DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-853/S-012 & 014

Merck & Co., Inc.
Attention: Kenneth A. Kramer
Manager, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Mr. Kramer:

Please refer to your supplemental new drug application 012 dated August 22, 2002, received August 23, 2002 and supplemental new drug application 014 dated July 14, 2004, received July 15, 2004 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cuprimine (penicillamine) Capsules 125 mg and 250 mg.

We acknowledge receipt of your submission dated July 08, 2004 for supplement 012.

Your submission of April 23, 2004 constituted a complete response to our October 08, 2003 action letter for supplement 012. We acknowledge that this is the first review cycle for supplement 014.

Supplemental new drug application 012 provides for a new subsection titled *"Geriatric Use"* which has been added to include information regarding the use of Cuprimine in the elderly. Pharmacokinetic data have been added under CLINICAL PHARMACOLOGY to support the new *"Geriatric Use"* text regarding renal excretion.

Supplemental new drug application 014 provides the following changes:

- WARNINGS, *Pregnancy* – adding category statement, Category D and pregnancy text elements referenced in 21 CFR 201.57(f)(6)(d);

- PRECAUTIONS, *Carcinogenesis* – revisions to "Carcinogenesis, Mutagenesis, Impairment of Fertility" and text about the mutagenic effect of penicillamine

- PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility and text about the mutagenic effect of penicillamine

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Barbara Gould, Regulatory Project Manager, at (301) 827-2506.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, &
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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

/s/

Sharon Hertz

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