CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-923

Administrative Documents

LABELING REVIEW

NDA: 20-923

DRUG: Optiray Pharmacy Bulk Package

SPONSOR: Mallinckrodt Medical, Inc.

DATE OF SUBMISSION: September 30, 1997

BACKGROUND: This new drug application provides for Pharmacy Bulk Packages of Optiray 240 mg, Optiray 320 mg, and Optiray 350 mg filled with 200 mL of solution in 250 mL bottles. A comparison between the most recently approved labeling for NDA 19-710, Optiray and the proposed labeling for NDA 20-923, Optiray Pharmacy Bulk Package was completed. Any differences between the two labels are noted below:

1. **STORAGE** section, 1st paragraph:

Currently approved labeling (NDA 19-710) reads:

"Store below 30 °C (86°F)."

Proposed labeling (NDA 20-923, Optiray Pharmacy Bulk Package) reads:

[redacted]

Comment: This change follows the U.S.P. 23. We recommend the following change:

Storage: Store at USP controlled room temperature, 20 °C to 25 °C (68 °F to 77 °F).

ACCEPTABLE ☑ **UNACCEPTABLE** ☐

/S/

Eldon Leutizinger, Ph.D

Recommendation: Pending that all changes to the labeling are found acceptable the New Drug Application Pharmacy Bulk Package can be approved. Otherwise, the Pharmacy Bulk Package should be approved on marked-up draft labeling.

/S/

Catalina Ferre-Hockensmith
Consumer Safety Officer

/S/ 7/13/98

Concur:
Robert K. Leedham Jr.
Supervisory Consumer Safety Officer

/S/

Eldon Leutzinger, Ph.D.
Supervisory Chemist

/S/ 5/26/98

Concur:
Patricia Y. Love, M.D., M.B.A.
Director, Division of Medical
Imaging and Radiopharmaceutical
Drug Products

A/W see attached
comments in Dms Docs

/S/

DIVISION DIRECTOR BRIEF MEMO TO THE FILE

NDA:	20-923
DRUG:	Optiray (ioversol) Pharmacy Bulk Package
INDICATION:	Intra-arterial, intravenous injection for iodinated contrast imaging
CATEGORY:	5C
SPONSOR:	Mallinckrodt Medical, Inc.
SUBMITTED:	October 1, 1997
PDUFA DATE:	October 1, 1998
COMPLETED:	May 26, 1998

/S/ 5/26/98

RELATED REVIEWS:

Chemistry - Yong de Lu 3/10/98, 4/23/98
Microbiology - V. Greenman 10/21/97
Project Manager - C. Ferre-Hockensmith

BACKGROUND: Mallinckrodt presently markets Optiray (ioversol injection) in 160, 240, 300, 320 and 350 mg/ml of organically bound iodine concentrations for a variety of intravenous and intraarterial indications. These include intraarterial indications of cerebral angiography, aortography, cardiac angiography and ventriculography, visceral angiography, peripheral angiography, and digital substraction angiography. The intravenous indications include head and body computerized tomography, and excretory urography. These indications are spread across all concentrations. All indications are found in the highest concentration (350 mg/ml). Also, the 350 and 320 mg/ml concentrations are approved for pediatric indications. For details please see the table on page 3.

Mallinckrodt submitted a for a pharmacy bulk package for the 240, 320 and 350 mg/ml concentrations. The bulk packages will be supplied as 200 ml solution in 250 ml volumes. Optiray in these concentrations is currently marketed in glass bottles. These are single use containers, only. The proposed application is for multi-use containers. The manufacturing controls and sterilization procedures are the same. The labeling and disposal statements have been revised. These data were reviewed by the chemists and microbiologists and were found to be acceptable with the following additions.

1. *The provision of the container labeling*
2. *The addition of the lot and expiration numbers to the containers*

These were supplied and found to be acceptable.

3. *A commitment "to add one batch of each strength in existing container/closure systems to stability studies and annually, and to report these data annually"*
4. *A commitment "to conduct long range stability studies should be performed at 25± 2 °C to confirm to ICH*

The sponsor agreed to both commitments.

In addition to the above, the proposed labeling does not contain the box around the warning statements for iodinated contrast agents. The must be added.

Also, in reviewing the package insert, there is a subtle difference in the terminology used to describe the sterile conditions of use. The approved labeling states that "under strict aseptic technique". The proposed pharmacy bulk package revisions has two similar statements. One is found under the Dosage and Administration; the other is just before the storage statement. In the dosage and administration section it states:

> "As with all contrast media, other drugs should not be mixed with ioversol solutions because of the potential for chemical incompatibility.
>
> If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.
>
> Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and should not be used if particulates are observed or marked discoloration has occurred.
>
> **Directions For Proper Use of Pharmacy Bulk Package:** The transferring of contrast agents from a Pharmacy Bulk Package should be performed in a suitable work area, such as a laminar flow hood, utilizing aseptic technique. The closure may be penetrated only one time utilizing a suitable transfer device."

Just before the storage statement, it states:

> **"Directions for Proper Use of Optiray, Pharmacy Bulk Package:**
> 1. The container closure may be penetrated only one time, utilizing a suitable sterile transfer device or dispensing set which allows measured distribution of the contents.
> 2. The transferring of Optiray from the Pharmacy Bulk Package is restricted to a suitable work area, such as a laminar flow hood, utilizing aseptic technique.
> 3. The withdrawal of container contents should be accomplished without delay. However, should this not be possible, a maximum time of 4 hours from initial closure entry is permitted to complete fluid transfer operations.
> 4. Temperature of container after the closure has been entered should not exceed 25°C (77°F)."

The words "strict aseptic technique" are not used in the revisions, however, these is accepted terminology for pharmacy bulk packages and can be different from the single dose package inserts. However, the titles of the two directions sections are very similar and redundant. After reading the first paragraph, there is not a statement to indicate that more information is presented later. Therefore, these two sections should be consolidated in one Drug Handling section. This section should be just before the storage statements. A phrase should be added to the end of the introductory Dosage and Administration section to refer to the reader to the Drug Handling section.

ACTION: Approval
Label revisions include 1) the box around the warnings, 2) the storage condition temperature change, and 3) the changes in drug handling noted above
Letter: Identify the 2 commitments

OPTIRAY APPROVED INDICATIONS BY CONCENTRATION & ROUTE OF ADMINISTRATION					
Route of Administration	**Concentration in mg/ml bound iodine**				
Intra-arterial	**160**	**240**	**300**	**320**	**350**
Aortography				X	
Cerebral		X	X	X	X
Coronary				X	X
Ventriculography				X	X
Visceral				X	
DSA	X				X
Pediatric angiocardiography				X	X
Peripheral angiography			X	X	X
Intravenous					
CT head & body		X	X	X	X
Excretory urography		X	X	X	X
Venography		X	X	X	X
Pediatric CT head & body				X	
Pediatric excretory urography				X	

10 pages redacted from this section of the approval package consisted of draft labeling

EXCLUSIVITY SUMMARY for NDA # 20-923 SUPPL #_____

Trade Name Optiray (Ioversol) Injection Pharmacy Bulk Package **Generic Name**_____

Applicant Name Mallinckrodt medical, Inc. **HFD-** 160

Approval Date 5/29/98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X/

   If yes, what type? (SE1, SE2, etc.) —

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /___/ NO /X/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

___

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /X/ NO /___/

If yes, NDA # 19-710 Drug Name Optiray

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____
_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____
_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____
_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

DEBARMENT CERTIFICATION

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

Edward R. Porter
Senior Regulatory Affairs Associate
Medical and Regulatory Affairs
Mallinckrodt Inc.

5-14-98
Date

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet) **Date**: March 19, 1998

To: Mary Hamilton
Manager, Regulatory Affairs Medical Imaging

Fax Number: (314) 654-3344 **Voice Number**: (314) 654-3272

From: Catalina Ferre-Hockensmith
Consumer Safety Officer

Fax Number: (301) 480-6036 **Voice Number**: (301) 443-3500

Message:

Please note that we do not consider this a formal communication.

NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

MEETING MINUTES

NDA:	20-923
DRUG:	Optiray (Ioversol Injection) Pharmacy Bulk Package
DATE/TIME:	Thursday, October 16, 1997, 2:30PM
LOCATION:	18B-37
SPONSOR:	Mallinckrodt Medical, Inc.
FDA ATTENDEES:	James Cheever, D.M.D., Associate Director, HFD-160 Young-De Lu, Ph.D., Chemistry Reviewer, HFD-160 Vivian Greenman, Ph.D., Microbiology Reviewer, HFD-805 Catalina Ferre-Hockensmith, Consumer Safety Officer, HFD-160
PURPOSE:	To determine the feasibility of the application for filing.
MICROBIOLOGY:	The application is adequate to file.
CHEMISTRY:	The application is adequate to file.
CONCLUSION:	The application is suitable for filing.

Prepared by: Catalina Ferre-Hockensmith

cc: Original NDA 20-923
HFD-160/Div. File
HFD-160/cheever/lu/hockensmith
HFD-160/greenman

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 20-923 Drug OPTIRAY (IOVERSOL) INJECTION PBP DATE 4/28/98

Applicant MALLINCKRODT MEDICAL, INC. CSO CATALINA FERRE-Hockensack /Phone 443-3500

User Fee Goal Date: 10/1/98

Arrange package in the following order:

		Check or Comment
1.	ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP X AE ____ NA ____ Yes X No ____
2.	Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes X No ____
3.	Completed copy of this CHECKLIST in package	Chem/Ther Types ____
4.	LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft ✓ Revised Draft ____ Final ✓
5.	PATENT INFORMATION	N/A ✓
6.	EXCLUSIVITY CHECKLIST	____
7.	PEDIATRIC PAGE	____
8.	DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	____
9.	Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo expaining why.	N/A

10. REVIEWS:

DIVISION DIRECTOR'S MEMO	If more than 1 review for any	____
GROUP LEADER'S MEMO	1 discipline, separate reviews	____
MEDICAL REVIEW	with a sheet of colored paper.	N/A
SAFETY UPDATE REVIEW	Any conflicts between reviews	N/A
STATISTICAL REVIEW	must have resolution documented	N/A
BIOPHARMACEUTICS REVIEW		N/A
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		N/A
Statistical Review of Carcinogenicity Study(ies)		N/A
CAC Report/Minutes		N/A
CHEMISTRY REVIEW		4/23/98
Labeling and Nomenclature Committee Review Memorandum		N/A
Date EER completed N/A (attach signed form or CIRTS printout)		OK ____ No ✓
FUR needed ____ FUR requested ____		
Have the methods been validated?		Yes (attach) ____ No ____
Environmental Assessment Review / FONSI		Review ____ FONSI ____
MICROBIOLOGY REVIEW		10/21/97
What is the status of the monograph?		____

11.	CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	✓
12.	MINUTES OF MEETINGS Date of End-of-Phase 2 Meeting N/A Date of pre-NDA Meeting N/A	✓
13.	ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes ____ Info Alert ____ Transcript ____ No mtg ✓
14.	FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	N/A
15.	If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes ____ No ✓ Yes, documentation attached ____ No, included in AP ltr ✓
16.	INTEGRATED SUMMARY OF EFFECTIVENESS	N/A
17.	INTEGRATED SUMMARY OF SAFETY	N/A

revision: 3/7/96

Catalina.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-923

OCT 27 1997

Mallinckrodt Medical, Inc.
675 McDonnell Blvd.
St. Louis, MO 63134

Attention: Clarice Kassoff
Senior Regulatory Affairs Associate

Dear Ms. Kassoff:

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: Optiray (Ioversol Injection) Pharmacy Bulk Package

Therapeutic Classification: Standard

Date of Application: September 30, 1997

Date of Receipt: October 1, 1997

Our Reference Number: 20-923

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 November 30, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Catalina Ferre-Hockensmith, Consumer Safety Officer, 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,

10/24/97

James R. Cheever, D.M.D.
Associate Director
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-928
HFD-160/Div. Files
HFD-160/CSO/cfh
HFD-160/el/yl/pc/vg
DISTRICT OFFICE

Drafted by: cfh/October 24, 1997/n20923pb.ack
Final:

ACKNOWLEDGEMENT (AC)