DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-041

NDA APPROVED

EMD Pharmaceuticals, Inc
3211 Shannon Road, Suite 500
Durham, NC 27707

Attention: Elliott T. Berger, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance

Dear Dr. Berger:

Please refer to your New Drug Application (NDA) dated June 16, 2006, received June 19, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyanokit (hydroxocobalamin for injection) 5 g for intravenous use.

We acknowledge receipt of your submissions dated April 3 and 7, May 30, July 28, September 8, October 5, 6, 9, 13, 20, 26, 30, and 31, November 1, 9, 15, and 20, and December 14 and 15, 2006.

This new drug application provides for the use of Cyanokit (hydroxocobalamin for injection) for the treatment of known or suspected cyanide poisoning.

We have completed our review of this application, as amended, and it is approved effective on the date of this letter, under the provisions of 21 CFR Part 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible), for use as recommended in the enclosed physician labeling text and required patient labeling text, with the minor editorial revisions listed below.

1. Add a RECENT MAJOR CHANGES section to the HIGHLIGHTS section of the physician labeling text that reads

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| Indications and Usage, Cyanide poisoning (1.1) | 12/2006 |
| Dosage and Administration, Recommended Dosing (2.1) | 12/2006 |

2. On the outer and inner cartons, vial label, and instruction card, replace each occurrence of:

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   with:

   For Intravenous Use
   To be reconstituted with 100 mL per vial of 0.9% Sodium Chloride Injection
   Diluent Not Included

   Ensure that the phrase "Diluent Not Included" is more prominent than the text immediately above it.

3. On the back of the instruction card, delete "and /" so that the sentence reads "Soot present around mouth, nose or oropharynx".

The final printed labeling (FPL) must be identical to, except for including the revisions listed, the enclosed labeling text for the package insert (submitted December 14, 2006), patient package insert (submitted December 14), and immediate carton and container labels (submitted December 13). These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as stated, in the physician labeling, carton and container labeling, and instruction card may render the product misbranded and an unapproved new drug.

Please submit either an electronic version or 12 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If paper copies are submitted, individually mount 6 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission as **"FPL for approved NDA 22-041."** Approval of this submission by FDA is not required before the labeling is used.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

**Subpart I Approval Requirements**

Approvals under 21 CFR Part 314, Subpart I, are subject to three requirements:

1. *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its

safety when used as indicated when such studies are feasible and ethical. We note that Cyanokit has an indicated use that will allow such prospective studies to be conducted in smoke inhalation victims suffering from cyanide exposure. As such events occur with reasonable frequency in the United States, we request that such a study or studies be completed on or before February 1, 2009, and that pediatric patients be included to the extent possible.

2. *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that Cyanokit can be safely used without restrictions on distribution or use and note your commitment to provide training to first-responders and others expected to administer this product.

3. *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We have concluded that the FDA-Approved Patient Labeling meets the requirements of this subsection. We remind you that the patient labeling must be available with the product to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced animal efficacy regulations.

**Postmarketing Study Commitments**

We remind you of your postmarketing study commitments specified in your submission dated December 15, 2006. These commitments are listed below.

1. Subpart I Confirmatory Clinical Study: To conduct a study in both adult and pediatric patients to verify and describe the clinical benefit of Cyanokit and to assess its safety when used as indicated.

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   | Protocol Submission: | February 1, 2007 |
   | Study Start: | May 1, 2007 |
   | Final Report Submission: | February 1, 2009 |

   Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing study commitment must be clearly designated "**Subpart I Postmarketing Study Commitments**."

2. Chemistry, Manufacturing, and Controls (CMC): To study in vitro the biochemical compatibility of hydroxocobalamin with the most frequently administered resuscitation drugs and blood products.

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| Protocol Submission: | May 1, 2007 |
| Study Start: | August 1, 2007 |
| Final report Submission: | February 1, 2008 |

3. Pharmacology/Toxicology (P/T): To perform Segment I (fertility and early embryonic development) studies, as per the ICH M3, S5A, S5B, and S5B(M) Guidances to Industry.

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| Protocol Submission: | March 1, 2007 |
| Study Start: | June 1, 2007 |
| Final report Submission: | June 1, 2008 |

4. P/T: To perform Segment II (embryofetal development) studies in two species, as per the ICH M3, S5A, S5B, and S5B(M) Guidances to Industry.

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| Protocol Submission: | March 1, 2007 |
| Study Start: | June 1, 2007 |
| Final report Submission: | June 1, 2008 |

5. P/T: To perform Segment III (peri- and post-natal development) studies, as per the ICH M3, S5A, S5B, and S5B(M) Guidances to Industry.

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| Protocol Submission: | March 1, 2007 |
| Study Start: | June 1, 2007 |
| Final report Submission: | January 1, 2009 |

6. P/T: To conduct a minimal in vitro genetic toxicology screen (one in vitro mutagenicity assay and one in vitro assay for chromosome damage) to characterize the toxicological safety of the drug product shelf life specifications (stability specifications).

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| Protocol Submission: | February 1, 2007 |
| Study Start: | April 1, 2007 |
| Final report Submission: | October 1, 2007 |

7. P/T: To conduct a toxicology study of adequate dose and duration to characterize the toxicological safety of the drug product shelf life specifications (stability specifications).

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| Protocol Submission: | February 1, 2007 |
| Study Start: | April 1, 2007 |
| Final report Submission: | October 1, 2007 |

8. P/T: To adequately assess photosafety to support the drug as described in the 2003 Guidance for Industry: Photosafety Testing.

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| Protocol Submission: | March 1, 2007 |
| Study Start: | June 1, 2007 |
| Final report Submission: | March 1, 2008 |

In addition, we remind you of your December 15, 2006, agreement to provide the following CMC information by June 30, 2007.

1. Available data supporting the identity of all impurities exceeding the identification threshold of (b)(4) in the drug substance.

2. Data supporting the safety of all impurities exceeding the qualification threshold of (b)(4) in the drug substance.

3. Available data supporting the identity of all impurities exceeding the identification threshold of (b)(4) in the drug product.

4. Data supporting the safety of all impurities exceeding the qualification threshold of (b)(4) in the drug product.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

As required by 21 CFR 314.640, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

The expiration dating period granted for Cyanokit is 30 months with storage conditions of 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

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

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

*{See appended electronic signature page}*

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures

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

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/s/

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Robert Meyer

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