CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-569

CHEMISTRY REVIEW(S)

NDA 21-569

Sodium Chloride, Injection, 0.9%, USP

Mallinckrodt Inc.
Tyco Healthcare

Mark Sassaman, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Pre-Marketing Division III, Branch V
for
Division of Medical Imaging and
Hematology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-569

2. REVIEW # 4

3. REVIEW DATE: 25 APR 2006

4. REVIEWER: Mark Sassaman, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application	27 SEP 2002
Amendment BC	08 NOV 2002
	08 MAY 2003
	10 JUN 2003
	09 JUL 2003
Amendment AC	28 JUL 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AZ	26 JAN 2006
Amendment BC	18 APR 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Tyco Healthcare Mallinckrodt
Address:	Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis MO 63134
Representative:	Edward R. Porter, Manager, Regulatory Affairs
Telephone:	(314)654-3334 (direct line) (314)654-2000 (company line)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Sodium Chloride Injection USP 0.9%
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.9% NaCl

13. ROUTE OF ADMINISTRATION: Parenteral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Sodium chloride, NaCl, Mol. Wt. 58.44

8742. Sodium Chloride. Salt, common salt. ClNa, mol wt 58.44. Cl 60.66%, Na 39.34%. NaCl. The article of commerce is also known as *table salt, rock salt* or *sea salt*. Occurs in nature as the mineral *halite*. Produced by mining (rock salt), by evaporation of brine from underground salt deposits and from sea water by solar evaporation. Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 722-730. Toxicity studies: E. M. Boyd, M. N. Shamas, *Arch. Int. Pharmacodyn.* **144**, 86 (1963). Comprehensive monograph: D. W. Kaufmann, *Sodium Chloride*, ACS Monograph Series no. 145 (Reinhold, New York, 1960) 743 pp.

Cubic, white crystals, granules, or powder; colorless and transparent or translucent when in large crystals. d 2.17. The salt of commerce usually contains some calcium and magnesium chlorides which absorb moisture and make it cake. mp 804° and begins to volatilize at a little above this temp. One gram dissolves in 2.8 ml water at 25°, in 2.6 ml boiling water, in 10 ml glycerol; very slightly sol in alcohol. Its solv in water is decreased by HCl. Almost insol in conc HCl. Its aq soln is neutral. pH: 6.7-7.3. d of satd aq soln at 25° is 1.202. A 23% aq soln of sodium chloride freezes at −20.5°C (5°F). LD_{50} orally in rats: 3.75 ±0.43 g/kg (Boyd, Shamas).

Note: Blusalt, a brand of sodium chloride contg trace amounts of cobalt, iodine, iron, copper, manganese, zinc is used in farm animals.

Caution: Not generally considered poisonous. Accidental substitution of NaCl for lactose in baby formulas has caused fatal poisoning.

USE: Natural salt is the source of chlorine and of sodium as well as of all, or practically all, their compds, e.g., hydrochloric acid, chlorates, sodium carbonate, hydroxide, etc.; for preserving foods, manuf soap, dyes; to salt them out; in freezing mixtures; for dyeing and printing fabrics, glazing pottery, curing hides; metallurgy of tin and other metals.

THERAP CAT: Electrolyte replenisher; emetic; topical anti-inflammatory.

THERAP CAT (VET): Essential nutrient factor. May be given orally as emetic, stomachic, laxative or to stimulate thirst (prevention of catarrh). Intravenously as isotonic solution to raise blood volume, to combat dehydration. Locally as wound irrigant, rectal douche.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]		3	Adequate	18 JUL 2003	Reviewed as part of original submission (Michael Theodorakis)
[redacted]	III			3	Adequate	10 FEB 2000	Reviewed as part of original submission (Michael Theodorakis)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-710; approved	Optiray (Ioversol) Injection
NDA	20-937; approved	Optimark (Gadoversetamide) Injection
NDA	20-976; approved	Optimark (Gadoversetamide) Injection in Pre-filled Ultraject Syringes

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox Memo	Approval	18 JUL 2003 22 JUL 2003	Tim McGovern
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS	In progress		
EA	Grant exemption	25 APR 2006	Mark Sassaman
Microbiology	Approval	11 MAY 2003	Stephen E. Langille

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-569

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Agency's concerns over a number of complaints the manufacturer had received regarding syringe failure resulted in improvements in both manufacturing and testing procedures; these improvements are described in detail in the amendment.

The company has also taken measures to initiate in-process controls during manufacture, update product specifications, revise the product stability protocol, test the drug product in a number of power injector devices, and provide an analysis of potential adverse events as requested by the Agency.

The concerns have been adequately addressed and, since there are no further issues outstanding, I recommend approval of the application pending fill-site inspection.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

[redacted]

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

From Review #1:

The drug substance, sodium chloride, is widely used in compounding, injections and other pharmaceutical preparations for administration to patients. Sodium chloride meets the USP, BP and EP compendial specifications. It is manufactured by [redacted]

The drug product, sodium chloride injection, 0.9%, is packaged in 50 and 125 mL [redacted] syringes, manufactured by Mallinckrodt Inc., Raleigh NC. The [redacted] (tip and cap) are composed of [redacted] rubber [redacted] The drug product meets the combined USP,

BP and EP compendial specifications. The drug product is [redacted] and it is preservative free. The syringes are disposable.

B. Description of How the Drug Product is Intended to be Used

From Review #1:

Sodium chloride injection, 0.9%, packaged in 50 mL syringes is indicated for use in flushing [redacted] Sodium chloride injection, 0.9%, packaged in 125 mL syringes is indicated for use in flushing [redacted] The 125 mL syringe is supplied with a luer lock adapter/nut adapter. The power injector that is recommended to be used is the Liebel-Flarsheim Optistar LE Contrast Delivery System. Both syringes are intended for single patient use.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has responded to all the concerns and questions posed by the FDA in an Approvable Letter, received 31 JUL 2003; a Clinical Concerns Letter, dated 26 AUG 2003; and a TCON follow-up meeting of 23 OCT 2003. The responses are satisfactory and represent a formal "tying up of loose ends" for a product deemed approvable in 2003.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Mark Sassaman, Ph.D./Date: 25 APR 2006
Branch Chief: Ravi Harapanhalli, Ph.D./Date
Project Manager: Lynn Henley/Date

C. CC Block

CC: Lynn Henley, Eldon Leutzinger, Karl Stiller

7 Page(s) Withheld

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_____ Deliberative Process

Withheld Track Number: Chemistry- 3

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/s/

Mark Sassaman
6/16/2006 08:31:52 AM
CHEMIST

Ravi Harapanhalli
6/16/2006 05:31:54 PM
CHEMIST

NDA 21-569

Sodium Chloride Injection, 0.9%, USP
(50 and 125 mL pre-filled syringes)

Mallinckrodt Inc.
Tyco Healthcare

Michael C. Theodorakis, Ph.D.

Division of New Drug Chemistry II
(HFD-820)

Division of Anesthetic, Critical Care,
and
Drug Addiction Drug Products
(HFD-170)

Chemistry Review Data Sheet

1. NDA 21-569

2. REVIEW # 3

3. DATE COMPLETED: July 30, 2003

4. **Michael C. Theodorakis, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original application	27-SEP-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AC	28-JUL-2003 (labeling)
Amendment AC	28-JUL-2003 (product complaints)

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt Inc. Tyco Healthcare
Address:	675 McDonnell Blvd P. O. Box 5840 Saint Louis, MO 63134
Representative:	Edward R. Porter Manager Regulatory Affairs
Telephone:	314-654-6061

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name Sodium Chloride Injection, 0.9%
c) Code Name/# :
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type : 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
505(b)(2)

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM:
Injection

12. STRENGTH/POTENCY:
0.9% NaCl

13. ROUTE OF ADMINISTRATION:
Parenteral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product - Form Completed

____x_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

8742. Sodium Chloride. Salt; common salt. ClNa; mol wt 58.44. Cl 60.66%. Na 39.34%. NaCl. The article of commerce is also known as *table salt, rock salt* or *sea salt.* Occurs in nature as the mineral *halite.* Produced by mining (rock salt), by evaporation of brine from underground salt deposits and from sea water by solar evaporation: Faith, Keyes & Clark's *Industrial Chemicals,* F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 722-730. Toxicity studies: E. M. Boyd, M. N. Shanas, *Arch. Int. Pharmacodyn.* **144,** 86 (1963). Comprehensive monograph: D. W. Kaufmann, *Sodium Chloride,* ACS Monograph Series no. **145** (Reinhold, New York, 1960) 743 pp.

Cubic, white crystals, granules, or powder; colorless and transparent or translucent when in large crystals. d 2.17. The salt of commerce usually contains some calcium and magnesium chlorides which absorb moisture and make it cake. mp 804° and begins to volatilize at a little above this temp. One gram dissolves in 2.8 ml water at 25°, in 2.6 ml boiling water, in 10 ml glycerol; very slightly sol in alcohol. Its soly in water is decreased by HCl. Almost insol in concd HCl. Its aq soln is neutral. pH: 6.7-7.3. d of satd aq soln at 25° is 1.202. A 23% aq soln of sodium chloride freezes at −20.5°C (5°F). LD_{50} orally in rats: 3.75 ±0.43 g/kg (Boyd, Shanas).

Note: ***Blusalt,*** a brand of sodium chloride contg trace amounts of cobalt, iodine, iron, copper, manganese, zinc is used in farm animals.

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USE: Natural salt is the source of chlorine and of sodium as well as of all, or practically all, their compds, e.g., hydrochloric acid, chlorates, sodium carbonate, hydroxide, etc.; for preserving foods; manuf soap, dyes—to salt them out; in freezing mixtures; for dyeing and printing fabrics, glazing pottery, curing hides; metallurgy of tin and other metals.

THERAP CAT. Electrolyte replenisher; emetic; topical anti-inflammatory.

THERAP CAT (VET): Essential nutrient factor. May be given orally as emetic, stomachic, laxative or to stimulate thirst (prevention of calculi). Intravenously as isotonic solution to raise blood volume, to combat dehydration. Locally as wound irrigant, rectal douche.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	4 and 1	Adequate	7/18/03	
[redacted]	III			3	Adequate	2/10/00	

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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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NDA	20-937; approved	Optimark (gadoversetamide) Injection
NDA	20-976; approved	Optimark in Prefilled Ultraject Syringes (gadoversetamide) Injection

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Completed	7/21/03	Michael Theodorakis
Pharm/Tox	Consult		Tim McGovern
Biopharm			
LNC			
Methods Validation	In-process		
OPDRA			
EA	Grant exemption		
Microbiology	Approval	5/11/03	Stephen E. Langille

The Chemistry Review for NDA 21-569

The Executive Summary:

I. Recommendations

A. Recommendation and Conclusion on Approvability:

In view of the recent submission dated 28-July-2003 which contains information about the failure rate of the syringes, there are two options that this reviewer recommends from the chemistry standpoint:

a. [redacted]

b. Issue an approvable letter with the combined comments from Chemistry Review #2 and Chemistry Review #3.

Either course would be acceptable to this reviewer.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

No Phase IV commitments were made.

II. Summary of Chemistry Assessments

See Chemistry Review # 1

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Review Chemist/MCTheodorakis/June 30, 2003
Team Leader/DLKoble/
CSO/SStradley

C. CC Block

5 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 4

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/s/

Michael Theodorakis
7/30/03 01:13:34 PM
CHEMIST

Dale Koble
7/30/03 01:30:14 PM
CHEMIST
See TL memo that covers CR#!, CR#2, and CR#3.

Chemistry Assessment Section

NDA 21-569

Sodium Chloride Injection, 0.9%, USP
(50 and 125 mL pre-filled syringes)

Mallinckrodt Inc.
Tyco Healthcare

Michael C. Theodorakis, Ph.D.

Division of New Drug Chemistry II
(HFD-820)

Division of Anesthetic, Critical Care,
and
Drug Addiction Drug Products
(HFD-170)

Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 21-569

2. REVIEW # 2

3. DATE COMPLETED: July 28, 2003

4. **Michael C. Theodorakis, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original application	27-SEP-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AC	23-JUL-2003 (labeling)
Amendment AC	23-JUL-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt Inc. Tyco Healthcare
Address:	675 McDonnell Blvd P. O. Box 5840 Saint Louis, MO 63134
Representative:	Edward R. Porter Manager Regulatory Affairs
Telephone:	314-654-6061

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name Sodium Chloride Injection, 0.9%
c) Code Name/# :
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type : 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(2)

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM:

Injection

12. STRENGTH/POTENCY:

0.9% NaCl

13. ROUTE OF ADMINISTRATION:

Parenteral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

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[redacted]	III			3	Adequate	2/10/00	

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18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Completed	7/21/03	Michael Theodorakis
Pharm/Tox	Consult		Tim McGovern
Biopharm			
LNC			
Methods Validation	In-process		
OPDRA			
EA	Grant exemption		
Microbiology	Approval	5/11/03	Stephen E. Langille

Chemistry Assessment Section

The Chemistry Review for NDA 21-569

The Executive Summary:

I. Recommendations

A. Recommendation and Conclusion on Approvability:

[redacted]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

No Phase IV commitments were made.

II. Summary of Chemistry Assessments

See Chemistry Review # 1

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Review Chemist/MCTheodorakis/June 30, 2003
Team Leader/DLKoble/
CSO/SStradley

C. CC Block

19 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 5

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/s/

Michael Theodorakis
7/30/03 09:21:36 AM
CHEMIST

Dale Koble
7/30/03 11:46:58 AM
CHEMIST
See TL memo on CR#1, CR#2, and CR#3.

NDA 21-569

Sodium Chloride Injection, 0.9%, USP
(50 and 125 mL pre-filled syringes)

Mallinckrodt Inc.
Tyco Healthcare

Michael C. Theodorakis, Ph.D.

Division of New Drug Chemistry II
(HFD-820)

Division of Anesthetic, Critical Care,
and
Drug Addiction Drug Products
(HFD-170)

Table of Contents

Executive Summary Section

Chemistry Review Data Sheet

1. NDA 21-569

2. REVIEW # 1

3. DATE COMPLETED: June 30, 2003

4. **Michael C. Theodorakis, Ph.D.**

5. **PREVIOUS DOCUMENTS**:

Previous Documents	Document Date
N/A Original application	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	27-SEP-2002
Amendment BC	08-NOV-2002
	08-MAY-2003
	10-JUN-2003
	09-JUL-2003

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Name:	Mallinckrodt Inc. Tyco Healthcare
Address:	675 McDonnell Blvd P. O. Box 5840 Saint Louis, MO 63134
Representative:	Edward R. Porter Manager Regulatory Affairs
Telephone:	314-654-6061

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name Sodium Chloride Injection, 0.9%
c) Code Name/# :
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type : 6
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)(2)

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM:

Injection

12. STRENGTH/POTENCY:

0.9% NaCl

13. ROUTE OF ADMINISTRATION:

Parenteral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

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Executive Summary Section

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Caution: Not generally considered poisonous. Accidental substitution of NaCl for lactose in baby formulas has caused fatal poisoning.

USE: Natural salt is the source of chlorine and of sodium as well as of all, or practically all, their compds, e.g., hydrochloric acid, chlorates, sodium carbonate, hydroxide, etc.; for preserving foods; manuf soap, dyes—to salt them out; in freezing mixtures; for dyeing and printing fabrics, glazing pottery, curing hides; metallurgy of tin and other metals.

THERAP CAT: Electrolyte replenisher; emetic; topical anti-inflammatory.

THERAP CAT (VET): Essential nutrient factor. May be given orally as emetic, stomachic, laxative or to stimulate thirst (prevention of calculi). Intravenously as isotonic solution to raise blood volume, to combat dehydration. Locally as wound irrigant, rectal douche.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]		4 and 1	Adequate	7/18/03	
[redacted]	III			3	Adequate	2/10/00	

[1] Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 -Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application
5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19-710; approved	Optiray (ioversol) Injection
NDA	20-937; approved	Optimark (Gadoversetamide) Injection
NDA	20-976; approved	Optimark in Prefilled Ultraject Syringes (Gadoversetamide) Injection

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Completed	7/21/03	Michael Theodorakis
Pharm/Tox	Consult		
Biopharm			
LNC			
Methods Validation	In-process		
OPDRA			
EA	Grant exemption		
Microbiology	Approval	5/11/03	Stephen E. Langille

Executive Summary Section

The Chemistry Review for NDA 21-397

The Executive Summary:

I. Recommendations

A. Recommendation and Conclusion on Approvability:

This Application is approvable from the chemistry standpoint. The deficiencies listed in the draft letter must be conveyed to the Applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

No Phase IV commitments were made.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, sodium chloride, is widely used in compounding injections and other pharmaceutical preparations for administration to patients. Sodium chloride meets the USP, BP and EP compendial specifications. It is manufactured by [redacted]

The drug product, sodium chloride injection, 0.9%, is packaged in 50 and 125 mL [redacted] syringes. The [redacted] closures (tip and cap) are composed of [redacted] rubber [redacted]. It is manufactured by Mallickrodt Inc., at Raleigh, NC. The drug product meets the combined USP, BP and EP compendial specifications. The drug product is [redacted] and it is preservative free. The syringes are disposable.

B. Description of How the Drug Product is Intended to be Used

Sodium chloride injection, 0.9%, packaged in 50 mL syringes is indicated for use in flushing [redacted]

Sodium chloride injection, 0.9%, packaged in 125 mL syringes is indicated for use in flushing [redacted]

The 125 mL syringe is supplied with a luer lock adapter/nut adapter. The luer lock adapter/nut is manufactured as device under 510 K862653.

The power injector that is recommended to be used is the Liebel-Flarsheim Optistar LE Contrast Delivery System. Both syringes are intended for single patient use.

C. Basis for Approvability or Not-Approval Recommendation

All CMC aspects have been adequately addressed and supported by data. The Applicant provided a narrative description and flow diagrams describing the manufacturing process. Also it included executed batch records for solution preparation and filling of one of the full scale batches used in the primary stability program for the drug, and blank master batch records that detail the intended commercial process up through filling of the product.

The Applicant conducted studies to specifically evaluate the potential for leaching [redacted] from the syringe barrel by subjecting samples of the syringe barrel to extreme conditions of extraction with various extraction media. Also the Applicant conducted studies to assess the biocompatibility [redacted] These studies showed that [redacted] composes the 50 mL and 125 mL syringe barrels is safe and compatible when in contact with Sodium Chloride Injection USP 0.9%.

It should be noted that [redacted] used for manufacturing the syringe barrels, the syringe barrels themselves, and the [redacted] closures have been already approved by this Agency for packaging injections under the following NDAs:

NDA 19-710, Optiray (ioversol) Injection,
NDA 20-937, OptiMark (gadoversetamide) Injection:
NDA 20-976, OptiMark (gadoversetamide) Injection:
(piston and tip cap)

Executive Summary Section

For determination of stability, three batches of sodium chloride injection 0.9% were manufactured at a scale of 10% of the maximum commercial batch size. All three batches were manufactured at the commercial site utilizing commercial scale equipment. Specifically, the size of the stability batches that were produced was [redacted] L while the maximum commercial scale batch is [redacted] L. Each batch was filled into 50 mL and 125 mL syringes. Three lots for each container size were placed on stability. One lot for each container was used for [redacted] studies. The Applicant provided 12 months stability data. Based on statistical analysis, the Applicant requested an [redacted] expiration dating period.

The Applicant requested a categorical exclusion pursuant to 21 CFR 25.31(C). This was based on the fact that sodium chloride is a natural substance, widely present in the biosphere.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Review Chemist/MCTheodorakis/June 30, 2003
Team Leader/DLKoble/
CSO/KACompton/

C. CC Block

56 Page(s) Withheld

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/s/

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7/22/03 05:31:18 PM
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Dale Koble
7/30/03 11:41:10 AM
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Michael Theodorakis
7/22/03 05:31:18 PM
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Dale Koble
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Dale Koble
7/30/03 11:44:19 AM
CHEMIST
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