

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-414

CORRESPONDENCE



DMF _____

9

Roche Products Limited
Attention: Mr. Jeremy Brace, Dept. of Regulatory Affairs
40 Broadwater Road
Welwyn Garden City
Hertfordshire AL7 3AY
ENGLAND

Dear Mr. Brace:

Your letter dated May 10, 1996 authorizes us to reference Drug Master File _____ for Pyridostigmine Hydrobromide Tablets 30 mg, USP in support of the Office of the Surgeon General, Department of the Army's drug product application, NDA 20-414. Your communication dated May 1996 was reviewed.

The information provided in the DMF has been reviewed in support of the Office of the Surgeon General, Department of the Army's NDA application and the following additional information is requested:

1. We request that a limit for total impurities for the new drug substance (n.d.s.), pyridostigmine bromide, be added to your acceptance specifications for this material.
2. All compendial analytical methods and procedures should be those of the USP. Please replace your _____ method with the USP method. Please specify which method is used for determination of _____ this should also be the USP method.
3. The names and codes for the impurities have been reversed in the illustration on page 82; please replace this page with a corrected version.
4. _____
5. As noted in the Manufacturing Process Validation Report (Appendix 5) use of the _____ is not justified. Please provide a

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

11. Please describe the actual laboratory testing (i.e., the Identification tests) you perform for acceptance of packaging components, such as blister packaging. We note in this regard that _____ packaging materials are often identified by _____ determinations. Your Appendix 8 (e.g., pages 375, 379) refers to laboratory testing and QC specifications, but this information was not included in the DMF.

12. Please update the stability data for the drug product batches cited in the DMF. The original information provided would not support an expiry beyond _____ months. We assume that since the submission of the DMF you have accumulated additional stability data.
We note that supporting information - i.e., data on the stability of the 60 mg Mestinon tablet, as well as data on the 30 mg product produced by you for the Department of the Army for investigational purposes (the IND product) - may be provided to support a longer expiration dating for the 30 mg tablet described in DMF _____

This information should be provided as an amendment to your Drug Master File. Please forward two (2) copies to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive, Room 2-14
Rockville, Maryland 20852

When you amend your Drug Master File _____ please notify the Office of the Surgeon General, Department of the Army in accordance with 21 CFR 314.420(c) and notify the review chemist at the address below that the DMF has been amended. Please provide a desk copy of the amendment to the review chemist to expedite the review of your DMF.

Dr. Janusz W. Rzeszotarski
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857.

DMF _____
Page 4

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

Sincerely yours.

/S/

Stanley W. Blum, Ph.D.
Chemistry Team Leader, DNDC-1
Division of Neuropharmacological Drug
Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research



DMF —

MAR 19 1997

Dear Dr. —

Your letter dated April 11, 1996 authorizes us to reference Drug Master File — for the drug substance, pyridostigmine bromide, in support of the Office of the Surgeon General, Department of the Army's drug product application, NDA 20-414. Your communication dated March 28, 1996 was reviewed.

The information provided in the DMF has been reviewed in support of the Office of the Surgeon General, Department of the Army's application and the following additional information is requested:

1. Please provide and incorporate into the requirements for your starting materials a specific method of identification, e.g., determination of the IR spectrum, for the starting material 3-hydroxypyridine. The comparison reference standard material should also be defined/described as being suitable for reference purposes.
2. Please revise the example description of the synthesis of the drug substance to include the molar quantities as well as the weights of materials employed. While we would prefer a more narrative descriptive style, the cookbook style you have used is acceptable; however, the molar quantities of reactants and reagents should be added.
3. All compendial methods should be those of the USP. Please replace the — test and other — methods with those of the USP. We note that "mutual recognition" between pharmacopeias has not yet been achieved, and therefore all pharmacopeial references must be to USP.
4. Please provide a purity profile of the pyridostigmine bromide drug substance; i.e., — chromatograms of several batches.
5. Please describe the container/closure system for storage of the pyridostigmine bromide drug substance, both for the stability program

samples and for routine storage.

6. Please describe the stability protocol, and provide test results.

This information should be provided as an amendment to your Drug Master File. Please forward two (2) copies to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive, Room 2-14
Rockville, Maryland 20852

When you amend your Drug Master File —, please notify the Surgeon General, Department of the Army in accordance with 21 CFR 314.420(c) and notify the review chemist at the address below that the DMF has been amended. Please provide a desk copy of the amendment to the review chemist.

Dr. Janusz W. Rzeszotarski
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857.

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

Sincerely yours.

/S/

Stanley W. Blum, Ph.D.
Chemistry Team Leader, DNDC-1
Division of Neuropharmacological Drug
Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DMF
Page 3

cc:

DMF (2 copies)
HFD-120/Div.File for NDA 20-414
HFD-120/CSO/RNighswander
HFD-120/JRzeszotarski
/SBlum
HFD-810/ONDC Division Director

Drafted by: SWBlum/March 19, 1997//n:\blum\20414.nds
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final: SWB 19-MAR-97

DEFICIENCY