CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-175

CORRESPONDENCE

N/S Nighswander

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 11 2000

NDA 21-175

INFORMATION REQUEST LETTER

Office of the Surgeon General
Department of the Army
Attention: Dr Ronald E. Clawson
Project Manager
MCMR-RCQ-RA
504 Scott Street
Fort Detrick, MD 21702-5012

Dear Dr Clawson:

Please refer to your December 1, 1999 new drug application for NAADS (atropine/pralidoxime multi-chamber auto-injector) injection (multi-chamber auto-injector).

We also refer to your submission dated March 27, 2000.

We are reviewing the chemistry section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. We note that your release specifications for the atropine component of the NAADS list the unknown, unidentified impurities as [redacted]. We further note that your stability protocol and reports list nine (9) individual unknown impurities identified only by their relative retention times (RRT), with the [redacted]. We also note that in the reported period of six (6) months of stability study only one of these potential unknown impurities [redacted] reached the quantifiable level. In addition we observe that the levels of [redacted]. We find the above mentioned specifications lacking scientific justification since none of the proposed levels was neither observed nor toxicologically qualified. Please resubmit the release and stability specifications to conform to the existing drug purity and stability guidelines. Further, please determine and provide the structure of any impurity/degradant that exceeds the level of [redacted] in the drug product.

If you have any questions, call Robbin Nighswander, R.Ph., Regulatory Management Offficer, at (301) 594-2850.

Sincerely,

4/11/00

/S/

Maryla Guzewska, Ph.D.
Chemistry Team Leader, Neurology Drugs for the Division of Neuropharmacological Drug Products, (HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

(b5)

8 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

MERIDIAN
MEDICAL TECHNOLOGIES

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FOR MEDICINE

18 December 2001

Dr. George Schieferstein
USAMMDA
622 Nieman Street
Frederick, MD 21702-5009

Dear George:

MMT has made the following changes, requested by the FDA, to the ATNAA labeling based on input from Mr. Robbin Nighswander.

1- Changed the wording for storage on:
   A: The Injector label
   B. The package Insert
   C: Interior Carton label
   D: Exterior Carton Label

2-Changed Injector label as follows:
   A: Include First three pictograms from revised instruction card and package insert.
   B. Pictogram 3 shall have the words: **10 SECONDS**

3-Modified the chemical description of atropine on the package insert.

4- Correct the empirical formula for pralidoxime

Attached is copy of the package insert with above revisions as well as a draft copy of the changed autoinjector label.

Thank you for all of your help in this matter.

Respectfully,

Thomas Freund
Manager, Meridian Regulatory Affairs

Meridian Medical Technologies
10240 Old Columbia Rd.
Columbia, MD 21046

410 309 6830 fax 410.309 1475
www.meridianmeds.com

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

NEW CORRESP

REPLY TO
ATTENTION OF:

February 10, 2000

NC

ORIGINAL

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application for Atropine and Pralidoxime Chloride Injection (Nerve Agent Antidote Delivery System) (NDA No. 21-175)

Robbin Nighswander, R.Ph
Division of Neuropharmacological
Drug Products (HFN-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike, Room 4049
Rockville, Maryland 20852-1420

Dear Mr. Nighswander:

Enclosed is an additional copy of volume 1.15 and volumes 1.23 through 1.27 as requested in a telephone conversation on February 4, 2000.

The New Drug Application for the Nerve Agent Antidote Delivery System (NDA No. 21-175) was filed with the Agency on December 6, 1999. The Agency inquired in a letter of January 6, 2000 about the status of pediatric studies required by 21 CFR 314.55. The Army requests a full waiver from pediatric assessments in accordance with 21 CFR 314.55(c)(2) because the multichambered autoinjector will be for military use only and will not be used in a pediatric population.

On January 7, 2000 the Agency informed Dr. Ronald Clawson that the name "NAADS" would be referred to the Agency's Naming Committee for review. For your information, the appropriate military designation for the multichambered autoinjector has been changed to "Antidote Treatment - Nerve Agent, Autoinjector."

Please contact Ms. Kathie Mantine at 301-619-2809 (alternate 7550), facsimile 301-619-7803, or electronic mail kathie.mantine@det.amedd.army.mil for regulatory questions. The point of contact at the U.S. Army Medical Materiel Development Activity for technical questions is Dr. George Schieferstein at 301-619-7843.

Sincerely,

Julie K. Zadinsky
Colonel, Army Nurse Corps
Deputy Chief of Staff for
Regulatory Compliance and Quality

Enclosure

Copies Furnished (wo/enclosure):

U.S. Army Medical Materiel Development Activity, ATTN: MCMR-SGS
U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

DEC 01 1999

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality

SUBJECT: New Drug Application for the Nerve Agent Antidote Delivery System, Volumes 1-27 (NDA No. 21-175)

Russell Katz, M.D.
Division of Neuropharmacological
Drug Products (HFN(120))
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike, Room 4049
Rockville, Maryland 20852-1420

Dear Doctor Katz:

The U.S. Army Office of The Surgeon General (OTSG) is submitting in duplicate, in accordance with Section 314.50 of Title 21 of the Code of Federal Regulations (21 CFR 314.50) and Section 505 (b) (2) of the Federal Food, Drug, and Cosmetic Act, a New Drug Application (NDA) (Form FDA 356h) for the Nerve Agent Antidote Delivery System (NAADS) (enclosure 1). The NAADS will deliver atropine (2.1 mg in 0.7 ml) and pralidoxime chloride (600 mg in 2 ml) from one autoinjector, through a single needle for self-aid and buddy-aid of service members who have been exposed to organophosphorous nerve agents.

Request for Priority Review

Currently, these antidotes are available in separate autoinjectors. The Atropen® (NDA 17-106) and Pralidoxime Chloride Injection (Combopen®, NDA 18-986) are approved by the Food and Drug Administration (FDA) (Agency). Meridian Medical Technologies, Inc. (MMT), our co-development partner and ultimate manufacturer, holds these NDAs. In a combat situation where a service member requires immediate treatment for exposure to nerve agents, the NAADS will deliver the needed antidotes quickly and efficiently by a single injection rather than the two separate injections which must be administered using the current system. The current system requires additional time to administer the antidotes since each drug must be given by a separate injection. To a potentially nerve-agent impaired service member, the decreased steps required to deliver the antidotes using the NAADS may provide a significant advantage. It is this ability of the NAADS to dramatically improve the protection offered to service personnel in life-threatening circumstances that leads the Army to request priority review of this application.

Agency Concurrence on 505(b)(2) Submission

At the April 9, 1999 pre-NDA meeting held between the Agency, the U.S. Army Medical Materiel Development Activity, and MMT, a topic of discussion was the higher dose of atropine delivered by the NAADS compared to the Atropen® (enclosure 2 provides the FDA's meeting minutes). Based upon information provided during that meeting, it was determined that there were no safety concerns associated with the increased atropine dosage. Supporting data is included in this application. During the meeting it was confirmed that this application could be filed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Therefore, in accordance with 21 CFR 314.54, this application does not include a Nonclinical Pharmacology and Toxicology Section, or a Statistical Section. In addition, there is no other pertinent data presented for section 21 CFR 314.50(g).

Also, at the April 9, 1999 meeting, Agency representatives inquired whether studies had been performed to demonstrate successful injection of the antidotes through clothing used to protect service members against chemical exposure. As a result of that question, a laboratory study was conducted which demonstrated that the NAADS completely delivered the antidotes through multiple layers of protective clothing without damage to the needle. That study is presented in the NDA (beginning on page 2024). Another inquiry was whether the service member was able to distinguish the NAADS from the Convulsant Antidote for Nerve Agent (anticonvulsant autoinjector--Diazepam) in the dark. A test with service members during the fall of 1999 will address this question and a report will be provided to the Agency.

Request for Waiver of "Rx only" Labeling

Finally, during this meeting, we communicated our intent to request a waiver of the "Rx only" statement from the NAADS labeling. This product will not be distributed to service members under a physician's prescription, but will be distributed to potentially large numbers of service members deployed to war zones or theaters of operations where they would be potentially at risk of nerve agent attack. Including "Rx only" on the label will be misleading and could cause unnecessary concern and confusion to medical personnel and service members being issued the NAADS.

Organization of Submission

The complete submission is organized into 27 volumes as follows:

a. Volume 1.1 contains the Application Form (FDA Form 356h), cover letter, Index (item 1), labeling (item 2), Overall Summary (item 3) and Letters of Cross Reference.

b. Volumes 1.2-1.11 contain the Chemistry, Manufacturing, and Controls Information (item 4.A).

c. Volumes 1.12-1.13 contain the Methods Validation Package (item 4.C).

d. Volume 1.14 contains Statements and Certifications including the Environmental Impact Assessment, Samples Statement (item 4.B), Patent Certification (item 14), Field Copy Certification (item 17), and four copies of the draft labeling (item 2).

e. Volumes 1.15-1.27 contain the Human Pharmacokinetic and Bioavailability information (item 6).

To aid in the review, additional review copies of volumes 1.6, 1.7, and 1.8 containing [redacted] manufacturing information are provided for the microbiologist's review. We have also provided extra copies of volumes 1.9 and 1.10 for the Center for Device and Radiological Health Review. Four complete sets of volumes 1.12 and 1.13 containing methods validation have been provided. Finally, five additional copies of volume 1.1 are provided.

We certify that this NDA does not include the services of any persons, debarred clinical investigators, or associated facilities under subsections 306 (a) or (b) in the conduct of any of the studies in this submission.

Finally, we look forward to cooperating with you and your staff in the review process in any way possible. Please do not hesitate to contact Dr. Ronald E. Clawson, Project Manager, Pharmaceutical Systems Division, U.S. Army Medical Materiel Development Activity, at 301-619-2051 if you have any questions or requests regarding this filing. As always, we want to cooperate fully with the FDA in all matters of mutual concerns.

Sincerely,

John S. Parker
Major General, Medical Corps
Commander

Enclosures

Copy Furnished (wo/enclosures):

U.S. Army Medical Materiel Development Activity, ATTN: MCMR-UMP