CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-569

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

tyco Healthcare

Mallinckrodt

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

Tele: 314 654-2000
www.mallinckrodt.com

11 July 2003

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Anesthetic, Critical Care and Addition Drug Products
5600 Fishers Lane
Rockville, Maryland 20857
Attention: Sara Stradely
Document Room 9B-45

Ref: NDA 21-569 Sodium Chloride Injection USP 0.9%
NDA Section 14 – Patent Certification

Tyco Healthcare Mallinckrodt has conducted a patent search with respect to Sodium Chloride Injection Syringe submitted in this NDA 21-569 and hereby declares that no relevant patents were found that claim the method of use proposed in this NDA.

Edward R. Porter

Edward R Porter

Manager Regulatory Affairs
Tyco Healthcare Mallinckrodt

EXCLUSIVITY SUMMARY

NDA # 21-569 SUPPL # 000 HFD # 160

Trade Name n/a

Generic Name Sodium Chloride Injection, USP 0.9%

Applicant Name Tyco Healthcare Mallinckrodt

Approval Date, If Known July 27, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

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 ☐

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.

Please note that the answer "Yes" to the previous question involves clinical data from published literature.

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 ☐

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

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 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 ☐

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

NDA# 016677 Sodium Chloride, NA-22 Soln/Injection (Abbott)

NDA# 018803 Sodium Chloride 0.9% Inj. (Hospira)

NDA# 019217 Sodium Chloride 0.9% Abb oject 10ML (Hospira)

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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.

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☐

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

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 ☐

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Lynn Henley
Title: Regulatory Project Manager
Date: July 20, 2006

Name of Office/Division Director signing form: George Q. Mills, M.D., M.B.A.
Title: Director, Division of Medical Imaging and Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE

)A/BLA # : 21-569 Supplement Type (e.g. SE5): n/a Supplement Number: n/a

Stamp Date: 1/27/06 Action Date: 7/27/06

HFD 160 Trade and generic names/dosage form: Generic name: Sodium Chloride Injection, USP 0.9%

Applicant: Tyco Healthcare Mallinckrodt Therapeutic Class: 2030900

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: For use in flushing compatible intravenous administration sets and indwelling intravascular access devices

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ction A: Fully Waived Studies

Reason(s) for full waiver:

x Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other: _____

studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ction D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-569
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

tyco Healthcare Mallinckrodt

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

Tele: 314 654-2000
www.mallinckrodt.com

11 July 2003

Food and Drug Administration
Center for Drug Evaluation & Research
Division of Anesthetic, Critical Care and Addition Drug Products
5600 Fishers Lane
Rockville, Maryland 20857
Attention: Sara Stradely
Document Room 9B-45

Ref: NDA 21-569 Sodium Chloride Injection USP 0.9%
NDA Section 16 – Debarment Certification

Tyco Healthcare Mallinckrodt hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act in Connection with this New Drug Application NDA 21-569.

Edward R. Porter

Manager Regulatory Affairs
Tyco Healthcare Mallinckrodt

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Mallinckrodt Inc.
P. O. Box 5840
St. Louis, MO 64134

2. TELEPHONE NUMBER *(Include Area Code)*

(314) 654-2000

3. PRODUCT NAME

Sodium Chloride Injection USP 0.9% (Saline Syringe)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-569

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

43-1479062

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Robert F. Ingham	Regulatory Affairs - Imaging	September 24, 2002

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

Office of Surveillance and Epidemiology

MEMO

To: George Q. Mills, M.D.
Division of Medical Imaging and Hematology Products

Through: Linda Y. Kim-Jung, Pharm.D., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support,
Office of Surveillance and Epidemiology
HFD-420; White Oak Bldg. 22, Mail Stop 4447

From: Laura Pincock, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support,
Office of Surveillance and Epidemiology
HFD-420; White Oak Bldg. 22, Mail Stop 4447

Date: May 30, 2006

Re: OSE Consult 06-0123
[redacted] (Sodium Chloride Injection, USP 0.9%)
50 mL in plastic syringes in cartons of 10 syringes
125 mL in plastic syringes in cartons of 20 syringes

NDA #: 21-569

This memorandum is in response to an April 23, 2006 request from your Division for a review of the proprietary name, [redacted] Upon the initial steps in the proprietary name review process, the Division of Drug Marketing, Advertising and Communications (DDMAC) did not recommend the use of the proposed proprietary name, [redacted] from a promotional perspective because it is overly fanciful and overstates the efficacy of the product. Specifically, DDMAC states:

[redacted]

As per email correspondence with the Division on May 22, 2006, the Division concurs with DDMAC's comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name, [redacted] since the Division supports DDMAC's objection of the name based on promotional concerns. We recommend the sponsor be notified immediately of the decision to object to the names based on the aforementioned concerns and request submission of an alternative proprietary name for NDA # 21-569. Please forward the alternate name for DMETS review upon submission.

If you have any questions for DDMAC, please contact Catherine Gray or Suzanne Berkman at 301-796-1200. If you have any other questions or need clarification, please contact the medication errors Project Manager, Diane Smith, at 301-796-0538.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laura Pincock
6/8/2006 03:11:38 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/8/2006 03:26:22 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director, DMETS in her absence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-569

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

Attention: Edward R. Porter
Manager, Regulatory Affairs

Dear Mr. Porter:

Please refer to the teleconference between representatives of your firm and FDA on September 24, 2003. The purpose of the meeting was to discuss the approvable letter dated July 31, 2003 for sodium chloride injection, USP 0.9%.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING ATTENDEES

Meeting Date: September 24, 2003

Location: teleconference

NDA: 21-569 (sodium chloride injection, USP 0.9%)

Sponsor: Mallinckrodt. Inc.

Type of Meeting: Guidance

Meeting Chair: Nancy Chang, M.D., Team Leader, Analgesics
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

Minutes Recorder: Sara E. Stradley, Regulatory Project Manager

Mallinckrodt	Title
Ron Brendel	Research Pharmacist
Karen Coulson	Director, R&D
Brian Doty	Director Pharmaceutical Science
Frank Fargo	Manager, R&D
Eric Hanford	Product Manager
Dave Kruse	Site Quality Manager
Marge Moutray	Manager, R&D
Alicia Naploi	Sr. Director, Regulatory and Clinical Affairs
Ed Porter	Manager, Regulatory Affairs
Nancy Schmich	Project Leader, R&D
FDA	**Title**
Celia Winchell, M.D.	Acting Deputy Director
Nancy Chang M.D.	Team Leader, Anesthetics
Arthur Simone, M.D., Ph.D.	Medical Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Mike Theodorakis, Ph.D.	Chemistry Reviewer
Sara Stradley, M.S.	Regulatory Project Manager

Meeting Objective: To discuss the July 31, 2003 approvable letter and the questions in the September 12, 2003 meeting package.

General Discussion: After brief introductions, the teleconference focused on the questions from the September 12, 2003 meeting package. The deficiencies from the July 31, 2003 approvable letter are listed in italics.

Chemistry

Our evaluation of the design, manufacturing, in-process specifications and sampling, drug product specification, drug product immediate carton, and product complaints indicate the drug product is significantly deficient in quality and performance.

1. *Provide improvements in the design (e.g. tip cap design, syringe barrel wall strength), component manufacturing (e.g., dimensional controls and sampling plan), drug product manufacturing, manufacturing in-process controls (e.g. a stratified sampling plan), drug product specifications and sampling (e.g. 100% testing), and packaging (more protective imeediate container and shipping container) to reduce the types of customer complaints that are being reported for the drug product. These complaints include:*

   a. *Cracked syringes*
   b. *Syringes missing tip caps or leaking at the tip cap*
   c. *Syringes missing components*
   d. *Misalignment of backer plate*
   e. *Syringes leaking at piston*
   f. *Hard to push syringes*
   g. *Syringes damaged due to inadequate packaging*
   h. *Syringes cracked during use*

Discussion

The Sponsor stated that they reviewed the safety and quality aspects of this issue and reviewed the marketed products. Based on this information, the Sponsor stated that the syringes do demonstrate appropriate quality and performance. The Sponsor stated that this data was submitted to the Agency.

The Division stated that they reviewed the data submitted at the end of the review cycle and found that most complaints were in the United States but the Sponsor's denominator included global distribution. The Division expressed concern that the Sponsor was not capturing all of

the global complaints and stated that the rates should be recalculated based on the U.S. distribution and complaints only.

The Division stated that often a factor of ten is used to compare the rate of reported complaints versus the actual rate of problems. The Division reiterated that the Sponsor should capture complaints in the U.S. market and redo the calculation using U.S. distribution data and include the factor of 10 in the calculation. The Sponsor agreed to recalculate the data.

The Division expressed concern about the number of complaints and stated that it is unacceptable for the syringes to have the current rate of deficiencies such as leakage, cracking, and missing components. It is an unreasonable defect rate. A common industrial goal for the defect rate would be 1:1,000,000. A decrease to 1/10 –1/4 of the current defect rate may be acceptable depending on the particular defect.

The Sponsor stated they will focus on demonstrating to the Division that there are appropriate controls in place during the manufacturing of the syringes. The Sponsor will provide additional information on the manufacturing process.

2. *Provide a stratified sampling plan for in-process controls and drug product specifications based on the variability associated with the manufacturing (e.g. [redacted] beginning to end of process, etc.)*

Discussion
The Sponsor stated that sampling is described in the NDA. The Division questioned if [redacted] were used and what type of variability is seen between the filling stations. The Sponsor stated that they can provide the detailed sampling plan and supporting SOPs.

3. *Provide updated drug product specification.*

   a. *In order to increase assurance of the tip cap-syringe integrity, increase the minimum acceptance criteria for tip cap removal force*

   b. *Include a specification for UV absorbance of the saline solution.*

Discussion
The Sponsor stated that they had provided data to demonstrate what has been historically seen for the tip caps for the 50 and 125 mL syringes. The Sponsor stated they could not tighten the lower end but could reduce the high end. The Division stated that this request was related to the drop testing at the Division and the complaints of missing tip caps. The

Division stated that when they dropped three separate syringes, the tip cap came off 2 of the 3 syringes. The Sponsor stated that the sample syringes sent to the Division were not packaged according to their standard packing configuration for shipping. The Division acknowledged this may have been the case but nonetheless emphasized the importance of the tip cap staying in place when the product is dropped.

The Sponsor stated they do not have a good mechanism to tighten the lower limit. The Division stated that it is related to improving the integrity of the product. The specification should be set at a point where the lower limit of tip cap removal force is sufficiently high to prevent the tip cap from dislodging when the product is dropped. The Sponsor stated they will reevaluate obtaining a tighter limit, and examine the controls during manufacturing.

The Sponsor stated that the UV absorbance test was used during the development phase and felt it was no longer needed for commercial testing. The Division reminded the Sponsor that there was one lot that failed UV absorbance which indicated cross contamination. The Sponsor stated that they believed proper controls have been put in place to prevent this from occurring again. Nonetheless, the Division stated that this test was an appropriate control. The Sponsor stated they will include this in the specification/stability testing in the commercial product.

4. *Provide a revised drug product stability protocol.*

   a. *Include specifications for UV absorbance of the saline solution, fill volume, and particulate matter*
   b. *Include testing of samples stored in three orientations, i.e. horizontal, tip-cap up and tip-cap down.*
   c. *Include the storage conditions*
   d. *Include a functionality test with appropriately justified injectors for both the 50 mL and 125 mL syringes.*

Discussion
The Sponsor stated they will incorporate the UV absorbance into the specifications.

The Sponsor stated they check the fill volume every 15 minutes by taking the average weight of the container.

The Division stated they are concerned with the 100% visual inspection process. The Division stated that when the facility was inspected, the inspector noted that the line inspector was looking elsewhere. The Sponsor stated that the FDA inspectors distracted the line inspectors and noted that the FDA inspector did not make this a significant observation.

Nevertheless, the Division pointed out that 100% visual inspection may be a suboptimal approach to quality control particularly if the data show that many syringes are removed during inspection. This would illustrate that distraction of the inspectors had the potential to place many defective syringes into circulation. The Division questioned if the Sponsors have compared the defects identified in the complaints and the defects noted during 100% visual inspection. The Division suggested that the Sponsor determine ways to improve the process. The Sponsor replied that the stratified plan should provide answers to many of these issues.

The Division questioned how many syringes are being removed during the 100% inspections for defects. The Sponsor stated this is recorded in the batch records and if the limits are exceeded, the lot is not released. The Sponsor will provide more detailed information on the defects seen during the 100% inspections.

The Division stated that three orientations need to be included in the drug product stability protocol as part of a methodical and systematic testing of the drug product. The Sponsor stated this would triple the amount of work required. However the Division stated that the amount of work would be minimal.

The Division stated that the Sponsor should justify the selection of injectors used for functional testing in relation to the injectors listed as compatible in the labeling.

5. *Provide functionality testing of the drug product in the power injectors in which it is to be used and include information in the package insert to identify appropriately compatible power injectors.*

Discussion
The Division stated that the addition of new injectors should be a CBE-0 and not reported in the annual report. This process may change in the future depending on the results. The Sponsor agreed to submit the information in a CBE-0.

6. *Consultation with the Agency on the potential applicability of a new initiative in process analytical technology to the improvement of the quality of the drug product may be appropriate and is encouraged.*

Discussion
The Division stated the Center has been examining process analytical techniques and including more instrumental analysis. It is a relationship based on total quality of the product. The Sponsor should consider the new PAT technology (e.g., near IR) for potential application to their drug product.

Clinical

The Division asked for the status of the Sponsor's response to the Divisions' earlier request (letter dated August 26, 2003) for further information related to the potential air emboli with their product. The Sponsor stated that they were working on a response. The Division requested that the Sponsor provide reports of all of the adverse events associated with their approved pre-filled syringes, regardless of cause. The Sponsor agreed to provide this information.

Action Items

- Recalculate the complaint data using U.S. distribution data and include a factor of 10 for reporting bias in the calculation.
- Provide the detailed sampling plan and supporting SOPs.
- Further investigate the tip cap removal force.
- Add UV absorbance to the drug product stability protocol and to the drug product specifications.
- Include testing of three different orientations (i.e. horizontal, tip-cap up and tip-cap down), to the drug product stability protocol.
- Investigate and provide the defect rates and the type of defects noted at time of 100% inspection.
- Provide reports of all adverse events, associated with Mallinckrodt's approved pre-filled syringes, regardless of the cause.

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/s/

Sara Stradley
10/23/03 03:36:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-569

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

Attention: Edward Porter
Manager Regulatory Affairs

Dear Mr. Porter:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sodium chloride injection, USP, 0.9%.

We also refer to the submission dated July 28, 2003, containing a list of adverse event reports for similar syringes containing contrast media.

We have reviewed the referenced material and have the following comments and recommendations.

1. Provide analysis and tabulation of adverse events that might be related to air emboli, such as strokes, as well as events that clearly document air emboli. Events reported to the Optiray and Optimark NDA's, as well as those reported to the device manufacturer should all be reported.

2. Provide root cause analysis for the air embolisms reported above, identifying both the source of the problem, e.g., operator, syringe, device, and the nature of the problem, e.g., lack of training, defective product, misuse of device. Interviewing the original reporters of these adverse events may be informative in this regard.

3. Investigate the probable source(s) of the air in cases where large-volume air emboli were reported.

4. Explain the following statement in the Optistar LE Contrast Delivery System Operator's Manual (page 5-1-1): "Failure to remove the syringe after completion of a procedure may lead to an inadvertent injection of air." Explain the possible consequences of leaving spent syringes connected to the tubing.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
8/26/03 04:08:05 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-569

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

Attention: Edward Porter
Manager, Regulatory Affairs

Dear Mr. Porter:

We received your August 5, 2003, correspondence on August 8, 2003, requesting a meeting to discuss the action letter dated July 31, 2003. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.

Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].

Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm.

You did not indicate the type of meeting requested. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C. The meeting is scheduled for:

Date: September 16, 2003
Time: 10:00 a.m. EST
Location: teleconference
CDER participants: Bob Rappaport, M.D., Acting Division Director
Nancy Chang, M.D., Medical Team Leader
Art Simone, M.D., Medical Reviewer
Dale Koble, Ph.D., Chemistry Team Leader
Mike Theodorakis Ph.D., Chemistry Reviewer

Since this meeting is to clarify the deficiencies listed in the July 31, 2003, action letter, no background material will be provided for this meeting.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
8/22/03 09:07:03 AM

FDA Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville, MD 20857

Memo to File: Post-Action Letter

NDA (serial) Number	**021-569 (N-000-BM)**
Sponsor:	Mallinckrodt, Incorporated
Generic Name:	Sodium Chloride Injection, USP 0.9%
Proprietary Name:	[redacted]
Pharmacologic Class:	Intravenous Solutions
Proposed Indication:	**"50 mL syringe** Sodium Chloride Injection, USP 0.9% is indicated for use in flushing compatible intravenous administration sets and indwelling intravascular access devices [redacted] **"125 mL syringe** Sodium Chloride Injection, USP 0.9% is indicated for use in flushing compatible intravenous administration sets and indwelling intravascular access devices [redacted]
Submission Date:	July 28, 2003
Receipt Date:	July 29, 2003
Clinical Reviewer:	Arthur Simone, MD, PhD
Completion Date:	August 5, 2003

Clinical concerns raised during the review process of NDA 21-569, Sodium Chloride Injection, USP 0.9%, were based initially on theoretical risks of air emboli, breaks in sterile technique, and syringe/tubing disconnects. When we were provided with complaints and adverse event reports for similar syringes containing contrast media, we found that all the theoretical risks for the saline syringes had actually been reported with their counterparts. Of particular concern, were multiple reports of air emboli (from Sponsor's search and AERS database search), some with radiographic evidence of air in the heart. Most disturbing was that the volume of air in at least two cases was greater than 100 mL, which exceeds the volume of air in the syringe and deadspace of the tubing combined, assuming a full syringe and use of a single set of the manufacturer recommended tubing. In addition, there were reports of two patients who suffered strokes and one who had slurred speech immediately following the injections; all possibly sequella of embolic air events. Also reported were multiple cases of chest pain and dyspnea, hypotension, arrythmias, and myocardial infarction which might possibly be attributable to air emboli. These reports were from institutions in different states suggesting the problem is widespread, but clearly not site/user specific.

The following are the incidents identified by the Sponsor and through AERS database. Of note, all reported events were with Optiray syringes intended for power injection. No events were reported in association with use of hand held syringes only (Optimark, Optiray Pharmacy Bulk Package). In addition, a search of the AERS database for events associated with sodium chloride injection (N16677) and lactated ringer's injection (N16682) revealed no cases of air emboli.

Optiray 240

MK200202-0332-1	Stroke

Optiray 320

MK200201-0157-1	Air embolism
MK200209-0204-1	Air emoblism (estimated at 100mL)
14251-99M/1049	Air embolism (20-25mL) report in AERS (ISR 3419264)
13970-99M/730	Air embolism report in AERS (ISR 3347639)
MK200301-0239-1	Air embolism (130-140mL) report in AERS (ISR 4047615)

Optiray 350

14959-00M/2225	Air embolism

Sponsor should provide the following.

1. Analysis and tabulation of adverse events database for events that might be related to air emboli, such as strokes, as well as events that clearly document air emboli. Events reported to the Optiray and Optimark NDA's, as well as those reported to the device manufacturer should all be reported.
2. Root cause analysis for the air embolisms reported above identifying both the source of the problem, e.g., operator, syringe, device, and the nature of the problem, e.g., lack of training, defective product, misuse of device. . Interviewing the original reporters of these adverse events may be informative in this regard.
3. Investigation of the probable source(s) of the air incases where large volume air emboli were reported.
4. Explain the following statement in the Optistar LE Contrast Delivery System Operator's Manual (page 5-1-1): "Failure to remove the syringe after completion of a procedure may lead to an inadvertent injection of air." Explain the possible consequences of leaving spent syringes connected to the tubing.

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/s/

Arthur Simone
8/20/03 03:50:33 PM
MEDICAL OFFICER

Nancy Chang
8/26/03 10:52:50 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-569

DISCIPLINE REVIEW LETTER

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

Attention: Edward R. Porter
Manager Regulatory Affairs

Dear Mr. Porter:

Please refer to your September 30, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for sodium chloride injection, USP, 0.9%.

We also refer to your submission dated June 2, 2003.

Our review of the tradename section of your submission is complete. We are forwarding you comments from the Division of Medication Errors and Technical Support (DMETS). DMETS disagrees with the proposal to market sodium chloride injection, USP, 0.9% under the name [redacted] DMETS has the following comments.

1. The trademark Ultraject® should appear only on the labels and labeling to indicate the packaging configuration, a prefilled plastic syringe containing an injectable pharmaceutical, and not in conjunction with the proprietary name. The presentation of the trademark, Ultraject® on the [redacted] product is different from the other two currently marketed products (OptiMARK, Optiray). The presentation of the trademark Ultraject® as part of the proprietary name and to indicate a packaging configuration could cause confusion.

2. The use of the established name, 0.9% Sodium Chloride Injection, USP to identify the product in lieu of use of a proprietary name is acceptable. Other trademarks that indicate a packaging configuration are ABBOJECT®, Thermoject®, and ADD-VANTAGE®. A review of some container and or carton labeling with the ABBOJECT® and Thermoject® trademarks indicates these trademarks are not presented in front of or associated with the proprietary name. These trademarks only identify a packaging configuration. The introduction of proprietary names employing a common prefix or the same trademark in the proprietary name, e.g., [redacted] *Saline*, [redacted] *Dextrose* and [redacted] *Lidocaine*, increases the chance of confusion between products. This can be especially worrisome if the

first medication becomes known as [redacted] or if the most popular medication becomes known as [redacted], because this situation will increase the risk of a communication or selection error. If future products are approved with the trademark Ultraject® as part of the proprietary name then it could result in additional confusion and medication errors, due to sound-alike and look-alike issues.

3. In addition, DMETS has reviewed the container labels, carton labeling and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. DMETS recommends the inclusion of a statement in the "Assembly and Inspection" section

[redacted]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
7/18/03 01:09:11 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 14, 2003

To: Edward Porter	**From:** Sara E. Stradley
Company: Mallinckrodt, Inc.	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
Fax number: 314-654-3344	**Fax number:** 301-443-7068
Phone number: 314-654-6061	**Phone number:** (301) 827-7430

Subject: NDA 21-569/CMC preliminary comments

Total no. of pages including cover: 3

Comments: Please respond and provide the information requested below as soon as possible

Document to be mailed: ☐ YES ☑ NO

The following comments refer to the container closure system.

1. Provide a description of the manufacturing process for the container closure components. Include the description of any additional materials (e.g., mold release agents) that are used in the manufacture and appropriate safety qualification of these materials.

2. Provide the chemical composition and appropriate information to support the safety of the [redacted] adhesive and printing ink used for the drug product labeling.

3. Provide the analytical methods, S1131 and S1132 cited in Volume 1.6, page 6.39, used in the adhesive and ink migration studies.

4. Provide report 1176/02/028 referenced in Volume 1.4, page 4.294 for the Simulation of Stresses from Shipping and Handling study for the drug product.

   Our evaluation of samples of the drug product indicated a lack of tip cap/syringe integrity when the drug product was dropped (in it's carton); additional samples of the to be commercialized drug product in the commercial packaging were requested on July 11, 2003. This potential issue with tip cap/syringe integrity will have to be appropriately addressed.

The following comments refer to the drug product manufacturing process.

5. Provide a specification for the [redacted]

6. Provide a detailed description of the procedure used for [redacted] of the syringe components (barrel, plunger, and tip cap), including any in-process controls.

The following comments refer to the drug product specifications.

7. Tighten the acceptance criteria for tip cap removal force.
   Provide data and justification for the proposed acceptance criteria (e.g., including maintenance of container closure integrity and sterility). Also, see comment 4 above.

8. Provide lower acceptance criteria for maximum piston release force and piston travel force. Additionally, provide a minimum for piston release force. Provide data and justification for the proposed acceptance criteria (e.g., functionality and maintenance of container closure integrity and sterility).

The following comments refer to the post-approval drug product stability protocol.

9. Provide a revised drug product stability protocol as follows:

   a. Include storage of the drug product in three orientations; i.e., horizontal, upright, and inverted.

   b. Include the storage conditions.

   c. Include tests for particulate matter, fill volume, and UV absorbance.

   d. Include a test with the power injector for the 50 mL syringe.

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/s/

Sara Stradley
7/14/03 03:30:22 PM
CSO

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: February 20, 2003	**DUE DATE:** May 23, 2003	**ODS CONSULT #:** 03-0068

TO: Bob Rappaport, M.D.
Acting Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Sara Stradley
Regulatory Project Manager
HFD-170

PRODUCT NAME: [redacted] (0.9% Sodium Chloride Injection, USP) **NDA #** 21-569	**NDA SPONSOR:** Mallinckrodt Inc.

SAFETY EVALUATOR: Scott Dallas, R.Ph.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, [redacted] to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS does not recommend use of the proprietary name [redacted]
2. DMETS recommends the trademark Ultraject® appear only on the labels and labeling to indicate the packaging configuration, a prefilled plastic syringe containing an injectable pharmaceutical, and not in conjunction with the proprietary name.
3. DMETS recommends implementation of the labeling comment outlined in section III.
4. DMETS would concur with the sponsor's use of the established name, 0.9% Sodium Chloride Injection, USP to identify the product in lieu of use of a proprietary name.
5. DDMAC finds the proprietary name [redacted] acceptable from a promotional perspective.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

5 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 9

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/s/

Bob Rappaport
7/31/03 08:15:18 PM

Memo of 5/21/03 Teleconference

Re: N21-569 NaCl (sodium chloride injection USP 0.9%)

Sponsor: Mallinckrodt, Inc.

Attendees:

Mallinckrodt, Inc.

Ed Porter, Project Manager
Other Mallinckrodt personnel

FDA
Art Simone, M.D.
Scott Dallas, Reviewer, Medication Errors
Denise Toyer, Director, Regulatory Affairs, OPSS/DMETS
Victoria Kao, B.S., Regulatory Project Manager

During this teleconference, the Sponsor committed to providing the following information to the Agency in support of the review of this NDA:

1) Copy of the Optistar LE manual
2) Information on medication errors and extravazation potential for two currently approved and marketed injectable products, Optiray and OptiMARK
3) Clarification on the following topics as pertained to N21-569 NaCl prefilled syringe and Optistar LE

    a) Potential for medication errors
    b) Extravazation potential with respect to use in adult and pediatric population
    c) Potential for Use of Optistar LE with products other than Mallinckrodt products
    d) Injection control and the capability for program override
    e) Injection rates
    f) Back pressure protection

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/s/

Victoria Kao
6/20/03 06:17:42 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-569

Tyco Healthcare Mallinckrodt
Attention: Edward R. Porter
Manager, Regulatory Affairs
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Dear Mr. Porter:

We acknowledge receipt on January 27, 2006, of your January 26, 2006, resubmission to your new drug application for Sodium Chloride 0.9% USP Pre-Filled Syringe.

We consider this a complete, class 2 response to our July 31, 2003, action letter. Therefore, the user fee goal date is July 27, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, call Lynn Henley, Regulatory Project Manager, at (301)796-1979.

Sincerely,

{See appended electronic signature page}

Lynn Henley
Regulatory Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Lynn Henley
4/23/2006 03:16:30 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-569

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

Attention: Edward R. Porter
Manager, Regulatory Affairs

Dear Mr. Porter:

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: Mallinckrodt Inc.

Review Priority Classification: Standard (S)

Date of Application: September 27, 2002

Date of Receipt: September 30, 2002

Our Reference Number: NDA 21-569

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 30, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care
And Addiction Drug Products, HFD-170
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Victoria Kao, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Victoria Kao
Regulatory Project Manager
Division of Anesthetic, Critical Care
and Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Victoria Kao
4/15/03 02:32:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Mallinckrodt Inc.
675 McDonnell Blvd.
P.O. Box 5840
St. Louis Missouri, 63043

Attention: Edward R. Porter
Manager Regulatory Affairs

Dear Mr. Porter,

Please refer to the meeting between representatives of your firm and FDA on. The purpose of the meeting was for Mallinckrodt Inc. to obtain FDA's feedback on an NDA, if filed, based on presented data.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-827-7416.

Sincerely,

Victoria Kao
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: July 17, 2002 Time: 3:30pm-4:30pm

Location: Parklawn Building, Potomac Conference Room

Sponsor: Mallinckrodt Inc.

Drug Name: 0.9% Sodium Chloride Injection, USP

Type of Meeting: Industry Meeting

Meeting Chair: Bob Rappaport M.D., Deputy Division Director

Minutes Recorder: Victoria Kao, Regulatory Project Manager

Mallinckrodt	**Title**
Tom Coogan	Product Manager
Karen Coulson	Project Director
Brian Doty, Ph.D.	Pharmaceutical Science Director
Lisa Niebruegge	Team Leader/Sr. Research Chemist
Edward Porter	Manager Regulatory Affairs
FDA HFD-170 Division of Anesthetic, Critical Care and Addiction Drug Products	**Title**
Bob Rappaport, M.D.	Deputy Division Director
Nancy Chang, M.D.	Medical Team Leader
Mike Sevka, M.D.	Medical Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Tim McGovern, Ph.D.	Supervisor, Pharmacology and Toxicology
Tom Permutt, Ph.D.	Statistics Team Leader
Victoria Kao	Regulatory Project Manager
FDA HFD-510 Division of Metabolic and Endocrine Drug Products	**Title**
David Lewis, Ph.D.	Chemistry Reviewer
FDA Division of New Drug Chemistry II	**Title**
Eric Duffy, Ph.D.	Director
FDA HFD-805 Microbiology	**Title**
Stephen Langille, Ph.D.	Microbiology Reviewer

Meeting Objective:
To give the sponsor an assessment of the requirements for approval of a 0.9% Sodium Chloride, USP, NDA.

Background:
Mallinckrodt and the Agency had a teleconference February 5, 2002, during which issues surrounding the proposed indication and usage as well as the need to identify the appropriate FDA center to review the application were discussed. The Sponsor stated that the proposed indication would be focused on the product being used as a flush. The Agency then suggested that a Request for Designation be filled out and submitted to the Agency's Ombudsman.

In a letter dated May 3, 2002, the Office of the Ombudsman issued a letter designating CDER as the appropriate review center. Thus HFD 170 DACCADP will be the lead review division for NaCl syringe 0.9% application.

Mallinckrodt requested this meeting to discuss the upcoming NDA submission.

MINUTES:
Following introductions, and a presentation by the sponsor, the discussion moved to questions the sponsor posed in the meeting briefing package submitted May 29, 2002.

Chemistry, manufacturing and controls (CMC) information and questions

Q9.4 Does the FDA find the proposed regulatory specifications for Sodium Chloride Injection 0.9% USP acceptable?

A. The Agency had the following comments:

1. The tests/acceptance criteria which are included in the current USP monograph are acceptable.
2. Justification should be provided for the syringe performance test acceptance criteria.
3. "Report values" for specific leachables should be supported by adequate container suitability studies.

Q9.5 Does the FDA find the proposed stability protocol acceptable?

A. The Agency had the following comments:

1. Number of batches, storage conditions, and testing schedule are acceptable.
2. An alternate thermal cycling study should be done (just above freezing to ca. 50°C)
3. Justify sideways storage orientation as worst-case scenario
4. Justify acceptance criteria for syringe performance tests

The Agency had these comments regarding available stability data *vs.* proposed shelf life:

1. Amount of submitted data will not support a [redacted] expiry.
2. Statistical analysis/extrapolation is a review issue, and applicability cannot be determined prior to reviewing stability data.

The Agency made the following requests/comments regarding container qualification studies:

1. Adequate container/closure suitability studies should be provided.
2. Long-term container qualification studies of NaCl solution stored in proposed syringes may be supportive.
3. The test syringes should be labeled with the proposed labeling to allow detection/determination of potential extractables arising from the inks, solvents, adhesives, etc. in the labels.

In addition, the Agency made the following requests:

1. Simulated shipping studies should be provided.
2. Vibration studies should be conducted.
3. Drop testing should include tests for breakage, cracks, excess particulate matter, and syringe/piston performance changes in addition to checks for potential compromise of container/closure integrity due to shipping stress.
4. The Sponsor should submit letters of authorization for the following:

    a. Type III DMF's for
    b. Type III DMF's for [redacted]

Discussion

Dr. David Lewis indicated that the USP Physical Tests for Containers (USP <661>) were not sufficient to support chemistry, manufacturing and controls information for the proposed syringe. Two levels of testing should be performed: 1) USP Physico-chemical and Biological Reactivity Testing per <87>, <88>, and <661>, and 2) Container qualification studies, to be run on filled syringes. The second (qualification) study should address the issue of extractables and leachables migrating from the syringe into the contained solution. The Sponsor indicated that they may respond to these issues by providing real time stability data on levels of extractables found in filled syringes.

The Agency also suggested a study with heat-cold cycling to mimic conditions of moving from air freight to warehouse or truck to address the freeze thaw failures. The Sponsor should justify sideways storage orientation as worst case.

Nonclinical Pharmacology and Toxicology

Q. 8.6 Is it acceptable to only include data in Section 5 Nonclinical Pharmacology and Toxicology which is appropriate for qualification studies performed on extracts from the container closure system?

A. Qualification studies for extractables/leachables from the container closure system and syringe components, as needed, should be included.

Microbiology

The Agency conveyed the following comments to the Sponsor:

1. Sterilization validation for both presentations should be provided.
2. [redacted] for syringe components contacting the product (barrel, tip, rubber stopper, etc.) should be provided.
3. The Sponsor should clarify whether there would be a [redacted] if the second cycle fails.

Human Pharmacokinetics and Bioavailability

Q. 8.7 Mallinckrodt proposes to request a waiver of evidence of in vivo bioavailability or bioequivalence per 21 CFR 320.22 (b)(1). Does the FDA find it appropriate?

A. The sponsor's proposal to request a waiver of evidence of in vivo bioavailability or bioequivalence is acceptable.

Clinical

Q. 9.8 Mallinckrodt proposes that no animal or human information be provided. It is proposed that the application rely on the Agency's finding of safety and effectiveness of the previously approved product. Is this acceptable?

A. The Sponsor should submit the following:

1. A separate NDA for each drug product if the 50 ml syringe size is not intended for use with power injectors.
2. Postmarketing assessment of the adverse event safety databases associated with the use of power injectors and saline products administered by them. This should include a search of the literature.
3. A discussion of the commercially available power injectors that will be compatible with the proposed drug products. Clarification of marketing intent for only the Optistar pump.
4. An assessment of the safety of pressure injections.
5. Assurance that air will not be injected through use of the syringes proposed for marketing with the proposed delivery system.
6. The labeling should clearly and prominently state that these products are intended for one time use and for one patient.
7. Clarification of the contents of the marketed product, and the set-up for the product in actual use.

Discussion

Dr. Chang inquired whether the proposed syringes could fit other currently marketed injectors and the Sponsor responded that the syringes were not compatible with any other injectors – that adapters were specific. The OptiStar's maximum delivery pressure is 300 psi.

The Agency raised concern about possible introduction of air during delivery due to injector failure or otherwise. [redacted] a consultant to Mallinckrodt from [redacted], replied that he personally had not experienced any machine failures, but he had heard of few instances of such. The Agency asked the Sponsor to submit a summary of all potential risks associated with sodium chloride injection and the power injector, e.g., vascular injury, tears, introduction of air, etc.

General Regulatory Discussion

The Agency clarified that a 505(b)(2) submission for this product is appropriate. Dr. Rappaport suggested that the Sponsor pursue a separate meeting with Agency's User Fee staff to discuss the appropriate fee.

Minutes prepared by Victoria Kao, Regulatory Project Manager

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/s/

Victoria Kao
1/15/03 01:47:37 PM

SPONSOR MEETING ATTENDEES

Meeting Date: February 5, 2002

Location: Parklawn Building, Conference **Rm** 9B-45 (10:00-11:00 AM)

Sponsor : Mallinckrodt/Tyco Healthcare

Type of Meeting: Industry Telecon

If there are any questions, please contact Vietoria Kao 301-827-7416

Mallinckrodt Inc.	Title
Ron Brendel	Research Pharmacist
Dr. Brian Doty	Pharmaceutical Science Director
Lisa Niebruegge	Team Leader/Sr. Research Chemist
Edward Porter	Manager, Regulatory Affairs
Marge Moutray	Manager of Pharmaceutical Science/LIMS
Tom Coogan	Product Manager

Appears This Way
On Original

Memo of teleconference 2-05-02

Re: Sodium Chloride Injection 0.9% USP

Sponsor: Mallinckrodt/Tyco Healthcare

Attendees:

Mallinckrodt

Ron Brendel
Dr. Brian Doty
Lisa Niebruegge
Edward Porter
Marge Moutray
Tom Coogan

FDA

Cynthia McCormick, M.D.
Bob Rappaport, M.D.
Michael Sevka, M.D.
Naiqi Ya, Ph.D.
Dale Koble, Ph.D.
Suliman Al-Fayoumi, Ph.D.
Tim McGovern, Ph.D.
Kathleen Haberny, Ph.D.
Tom Permutt, Ph.D.

FDA responded to questions posed in background package dated December 4, 2001.

CMC Question 9.5

Does the FDA find the proposed regulatory specifications for Sodium Chloride Injection 0.9% USP acceptable?

FDA Response: Premature to decide which tests are not necessary at release, e.g. [redacted] Acceptance criteria in the drug product specification should not just report values, they should have numeric values as limits.

CMC Question 9.6

Does the FDA find the proposed stability protocol acceptable?

FDA Response: Stability testing should be performed at all three orientations or at the worst case orientation that may affect the functionality of the syringes. ***Sponsor was asked to consider unanticipated effects of excess [redacted] All three or validate one time only on development batches and NDA batches. Post AP may not rule out variation uncertainties.***

CMC Question 9.7

Mallinckrodt proposes filing the submission with [redacted] accelerated and real time stability data. Is this acceptable?

FDA response: It is fileable. However, this data will not support the proposed shelf life of [redacted] The amount of extrapolation assigned to the drug product will depend upon the stability data, but would not exceed [redacted]

Additional CMC Comments

- Any drug substance specifications used in addition to USP should be submitted as a regulatory specification. [redacted] ***Bulk USP is not clean (?) as injection. If supplier has more tests that are better than USP - get them in NDA.***

- DMF(s) or manufacturing and quality control information should be provided for the syringes. ***Sponsor agreed to provide in submission. Sister company will make them. Sponsor was asked what the regulatory status of empty syringes is. They are distributed under as devices. Everything in this syringe has been approved with another drug in CDER. LOA will be required in the submission.***

- A limit on [redacted] may be required depending on the use of the drug product.

- Test for the ink and/or adhesive on the container label that migrates into the drug solution should be performed. ***Heat migration testing will be needed. DMF for ink will be needed. Sponsor agreed to provide info on safety of ink and/or adhesive either by DMF or certification.***

- Acceptance criteria for syringe function tests, e.g. piston release force and piston travel force, should be justified. ***Function testing/acceptance criteria need to be correlated with indication/use.***

- Ruggedness of the drug product should be studied, e.g. shipping studies or simulation, drop testing, etc.

- Provide an explanation for the footnote in the stability protocol on page 31. ***Functional testing should be as appropriate and complete as possible.***

Sponsor then informed us that they have decided to revise the proposed indication

[redacted] so that it can better conform with CDRH guidelines for that of an indication applicable to an accessory to a device. They aim to submit the application to CDRH.

Memo prepared by Vicki Kao 2/11/02

FILING MEETING MINUTES

Meeting Type: Filing Meeting

NDA: 21-569.

Filing Method: To be filed as 505(b)(2). It will reference the Agency's past finding of safety and efficacy of NaCl.

Drug Product: Sodium Chloride Injection USP 0.9%; to be used with OptiStar pump.

NDA PDUFA Goal Date: July 30, 2003

Proposed Indication: For use in flushing compatible intravenous administration sets and indwelling intravascular access devices.

Sponsor: Mallinckrodt Inc.

Filing Meeting Date: November 20, 2002

Minutes Recorder: Victoria Kao, Regulatory Project Manager

Attendees:

Bob Rappaport, M.D., Acting Division Director
Dominic Chiapperino, Ph.D., Chemistry Reviewer
Dale Koble, Ph.D., Chemistry Team Leader
Art Simone, M.D., Medical Reviewer
Nancy Chang, M.D., Medical Team Leader
Tim McGovern, Ph.D., PharmTox Team Leader
Steve Langille, Ph.D., Microbiology Reviewer (Consult to HFD-805)
Victoria Kao, B.S., Regulatory Project Manager

A brief history on this product was presented: Mallinckrodt and the Agency had a teleconference February 5, 2002, during which issues surrounding the proposed indication and usage as well as the need to identify the appropriate FDA center to review the application were discussed. The Sponsor stated that the proposed indication would be focused on the product being used as a flush. The Agency then suggested that a Request for Designation be filled out and submitted to the Agency's Ombudsman.

In a letter dated May 3, 2002, the Office of the Ombudsman issued a letter designating CDER as the appropriate review center. Thus HFD 170 DACCAPD will be the lead review division for NaCl syringe 0.9% application .

The Agency and Sponsor met on July 17, 2002, to discuss an NDA submission for this product.

CHEMISTRY

The RLD for this product is N16-677, Baxter's 0.9% Sodium Chloride in a Plastic Container. The application also refers to N19710 for Optiray, an approved NDA for a separate Mallinckrodt prefilled [redacted] syringe product. The current NaCl syringe utilizes the same [redacted]

These questions were conveyed to the Sponsor on November 18, 2002 :

"1) For inspection sites, we were given site/facilities for drug substance and drug product and drug product manufacture. Please confirm that there are no additional sites where any of the following are performed:

a. Testing of finished product or bulk drug
b. packaging
c. labeling
d. sterilization

2) Please provide a statement to the effect that you are ready (or the date you will be ready) for site inspection."

As of the filing meeting, the Sponsor has not provided a response. However Dr. Koble confirmed that they would not be filing issue unless any of the sites will not be ready within 6 months of NDA submission.

3) Dr. Chiapperino will review the jackets again to make sure there is adequate performance data for a review of whether the syringe can withstand pressure during administration. There could be some data from N19710 for Optiray referred to earlier.

PHARMTOX

Dr. McGovern asked that the Sponsor be reminded that extractables need to be qualified as soon as possible. Dr. Chiapperino said that he has data on extractables in his portion of the application. They will confer and request additional data if needed. This will not be a filing issue.

CLINICAL

1) Dr. Simone pointed out that one reference article is untranslated from Japanese. Sponsor will be asked for translation.

2) There is some concern regarding the possible introduction of air bubbles in lines during administration by the OptiStar pump. THIS CONCERN WILL BE CONVEYED TO SPONSOR IN A SEPARATE LETTER WITHIN 14 DAYS AFTER THE FILING DATE.

Minutes prepared by Victoria Kao, Regulatory Project Manager, November 21, 2002.

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/s/

Victoria Kao
11/22/02 05:16:43 PM

CC: File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Ombudsman
5600 Fishers Lane (HF-7)
Room 14B-03
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

May 3, 2002

Edward R. Porter
Manager, Regulatory Affairs
Mallinckrodt, Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, MO 63134

Re: Request for Designation
Sodium Chloride Flush Syringes
Our file: RFD 2002.016

Dear Mr. Porter:

The Food and Drug Administration (FDA) has completed its evaluation of the above-referenced request for designation (RFD), which was received and filed by this office on February 25, 2002, and the additional information you provided by email on April 10, 2002. By mutual agreement, the review period for this RFD was extended to May 3, 2002.

The RFD covers Mallinckrodt's prefilled, single-use, [redacted] 0.9% sodium chloride injection in two syringe sizes, 50 mL and 125 mL. The products are designed to be used with Mallinckrodt's Optistar [redacted], a device that injects contrast agents into the vascular system during magnetic resonance imaging procedures.

[redacted]

[redacted]

You may request reconsideration of this decision within 15 days of receipt of this letter. See 21 CFR § 3.8(c). If you have any questions about this designation letter, please contact Suzanne O'Shea, of this office, at 301-827-3390.

Sincerely yours,

Steven H. Unger
Ombudsman