the applicant's knowledge, a drug has not previously been approved under section 505(b) of the act containing any active moiety in OptiMARK™ (gadoversetamide injection).

DEBARMENT CERTIFICATION

This certifies that Mallinckrodt Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [U.S.C. 306 (a) or (b)], in connection with this new drug application.

FIELD COPY OF CMC SECTION OF NDA SUBMISSION TO THE DISTRICT OFFICE

This certifies that Mallinckrodt Inc. has provided to its home FDA district office the required field copy of the application that contains the technical section described in 314.50 (d)(1), a copy of the information required under 314.50 (a) and (c), and certifies that the field copy is a true copy of the technical section contained in the archival and review copies of the application.

USER FEE FOR NEW DRUG APPLICATION

Mallinckrodt Inc. has forwarded a check for the full amount of the User Fee for a New Drug Application to the Food and Drug Administration at P. O. Box 360909, Pittsburgh, PA 15251-6909. Photocopies of the letter and check are provided.

Mary E. Hamilton
Manager, Regulatory Affairs
Medical Imaging

23 February 98
Date