CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-569

APPROVABLE LETTER

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

We acknowledge receipt of your submissions dated November 8, 2002; January 31, February 27, May 8, 20, and 22, June 2, and 10, July 9, 11, 17, 18 (2), 23, 24, and 28 (2), 2003.

We also acknowledge receipt of your submission dated July 29, 2003. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following deficiencies.

Our evaluation of the design, manufacturing, in-process specifications and sampling, drug product specifications, 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 immediate 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 the backer plate

e. Syringes leaking at the piston

f. Hard to push syringes

g. Syringes damaged due to inadequate packaging

h. Syringes cracking during use

2. Provide a stratified sampling plan for in-process controls and drug product specifications based upon the variability associated with the manufacturing (e.g.,

3. Provide an 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.

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 power injectors for both the 50 mL and 125 mL syringes.

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.

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.

In addition, you must submit draft labeling for the drug. The labeling should be identical in content to the enclosed draft labeling (text for the package insert, immediate container and carton labels).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Sara 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

10 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Approvable Letter # 1 / 1

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/s/

Bob Rappaport
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