CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-569

MEDICAL REVIEW

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 Tel:(301)443-3741

DIVISION DIRECTOR'S ACTION MEMORANDUM

DATE: July 31, 2003

TO: File, NDA 21-569

FROM: Bob A. Rappaport, M.D.
Director (Acting)
Division of Anesthetic, Critical Care and Addiction Drug Products

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

Background:

NDA 21-569 for Sodium Chloride Injection, 0.9%, USP (50 and 125 mL pre-filled syringes) was submitted by Mallinckrodt, Incorporated on September 30, 2002. The application was submitted under 21CFR§505(b)(2) to DACCADP in CDER after the sponsor received a response to their Request for Designation from the FDA's Office of the Ombudsman.

The clinical portions of this application were reviewed by Arthur Simone, M.D., Ph.D. under the supervision of Nancy Chang, M.D. This memo will serve to summarize their review, as well as the reviews written by the other members of the team: Timothy McGovern, Ph.D., pharmacology/toxicology; and, Michael C. Theodorakis, Ph.D., chemistry, manufacturing and controls (CMC) under the supervision of Dale Koble, Ph.D.

The sponsor's proposed indications for these products read as follows:

50 mL syringe

Sodium Chloride Injection, USP 0.9% is indicated for use in flushing [redacted]

125 mL syringe

Sodium Chloride Injection, USP 0.9% is indicated for use in flushing [redacted]

There were no clinical trials submitted in support of this application. The sponsor did submit literature in support of the efficacy and safety of these products. In addition they referenced the Agency's findings of safety and efficacy for NDA 16-677 (Sodium Chloride, 0.9% in Plastic Container). However, the proposed indications for the products in this submission are different from the indication for the reference-listed product.

Efficacy:

The clinical review team has determined that there is sufficient evidence in the literature to a support extrapolation of efficacy in adults from similar syringes filled with normal saline solutions.

Safety—Nonclinical:

There were no nonclinical safety studies performed in support of this submission, and Dr. McGovern has concluded that there are no nonclinical safety issues relevant to clinical use. The sponsor did conduct a series of biocompatibility studies for [redacted] that is also a component of several approved pre-filled syringes. Those studies did not demonstrate a potential for adverse events.

Safety—Clinical

Dr. Simone has described four potential clinical safety concerns that could be associated with use of these products.

1. The syringes contain a small but clinically significant quantity of air. Use in a mechanical injector that does not detect air and does not stop injection when air is detected could result in morbidity, and possibly mortality should the injection be delivered into the circulation.

2. Delivery of up to 100 mL or more of saline, along with significant volumes of contrast media, over a short period of time could cause significant physiological

derangements, particularly in younger pediatric patients, e.g., in a 20 kg child, the 100 mL would represent 10% of the total blood volume.

3. Extravasation of these volumes of saline, particularly in infants and smaller children, could result in compartment syndromes at peripheral access sites.

4. The high pressures needed to generate the proposed flow rates could be sufficient to cause tubing to disconnect, potentially resulting in blood loss through the vascular access, air emboli, loss of sterility, and loss of injectate. The 50 mL syringe has a [redacted] and the 125 mL syringe comes with a special adapter that locks the tubing to the syringe, helping to minimize the risk.

Dr. Simone has proposed that appropriate labeling, including warnings, instructions, and appropriate dosing/volume and/or patient population restrictions, could sufficiently reduce the risks to a clinically supportable level. In addition, specifically in regard to air emboli, he has suggested the addition of an "Air Check" key that must be pressed in order to make the "Start" key active on all compatible and recommended power injectors. Some of the compatible injectors currently marketed already have this safety feature.

Chemistry, Manufacturing and Controls:

The Office of New Drug Chemistry has determined that from a risk management perspective a facility inspection for the site of sodium chloride drug substance manufacture is not required.

The CMC review team has delineated a number of concerns regarding the quality of these products:

1. The design and performance of the attachment of the tip cap to the syringe lack robust integrity. The team performed drop tests of the syringes in their immediate cartons from a height of approximately 4 feet. The majority of the samples lost their caps.

2. The design and composition of the immediate carton for the syringes provides inadequate protection. The sponsor has not provided data on the protection (container closure integrity) provided the syringe by the immediate carton.

3. No data has been submitted in support of the portions of the label that address functional compatibility of the syringes with the stated power injectors.

4. Drug product complaint data for Mallinkrodt's similar Optiray and Optimark products reveal:

    a. More than twelve reports for missing, leaking or damaged tip caps.
    b. More than ten reports for cracked syringes delivered to customers.
    c. Several reports of damaged immediate cartons delivered to customers.
    d. Multiple reports of leaking syringes noted by customers upon delivery.

e. More than 45 reports of syringes cracking during use.
f. Reports of missing components, defective backer plates and sticking or hard to push plungers.

5. Product complaints averaged approximately 150 per year.

Dr. Koble, in his Executive Summary Memo, has concluded that:

> The drug product deficiencies are of a sufficient frequency and type that from a chemistry, manufacturing and controls perspective an "approvable" action is recommended.

In addition, Dr. Koble's memo also suggests that the sponsor should:

1. Provide an appropriate sampling plan for in-process controls and drug product specifications.

2. Provide updated drug product specifications for minimum acceptance criteria for tip cap removal force and for UV absorbance of the saline solution.

3. Provide a revised drug product stability protocol including specifications for UV absorbance, testing of samples in three different orientations, storage conditions, and a functionality test with appropriately justified power injectors for both syringes.

4. Provide functionality testing of the products in the Power Injectors in which the are to be used, identifying adequately tested and appropriately compatible injectors in the label.

5. Consult with the Agency regarding the potential applicability of our new in process analytical technology initiative to your product.

Nomenclature:

The sponsor initially requested the tradename ' [redacted] This proprietary name was reviewed in consultation by the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety. They found that the trademark "Ultraject®" appeared in the labels and labeling of other Mallinckrodt syringe products specifically to indicate the packaging configuration of a prefilled plastic syringe containing an injectable pharmaceutical, and that it was not associated with the proprietary name. DMETS recommended that this product maintain that paradigm in order to provide consistency and reduce the risk of medication errors. The sponsor has agreed to this change.

Comments:

The sponsor has provided sufficient information to establish the efficacy and safety of their products when used according to the current draft labeling. This draft has been modified from the sponsor's original submission and has been found to be acceptable by the sponsor. The labeling now provides sufficient warning and precaution language to reduce the risk of volume overload, fluid extravasation, and air embolus to levels that would be associated with misuse of similar products. Further attempts to bring the incidence of these adverse events towards zero will require major changes in the manufacturing of these products and/or more extensive controls on behavioral factors affecting use.

The use of the 125 mL syringe in a power injector in pediatric patients remains of concern. Fluid overload resulting in significant morbidity remains a possibility in that setting. Thus, the labeling has been changed to incorporate appropriate warnings and to delineate the safe use of these products in the pediatric patient population. The sponsor has concurred with these changes.

The extensive product quality deficiencies outlined above raise concerns that clinically significant complications could occur at unacceptable rates in association with these products. For example, loose tips and cracked barrels could result in loss of sterility with potential for sepsis. Syringes cracking during use could result in blood loss, loss of sterility, or complications associated with delayed or repeated procedures. While additional cautions and warnings have been added to the labeling, the extensive nature of these problems could result in unacceptable morbidity in the clinical setting. These product quality deficiencies must be corrected prior to marketing.

Other CMC deficiencies have been enumerated above. A letter outlining the product quality and general CMC deficiencies will be forwarded to the sponsor.

Action: **Approvable**

cc.Division File: NDA # 21-569, A. Simone, N. Chang, R. Meyer
ec.DFS: NDA # 21-569 (N000)

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/s/

Bob Rappaport
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MEDICAL OFFICER

Division Director's Action Memorandum

NDA:	21-569
Product:	Sodium Chloride Injection, 0.9% (50 and 125 mL pre-filled syringes)
Sponsor:	Mallinckrodt
Today's date:	July 27, 2006
Submission date:	January 27, 2006 (a response to the July 31, 2003 action letter)
Author:	Dwaine Rieves, MD Deputy Division Director/Acting Division Director

Dwaine Rieves 7-26-06

1. Overview:

This NDA submission was a response to an approvable letter issued in 2003. The product consists of two presentations (50 mL and 125 mL) of saline for injection. This presentation is specifically for use in the administration of intravenous contrast agent. The approvable letter from 2003 cited two main areas of concern: CMC deficiencies and the need for revised labeling. These deficiencies have been resolved and the application is approved. Listed below is a brief summary of the major review findings. I concur with all reviewer findings and the drug approval.

2. Clinical:

Dr. Louis Marzella performed the review of the clinical information and proposed labelling. He concurs with the approval. The supportive clinical safety and efficacy data were previously reviewed (in 2003) by Dr. Arthur Simone and were determined to be acceptable.

3. CMC:

Dr. Mark Sassaman performed the review of the response to the CMC deficiencies and determined that the sponsor has sufficiently resolved all issues cited in the 2003 letter. Dr. Sassaman regards the supplied information as acceptable for approval.

4. Microbiology:

Dr. Stephen Langille revised the microbiology information (supplied and reviewed in 2003) and determined that the information was acceptable to support the approval.

5. Facilities:

A facilities inspection was completed on July 25, 2006 and the inspection findings supported the approval.

6. Pharm/Toxicology:

The pharmacology and toxicology information was supplied and reviewed in 2003 by Dr. Timothy McGovern. The review found the information sufficient for approval.

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/s/

Rafel Rieves
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MEDICAL OFFICER

June 29, 2006

Division of Medical Imaging and Hematology Products

Clinical Review

NDA# 021-569
Sponsor: Mallinckrodt, Incorporated
Generic Name: Sodium Chloride Injection, USP 0.9%
Proprietary Name: [redacted]
Pharmacologic Class: Intravenous Solutions
Reviewer: Louis Marzella M.D., Ph.D.

Material Reviewed
Product's Package Insert, Package inserts of competitor products, medical officer review of original NDA. The pending consultation request for review of trade name is noted.

Background
This NDA submission consists of the sponsor's response to an approvable letter issued on in July, 2003. The original NDA was submitted as a 505(b)(2) request with the basis for clinical safety and efficacy supported by published literature. The original CMC and medical team determined the application could not be approved until certain items were addressed. These items are noted in the attached "approvable" letter and generally relate to manufacturing issues. CMC review of this 2006 submission has determined that the non-label-related items are sufficiently addressed. This review document pertains to the revised product labeling; specifically determining whether the proposed labelling addresses the labelling items described in the July, 2003 approvable letter."

Recommendations
The reviewer recommends the following changes to the package insert for the present product.

1) Update of the safety information in the label to include the observations described in the MO review of the original NDA.
2) Changes to the format of the warnings and precautions section to add new precautions, add headers to make information more prominent, decrease redundancy.

See attached label review.

10 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2

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/s/

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MEDICAL OFFICER

George Mills
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MEDICAL OFFICER

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

REVIEW AND EVALUATION OF CLINICAL DATA

NDA#	**021-569**
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 [redacted]
Submission Date:	September 30, 2002
Clinical Reviewer:	Arthur Simone, MD, PhD
Completion Date:	July 30, 2003

Primary Clinical Review

1. Recommendations

From a clinical perspective, sufficient information has been provided by the Sponsor to support the safety and efficacy of the [redacted] when used as an intravascular flush in adults. Data demonstrating safety and efficacy in pediatric populations is limited. Use of this product in the pediatric population should be limited to those patients who will be able to tolerate the volumes of fluid potentially administered by this product and expected to be administered in the course of their procedure.

2. Summary of Clinical Findings

2.1 Efficacy

The Sponsor has submitted this NDA as a 505(b)(2) application citing the FDA's findings of safety and efficacy in Sodium Chloride 0.9% In Plastic Container (NDA 016-677) and findings in the literature. There are two indications for the Reference Listed Drug: a source of water and electrolytes, and a priming solution in hemodialysis procedures. The proposed indication is different from that of the Reference Listed Drug and other NDAs for Sodium Chloride Injection USP 0.9% in that the [redacted] is intended for use in contrast media power injection devices and specifically designed to be the only prefilled syringes of saline flush solutions for use with Mallinckrodt power injectors. There were no clinical trials conducted in support of this NDA.

Preservative-free normal saline solutions have a long history of use by intravenous administration for fluid resuscitation, delivery of pharmacologically and chemically compatible medications, and maintenance of venous access patency. Similarly, there is a substantial history of use of preservative-free normal saline administered intra-arterially to maintain the patency of arterial access and to flush compatible medications, particularly radio-opaque dyes, into the arterial system. The medical literature is replete with articles that support the efficacy of normal saline used in each of these circumstances in adults.

Provided the medications to be injected and then flushed by the [redacted] are compatible both physically and chemically with normal saline, there is sufficient evidence in the literature to support a finding of efficacy.

2.2 Safety

As with efficacy, there is ample literature to support the safety of preservative-free normal saline for flushing medications with which it is physically and chemically

compatible through vascular access tubing and devices. There are safety concerns related to the mechanics by which such flushing of medications occurs and much of the literature provided by the Sponsor was selected to address those concerns. Below, each safety issue is presented along with the response of the Sponsor.

1. **Air Emboli**. The [redacted] contain small but clinically significant amounts of air, approximately 1 mL in the specimens we received. Use in a mechanical injector that does not detect air and stop injection when air is detected can result in significant morbidity and possible mortality particularly if the injection is made on the arterial side of the circulation. In fact, the Sponsor has submitted postmarketing adverse event data, for similar syringes containing contrast media that include at least two reports of air injection in one year associated with the use of these syringes, one of which resulted in permanent neurological sequellae.
Proposed warnings on the package, syringe label, and package insert regarding this risk are appropriate and will help to minimize inadvertent injection of air. Use of the syringes in compatible Mallinckrodt injectors has the added benefit that the user must press the "Air Check" key to make the "Start" key active. However, considering the availability of the technology and the severity of the outcomes of air emboli, it would seem that the safest approach might be the combination of warnings, "air check" keys, minimizing or eliminating air from the syringes, and injection devices that allow for purging of air as well as its detection and the stoppage of infusion once it is detected.

2. **Fluid Overload**. The proposed products are large volume syringes that are intended for the delivery of 100 mL or more of saline over a short period of time. Flush syringes containing smaller volumes of saline have already been approved for similar indications. At least one of the devices for which these syringes are to be used also provides for a "Drip Mode" used to maintain patency of the vascular access. This is done by interrupting the minimum drip rate of 0.1 mL/sec (360 mL/h) at timed intervals to deliver an operator set volume per unit of time when the device is not being used to flush contrast media into the vascular system. Thus, this fluid volume needs to be considered in addition to that of the injected contrast media and saline flush when determining the overall fluid load for the patient. The typical saline flush, used in medical practice, varies from 10-60 mL, and the volume of the injected contrast media is variable often depending on the procedure and the patient's weight. In some patients, particularly infants and small children, the volumes administered: contrast media, flush and "drip mode," may be substantial and may cause physiological derangements related to fluid overload. The label will need to reflect the typically administered volumes associated with the intended use of the [redacted] and should provide data-based guidance on minimizing the overall fluid load to the patient. The Sponsor is currently addressing this issue [redacted]

3. **Extravasation**. Although osmotic damage and direct cellular toxicity are more of a concern with extravasated contrast media than normal saline, ischemia secondary to impaired circulation and mechanical compression injuries to nerves and other tissues may result from large volumes of extravasated normal saline. This is particularly true in smaller patients such as infants and young children in whom the flush volumes combined

with drip flows could be sufficient to cause compartment syndromes at peripheral vascular access sites. The relatively high pressures achieved by the power injectors may also contribute to this risk.
The Sponsor has provided literature suggesting that the incidence of extravasation is relatively low, < 1%, and has indicated that the volumes to be injected for flushing medications are adjustable on the pumps compatible with the [redacted] These two factors coupled with appropriate precautions, dosing and patient selection information in the label should reduce the risk associated with normal saline extravasation to a point where it is outweighed by the advantages of using the product.

4. **High Injection Pressures**. High pressures are needed to generate flows of 10 mL/sec, up to 200 PSI at the syringe plunger. Much of this pressure is dissipated in ejecting solution from the syringe, however, pressure in the tubing, especially if the vascular access device is of small bore, can be sufficient to cause disconnects at the any interconnection point from the syringe to the vascular access device. Risks associated with such disconnections include blood loss through the vascular access – especially with arterial lines, air emboli – particularly with central venous access, break in sterility with associated risk of infection, and loss of injectate with associated loss of efficacy for the procedure, i.e., contrast media is not fully or properly flushed requiring repeat injection with the inherent risks thereof.
To minimize these risks, the Sponsor's 50 mL syringe has a [redacted] and the 125 mL syringe comes with a special adapter which locks the tubing to the syringe. Appropriate labeling to warn of the risk of disconnect and thus the need to use appropriate tubing and the adapter, with the 125 mL syringe, along with clear and easy to follow instructions for using the adapter should adequately minimize this risk.

2.3 Other Relevant Information

The sponsor provided a summary of the product complaints and adverse events reported between January 2001 and December 2002 for the Optiray 125 mL power injector syringe and the Optiray and OptiMARK hand held syringes. These syringes are similar to those contained in the current application, but they are pre-filled with contrast media rather than saline. During that time period, the Sponsor states at total of [redacted] syringes were distributed worldwide.

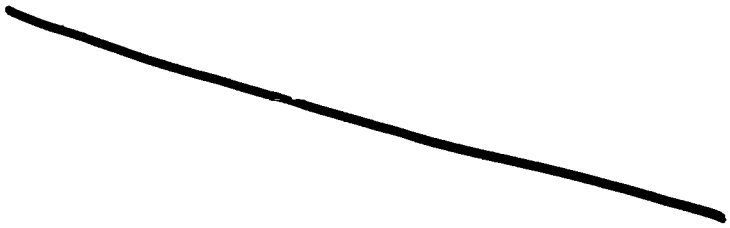
There were 291 product complaints during that time, the vast majority of these were "syringe tip cap – fell off or missing" and "cracked/leaking [redacted] before use." There were also a significant number of reports of "syringe burst during injection." The first two complaints raise concerns regarding sterility and the risk of infection if a damaged product goes undetected and is used on a patient. The last complaint both emphasizes the concerns stated in the safety section and raises the additional safety concerns of break in sterile technique and blood loss through the vascular access – particularly arterial access.

There were 331 adverse event reports total for the Optimark, and Optiray 240, 300, 320, and 350 during 2001 some of which suggest that the concerns raised regarding the safety

of the [redacted] are more than just theoretical. Among these were two patients who suffered strokes and one who had slurred speech immediately following the injections, raising the concern of air emboli expressed in the Safety section above. There were multiple cases of chest pain and dyspnea, hypotension, arrythmias, and myocardial infarction which might possibly be attributable to air emboli or product contamination, as well as one case of chest pain where the patient "was injected with ... air into the heart" which was found by roentgenography and had to be evacuated. In addition there were at least two cases of sepsis that might possibly be attributable to product contamination, although defective syringes were not reported in association with these cases.

2.4 Dosing

The proposed label indicates that typical normal saline flush volumes following contrast agent administration are 10 to 25 mL per injection at rates not to exceed 10 mL/sec, and that typical infusion rates for drip volumes used to maintain patency of vascular access are in the range of 0.5 to 1 mL/min.



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