CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-041

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-041

NAME OF APPLICANT / NDA HOLDER
EMD Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Cyanokit ®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Hydroxocobalamin	2.5 g

DOSAGE FORM
Lyophilized Hydroxocobalamin Dark Red Powder for IV Use

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

or each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the rmation described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, plete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,834,448	11/10/1998	11/14/2016

d. Name of Patent Owner
Merck Patent Gessellschaft mit beschraenker Haftung (Merck Patent GmbH)

Address *(of Patent Owner)*
Frankfurter Strasse 250

City/State
Darmstadt, Germany

ZIP Code	FAX Number *(if available)*
64271	+49 6151 72 7191
Telephone Number	**E-Mail Address *(if available)***
+49 6151 72-0	

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Elliott Berger
EMD Pharmaceuticals, Inc.

Address *(of agent or representative named in 1.e.)*
3211 Shannon Road, Suite 500

City/State
Durham, North Carolina

ZIP Code	FAX Number *(if available)*
27707	(919) 401-7180
Telephone Number	**E-Mail Address *(if available)***
(919) 401-7100	elliott.berger@emdpharmaceuticals.com

f. the patent referenced above a patent that has been submitted previously for the proved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*: **15** — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* "Cyanokit® is indicated for the treatment of known or suspected cyanide poisoning." (See "Indications and Usage" section in proposed labeling)	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	June 12, 2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name James N. Czaban	
Address Heller Ehrman LLP 1717 Rhode Island Avenue, NW	City/State Washington, DC
ZIP Code 20036	Telephone Number (202) 912-2000
FAX Number *(if available)* (202) 912-2020	E-Mail Address *(if available)* james.czaban@hellerehrman.com

PSC Media Arts (301) 443-1090 EF

EXCLUSIVITY SUMMARY

NDA # 22041 SUPPL # HFD # 170

Trade Name Cyanokit

Generic Name hydroxocobalamin

Applicant Name EMD Pharmaceutical, Inc

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement? YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Seven

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 85-998 HYDROXOCOBALAMIN INJECTION USP
[Watson Laboratories, Inc.] Approved 1978.

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study	Purpose
EML 015722-H101	safety, tolerability, pharmacokinetics

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

The single investigation was both essential and new.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
YES ☒	! NO ☐
Explain: Study was carried out under the direction of Merck KGaA, the parent company of EMD Pharmaceutical.	! Explain:
Investigation #2	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Matthew Sullivan
Title: Regulatory Project Manager
Date: November 26, 2006

Name of Office/Division Director signing form: Bob Rappaport
Title: Director, Division of Anesthesia, Analgesia and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : N 22-041 **Supplement Type (e.g. SE5):** n/a **Supplement Number:** n/a

Stamp Date: June 19, 2006 **Action Date:** December 19, 2006

HFD 170 **Trade and generic names/dosage form:** Cyanokit (hydroxocobalamin)

Applicant: EMD Pharmaceuticals, Inc **Therapeutic Class:** 8031501

Indication(s) previously approved: (none)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of known or suspected cyanide poisoning

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☒ **Other:** Orphan drug indication, so no pediatric studies required under PREA.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 22-041
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Matthew Sullivan
11/26/2006 02:23:21 PM

1.7 Debarment Certification

EMD Pharmaceuticals, Inc hereby certifies that it did not and will not use in any capacity, the services of any person debarred under subsection (a) or (b) of the Federal Food, Drug and Cosmetics Act (Section 306 (a) or 306 (b)), in the preparation of the New Drug Application for Cyanokit®.

Elliott Berger, PhD
VP Regulatory Affairs and Quality Assurance
EMD Pharmaceuticals, Inc
3211 Shannon Road, Suite 500
Durham, NC 27707
U.S.A.

07 June 2006
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

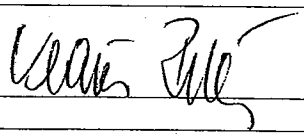
Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attachment 1	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Klaus K Rueth	Chief Financial Officer
FIRM / ORGANIZATION EMD Pharmaceuticals, Inc	
SIGNATURE 	DATE 6/8/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (4/06)

PSC Graphics: (301) 443-1090 EF

Form FDA 3454

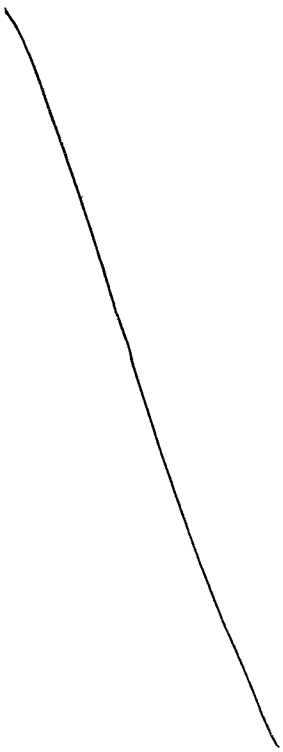
Attachment 1

Clinical Investigators

Principal Investigator Protocol EML015722H101
Priv. Doz. Dr. med. Georg Golor
Parexel International GmbH
Klinikum Westend, Haus 17
Spandauer Damm 130
14050 Berlin
Germany

b(4)

Subinvestigators to Priv. Doz. Dr. med. Georg Golor
Sara



[1]A completed financial disclosure form was not collected from [redacted] was involved in study related procedures (measurement of vital signs) in September and October 2004. He resigned from his activities at Parexel International GmbH before the absence of his financial disclosure form was noticed.

Office Director's Sign-Off Memorandum

Date:	Friday, December 15, 2006
NDA:	22-041
Sponsor:	EMD Pharmaceuticals, Inc.
Proprietary Name:	Cyanokit (hydroxocobalamin, lyophilized) for injection
Author:	Robert J. Meyer, MD Director, Office of Drug Evaluation II

Introduction: This is a first-cycle application for this new drug application of a cyanide poisoning antidote. Because of the need for additional approved antidotes against cyanide toxicity (especially in light of the potential for use of cyanide by terrorists or use against our military personnel in the battlefield), this drug was given a priority review. The product itself is a kit with two 2.5 gm vials of hydroxocobalamin, a vitamin B12 analogue that can "scavenge" cyanide on a 1:1 molecular basis to become cyanocobalamin (or vitamin B12), along with IV tubing and spikes to allow diluent transfer. It does not, however, contain diluent. A lethal oral dose in humans would be in the range of 200 mg and above, so the dose of this drug (5 – 10 gm) should be sufficient to complex cyanide in many lethal exposures. The diluent proposed for reconstituting the drug is normal saline, which is not included in the Cyanokit. Because controlled trials with humans are neither feasible nor ethical, the primary efficacy data from this drug have been developed in animals, with controlled safety data from human volunteers exposed to drug, but not cyanide. Therefore the approval will occur under subpart I or the animal rule.

I refer the reader to the summary memorandum of Dr. Bob Rappaport for details, as his memorandum will be the memorandum of record. I am in substantial agreement with that memorandum's observations, conclusions and recommendations. I will highlight a few selected points from my review of the action package.

CMC: At the time of the review of the package, there was an outstanding site inspection, but this has now been conducted and an overall acceptable recommendation has been issued for this drug product. From a review standpoint, all necessary CMC issues have been resolved. Currently, the data available only allow for a — month expiry, which the sponsor would like to extend due to the likelihood of this drug being stockpiled. The limiting factor in the expiration date is the presence of drug-related degradants, many of which would likely remain active in their cyanide complexing properties. Nonetheless, not all of these have been identified or qualified. Data that may support longer expiration dating period can be considered post-approval. Also, as per the CMC review and Dr. Rappaport's memo, the sponsor is being asked for additional information on the compatibility of the IV infusion set provided in the kit with the drug. This is not felt to be substantial enough of an issue to preclude approval.

b(4)

Pharm/Tox: This drug will be approved under the animal rule, therefore the animal testing is of paramount importance in assessing the efficacy of this drug, as well as informing the safety. I will not recapitulate the beagle dog efficacy data here, as that is available in the pharm/tox and medical reviews (as well as the signatory memorandum).

I do need to state, however, that the animal rule ordinarily calls for data from two species to support approval. However, this approval is based on one solitary animal study. The reasons why one would allow this are as follows:

1. The toxicity of cyanide (in poisoning cytochrome oxidases and thereby inhibiting oxidative phosphorylation or aerobic metabolism) is well understood and should be preserved and monotonic between species.
2. The dog study was well-conducted and impressive in its results in rescuing dogs that were already moribund from cyanide.
3. While controlled human data are not available, uncontrolled data were available and submitted by the sponsor. These studies were reports of the Cyanokit use in fire and suicide victims in France. While the data cannot be considered definitive for approval, they do support that many patients treated with Cyanokit after what would be projected to be lethal exposures can recover; particularly if the patient is found before full cardiac arrest occurs.

Again, I refer readers to the appropriate memos, including Dr. Rappaports for details of the dog study and other animal safety data. The pharm/tox team have a number of data needs that can and should be addressed post-approval (e.g., reproductive toxicology) as they inform labeling, but would not change the approval decision.

Clinical: The sponsor presented data from four "studies" on the efficacy of Cyanokit (designated Baud 1, 2 and 3, and Fortin) in cyanide poisoning and one study of the clinical safety of the drug (Study EML 015722-H101) given to non-cyanide exposed volunteers. Dr. Simone and Rappaport have summarized these data well. Of the efficacy reports, the Baud-3 experience is perhaps the most compelling, as this reported the use of Cyanokit in the setting of 14 non-fire-related settings, mostly suicidal ingestions. Since these patients were not otherwise burned or exposed to other fire-related toxins, the results are less confounded, though still uncontrolled. Ten of these 14 patients survived, many of them with initial cyanide levels that would have been predictive to be lethal. These clinical data in general suggest that the dog data does indeed predict human benefit for Cyanokit in the clinical setting.

The safety of the drug was reasonably established for this indication, with human data both from study H101 and from the Baud/Fortin experiences. The major safety issues relate to the effects of the drug in terms of its deep red coloration (it causes chromoturia when excreted unchanged in the urine and discoloring of the skin for several days to weeks), hypertension and some allergic, urticarial-type reactions. These are acceptable considering the proposed use and it should also be noted that most patients who have significant cyanide exposure will by hypotensive, so the direct hypertensive effect of the drug, reportedly due to nitric oxide scavenging, in these individuals would be restorative (in addition to the secondary effect of the drug on complexing cyanide).

Labeling and nomenclature: The main issue in labeling is that under the subpart I rule, the drug needs to have patient labeling and this is being developed with OSE and OND personnel and the company. DMETS has raised objections to the naming of Cyanokit due to its similarity to a discontinued vitamin B12 (Cyanoject). While name confusion is theoretically possible, given the vast differences in the way this drug will be used from a

vitamin supplement, given the fact that Cyanoject is no longer available and given the large differences in dosing (gm for Cyanokit vs mg of Cyanoject), I believe approving the drug with its current name is defensible. The company has been alerted to the name issue, but if a new name is not identified, I would not hold up approval for this issue alone.

A secondary issue with the PLR format is the correct date for the approval of hydroxocobalamin as an NME. This molecule was approved years ago as a vitamin precursor in much lower doses (with the correct date being 1975). Under the PLR, that is the date that must be cited for this drug, but this new use is so different and the dosing so much extraordinarily higher, that we wish to capture this approval in the labeling as well. This will be done, on advice from the authors of the PLR, in the recent changes subsection of the Highlights section.

Inspectional Issues: The inspection by DSI of the sites that did the pharmacokinetic assessments in the clinical/clinical pharmacology studies showed a number of issues in record keeping and standardized assay procedures (e.g., running of QC samples, standards, and documentation of handling of samples) that call into question the validity of the PK findings. This must be put into perspective, however. First, the PK data are not strictly pivotal in this application, as this is not based on comparative bioavailability or bioequivalence to an approved product. Second, these errors would have increased the "noise" of the study results, which would have limited the chance of showing a meaningful, consistent effect of dose in the exposures. Rather, the results of the PK studies showed good dose-proportionality and otherwise internally consistent data strongly suggesting the procedures, if not optimally or optimally documented, were sufficient. While the DSI-documented deficiencies would not be acceptable for a BE study or a pivotal BA study, given the results, their place in this overall evaluation of Cyanokit and the importance of having another cyanide antidote approved, we are accepting the results of these studies as sufficiently supportive and informative for the purposes of this NDA. This was discussed with the clinical team and the PK reviewers, who agreed.

Regulatory Conclusions: This drug can be approved given the data provided. With the animal rule, the sponsor has to commit to accrue and report data on the use of the drug in humans as it becomes available, and there are a number of CMC agreements and Pharm/tox phase 4 studies that have been negotiated with the sponsor. PREA does not apply to this drug as this use is designated as an orphan indication, so no pediatric studies are required. Nonetheless, we will encourage the inclusion of pediatric patients in the post-approval clinical assessments. Other PMC studies include:

- Segments I, II and III reproduction and developmental toxicology studies
- Photosafety testing
- Safety qualification of the proposed specified and unspecified drug substance and drug product impurities which exceed ICH thresholds.
- Compatability testing of the drug with other resuscitative medications to inform labeling as to administration in the same IV access.

I agree with Dr. Rappaport that the tissue distribution study suggested by the pharm/tox team as a phase 4 commitment should not be required.

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/s/

Robert Meyer
12/15/2006 01:58:38 PM
MEDICAL OFFICER

DIVISION DIRECTOR SUMMARY REVIEW AND RECOMMENDATION FOR APPROVAL

DATE:	December 7, 2006
DRUG:	Cyanokit (hydroxycobalamin) lyophilized powder for injection, 2.5 g in each of two glass containers; and spike and IV tubing system
NDA:	22-041
NDA Code:	Type 3P NDA
SPONSOR:	EMD Pharmaceuticals, Inc.
INDICATION:	For the treatment of known or suspected acute cyanide poisoning

EMD Pharmaceuticals, Inc. submitted NDA 22-041 in support of marketing approval for Cyanokit, on June 19, 2006.

Cyanokit consists of two glass containers containing 2.5 g each of hydroxycobalamin lyophilized powder for injection, and a spike and IV tubing system for IV administration of the drug product. Each container is to be filled with 100 mL of sterile saline and administered over a period of 7.5 minutes. A second dose total dose of 5 g may be administered over 15 minutes to 2 hours as needed. This high dose formulation of hydroxycobalamin has been developed by the sponsor for the treatment of acute cyanide poisoning based on the high affinity of the cyanide ion for cobalt compounds, thus allowing for removal of the cyanide ions from their binding sites on cytochrome oxidase, binding of these ions to the cobalt site of the hydroxycobalamin, and excretion of this complex in the urine.

Efficacy for this application was based on a study in beagle dogs, under 21 CFR §314.600, Subpart I (the "Animal Efficacy Rule"), as it would not be possible to perform a prospective, randomized, controlled trial in human subjects. The Animal Rule allows for the critical efficacy data to be obtained from appropriately and well-designed animal studies when efficacy studies in human studies would be unethical to perform. The animal efficacy data was supported by four uncontrolled, open-label studies (three of which were retrospective) and a safety and pharmacokinetic study performed in normal volunteers.

Review of the CMC portion of this application was completed by Milagros Salazar, Ph.D. Review of the general pharmacology and toxicology data presented in this application was completed by L. Steven Leshin, D.V.M., Ph.D. A supervisory review was provided by Daniel Mellon, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by David Lee, Ph.D. A statistical review of the animal efficacy study was completed by James Gebert, Ph.D. The clinical review was completed by Arthur Simone, M.D., Ph.D. Consultation on this application was also obtained from the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Office of Surveillance and Epidemiology (OSE).

Efficacy:

Animal Study

This efficacy trial was conducted in anesthetized beagle dogs that had been poisoned with potassium cyanide solutions. The cyanide solution was administered intravenously until the animals became apneic and then for an additional three minutes. The dogs were mechanically ventilated and administered normal saline or hydroxycobalamin 75 mg/kg or 150 mg/kg intravenously. Attempts to wean the animals from ventilation began 15 minutes after treatment and continued intermittently for 2 hours. Animals that could not be weaned from ventilation were then euthanized. Survival was assessed at four hours after completion of the infusion and at Day 14 following the treatment. The 75- and 150-mg/kg doses correspond to 5-g and 10-g doses, respectively, for a 70-kg adult.

Dr. Simone's Table 4 (page 29 of his review) summarizes the results of this study and is reproduced below:

Table 1 Dog Survival (from the primary Pharmacology-Toxicology review)

Dose		**Vehicle 0.9% Saline, IV**		**Hydroxocobalamin 75 mg/kg, IV**		**Hydroxocobalamin 150 mg/kg, IV**	
Gender		**M**	**F**	**M**	**F**	**M**	**F**
Body Weight Day 1 (kg)		10.3 ± 2.1	7.6 ± 0.3	10.0 ± 1.3	8.2 ± 1.0	9.9 ± 1.5	8.1 ± 0.6
Total KCN (mg/kg)		2.3 ± 0.1	2.3 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	2.3 ± 0.2
Overall by Treatment		2.3 ± 0.2		2.4 ± 0.2		2.2 ± 0.2	
		KCN doses were within 88% of target dose of 2.5 mg/kg KCN					
Time to Apnea (min)		2.8 ± 0.3	2.8 ± 0.5	2.9 ± 0.6	2.9 ± 0.4	2.4 ± 0.4	2.8 ± 0.5
Total N		**8**	**9**	**10**	**9**	**9**	**9**
Incidence and Time of Death	<4 hr	6	4		1		
	1						
	2		2				
	3	1			1		
	4	1		1	1		
	14		3				
	15			9	6	9	9
% Survival for 14/15 days		**0%**	**33.3%**	**90%**	**66.7%**	**100%**	**100%**

Mean ± SD

The animals treated with hydroxycobalamin exhibited a more rapid recovery of mean arterial blood pressure than the placebo-treated animals, beginning at the initiation of treatment. They also demonstrated a more rapid recovery of minute-volume ventilation. Lower incidences of lethargy, ataxia, dementia and paresis were observed in the hydroxycobalamin-treated animals compared to the placebo-treated animals. Hydroxycobalamin-treated animals also had fewer and less severe brain lesions at necropsy than placebo-treated animals.

Study Baud-1

This was a prospective, open-label, uncontrolled study of hydroxycobalamin administered to adult smoke inhalation victims by the Paris, France Fire Brigade between 1987 and 1994. Additional data was subsequently collected from hospital records retrospectively. Patients were assessed at the scene and treated with a 5-g infusion of hydroxycobalamin over 15 to 30 minutes. One or two additional 5-g doses were administered as needed when there was a partial response to the initial treatment. Oxygen was administered to all patients and other supportive measures such as volume replacement, assisted ventilation, administration of catecholamines, etc. were taken as needed based on the patient's condition. Patients were transferred to hospital after treatment and stabilization, and admitted to the ICU. Blood pressure and heart rate were measured on discovery, prior to and after treatment with hydroxycobalamin, and on hospital admission.

Dr. Simone's Table 25 on page 94 of his review summarizes the results of the study and is reproduced below:

Table 2 Clinical Outcomes for the Study

Clinical Outcome	Number of Patients (%)
Survival	50/69 (72%)
Death	19/69 (28%)
Causes of Death:	
Decerebration	13/19 (68%)
Septic Shock	5/19 (26%)
Hypoxemic Pneumonia	1/19 (5%)
Neurologic Symptoms:	
On Initial Examination	66/69 (96%)
Resolved	38/66 (58%)
Neuropsychiatric Sequelae at Discharge	9/66 (14%)
Patient Death	19/66 (29%)

The study's predefined threshold blood cyanide (BCN) levels for toxicity and potential lethality were 39 μmol/L and 100 μmol/L, respectively. Dr. Simone employed a threshold of 40 μmol/L for toxicity to maintain consistency between studies. Of the 60 patients who had documented BCN levels, 42 had toxic levels of cyanide, i.e., BCN $\geq$ 40 μmol/L, and of these, 28 (67%) survived. The survival rate was further subdivided as follows:

- 17 (74%) out of 23 patients with initial BCN $\geq$ 40 μmol/L and < 100 μmol/L survived
- 11 (58%) out of 19 patients with initial BCN concentrations $\geq$ 100 μmol/L survived

Dr. Simone's Table 26 (page 96 of his review) summarizes the data obtained from this study and is reproduced below:

Table 3 Summary of Efficacy Findings for the Study

Parameter	BCN ≥ 40 µmol/L					BCN < 40 µmol/L				
	BCO ≥ 1 mmol/L	BCO < 1 mmol/L	In Cardiac Arrest	Not in Cardiac Arrest	Group Summary	BCO ≥ 1 mmol/L	BCO < 1 mmol/L	In Cardiac Arrest	Not in Cardiac Arrest	Group Summary
Number of Patients	36	4	11	31	42	16	3	2	19	21
Median (Mean) CN level (µmol/L)	98 (121)	64 (64)	139 (141)	89 (102)	96 (112)	13 (11)	0 (6)	11 (11)	8 (9)	8.1 (9)
Range of CN levels (µmol/L)	40-250	41-87	40-239	41-250	40-250	0-27	0-19	0-21	0-27	0-27
Survival	24 (67%)	2 (50%)	2 (18%)	26 (84%)	28 (67%)	13 (81%)	3 (100%)	0 (0%)	18 (95%)	18 (86%)
Mean Dose of OH-Co (g)	5	5	5	5	5	5	5	5	5	5
Mean Infusion time (min)	32	28	20	35	31	31	63	30	36	32
Median (Mean) Age (y)	43 (50)	51 (52)	37 (45)	49 (51)	42 (50)	49 (48)	55 (51)	36 (36)	48 (49)	46 (50)
Age range (y)	21-89	25-82	25-83	21-89	21-89	20-94	31-68	33-38	20-94	20-94
Survivors Age ≥ 65	2/8	1/1	0/2	3/7	3/9	1/2	1/1	0/0	2/3	0
Survivors Age ≥ 75	1/5	1/1	0/2	2/5	2/6	1/2	0/0	0/0	1/2	0
Survivors without neurological sequelae	18 (75%)	2 (100%)	2 (100%)	20 (77%)	21 (75%)	10 (77%)	3 (100%)	0 (0%)	15 (83%)	3/19 (16%)

Although interpretation of these data is difficult due to the uncontrolled design of the study, it is striking that 67% of patients with BCN levels greater than or equal to 40 µmol/L survived and 58% of patients with BCN levels of greater than or equal to 100 µmol/L survived.

Study Baud-2

This was a retrospective study that evaluated the use of hydroxycobalamin in smoke inhalation victims with suspected cyanide toxicity at fire scenes and in hospital ICUs between 1988 and 2004 in Paris, France. Patients treated with alternative treatments for cyanide poisoning in addition to hydroxycobalamin were included in the study. Dr. Simone's Table 28 (page 102 of his review) summarizes the data collected in this study and is reproduced below:

Table 4 Summary of Efficacy Findings for the Baud-2 Study

Parameter	BCN ≥ 40 µmol/L					BCN < 40 µmol/L				
	BCO ≥ 1 mmol/L	BCO < 1 mmol/L	In Cardiac Arrest	Not in Cardiac Arrest	Group Sum-mary	BCO ≥ 1 mmol/L	BCO < 1 mmol/L	In Cardiac Arrest	Not in Cardiac Arrest	Group Sum-mary
Number of Patients	7	1	3	5	8	28	25	14	39	53
Median (Mean) CN level (µmol/L)	81 (104)	68 (68)	67 (89)	81 (106)	75 (99)	12 (15)	8 (12)	21 (22)	7 (11)	9 (14)
Range of CN levels (µmol/L)	47-165	N/A	47-154	62-165	47-165	3-38	4-29	9-38	3-30	3-38
Number in Cardiac Arrest	3	0	3	0	3	6	8	14	0	14
Survival	4 (57%)	1 (100%)	0 (0%)	5 (100%)	5 (63%)	14 (50%)	15 (60%)	1 (7%)	28 (72%)	29 (55%)
Mean Dose of OH-Co (g)	8.6	2.5	13.3	4.5	7.8	6.4	7.6	9.2	6.2	7.0
Mean Infusion time (min/1g of OH-Co)	22	Not known	27	6	22	6	14	18	5	10
Median (Mean) Age (y)	48 (51)	60 (60)	42 (39)	60 (60)	49 (53)	58 (55)	52 (55)	50 (51)	53 (56)	52 (51)
Age range (y)	29-79	N/A	29-48	50-79	29-79	20-87	22-92	22-73	20-92	20-92
Survivors Age ≥ 65	2/2	N/A	N/A	2/2	2/2	3/8	4/8	0/3	7/13	7/7
Survivors Age ≥ 75	1/1	N/A	N/A	1/1	1/1	2/4	1/3	0/2	2/7	2/2
Survivors without neurological sequelae	3 (75%)	1 (100%)	N/A	3 (60%)	3 (60%)	10 (71%)	9 (60%)	0 (0%)	19 (49%)	19 (66%)

The results of this study, as in Baud-1, reveal compelling data suggesting that victims of cyanide toxicity with clearly toxic and potentially lethal levels of cyanide may be responsive to treatment with hydroxycobalamin. Sixty-three percent of patients with BCN levels greater than or equal to 40 µmol/L survived and 67% with BCN levels greater than or equal to 100 µmol/L survived.

Study Baud-3

This was a retrospective study that evaluated the use of hydroxycobalamin in victims of severe, acute cyanide poisoning by ingestion or inhalation from sources other than fire at two hospitals in Paris between 1988 and 2003. Patients who had been treated with alternative antidotes in addition to hydroxycobalamin were included in the study.

Dr. Simone's Table 31 on page 108 of this review summarizes the data collected in this study and is reproduced below:

Table 5 Summary of patient exposures and initial assessments.

Patient Number	Age (years)	Gender	Initial BCN (µmol/L)	Initial Blood pressure (mmHg)	Initial Heart rate (bpm)	Initial Respiratory rate (bpm)	Initial GCS	OH-Co Dose (g)	Outcome
136	25	Male	125	150/90	100	--	15	5	Survived
137[1]	28	Female	154	110/60	120	8	12	10	Survived
138	51	Male	103	0/0	0	0	3	10	Survived
139	27	Male	150	95/50	110	3	3	20	Died Day 4 (shock)
141	32	Male	125	65/--	80	--	15	10	Survived
142	52	Male	158	200/120	110	25	15	5	Survived
143[1]	39	Male	238	120/70	90	14	12	10	Died Day 3 (brain death)
144[2]	32	Female	196	0/0	0	0	3	15	Died Day 4 (brain death)
145	64	Male	260	50/0	30	--	3	10	Died Day 10 (brain death)
146	38	Male	13	130/80	72	18	15	5	Survived
147[3]	15	Male	217	100/--	120	--	15	5	Survived
148[1]	44	Male	--	80/--	120	0	3	9	Survived
152[1]	40	Male	170	90/60	80	--	15	10	Survived
153	22	Male	--	115/80	140	20	15	5	Survived
Mean (SD)	36 (13)	n.a.	159 (54)	93 (54) 56 (40)	84 (45)	10 (10)	10 (6)	9 (4)	n.a.
Range	15-64	n.a.	0-200	0-200 0-120	0-140	0-25	3-15	5-20	n.a.

[1] Patient also received sodium thiosulfate as cyanide antidote therapy.
[2] Patient also received sodium thiosulfate and dicobalt edetate as cyanide antidote therapy.
[3] Patient also received dimercaprol (British anti-Lewisite [BAL]) and dimethyl-succinic acid as mercury antidote therapy.

This study is unique in that: most patients were exposed to cyanide by ingestion rather than inhalation; the exposure was limited primarily to cyanide, i.e., the poisoning was not due to a combination of toxins as was often the case for the smoke-inhalation victims; the poisoning was not complicated by other acute injuries such as burns and trauma frequently associated with the smoke-inhalation studies; and the doses of cyanide to which patients were exposed were relatively large compared to those of the smoke-inhalation victims. Thus, it may provide more accurate outcome data.

As in Baud-1 and Baud-2, this study provides significant support for the efficacy of hydroxycobalamin in the treatment of cyanide poisoning. The fact that seven of the survivors had initial lethal BCN levels is striking. Additionally, 90% of the surviving subjects had no neurological sequelae.

Study Fortin

This was a retrospective study that evaluated the use of hydroxycobalamin by the Paris Fire Brigade in smoke inhalation victims with suspected cyanide toxicity at fire scenes between 1995 and 2003. Data were collected from the records of the Fire Brigade and the hospital where the patients were admitted. Soot in the patients' airways was used as a surrogate marker in an effort to distinguish between patients more or less likely to have inhaled toxic levels of cyanide.

Dr. Simone's Table 33 (page 117 of his review) summarizes the data collected in this study and is reproduced below:

Table 6 Summary survival data for Fortin Study

	Soot present in airways			No soot in airways[1]		
	In Cardiac Arrest	Not in Cardiac Arrest	Total	In Cardiac Arrest	Not in Cardiac Arrest	Total
Evaluable Patients	19	53	72	19	10	29
Survival:[2]						
Overall	1 (5%)	25 (47%)	26 (36%)	1 (5%)	4 (40%)	5 (17%)
Age < 18 y	0/3 (0%)	0/2 (0%)	0/5 (0%)	0/4 (0%)	1/1 (100%)	1/5 (20%)
Age ≥ 18 y	1/16 (6%)	21/51 (41%)	26/67 (39%)	1/15 (7%)	3/8 (38%)	4/23 (17%)
Age ≥ 65 y	1/4 (25%)	4/9 (44%)	5/13 (38%)	1/4 (25%)	2/2 (100%)	3/6 (50%)
Age ≥ 75 y	1/4 (25%)	3/7 (43%)	4/11 (36%)	0/1 (0%)	1/1 (100%)	1/2 (50%)
Mean Dose of OH-Co (g)	6.3	4.9	4.8	4.0	4.4	4.3

[1] Includes patients for whom it was documented that no soot was present and those for whom there was no documentation and who, therefore, were assumed not to have been intubated.
[2] Includes only those patients who were know to survive until transferred out of the ICU.

As Dr. Simone notes in his review, also on page 117:

> As was noted in the Baud smoke-inhalation studies, those patients presenting in cardiac arrest had the lowest survival rates. This was true regardless of the presence or absence of soot in the airway. Overall survival was greater for pediatric and elderly patients when no soot was present in the airways; however, the opposite was true for patients ages 18-65 years old. The significance of this result is questionable at best based on the limitations of the data and of the assumption that blood cyanide levels can be estimated by the presence of soot in the airways.

Nevertheless, the results of this study are again supportive of significant efficacy for hydroxycobalamin in the treatment of cyanide poisoning due to smoke inhalation, at least for patients not already in cardiac arrest.

Clinical Safety:

Unfortunately, the French studies provide only limited information on the safety of Cyanokit due to their uncontrolled design and the confounding impact of smoke inhalation and burns in three of these studies. Erythema, rash and chromaturia occurred with substantial frequency in these studies. The most valuable safety data comes from the safety and tolerability study in healthy volunteers.

Study EML 015722-H101

This was a double-blind, randomized, placebo-controlled, single-ascending dose study that evaluated the safety and tolerability of four doses of hydroxycobalamin, 2.5, 5, 7.5 and 10 g administered over 7.5, 15, 22 and 30 minutes, respectively, in healthy adult volunteers. Pharmacokinetic data was also obtained.

There were no deaths or serious adverse events in this study. In general, adverse events were uncommon in the two lower-dose groups. The most common adverse events included chromaturia, erythema, rash, increased blood pressure, nausea, headache, chest discomfort, injection site reactions and allergic reactions. Increases in diastolic blood pressure, a pustular rash, headache, nausea and chest discomfort occurred more frequently in the two higher-dose groups compared to the two lower-dose groups. Dosing was discontinued in the 10-g dose group due to adverse events including the second allergic reaction (see below) and an episode of moderately severe hypertension lasting several hours.

Elevations in diastolic and systolic blood pressure were seen in all dose groups, occurring shortly after the initiation of infusion and generally resolving without intervention within 4 to 8 hours after the completion of treatment. While these changes were mostly modest, some of the subjects experienced potentially clinically dangerous increases. For patients suffering from cyanide toxicity, these changes may actually be beneficial, as these patients often experience hypotension and shock. In fact, a not uncommon finding in the

French studies was that patients who presented in shock or cardiac arrest had restoration of circulation following treatment with hydroxycobalamin.

Two subjects experienced allergic reactions, neither event severe. However, treatment was discontinued for one of these patients. While some laboratory abnormalities (decreased lymphocyte percentage with increased neutrophil percentage and normal cell count, elevated C-reactive protein, and leukocytosis) were noted in the hydroxycobalamin-treated subjects and were not seen in the placebo-treated subjects, these changes were not marked and were not associated with clinically apparent adverse events.

Nonclinical Safety:

The following studies were either not performed or the studies submitted with the application were considered inadequate by Drs. Leshin and Mellon:

- Segments I, II and III reproduction and developmental toxicology studies
- Photosafety testing
- Safety qualification of the proposed specified and unspecified drug substance and drug product impurities which exceed ICH thresholds, i.e., minimal in vitro genetic toxicology screen and a toxicology study of adequate duration to support the proposed clinical trial
- Adequate data to support the safety of cyanocobalamin, the major metabolite of hydroxycobalamin in the presence of cyanide. This may either be addressed by providing information on the purity of the cyanocobalamin used in the existing toxicology studies, or via an additional study with well-characterized cyanocobalamin chemical substance.
- Tissue distribution studies, including distribution in breast milk.

Drs. Leshin and Mellon conclude that these studies may be completed in the post-marketing period as they will clearly provide important information for labeling, but will not provide essential pre-approval information considering the urgent need for the availability of life-saving treatments for cyanide poisoning.

Clinical Pharmacology and Biopharmaceutics:

Dr. Lee has determined that the data submitted in this application is adequate to support approval and that no Phase 4 commitments are required from a clinical pharmacology and biopharmaceutics perspective.

Chemistry, Manufacturing and Controls:

Dr. Salazar has recommended that Cyanokit is approvable from a CMC perspective with the following Phase 4 commitment:

- Provision of physiochemical and biological testing data for the IV infusion set.

Dr. Salazar notes that this data may be submitted post-marketing approval because:

- The infusion set is composed of materials that have, for the most part, identical to another infusion set that has been approved under a 501(k) application, and both sets are manufactured by the same manufacturer.

- Adequate data was submitted in a compatibility study to demonstrate that the product does not change its quality attributes.

- There is an urgent need for this product.

Nomenclature:

The Division of Medication Errors and Technical Support (DMETS) has recommended against the use of the trade name Cyanokit. Their recommendation is based on possible look-alike confusion with Cyanoject. Cyanoject is no longer marketed in the U.S., but generic formulations remain on the market, and the name Cyanoject is still found in commonly used clinical references. Cyanoject contains an injectable formulation of cyanocobalmin in doses of 1000 mcg, 10 mg and 30 mg for intramuscular or deep subcutaneous injection, and is indicated for the treatment of Vitamin B12 deficiency or pernicious anemia, and for use in the Schilling Test for Vitamin B12 deficiency.

Inspections:

As of today, the report regarding the recently performed inspection of the safety and pharmacokinetics study is pending. In addition, one CMC inspection (of the manufacturer of the drug product) is also pending.

Discussion:

Cyanide toxicity is common in fire victims and usually results in severe morbidity or death. It is also seen in deliberate or inadvertent poisonings. Additionally, the possibility exists that cyanide could be used in terrorist attacks or as a chemical weapon of war. While there are approved and unapproved products available for the treatment of cyanide toxicity, these products have significantly unfavorable toxicity profiles of their own. Clearly, there is an urgent need for new treatments for cyanide toxicity that have more acceptable side effect profiles.

The sponsor has provided compelling evidence to support the efficacy of the hydroxycobalamin component of Cyanokit as a treatment for cyanide toxicity. The results of the animal efficacy study are striking. The majority of the beagle dogs, despite lethal levels of cyanide, survived without neurological sequelae following treatment with hydroxycobalamin at doses that were equivalent to the proposed human doses. While the French clinical studies are limited by their open-label, uncontrolled design, they nevertheless provide strong support for efficacy based on the fact that significant numbers of patients with toxic and even lethal levels of cyanide survived after treatment with hydroxycobalamin at the high doses proposed for the Cyanokit product.

The safety profile of this product appears to be relatively benign, with hypertension being the most clinically relevant adverse event seen in both the normal volunteer and the animal studies. Importantly, this effect could be beneficial in cyanide poisoned patients who frequently suffer from hypotension and shock due to the cyanide. The French data seems to be supportive of this possible benefit in that many of the patients with toxic cyanide levels who were in shock or cardiac arrest on initial evaluation had restoration of circulation after treatment. While allergic reactions do occur with exposure to hydroxycobalamin, in the expected treatment settings appropriate interventions would normally be available.

I concur with the CMC and Pharm/Tox reviewers that the data and studies that have not yet been adequately addressed in this application may be obtained and submitted in the post-marketing period. This determination is based on the relatively low risks associated with the absence of this information for this product and the urgent need for its availability as a life-saving treatment for patients who would otherwise die or suffer significant morbidity. However, I do not agree with the need for a tissue distribution study. Drs. Leshin and Mellon recommended this study as a way to provide data that could be included in the label and that would, thereby, aid practitioners in determining when a patient may no longer be at risk from sun exposure and/or when a lactating woman may reinitiate breast feeding. I do not think that it is likely that the data that might be obtained from this study would allow us to make additional clinical recommendations beyond those that have already been included in the package insert.

I do not agree with the recommendation from DMETS that the proposed trade name poses a significant risk of name confusion. In addition to the fact that Cyanoject is no

longer marketed in the U.S., Cyanokit will primarily be used by first responders, e.g., EMS providers and fire fighters, and will not generally be located in the same formularies as the generic Cyanoject products. Additionally, the low doses of cyanocobalamin in the Cyanoject products would not likely be harmful to cyanide-toxic patients. While the accidental administration of one of these products to a cyanide-poisoned patient in an emergency room remains a possibility and could result in a delay of appropriate treatment, I think that this is a highly unlikely scenario. The packaging of these products is also quite different and the products themselves are different in their appearance and obvious features related to route of administration.

Action recommended by the Division:

Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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

/s/

Bob Rappaport
12/7/2006 11:16:55 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-041

OFFICE DIRECTOR MEMO

ACTION PACKAGE CHECKLIST

BLA # / NDA # 22041	BLA STN# / NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Cyanokit Established Name: hydroxocobalamin Dosage Form: Lyophilized Powder for Injection		Applicant: EMD Pharmaceutical, Inc
RPM: Matthew Sullivan		Division: HFD-170 / Phone # 796-1245

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	December 19, 2006 December 15, 2006
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☐ Requested in AP letter ☒ Received and reviewed

❖ Application Characteristics

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): 3

NDAs, BLAs and Supplements:
☒ Fast Track
☒ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☒ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☒ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Division Director – December 7, 2006 Office Director – December 15, 2006
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	December 14, 2006
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	June 19, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	December 14, 2006
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	November 1, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	December 13, 2006

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS November 13, 2006 ☒ DSRCS December 12, 2006 ☐ DDMAC ☒ SEALD October 11, 2006 December 7, 2006 December 11, 2006 ☐ Other reviews ☐ Memos of Mtgs

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	RPM Filing review – August 17, 2006 ADRA review -
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	July 25, 2006 August 9, 2006 October 10, 2006 (3) October 12, 2006 October 17, 2006 October 18, 2006 (2) October 19, 2006 October 25, 2006 November 14, 2006 November 17, 2006 December 12, 2006 December 15, 2006
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	November 27, 2006
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg February 10, 2006
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	Special Protocol Assessment for animal efficacy study: April 8, 2004 Pre-IND: April 29, 2003

❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
❖ CMC/Product review(s) *(indicate date for each review)*	Primary – December 14, 2006
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☐ None Statistical review of stability studies – December 14, 2006
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	November 2, 2006 ☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: December 13, 2006 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Primary – December 5, 2006 Secondary – December 5, 2006 Addendum – December 15, 2006
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☐ None requested November 17, 2006

❖ Clinical review(s) *(indicate date for each review)*	December 1, 2006
Financial Disclosure reviews(s) or location/date if addressed in another review	Discussed in MO review of December 1, 2006
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	Discussed in MO review of December 1, 2006
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	November 16, 2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	November 17, 2006 [animal efficacy study]
• Bioequivalence Studies	
• Clin Pharm Studies	December 12, 2006
❖ Statistical Review(s) *(indicate date for each review)*	☐ None November 14, 2006
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None November 27, 2006 Addendum: December 15, 2006

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, December 12, 2006 2:51 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: RE: NDA 22-041 Cyanokit - Tox Question

Elliott –

Your approach is acceptable. However, please note comments in Notes 2 and 3 in the ICH-S2b Guidance for Industry concerning the mouse lymphoma assay. These items should be incorporated to ensure that clastogenicity is appropriately assessed.

Matt

From: elliott.berger@emdpharmaceuticals.com [mailto:elliott.berger@emdpharmaceuticals.com]
Sent: Tuesday, December 12, 2006 11:55 AM
To: Sullivan, Matthew
Cc: cindy.marshall@emdpharmaceuticals.com
Subject: NDA 22-041 Cyanokit - Tox Question

Matt

In our discussion yesterday, Dr. Mellon noted that per ICH Guidance, 3 studies wold be required to "qualify" the impurities, namely an *in vitro* mutagenicity test, an *in vitro* clastogencicity test and a general toxicity study. We want to confirm that the following will be acceptable:

- *In Vitro* Mutagenicity Test - Ames Test
- *In Vitro* Clastogenicity Test - Mouse Lymphoma Assay (we had done this test as part of the core Tox package and would like to use this for clastogenicity in order to compare results if necessary)
- General Toxicity - Single Dose Study with 14 Day follow-up

Thanks

Elliott T. Berger, Ph.D.
Vice President, Regulatory Affairs & Quality Assurance
EMD Pharmaceuticals, Inc.
(919) 401-7107 Phone
(919) 401-7191 Fax

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/s/

Matthew Sullivan
12/15/2006 02:22:24 PM
CSO

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, December 14, 2006 3:32 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: RE: NDA 22-041 Cyanokit - Revised PI
Attachments: Phase 4 Commitments v2.doc

Here is the post-marketing commitment information.

As with the carton/container and PI, please shoot with an email with your concurrence, or issues.

Matt

From: elliott.berger@emdpharmaceuticals.com [mailto:elliott.berger@emdpharmaceuticals.com]
Sent: Thursday, December 14, 2006 12:04 PM
To: Sullivan, Matthew
Cc: cindy.marshall@emdpharmaceuticals.com
Subject: NDA 22-041 Cyanokit - Revised PI

Matt

Attached is the revised PI. There are only a couple of places where we actually made "content" revisions, all others were really editorial in nature.

Elliott T. Berger, Ph.D.
Vice President, Regulatory Affairs & Quality Assurance
EMD Pharmaceuticals, Inc.
(919) 401-7107 Phone
(919) 401-7191 Fax

1. Conduct a study in both adults and pediatrics to verify and describe the clinical benefit of Cyanokit and to assess its safety when used as indicated.

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

2. Study the in-vitro and biochemical compatibility of hydroxocobalamin with the most frequently administered resuscitation drugs and blood products.

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

3. Perform Segment I (Fertility and Early Embryonic Development) studies, as per ICHM3, S5A, S5B, and S5B(M) Guidances to Industry.

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

4. Perform Segment II (Embryofetal Development) studies in two species, as per ICHM3, S5A, S5B, and S5B(M) Guidances to Industry.

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

5. Perform Segment III (Peri- and Post-natal Development) studies, as per ICHM3, S5A, S5B, and S5B(M) Guidances to Industry.

Protocol Submission: March 2007
Study Start: June 2007
Final report Submission: Jan 2009

6. 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).

Protocol Submission: Feb 2007
Study Start: April 2007
Final report Submission: October 2007

7. Conduct a toxicology study of adequate dose and duration to characterize the toxicological safety of the drug product shelf life specifications (stability specifications).

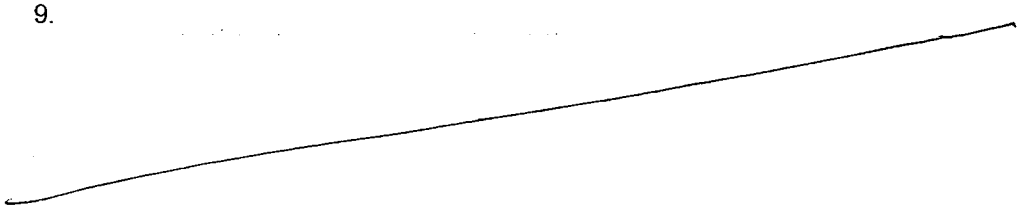
Protocol Submission: Feb 2007
Study Start: April 2007
Final report Submission: October 2007

8. Adequately assess photosafety to support the drug as described in the 2003 Guidance for Industry: Photosafety Testing.

b(4)

Protocol Submission:	March 2007
Study Start:	June 2007
Final report Submission:	March 2008

9.



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/s/

Matthew Sullivan
12/15/2006 12:19:45 PM
CSO

ADRA Rev #1 of Action Package for NDA 22-041, Cyanokit (hydroxocobalamin) Lyophilized Powder for Injection

Reviewer: Lee Ripper, HFD-102
Date received: 11/28/06
Date of review: 12/5/06; *12/15/06*
Date original NDA received: 6/16/06
UF goal date: 12/19/06, action goal date 12/15/06

Proposed Indication: Tx of known or suspected cyanide poisoning
Action type: AP
RPM: Matt Sullivan
Drug Classification: 3PV, Subpart I (animal rule)
505(b)(1) application

Debarment Certification: AC
Financial Disclosure: Not needed; subpart I approval, efficacy based on animal study; human data considered to be supporting data
Safety Update: 10/6/06; MOR p.65 notes that SU information was incorporated into the review.
Risk Management Plan: OSE review 11/16/06
Clinical Inspection Summary: The efficacy study in dogs was audited. No issues were raised. *Clin Pharm inspection of 3 sites resulted in a 483 at each site. See 12/15/06 Addendum to Clin Pharm Review and Office Director's Review.*
ODS/DMETS Review of Proprietary Name: 11/13/06, does not recommend the use of the proprietary name Cyanokit. Review includes review of labels. DR ltr out 11/17/06. *DD and OD reviews find name Cyanokit acceptable.*
DSRCS Review of PPI: *12/12/06.*
DDMAC Review: None in pkg; DMETS review says DDMAC finds the proprietary name Cyanokit acceptable. *RPM sent consult to DDMAC 12/6/06. No written review in DFS. DDMAC told RPM they had no additional comments beyond those already provided by SEALD.*
SEALD Review of PLR: 10/11/06. *Review of pharmacologic classification 12/11/06.*
EA: CMC review states that categorical exclusion was claimed and granted.
EER: *AC 12/13/06*
PSC/WU Mtg: 11/27/06

CMC section to Rick Lostritto, 12/5: Dr. Lostritto emailed that he does not need to see the package.
P/T section to Ken Hastings, 12/5: Dr. Hastings emailed that he will review the package if Dr. Meyer requests; otherwise, he does not need to see it. *Review dated12/13/06.*

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/s/

Leah Ripper
12/15/2006 06:20:06 PM
CSO

MEMORANDUM
Dec. 13, 2006

TO: File
FROM: Kenneth L. Hastings, Dr.P.H., D.A.B.T.

SUBJECT: NDA 22-041

I concur with Drs. R. Daniel Mellon and Lawrence Leshin that the marketing application for Cyanokit (hydroxycobalamin) may be approved based on review of submitted nonclinical data. The post-marketing commitments concerning reproductive toxicology studies, qualification of impurities, and other issues are reasonable.

_____
Kenneth L. Hastings, Dr.P.H., D.A.B.T.
Associate Director
Office of New Drugs

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/s/

Kenneth Hastings
12/13/2006 04:03:28 PM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 12, 2006

TO: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

VIA: Matthew Sullivan, M.S., Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for Cyanokit (hydroxocobalamin) powder for solution, for intravenous use, NDA 22-041

Background and Summary

EMD pharmaceuticals submitted an NDA on June 16, 2006, for Cyanokit (hydroxocobalamin) powder for solution, for intravenous use, NDA 22-041, for the treatment of known or suspected cyanide poisoning. Priority review status was granted and the NDA will be considered for approval under the Subpart I regulations (Approval for new drugs when human efficacy studies are not ethical or feasible).

Patient information for Cyanokit is required under Subpart I (314.610(b)(3).

Comments and Recommendations

1. See the attached patient information for our suggested revisions (marked and clean). We have removed unnecessary information, simplified language where possible, and lowered the reading level from a grade level of 10.2 to 6.7 (Flesch-Kincaid Grade Level). Patient information should be written at no higher than an 8th grade reading level in order to enhance comprehension among a broad range of patients, including those with lower literacy levels. Approximately 50 percent of U.S. adults comprehend written information when written at or less than an 8th grade reading level.
2. Cyanokit will only be used in emergency situations in the field or hospital. The patient will not receive the patient information with the administration of the product. The sponsor should state the planned mechanism for dispensing this required information to a patient.

Please call us if you have any questions.

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

✓ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

FDA-Approved Patient Labeling

Patient Information
Cyanokit (hydroxocobalamin) powder for solution, for intravenous use
Treatment for known or suspected cyanide poisoning

What is Cyanokit?

Cyanokit is an emergency treatment (antidote) used in patients with known or suspected cyanide poisoning. Cyanide is a chemical poison. Cyanide poisoning can happen from:

- breathing smoke from household and industrial fires
- breathing or swallowing cyanide
- having your skin exposed to cyanide

Cyanide poisoning is a life-threatening condition because cyanide stops your body from being able to use oxygen. You can die if your body does not have enough oxygen.

Cyanokit was approved for the treatment of known or suspected cyanide poisoning based on testing:

- how well it worked in animals (It is not ethical to poison people with cyanide in order to test a treatment.)
- its safety in people with cyanide poisoning

How is Cyanokit used?

Cyanokit is given through a vein (intravenous or I.V,) over 15 minutes by an emergency care provider or doctor. A second dose may be given to you if needed.

What are possible side effects with Cyanokit?

Serious side effects may include:

- **allergic reactions.** Signs of a serious allergic reaction include chest tightness, trouble breathing, swelling, hives, itching, and a rash.
- **increased blood pressure**

Other side effects may include:

- **red colored urine**
- **red colored skin and mucous membranes, acne-like rash**
- **nausea, vomiting, diarrhea, bloody stools, trouble swallowing, stomach pain**
- **throat tightness, dry throat**
- **headache, dizziness, memory problems, restlessness**
- **infusion site reaction**
- **eye swelling, irritation, or redness**
- **swelling of feet and ankles**
- **irregular heart heat, increased heart rate**
- **fluid in lungs**

These are not all the side effects with Cyanokit.

After treatment with Cyanokit:

- **Skin and urine redness.** Skin redness may last up to 2 weeks. Avoid sun exposure while your skin is red. Urine redness may last up to 5 weeks.
- **Acne-like rash.** An acne-like rash may appear 7 to 28 days after treatment with Cyanokit. This rash usually goes away without any treatment.
- **Breastfeeding.** Talk to your doctor if you breastfeed. The ingredient in Cyanokit may pass into your breastmilk. You and your doctor can decide when and if you can breastfeed your baby again

Talk to your doctor about any side effect that bothers you or that does not go away.

[insert manufacturer contact information]

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/s/

Jeanine Best
12/12/2006 01:41:11 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
12/12/2006 04:44:15 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 11, 2006

FROM: Nilufer Tampal, Ph.D.
Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-041, Cyanokit (Hydroxocobalamin) Lyophilized Powder (5.0 g) for IV Infusion, Sponsored by EMD Pharmaceuticals.

TO: Robert Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

At the request of DAARP, the Division of Scientific Investigations (DSI) conducted audits of the following safety and pharmacokinetic, and non clinical studies:

Study: **EML 015722-H101:** A double-blind, randomized, placebo-controlled, single-ascending-dose study, with a 4-week follow-up, of the safety, tolerability and pharmacokinetics of 4 intravenous doses (2.5g, 5g, 7.5g and 10g) of hydroxocobalamin in healthy subjects [——— *Study #: 07/59487-03 (clinical)and 66344 (Bioanalytical)*]

Study: **N106342:** Efficacy of Intravenous Hydroxocobalamin (Cyanokit®) Administration Following Intravenous Poisoning with Potassium Cyanide in Adult Beagle Dogs (——— *Study # 66346*)

b(4

Study EML 015722-H101 is pivotal for the approval of NDA 22-041 as this is the only clinical study submitted which provides safety and pharmacokinetic information in humans.

Animal efficacy information is the basis for clinical indication in this NDA. Study N106342 is the pivotal non clinical study to support the clinical indication.

The clinical and analytical[1] portions of Study EML 015722-H101 were conducted at [redacted] respectively. In addition, DAARP requested audit of clinical laboratory parameters due to the high number of abnormal clinical laboratory values that were attributed to interference from hydroxocobalamin (OH-Co). The clinical laboratory evaluations for the study were performed at [redacted].

b(4)

The in-life portion of Study N106342 was conducted at [redacted]. This portion was audited earlier by DSI with no objectionable findings that affected the study outcome. DSI's review of the audit dated 11/15/06 was forwarded to DAARP. In addition to the in-life portion, DAARP requested audit of the bioanalytical portion[1] at [redacted] This report is limited to the audit of analytical portion for Study N106342. (The audit of blood cyanide analysis at [redacted] was not requested for audit and was not audited by DSI)

Following the inspections at [redacted] and [redacted], Form 483 was issued. The inspection at [redacted] included analytical audits of Studies EML 015722-H101 and N106342, as both studies used the same assays. Form 483 was issued at the conclusion of the inspection at [redacted] DSI's evaluation of the significant items follows:

STUDY EML 015722-H101

Clinical Site: [redacted]

1. **Failure to assure that subjects were administered treatments according to the randomization code.**
   The firm failed to retain the sealed codes that were provided with the treatment kits for this double blinded study. According to the firm, the sealed codes were destroyed following the study. Therefore, placebo and drugs administered to the subject could not be confirmed during the inspection.

[1] The analytical portion for Study EML 015722-H101 included assay of total cobalamins in plasma and urine, and free cobalamin in plasma. For Study N106342, the analytical portion included analysis of total cobalamins and cyanocobalamin in plasma.

2. **Immediate storage of blood samples at 4°C following collection cannot be determined.**
For preparation of plasma samples for free cobalamin, the protocol required that subject blood samples be stored on ice immediately after collection to minimize protein binding post collection. There was no documentation to assure that the blood samples were immediately transferred to ice bath.

3. **Time elapsed between blood sample collection and blood gas analysis cannot be determined.**
Blood gas analysis was not performed at bedside as required by the protocol. The analyzer was located in a different room from the clinic. Although time of analysis was recorded on analyzer printouts, the accuracy of the time is questionable as there were instances where time of analysis was prior to time of blood collection. There was no documentation that the analyzer's internal clock was synchronized with the clinic clock. Therefore, it is not known if blood gas was analyzed immediately after collection. The medical office should evaluate the impact of this finding on the accuracy of the blood gas results.

4. **Centrifuge records were incomplete.**
The logs fail to record the dates and the settings of centrifugation. b(4)

Clinical Laboratory: ———————————

As described in the NDA, the sponsor attributed the high number of abnormal clinical laboratory results to colorimetric interference of hydroxocobalamin (OH-Co) with the measurement of urine, hematology and coagulation parameters. To investigate the interference of OH-Co on the clinical laboratory measurements, ——————— conducted an exploratory study —-19453. The DSI inspection audited both Study —-19453 and analyses of clinical samples from Study EML 015722-H101. The inspection revealed the following findings:

5. **Failure to assure that same analyzer brand and model were used for the exploratory and clinical studies and failure to specify which exploratory tests were conducted at the two facilities.**
The inspection found that only the exploratory tests for clinical chemistry were performed in ——————— / in ———————; the exploratory tests for urine, hematology and coagulation parameters were conducted at their other facility in ——————— The firm had no

documentation to demonstrate that the same brand and model of analyzers used in Study EML 015722-H101 were used for the exploratory work for urine analysis[2] and coagulation parameters at the Brandenburg facility. Therefore, DSI cannot confirm the basis for extrapolation of the interference results (absolute values and trends) from the exploratory Study —-19453 to Study EML 015722-H101 for urine analysis and coagulation parameters.

6. **Failure to document preparation of OH-Co stock and spiking solutions used for the exploratory investigation.**
To investigate the interference of OH-Co concentrations, ———— measured clinical laboratory parameters in whole blood, plasma and urine that were spiked with varying concentrations of OH-Co in Study —-19453. However, the firm failed to document the preparation of the OH-Co spiking solutions. Therefore, the accuracy of the OH-Co concentrations in the pooled human matrix used for the exploratory study —-19453 cannot be assured.

b(4)

Similarly, during analysis of clinical laboratory samples for Study EML 015722-H101, there was no documentation for preparation of OH-Co controls for the color index tests[3] used to estimate OH-Co concentrations in clinical samples. Thus, the reliability of the correlation of interference between the exploratory and clinical studies based on color intensity cannot be assured.

7. **Training certificate for the analyst was not signed and dated.**
The analyzers for clinical chemistry (' ———————— ,) in Study —19453 were leased. The certificate for training does not identify the analyzer and the analyst, and was not signed and dated.

---

[2] During the inspection the firm stated that same instrument was used for urine analysis in both studies because the same urine analysis strips (Multistix) were used in both studies. According to the firm, these strips can be read only by Clintek instruments.

[3] In the color index test, the color intensity of the clinical samples was visually compared to the color intensity of the OH-Co controls to estimate OH-Co concentrations. The estimated OH-Co concentrations were then used to evaluate extent of interference in the clinical samples based on the exploratory data from the Study —19453.

Analytical Site: [redacted]

8. **Lack of adequate documentation for the following aspects of the studies:**

   a. **Processing of QCs with subject samples.**
   At least two analysts were involved in processing of subject samples in each analytical run. There was no documentation to confirm that each analyst who processed subject samples also processed QCs. During the inspection, the firm stated that their practice allows one analyst to exclusively process QCs and the other to process only subject samples. Processing of QCs with subject samples by each analyst is essential to assure that all samples are handled identically. This enables QCs to reflect the accuracy of the subject concentrations.

b(4)

   b. **Time of removal from freezer and processing of QCs.**
   There was no documentation of when QCs were removed from the freezer and when QCs were processed for analysis. Therefore, it is not known if QCs remained at bench-top for the same duration as the subject samples prior to analysis.

9. **No internal standard was used in the assays.**
   Specifically the total cobalamin assay in plasma does not include an internal standard to normalize the variability during sample processing. Due to the high run failure rate (20-30%) found in this audit for total cobalamins, the failure to utilize an internal standard is of concern.

10. **No objective criteria for selecting pharmacokinetic (PK) repeats.**
   The sponsor identified the PK repeats without providing objective criteria. In addition, firm selected repeats for confirmation purposes without established criteria. Majority of these repeats for total coblamins in urine and plasma matched the original values. However, 44% (12 of 27) of the repeats for free cobalamin differed from their original values by >30%, suggesting the lack of reproducibility and confidence in the free cobalamin assay.

b(4)

STUDY N106342

Analytical Site: [redacted]

The analytical findings for Study N106342 were similar to the analytical observations for the human study EML 015722-H101.

However, unlike the human study, the findings do not significant impact Study N10632, as the QCs were processed by the same analyst who processed subject samples. Therefore, accuracy of QC results is indicative of the accuracy of animal concentrations.

Conclusions:

Clinical: Study EML 015722-H101

DSI recommends that the medical officer evaluate the significance of the following findings on the acceptance of the clinical results for Study EML 015722-H101:

A. The treatments (placebo or drug) administered to subjects in Study EML 015722-H101 cannot be confirmed during the inspection due to the lack of sealed codes (Item 1).

B. Immediate analysis of blood gas following collection cannot be established (Item 3).

C. With regard to interference of OH-Co concentrations on the measurement of clinical laboratory parameters:

b(4)

i. There was no documentation that the same model and brand of analyzers for urine analysis and coagulation parameters were used in the exploratory Study ~-19453 and Study EML 015722-H101 (Item 5). In light of this finding, DSI cannot confirm the basis for extrapolation of interference results from the exploratory study to Study EML 015722-H101 for urine analysis and coagulation parameters.

ii. Due to the lack of documentation to confirm accurate preparation of OH-Co controls, the correlation between interference and OH-Co concentrations for various clinical laboratory parameters in the exploratory Study ~-19453 cannot be assured (Item 6).

Analytical: Study EML 015722-H101

D. The accuracy of concentrations for total cobalamin in plasma and urine, and free cobalamin in plasma cannot be assured in Study EML 015722-H101, as handling of QCs with subject samples was not assured (Item 8).

E. The accuracy of free cobalamin concentrations in Study EML 015722-H101 cannot be assured as:

a. There was no assurance that blood samples were stored at 4C immediately following collection to minimize protein binding post collection (Item 2).

b. The PK repeat data suggests lack of reproducibility of the assay in incurred samples (Item 10).

Analytical: Study N106342

F. There were no significant findings that affected the analysis of total cobalamins and cyanocobalamin in Study N106342.

After you have reviewed this memo, please append it to the original NDA submission.

Nilufer Tampal, Ph.D.

Sriram Subramaniam, Ph.D.

Final Classifications:
VAI:
VAI:
VAI:

b(4)

cc:
DSI/RF
DSI/GLPBB/Tampal/Subramaniam/Himaya/CF
OND/DAARP/Simone/Raheja/Matthew Sullivan(NDA 22-041)
OCP/DCP2/David J. Lee/Doddapaneni (NDA 22-041)
Draft: SS 12/8,11/06
Edit: NT 12/8/06, JAO & MKY 12/11/06
DSI 5720; O:\BE\EIRCOVER\22041emd.cyn.doc
FACTS 759380

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/s/

Sriram Subramaniam
12/12/2006 12:04:19 PM
PHARMACOLOGIST
The paper copy was signed by Drs. Viswanathan and Subramaniam, and signed for Dr. Tampal on December 12, 2006.

Meeting Summary: Established Pharmacologic Classification Study Endpoints and Label Development (SEALD) Team

Application Number: 22-041/S-000
Review Division: Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Review Team: Cyanokit Review Team
Meeting Date: December 8, 2006

Drug Names: Cyanokit (hydroxocobalamin)
Regulatory Project Manager: Matthew Sullivan
Medical Officer: Arthur Simone

SEALD Label Initiatives Specialist(s): William Pierce
Concurrence(s): Lilliam Rosario, Acting SEALD Labeling Team Leader
Through: Laurie Burke, Director SEALD

Background:

On December 8, 2006, SEALD-Labeling team members met with the Cyanokit review team to discuss the pharmacologic classification terminology for inclusion in the Highlights of labeling for Cyanokit (hydroxocobalamin) as required in the CFR 201.57(a)(6).

The teams decided that "**antidote**" adequately describes the established pharmacological class for Cyanokit (hydroxocobalamin). Thus, the indication statement would read:

> *"Cyanokit contains hydroxocobalamin, an **antidote** indicated for the treatment of known or suspected cyanide poisoning. (1.1)....*

The SEALD-labeling team requests that the Cyanokit Review Team document the rationale for the pharmacological classification designation of Cyanokit in the appropriate NDA review. Based on these discussions, we suggest this information be included in the "Labeling Review" section of the medical officer's NDA review template.

Established Pharmacologic Classification of Cyanokit (hydroxocobalamin) and sodium nitrite/sodium thiosulfate:

The scientific validity AND clinical meaningfulness for proposed pharmacological classification terms were examined for hydroxocobalamin, sodium nitrite/sodium thiosulfate, and related products.

Scientific Validity:

- The mechanism of action for hydroxocobalamin is to bind to cyanide ions by substituting the hydroxo ligand linked to the trivalent cobalt ion to form cyanocobalamin; a stable, nontoxic compound excreted in the urine.

- "**Antidote**" is a scientifically valid physiological effect term for hydroxocobalamin in this indication ["antidote: an agent that neutralizes a poison or counteracts its effects" (Stedman's, 2006)].
- The pharmacologic classification term "vitamin analog" is a valid chemical structure term for use as a pharmacologic classification for hydroxocobalamin *(also see Clinical Meaningfulness below).*

Clinical Meaningfulness:

- The pharmacologic classification term "vitamin analog" was deemed not to be clinically meaningful for this product in this indication. "Vitamin analog" used alone as a pharmacologic classification may be misleading and confused with cyanocobalamin (B12, indicated for pernicious anemia) or other vitamins used for vitamin supplementation.
- "**Antidote**" was determined to be a clinically meaningful term to describe hydroxocobalamin..
- More specific pharmacologic classification terms for Cyanokit (hydroxocobalamin) such as "vitamin analog antidote", were deemed to provide limited additional clinical meaning to the **"antidote"** pharmacologic classification for this indication and was omitted.

The established pharmacologic classification (i.e., "**antidote**") was determined to be a scientifically valid and clinically meaningful established pharmacologic classification for Cyanokit (hydroxocobalamin).

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/s/

William Pierce
12/8/2006 04:59:59 PM
INTERDISCIPLINARY

Lilliam Rosario
12/8/2006 09:14:31 PM
PHARMACOLOGIST

Laurie Burke
12/11/2006 07:26:47 PM
INTERDISCIPLINARY

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, November 30, 2006 12:51 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: cindy.marshall@emdpharmaceuticals.com
Subject: CMC IR 11-30-06

Attachments: IR 11-30-06 CMC.doc

Elliott –

As promised, here is another information request. CMC has requested a response by Monday.

Thanks
Matt

IR 11-30-06
CMC.doc (39 KB)

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration

Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

Provide responses to the following CMC comments by December 4, 2006.

1. Revise the impurity limits in the drug substance hydroxocobalamin as recommended and list the identified impurities (— and — by their abridged chemical names:

	≤	%
Impurity		%
Impurity		%
Impurity		%
Impurity		%
Individual drug related unspecified impurity	≤	%
Total (sum of all reportable related impurities ≥ %)	≤	%

b(4)

2. Revise the release and shelf life impurity limits in the drug product (hydroxocobalamin for injection, 2.5g) as recommended and list the identified impurities , and — by their abridged chemical names:

	≤	
Impurity		
Impurity		
Impurity		
Impurity		
Impurity		
Impurity		
Impurity at		
Impurity at		
Individual drug related unspecified impurity	≤	
Total (sum of all reportable related impurities ≥ %)	≤	

b(4)

3. Explain why all the stability data of Batches 2079, 2080 and 2081 stored at 25°C/60% RH, have identical values for the content of Impurity on each time point reported.

b(4)

4. Provide a commitment that by June 30, 2007, the following additional data would be submitted to the NDA:
   (a) Data supporting the identity of all impurities exceeding the identification threshold of —% in the drug substance.
   (b) Data supporting the safety of all impurities exceeding the qualification threshold of —% in the drug substance.

(c) Data supporting the identity of all impurities exceeding the identification threshold of —%% in the drug product.

b(4)

(d) Data supporting the safety of all impurities exceeding the qualification threshold of —% in the drug product.

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/s/

Matthew Sullivan
11/30/2006 02:03:57 PM
CSO

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, November 14, 2006 5:48 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: FW: NDA 22-041 - Cyanokit - Questions

Elliott -

Please find attached our responses to the three questions that you posed to us on 11/9.

Please let me know if it doesn't come through OK.

Matt

---

b(4)

1 - Does this mean that Dr. Salazar does not accept our proposed Spec?

RESPONSE: Affirmative

2 - Is there other data we can provide, e.g., information on total exposure to this impurity from multiple dose tox studies, that would support the higher specification limit for ——— that we have proposed

RESPONSE: A minimal in vitro genetic toxicology screen (one in vitro mutagenicity assay and one in vitro assay for chromosome damage) should be completed, with material containing the amount of impurity at or exceeding the proposed specification limits of —% for Impurity with ——; —% for main impurity, ——— and — for Total Impurities. The proposed specifications based on the proposed —— shelf life will exceed the ICHQ3B threshold for qualification. If the sponsor agrees to a shorter expiration date, as recommended by the chemistry review team, the genetic toxicology studies would only be required to support anything greater than a 25 month shelf life.

3 - Can we get some general feedback on our proposed shelf life specifications as there are other limits that we have proposed that exceeded the levels in tox studies

RESPONSE:
1.- Hydroxocobalamin assay: ——— g/vial, equivalent to ———of the labeled amount as shelf life specification limit.

2.- Related Substances (% w/w) for release and shelf life specification limits:

b(4)

Impurity I	
Impurity I	
Impurity	
Impurity	
Impurity	
Impurity	
Impurity at	
Impurity at	
Any other unspec. impurity	—
Total content of impurities	—

3.- The expiration dating period granted is for the lyophilized product is —months with storage conditions of 252C (77C); excursions permitted to 15-300C (59-86CF) [see USP

Controlled Room Temperature].

The expiration period was based on the [redacted] qualification level for the Main Impurity of

b(4)

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ON ORIGINAL

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/s/

Matthew Sullivan
11/28/2006 04:28:52 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-041

DISCIPLINE REVIEW LETTER

11/17/06

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Cyanokit (hydroxocobalamin).

The Division of Medication Errors and Technical Support (DMETS) review of your submission is complete and the proprietary name, Cyanokit, in not recommended. In reviewing the proprietary name, the primary concern relating to look-alike confusion with Cyanokit is Cyanoject. Additionally, DMETS has concerns with this proposed packaging configuration because its design is error prone.

Cyanoject was identified as a name with a similar appearance to Cyanokit. The product named "Cyanoject" is no longer marketed in the United States. However, generic injectable formulations of the active ingredient, Cyanocobalamin, remain on the market and the name "Cyanoject" is still found in commonly used references, including Drug Facts and Comparisons and Clinical Pharmacology Online. We have learned from post-market surveillance that it is plausible for a generic equivalent to be dispensed for the discontinued product when the discontinued drug name appears in common drug references. Therefore, it is possible for prescriptions to be written for Cyanoject in which case a pharmacist would dispense the generic formulation of Cyanocobalamin.

Confusion may also arise from the similarity of the active ingredients in both products. Each molecule of Hydroxocobalamin (the active ingredient in Cyanokit) combines with one molecule of cyanide to form Cyanocobalamin (the active ingredient in Cyanoject). Both Hydroxocobalamin and Cyanocobalamin are commonly known as Vitamin B-12. However, Cyanocobalamin is indicated only for the treatment of B-12 deficiency or pernicious anemia, or as the Schilling Test to determine B-12 Deficiency. Whereas hydroxocobalamin is also indicated for treatment of B-12 deficiency at much smaller doses (30 mcg to 200 mcg) in addition to the proposed indication for known or suspected cyanide exposure. Cyanocobalamin, the active ingredient in Cyanoject, is administered at the

recommended dose of 30 mcg, 100 mcg, 200 mcg, or 1000 mcg per day via intramuscular or deep subcutaneous injection. The 100 mcg or 200 mcg dose may be given once a month.

The two names share some orthographic similarities. The two names share an identical beginning 'Cyano-' and both names end with the same letter 't' which contributes to the look-alike properties. Furthermore, the letters '-ki' in Cyanokit and the letters '-jec' in Cyanoject can look similar when scripted.

Cyanoject and Cyanokit have some different product characteristics, such as; vial strength (1000 mcg, 10 mg, or 30 mg vs. 2.5 g), prescribed dose (30 mcg, 100 mcg, 200 mcg, or 1000 mcg vs. 5 g) and route of administration (intramuscular or deep subcutaneous vs. intravenous infusion). However, the setting of use for both products may overlap in an inpatient setting, such as a hospital, where both may be administered via injection.

A prescription for Cyanoject should specify the microgram or milligram dose and the route of administration which may help to differentiate it from a prescription for Cyanokit. A prescription for Cyanoject should also specify a dosage frequency such as daily or monthly. However, it is possible that a prescriber in an inpatient setting could order the Cyanoject as a one time dose (e.g., Cyanoject #1 now) as part of an order for a Schilling Test, which has a standardized dose of 1000 mcg. Cyanokit could also be ordered as "Cyanokit, #1, now" which increases the potential for confusion. Because both Cyanoject and Cyanokit contain Vitamin B12 derivatives, it may be difficult for a healthcare professional to recognize an error before the wrong product is administered. DMETS cannot comment on the clinical significance should confusion occur and the wrong product be administered. However, the potential for patient harm may be severe should a patient with cyanide poisoning be treated with the wrong product.

Therefore, due to the potential for confusion with Cyanoject, DMETS does not recommend the use of the proposed proprietary name Cyanokit.

Additionally, DMETS reviewed the labels and labeling from a safety perspective. We have identified the following areas of improvement, which may minimize potential user error.

A. GENERAL COMMENTS

1. We note that you have proposed to label this product Cyanokit 2.5 g. This name is misleading for two reasons:

   (a) The kit contains 5 g of the active ingredient, Hydroxocobalamin, rather than the labeled 2.5 g. The name and strength recommended for the kit are:

TRADENAME 5.0 g

(b) The term "Cyanokit" refers to the entire contents of the unit and not just the active ingredient, Hydroxocobalamin. The name Cyanokit, specifically the suffix '-kit' describes the entire contents of the package which includes the two vials of Hydroxocobalamin, two transfer spikes, and one sterile IV infusion set. Thus the principal display panel should indicate all components contained in the carton. Therefore, the non-proprietary name, Hydroxocobalamin, should not appear in conjunction with this name. Conversely, the non-proprietary name should be the only name that appears on the container label of active drug. In summary, the proprietary name, Cyanokit, should only be used on the carton and insert labeling with no non-proprietary name associated with it. The active drug substance should be labeled only with its non-proprietary name.

2. The proper names for the diluents should be used in all labels and labeling (e.g., 0.9% Sodium Chloride Injection, not "Sterile Saline (0.9% NaCl) and 5% Dextrose Injection, not "5% dextrose (D5W)."

3. The letter 'C' in Cyanokit is shaped like a wrench or a cellular receptor which is distracting and makes the proprietary name more difficult to read. It is recommended that a regular letter 'C' be used for the font in the proprietary name. Additionally, the same graphic is included as a large symbol on the carton labeling. Please remove the graphic as it distracts away from the important information.

4. For the storage directions provide the following revisions:

(a) Add the text "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. This statement is to replace the originally proposed in the application.

(b) Add the text "at temperatures not exceeding 40°C (104°F)," so the statement reads "Stable up to 6 hours after reconstitution at temperatures not exceeding 40°C (104°F)." Also add the statement, "Discard the unused portion."

B. CONTAINER LABEL (Hydroxocobalamin, 2.5 g Vial)

1. Refer to General Comments A1 to A4.

2. The name in the container label for this product should read "Hydroxocobalamin for Injection, 2.5 g ". The route of administration statement "for Intravenous Use" should be relocated to appear below the non-proprietary name. Additionally, increase the prominence of this statement. A statement regarding the conditions for reconstitution is also recommended, see example below:

Hydroxocobalamin for Injection, 2.5 g
For Intravenous Use -
To be reconstituted with 100 mL of 0.9% Sodium chloride Injection

Also, revise the composition statement as follows:
"Vial Contents:
Hydroxocobalamin lyophilized powder, 2.5 g
Hydrochloric acid for pH adjustment "

3. The prominence of the strength (2.5 g/vial) should be increased. Furthermore, it is recommended to express the strength as "2.5 g per vial". On all labels and labeling, it should be apparent that each vial contains 2.5 g of hydroxocobalamin, Also, it is recommended to add a statement to the container label indicating that this vial is a component of Cyanokit. This statement should not override the prominence of the non-proprietary name and is intended to provide tracking information of the kit components.

4. It is recommended to add the following text to the fill line:
"FILL LINE"
(Upright position)

C. CARTON LABELING (Hydroxocobalamin, 2.5 g Vial Carton)

Refer to General Comments A1 to A4.

D. CARTON LABELING (Outer Carton Labeling for Cyanokit Unit)

b(4)

1. Refer to General Comments A1 to A4.

2. Add the following text to the frontal panel:
Kit contents:
2 Vials, each containing Hydroxocobalamin for Injection, 2.5 g
Intravenous administration set
2 Transfer spikes
1 Quick Use Reference Guide
1 Package Insert

Diluent is not included.

E. INSTRUCTIONS FOR USE CARD

1. Refer to General Comments A1-A4.

2. The contents of each Cyanokit unit should be listed on the card, such as "each unit contains 2 vials of Hydroxocobalamin 2.5 g"

3. The wording "Repeat for Adult", specifically the use of the word "adult" is questionable. Cyanokit is not indicated or intended for use in children, but this wording implies otherwise.

4. The following revisions to the check list are recommended:

Starting Dose: 5 grams (2 vials)
1. **Reconstitute**
   Add 10 mL of 0.9% Sodium chloride for Injection to vial using transfer spike. Fill to line. Vial in upright position.
2. **Mix**
   Rock or rotate vial for 30 seconds to mix solution. Do not shake.
3. **Infuse First Vial**
   Use vented IV tubing to hang and infuse over 7.5 minutes.
4. **Infuse Second Vial (— Step 1. and 2. before second infusion)**
   Use vented IV tubing to hang and infuse over 7.5 minutes.

b(4)

5. Revise the text that references the Package Insert such as, "See Package Insert for **alternate diluents, incompatibilities with other drugs and** full prescribing information."

6. We recommend that important safety information also be included on this card, perhaps on the back. Specifically, bulleted statements reminding practitioners of topics such as:

   (a) Guidance on appropriate patient selection for use of Cyanokit.

   (b) Physical and chemical incompatibilities that may necessitate the use of a separate intravenous line for administration.

   (c) A list of compatible diluents and intravenous solutions.

   (d) Other monitoring requirements such as blood pressure monitoring and monitoring for hypersensitivity, and interventions that may be required to manage these events.

F. PACKAGE INSERT LABELING

1. HIGHLIGHTS OF PRESCRIBING INFORMATION:
DOSAGE AND ADMINISTRATION section

We recommend that a statement reminding the practitioner of important incompatibilities with Cyanokit be placed in the HIGHLIGHTS OF PRESCRIBING INFORMATION [e.g., There are a number of drugs and blood products that are incompatible with Cyanokit, thus Cyanokit may require a separate intravenous line for administration (2.3)]

2. FULL PRESCRIBING INFORMATION:
DOSAGE AND ADMINISTRATION section

(a) Directions for Reconstitution sub-section

The complete directions on preparation and administration of Cyanokit need to be included in the PI. This information should be consistent with the "Instructions for Use" card. Specifically, this section should state that the complete dose of 5 g should be comprised of two 2.5 g vials that are reconstituted and prepared as directed.

(b) Incompatibility sub-section

In the chemical incompatibility paragraph, we recommend that you define the term as you did in the physical incompatibility paragraph (e.g., particle formation). Additionally, this sub-section follows the Use With Other Cyanide Antidotes section where it may be overlooked by the reader. We recommend that a statement regarding the number of important incompatibilities with Cyanokit be prominently featured within the first three paragraphs of the DOSAGE AND ADMINISTRATION section.

(c) Rate of Infusion sub-section

The complete recommendations of the rate of infusion for Cyanokit need to be included in the PI. This information should be consistent with the "Instructions For Use" card. Specifically, this section should state that one reconstituted vial (2.5 g) should be infused over 7.5 minutes and then followed by the second reconstituted vial (2.5 g) which should be infused over 7.5 minutes, for a total initial dose of 5 g administered over 15 minutes. This section should also include rate of infusion information for the optional second dose which ranges from 15 minutes (for patients in extremis) to 2 hours.

3. PATIENT COUNSELING INFORMATION section

This section should note that Cyanokit may cause the patient's urine to turn red. Revise accordingly. As currently written, the FDA Patient Approved Labeling section contains this side effect but it should also be in the PATIENT COUNSELING INFORMATION section for the prescriber.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with

the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Parinda Jani
11/17/2006 12:57:56 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 16, 2006

TO: Bob Rappaport, M.D., Director
Division of Analgesics, Anesthetics, & Rheumatology Products, HFD 170

THROUGH: Gerald Dal Pan, MD, M.H.S., Director
Office of Surveillance and Epidemiology, HFD-400

FROM: OSE Cyanokit RiskMAP Team

DRUG: Cyanokit (hydroxocobalamin)

NDA: 22-041

SPONSOR: EMD Pharmaceuticals

SUBJECT: OSE Review of Risk Management Plan

PID #: 2006-315

INTRODUCTION / BACKGROUND

This consult follows a request by the Division of Analgesics, Anesthetics, & Rheumatology Products (DAARP), for the Office of Surveillance and Epidemiology (OSE) to review a risk management plan (RMP) submitted by EMD Pharmaceuticals to manage the risks associated with the use Cyanokit (hydroxocobalamin), a product indicated for the treatment of known or suspected cyanide poisoning. The primary risks associated with the use of Cyanokit are hypertension and hypersensitivity reactions, events that have been observed both in healthy subjects who received Cyanokit and in patients who were treated with Cyanokit for smoke inhalation. The Sponsor proposes routine training on reconstitution and infusion of the product and routine pharmacovigilance as the management plan for Cyanokit.

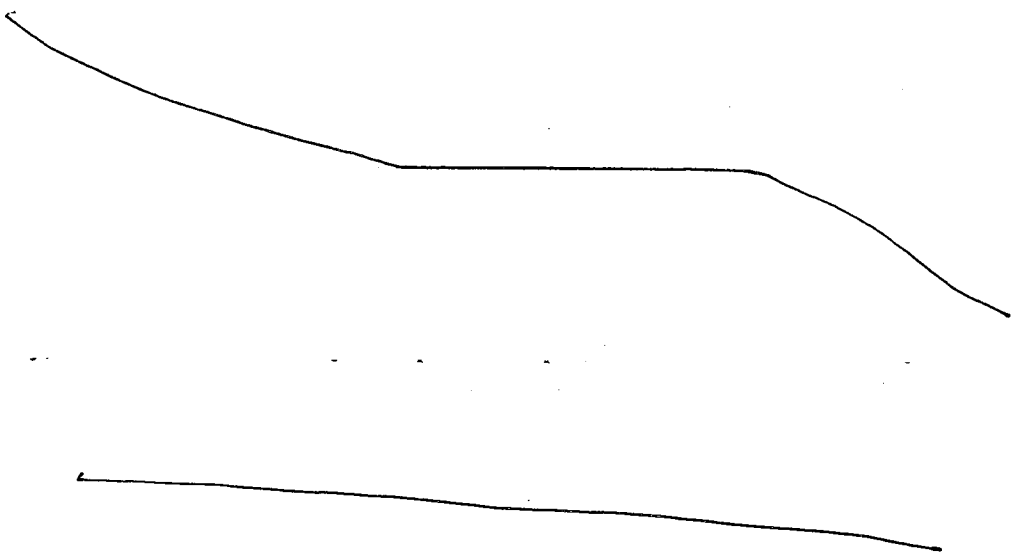
Cyanokit was studied in 136 healthy subjects in a placebo-controlled, single-ascending dose study that examined the safety, tolerability, and pharmacokinetics of Cyanokit. A total of 84 patients received Cyanokit in this study. Hypertension described as systolic blood pressure exceeding 180 mmHg or diastolic blood pressure exceeding 110 mmHg occurred in 18% of

subjects who received 5 grams of hydroxocobalamin and in 28% of subjects who received 10 grams of hydroxocobalamin[1]. According to the labeling the increases were generally transient, and only one patient required additional treatment for the hypertension. Regarding the time course of hypertension, the submission indicated that blood pressure increases were observed beginning at 5 minutes after initiation of the hydroxocobalamin infusion, peaking 20 to 30 minutes after initiation of the infusion, and subsequently declining toward baseline.[2] The RMP submission does not describe the extent (in mmHg) of the blood pressure increases over baseline (either the mean increase or the maximum increase). One healthy volunteer required treatment for hydroxocobalamin-induced hypertension.

Cyanokit was studied in an additional 245 patients with smoke inhalation who had known or suspected cyanide poisoning. Hypertension was observed in some of these patients, but the Sponsor states that the blood pressure changes did not appear to pose additional risk to patients. The Sponsor acknowledged that one patient had a hypertension-related adverse event (not further explained), but no patients experienced a cerebrovascular accident as a result of hydroxocobalamin-associated hypertension. The reviewing division is reviewing the details of the adverse events that occurred within the clinical trial.

Skin erythema and rash occurred in 94% and 20%, respectively, in patients who received 5 grams of hydroxocobalamin and in 100% and 44%, respectively, in patients who received 10 grams of hydroxocobalamin. Additionally, two subjects in the healthy patient study experienced systemic hypersensitivity reactions, including chest tightness, edema, urticaria, pruritus, and dyspnea, in addition to skin rash.

REVIEW OF SPONSOR'S RISK MANAGEMENT PLAN



b(4)

[1] The initial dose of Cyanokit is 5 grams infused over 15 minutes. A second dose of 5 grams may be administered in severe cases.

[2] Fortin Study Cardiovascular Addendum. EMD Pharmaceuticals submission 6/16/2006.

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 2

OSE Cyanokit RiskMAP ReviewTeam

Mary Dempsey, Risk Management Program Coordinator, OSE-IO
Jodi Duckhorn, MA, Patient Information and Research Team Leader, DSRCS
Claudia B. Karwoski, Pharm.D. Team Leader Risk Management Team, OSE-IO
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Nora Roselle, Pharm.D. Safety Evaluator Team Leader, DMETS
Joyce Weaver, Pharm.D., Senior Drug Risk Management Analyst, OSE-IO (Lead)

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

/s/

Mary Dempsey
11/16/2006 10:15:25 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
11/16/2006 05:12:53 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mail Stop 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE REVIEW #:** 06-0207
July 20, 2006	October 19, 2006	
DOCUMENT DATE:	**PDUFA DATE:** December 19, 2006	
June 16, 2006 and July 5, 2006		

TO: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

THROUGH: Nora Roselle, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Laura L. Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Cyanokit**
Each unit contains 2 vials Hydroxocobalamin for Injection
2.5 g/vial

NDA #: 22-041

NDA SPONSOR: EMD Pharmaceuticals, Incorporated

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Cyanokit.

2. DMETS recommends implementation of the comments outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name "Cyanokit" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: August 7, 2006

NDA# 22-041

NAME OF DRUG: Cyanokit
Each unit contains 2 vials Hydroxocobalamin for Injection
2.5 g/vial

NDA HOLDER: EMD Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products, for assessment of the proprietary name, Cyanokit, regarding potential name confusion with other proprietary and/or established drug names. Additionally, the Sponsor has submitted draft container labels, carton, and insert labeling for review and comment from a medication error perspective.

PRODUCT INFORMATION
Cyanokit contains Hydroxocobalamin, a molecule which can bind one cyanide ion by substituting the hydroxo ligand linked to the trivalent cobalt ion, to form Cyanocobalamin. Cyanocobalamin is excreted in the urine. Cyanokit is proposed to be indicated for the treatment of known or suspected cyanide poisoning. If clinical suspicion of cyanide poisoning is high, Cyanokit should be administered without delay.

Each Cyanokit unit consists of the following: 1) two 250 mL glass vials sealed with rubber stoppers and caps with plastic lids, each containing 2.5 g of lyophilized hydroxocobalamin; 2) two sterile transfer spikes; and 3) one sterile intravenous infusion set. The initial dose of Cyanokit is 5 g (two 2.5 g vials) administered as an intravenous infusion over 15 minutes. Depending on the severity of the poisoning and the clinical response, an additional 5 g may be administered by intravenous infusion up to a total of 10 g. The rate of infusion for the second dose ranges from 15 minutes (for patients in extremis) to 2 hours based upon the patient's condition. Each vial of Cyanokit (2.5 g) is to be reconstituted with 100 mL of diluent using the supplied sterile transfer spike. The recommended diluent is 0.9% Sodium Chloride. Lactated Ringers Solution and 5% Dextrose have also been found to be compatible. The mark on the glass vial represents the filling line for a 100 mL volume of diluent. After the diluent is added to the vial, the vial should be rapidly inverted or rocked (not shaken) for at least 30 seconds prior to infusion. The vial is then hung using the vented intravenous tubing and infused over 7.5 minutes. A second 2.5 g vial is prepared and administered over 7.5 minutes for a total dose of 5 g over 15 minutes.

In lyophilized form, Cyanokit should be stored at temperature up to 30°C (86°F). Brief exposure to temperatures up to 40°C (104°F) may be tolerated but exposure should be minimized. After reconstitution, the solution is good for 6 hours at a temperature not exceeding 40°C (104°F).

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Cyanokit to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for the proposed name consisting of two written pharmacy requisition slips and one verbal requisition request, involving health care practitioners within FDA. This exercise was conducted to simulate the ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Cyanokit. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the tradename "Cyanokit" from a promotional perspective.

2. The Expert Panel identified ten proprietary names that were thought to have the potential for look-alike or sound-alike confusion with Cyanokit. These products are listed in Table 1 (pages 4-6), along with the dosage forms available and usual dosage.

---

[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

[4] Phonetic and Orthographic Computer Analysis (POCA)

[5] WWW location http://www.uspto.gov/tmdb/index.html.

6 Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: CYANOKIT: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose	Other
Cyanokit	Hydroxocobalamin for injection 2.5 g/vial Each unit contains: 1) two 250 mL glass vials, each containing 2.5 g of lyophilized Hydroxocobalamin powder; 2) two sterile transfer spikes; 3) one sterile intravenous infusion set	5 g (two 2.5 g vials) administered consecutively as an intravenous infusion over 15 minutes. Depending on the severity of the poisoning and the clinical response, an additional 5 g may be administered by intravenous infusion up to a total of 10 g. The rate of infusion for the second dose ranges from 15 minutes (for patients in extremis) to 2 hours based upon the patient's condition	N/A
Cyclocort	Amcinonide Ointment: 0.1% (15g, 30g, 60g tubes) With Aquatain Cream: 0.1% (15g, 30g, 60g tubes) With Aquatain Lotion: 0.01% (20 mL, 60 mL)	Adults: Apply sparingly to the affected area two to three times daily. Children: Apply sparingly to affected area once daily.	LA
Synacort	Hydrocortisone Cream: 1%, 2.5 %	Children >2 years and Adults: Topical: Apply to affected area 2-4 times/day. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary	LA
Cyanokit	Hydroxocobalamin *Marketed in France, Poland, Hong Kong, and Norway*	No specific information is available on foreign product(s) but product is the same active ingredient as the proposed product.	LA/SA
Senokot **Senokot-S** **OTC**	Sennosides Tablets: 8.6 mg (Senokot) SenokotXTRA Tablets (17.2 mg) Sennosides/Docusate Sodium Tablets: 8.6 mg/50 mg (Senokot-S) Senokot Wheat Bran Fiber Supplement Senokot Childrens' Laxative Syrup is no longer marketed (8.8 mg/5mL)	Senokot/SenokotXTRA Adults: 1—2 tablets (8.6—17.2 mg sennosides) orally twice daily. Maximum dose: 4 tablets (748 mg standardized senna concentrate) twice daily. Children > 27 kg: 1 tablet (187 mg standardized senna concentrate) orally at bedtime. Maximum dose is 2 tablets (374 mg standardized senna concentrate) twice daily. Senokot-S Adults and adolescents ≥ 12 years: 2—4 tablets orally daily. Doses may be taken as a single dose or in divided doses, with doses preferably in the evening. Children 6—11 years: 1—2 tablets orally daily. Doses may be taken as a single dose or in divided doses, with doses preferably in the evening. Children 2—5 years: 1 tablet orally daily, preferably in the evening.	SA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Cyanokit	Hydroxocobalamin for Injection 2.5 g/vial Each unit contains: 1) two 250 mL glass vials, each containing 2.5 g of lyophilized Hydroxocobalamin powder 2) two sterile transfer spikes, 3) one sterile intravenous infusion set	5 g (two 2.5 g vials) administered consecutively as an intravenous infusion over 15 minutes. Depending on the severity of the poisoning and the clinical response, an additional 5 g may be administered by intravenous infusion up to a total of 10 g. The rate of infusion for the second dose ranges from 15 minutes (for patients in extremis) to 2 hours based upon the patient's condition.	N/A
Cyanoject	Cyanocobalamin Injection: 1000 mcg/mL (1 mL, 10 mL and 30 mL vials) *Preparation is no longer marketed but generics remain available.*	Injection for Schilling Test to determine B12 deficiency (1000 mcg intramuscular injection) B12 Deficiency: Intramuscular or Deep Subcutaneous: Adults: Initial: 30 mcg/day for 5-10 days; maintenance: 100-200 mcg/month Pernicious anemia: Intramuscular or Deep Subcutaneous: Adults: 100 mcg/day for 6-7 days; if improvement, administer same dose on alternate days for 7 doses, then every 3-4 days for 2-3 weeks; once hematologic values have returned to normal, maintenance dosage: 100 mcg/month	LA
Sinemet **Sinemet CR**	Carbidopa/Levodopa Tablets: 10 mg/100 mg, 10 mg/250 mg, 25 mg/250 mg Extended-Release Tablets: 25 mg/100 mg, 50 mg/200 mg	Oral dosage (regular-release tablets): Adults: The recommended initial dose is one carbidopa 25 mg/levodopa 100 mg tablet orally three times per day. Dosage may be increased by one tablet every day or every other day, as necessary, until a maximum of eight tablets per day is reached. Oral dosage (extended-release tablets): Adults: The initial dose is one carbidopa 50 mg/levodopa 200 mg tablet orally twice daily. Most patients have been adequately treated with the extended-release tablets in doses that provide 400—1600 mg of levodopa per day. The dosing intervals should be 4—8 hours apart during the waking day. Dosage adjustments should generally be made at 3-day intervals.	SA
Cytotec	Misoprostol Tablets: 100 mcg, 200 mcg	Adults, including the elderly: 200 mcg orally four times per day, with meals and at bedtime. May reduce to 100 mcg orally four times daily in those who do not tolerate 200 mcg dose.	SA
Azactam	Aztreonam Premixed Solution for Injection: 1 g/50 mL, 2 g/50 mL For Injection: 500 mg, 1 g, 2 g	Adults and adolescents: 1—2 g intravenously every 8—12 hours for moderately severe systemic infections. For severe, life-threatening infections, 2 g every 6—8 hours. Children and infants $\geq$ 1 month of age: 30 mg/kg every 6—8 hours depending upon the severity of the infection.	LA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Cyanokit	Hydroxocobalamin for Injection 2.5 g/vial Each unit contains: 1) two 250 mL glass vials, each containing 2.5 g of lyophilized Hydroxocobalamin powder, 2) two sterile transfer spikes, 3) one sterile intravenous infusion set	5 g (two 2.5 g vials) administered consecutively as an intravenous infusion over 15 minutes. Depending on the severity of the poisoning and the clinical response, an additional 5 g may be administered by intravenous infusion up to a total of 10 g. The rate of infusion for the second dose ranges from 15 minutes (for patients in extremis) to 2 hours based upon the patient's condition.	N/A
Monoket	Isosorbide Mononitrate Tablets: 10 mg , 20 mg	Adults: 20 mg orally twice daily, with doses given 7 hours apart ('asymmetric' or 'eccentric' dosing, to allow a 12 hour nitrate-free interval). However, a starting dose of 5 mg may be appropriate in patients with small stature, which should be increased to at least 10 mg by day 2—3 of therapy.	LA
Cancidas	Caspofungin For Injection: 50 mg, 70 mg	70 mg infusion as a loading dose on day 1, followed by 50 mg infusion once daily, administered over 1 hour. Duration of treatment is based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.	LA
*Frequently used, not all-inclusive **LA (look-alike), SA (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Cyanokit with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the ordering process. Two pharmacy requisition orders were written, each consisting of a combination of marketed and unapproved drug products and an order for Cyanokit (see page 7) were written. These orders were optically scanned and one order was delivered to a random sample of the participating health professionals via e-mail. In addition, a verbal pharmacy requisition request was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN ORDER	VERBAL ORDER
Requisition Order 1: 41 | Cyanokit 2 vials Requisition Order 2: 41 | Cyanokit 2 vials	"order code 41, Cyanokit, 2 vials,"

2. Results for Cyanokit:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. The majority of misinterpretations were misspelled/phonetic variations of the name, Cyanokit. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Cyanokit, the primary concerns relating to look-alike and sound-alike confusion with Cyanokit are Cyclocort, Synacort, Cyanoject, Cyanokit, Senokot, Sinemet, Cytotec, Azactam, Monoket, and Cancidas. DMETS also reviewed the labels, labeling, and proposed packaging and have safety concerns with the design of this product. We have many suggestions for improvement which can be found in Section III of this review.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of Cyanokit.

Upon further review of the names identified as primary concerns, it was determined that the proposed proprietary name, "Cyanokit", is marketed as a foreign proprietary name for the same active ingredient, Hydroxocobalamin, in France, Poland, Hong Kong, and Norway. Thus, the foreign proprietary name, Cyanokit, will not be discussed further. Additionally, the names Sinemet, Cytotec, Azactam, Cancidas, and Monoket were not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Cyanokit, in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, and dosage form.

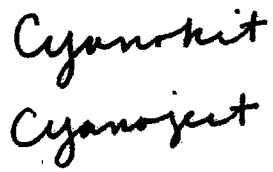
With respect to the remaining names of concern we have the following comments:

1. Cyanoject was identified as a name with a similar appearance to Cyanokit. The product named "Cyanoject" is no longer marketed in the United States. However, generic injectable formulations of the active ingredient, Cyanocobalamin, remain on the market and the name "Cyanoject" is still found in commonly used references, including Drug Facts and Comparisons and Clinical Pharmacology Online. We have learned from post-market surveillance that it is plausible for a generic equivalent to be dispensed for the discontinued product when the discontinued drug name appears in common drug

references. Therefore, it is possible for prescriptions to be written for Cyanoject in which case a pharmacist would dispense the generic formulation of Cyanocobalamin.

Confusion may also arise from the similarity of the active ingredients in both products. Each molecule of Hydroxocobalamin (the active ingredient in Cyanokit) combines with one molecule of cyanide to form Cyanocobalamin (the active ingredient in Cyanoject). Both Hydroxocobalamin and Cyanocobalamin are commonly known as Vitamin B-12. However, Cyanocobalamin is indicated only for the treatment of B-12 deficiency or pernicious anemia, or as the Schilling Test to determine B-12 Deficiency. Whereas hydroxocobalamin is also indicated for treatment of B-12 deficiency at much smaller doses (30 mcg to 200 mcg) in addition to the proposed indication for known or suspected cyanide exposure. Cyanocobalamin, the active ingredient in Cyanoject, is administered at the recommended dose of 30 mcg, 100 mcg, 200 mcg, or 1000 mcg per day via intramuscular or deep subcutaneous injection. The 100 mcg or 200 mcg dose may be given once a month.

The two names share some orthographic similarities. The two names share an identical beginning 'Cyano-' and both names end with the same letter 't' which contributes to the look-alike properties. Furthermore, the letters '-ki' in Cyanokit and the letters '-jec' in Cyanoject can look similar when scripted (see below).



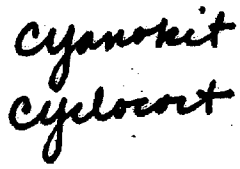
Cyanoject and Cyanokit have some different product characteristics, such as; vial strength (1000 mcg, 10 mg, or 30 mg vs. 2.5 g), prescribed dose (30 mcg, 100 mcg, 200 mcg, or 1000 mcg vs. 5 g) and route of administration (intramuscular or deep subcutaneous vs. intravenous infusion). However, the setting of use for both products may overlap in an inpatient setting, such as a hospital, where both may be administered via injection.

A prescription for Cyanoject should specify the microgram or milligram dose and the route of administration which may help to differentiate it from a prescription for Cyanokit. A prescription for Cyanoject should also specify a dosage frequency such as daily or monthly. However, it is possible that a prescriber in an inpatient setting could order the Cyanoject as a one time dose (e.g., Cyanoject #1 now) as part of an order for a Schilling Test, which has a standardized dose of 1000 mcg. Cyanokit could also be ordered as "Cyanokit, #1, now" which increases the potential for confusion. Because both Cyanoject and Cyanokit contain Vitamin B12 derivatives, it may be difficult for a healthcare professional to recognize an error before the wrong product is administered. DMETS cannot comment on the clinical significance should confusion occur and the wrong product be administered. However, the potential for patient harm may be severe should a patient with cyanide poisoning be treated with the wrong product.

Therefore, due to the potential for confusion with Cyanoject, DMETS does not recommend the use of the proposed proprietary name Cyanokit.

2. Cyclocort was identified as a name with a similar appearance to Cyanokit. Cyclocort is the proprietary name for Amcinonide, a corticosteroid preparation available as a cream, ointment, or lotion which is indicated to treat dermatoses. Cyclocort is available as a 0.1% strength, which is applied sparingly to the affected area two to three times daily. Cyclocort may be applied once daily in children.

The two names share some orthographic similarities. Both names share an identical beginning 'Cy-' and end with the same letter 't'. However, the middle portion of each name '-anoki-' vs. '-clocor-' look distinguishable when scripted and may help to differentiate the two names orthographically. Furthermore, the letter 'k' in Cyanokit and the letter 'l' is Cyclocort each contribute an upstroke in different positions of each name which may also help to differentiate the two names (see page 9).



Cyclocort and Cyanokit have different product characteristics, such as; strength (0.1% vs. 2.5 g), prescribed dose (a small amount to affected areas vs. 5 g), route of administration (topical vs. injection), and dosage frequency (once, twice, or three times a day vs. single dose, may be repeated once). As both Cyclocort and Cyanokit are available as a package with one strength, it is possible to see prescriptions for each with the quantity and directions "dispense 1, as directed" which increases the potential for confusion between the two names. However, a prescription for Cyclocort should also specify the dosage form (cream, ointment, or lotion) which may help to differentiate between the two names. Additionally, Cyclocort is primarily an outpatient drug, whereas Cyanokit will be prescribed for a specific patient population as part of emergency treatment for suspected Cyanide exposure. Cyanokit is not likely to be stocked by retail pharmacies as such patients may need to be hospitalized with additional supportive treatment. Cyanokit will be administered by a healthcare professional in an inpatient setting. Thus, the setting of use for these two medications is very different and is not likely to overlap.

DMETS believes the different context of use and dosage forms for Cyclocort and Cyanokit decrease the risk for confusion between Cyclocort and Cyanokit.

3. Synacort was identified as a name with a similar appearance to Cyanokit. Synacort is a proprietary name for Hydrocortisone cream, which is indicated to treat dermatoses. Synacort is available as a 1% or 2.5% strength, which is applied to the affected area two to four times daily. Synacort may be used in children and adults greater than 2 years of age.

The two names share some orthographic similarities. Both names share similar looking beginnings ('Sy-' vs. 'Cy-') and end with the letter 't' . However, the middle portion of each name '-anoki-' vs. '-nacor-' look distinguishable when scripted and may help to differentiate the two names. Furthermore, the letter 'k' in Cyanokit contributes an upstroke which may also help to differentiate the two names.

cyanokit
synacort

Synacort and Cyanokit have different product characteristics, such as; strength (1% or 2.5% vs. 2.5 g), prescribed dose (a small amount to affected area vs. 5 g), route of administration (topical vs. injection), and dosage frequency (two to four times a day vs. single dose, may be repeated once). DMETS notes that two strengths are similar numerically ("2.5") however the unit of measure (% vs. g) may help differentiate. Additionally, Synacort has two strengths. As both Synacort and Cyanokit are available as a package, it is possible to see prescriptions for each with the directions "dispense 1, as directed" which increases the potential for confusion between the two names. However, a prescription for Synacort should also specify the strength (1% or 2.5%) which may help to differentiate between the two names. Additionally, Synacort is primarily an outpatient drug, whereas Cyanokit will be prescribed for a specific patient population as part of emergency treatment for suspected Cyanide exposure. Cyanokit is not likely to be stocked by retail pharmacies as such patients may need to be hospitalized with additional supportive treatment. Cyanokit will be administered by a healthcare professional in an inpatient setting or in the field in a disaster response setting. Thus, the conditions of use for these two medications is very different and is not likely to overlap.

DMETS believes the lack of convincing look-alike similarity, as well as the different context of use with product strengths for Synacort and Cyanokit decrease the risk for confusion between Synacort and Cyanokit.

4. Senokot was identified as a name with similar sound to Cyanokit. Senokot is the brand name for a non-prescription product line of laxative and fiber supplement products. Senokot laxative products contain sennosides as the active ingredient. Senokot contains 8.6 mg sennosides, Senokot-S contains 8.6 mg sennosides with 50 mg of docusate (a stool softener), and SenokotXTRA contains 17 mg of sennosides. The recommended dose of Senokot/SenokotXTRA is 8.6 mg or 17.2 mg of sennosides orally twice a day. Senokot-S may be taken as one to four tablets orally daily as a single dose or in divided doses.

Senokot and Cyanokit share some phonetic similarities. The 'Cy-' beginning of Cyanokit is pronounced with a soft letter 'c' which sounds similar to the letter 's' sound that begins Senokot. However, the middle portions of each name sound distinctive due to the vowels (short letter 'e' vs. long letter 'a') which may help to differentiate the two names. Additionally, the endings of both names (-kot vs. –kit) sound distinctive. Furthermore, Senokot contains three syllables when pronounced, whereas Cyanokit contains four syllables when pronounced, which may further help to differentiate between the two names.

Senokot and Cyanokit have different product characteristics, such as; strength (8.6 mg or 17.2 mg vs. 2.5 g), prescribed dose (8.6 mg or 17.2 mg vs. 5 g), route of administration (oral vs. injection), and dosage frequency (two to four times a day vs. single dose, may be repeated once). A prescription for Senokot should specify the strength or quantity of tablets which may help to differentiate it from a prescription for Cyanokit. Cyanokit is not likely to be stocked by retail pharmacies as such patients may need to be hospitalized with additional supportive treatment. Cyanokit will be prescribed for a specific patient

population as part of emergency treatment for suspected Cyanide exposure and will be administered by a healthcare professional in an inpatient setting.

DMETS believes phonetic differences along with the different context of make it unlikely for Senokot and Cyanokit to be confused.

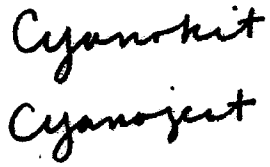
III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Cyanokit. In reviewing the proprietary name, the primary concern relating to look-alike confusion with Cyanokit is Cyanoject. Additionally, DMETS has concerns with this proposed packaging configuration because its design is error prone.

Cyanoject was identified as a name with a similar appearance to Cyanokit. The product named "Cyanoject" is no longer marketed in the United States. However, generic injectable formulations of the active ingredient, Cyanocobalamin, remain on the market and the name "Cyanoject" is still found in commonly used references, including Drug Facts and Comparisons and Clinical Pharmacology Online. We have learned from post-market surveillance that it is plausible for a generic equivalent to be dispensed for the discontinued product when the discontinued drug name appears in common drug references. Therefore, it is possible for prescriptions to be written for Cyanoject in which case a pharmacist would dispense the generic formulation of Cyanocobalamin.

Confusion may also arise from the similarity of the active ingredients in both products. Each molecule of Hydroxocobalamin (the active ingredient in Cyanokit) combines with one molecule of cyanide to form Cyanocobalamin (the active ingredient in Cyanoject). Both Hydroxocobalamin and Cyanocobalamin are commonly known as Vitamin B-12. However, Cyanocobalamin is indicated only for the treatment of B-12 deficiency or pernicious anemia, or as the Schilling Test to determine B-12 Deficiency. Whereas hydroxocobalamin is also indicated for treatment of B-12 deficiency at much smaller doses (30 mcg to 200 mcg) in addition to the proposed indication for known or suspected cyanide exposure. Cyanocobalamin, the active ingredient in Cyanoject, is administered at the recommended dose of 30 mcg, 100 mcg, 200 mcg, or 1000 mcg per day via intramuscular or deep subcutaneous injection. The 100 mcg or 200 mcg dose may be given once a month.

The two names share some orthographic similarities. The two names share an identical beginning 'Cyano-' and both names end with the same letter 't' which contributes to the look-alike properties. Furthermore, the letters '-ki' in Cyanokit and the letters '-jec' in Cyanoject can look similar when scripted (see below).



Cyanoject and Cyanokit have some different product characteristics, such as; vial strength (1000 mcg, 10 mg, or 30 mg vs. 2.5 g), prescribed dose (30 mcg, 100 mcg, 200 mcg, or 1000 mcg vs. 5 g) and route of administration (intramuscular or deep subcutaneous vs. intravenous infusion). However, the setting of use for both products may overlap in an inpatient setting, such as a hospital, where both may be administered via injection.

A prescription for Cyanoject should specify the microgram or milligram dose and the route of administration which may help to differentiate it from a prescription for Cyanokit. A prescription for

Cyanoject should also specify a dosage frequency such as daily or monthly. However, it is possible that a prescriber in an inpatient setting could order the Cyanoject as a one time dose (e.g., Cyanoject #1 now) as part of an order for a Schilling Test, which has a standardized dose of 1000 mcg. Cyanokit could also be ordered as "Cyanokit, #1, now" which increases the potential for confusion. Because both Cyanoject and Cyanokit contain Vitamin B12 derivatives, it may be difficult for a healthcare professional to recognize an error before the wrong product is administered. DMETS cannot comment on the clinical significance should confusion occur and the wrong product be administered. However, the potential for patient harm may be severe should a patient with cyanide poisoning be treated with the wrong product.

Therefore, due to the potential for confusion with Cyanoject, DMETS does not recommend the use of the proposed proprietary name Cyanokit.

Additionally, DMETS reviewed the labels and labeling from a safety perspective. We have identified the following areas of improvement, which may minimize potential user error.

A. GENERAL COMMENTS

1. We note the sponsor has proposed to label this product Cyanokit 2.5 g. This name is misleading for two reasons:

   a. The kit contains 5 g of the active ingredient, Hydroxocobalamin, rather than the labeled 2.5 g.

   b. The term "Cyanokit" refers to the entire contents of the unit and not just the active ingredient, Hydroxocobalamin. The name Cyanokit, specifically the suffix '-kit' describes the entire contents of the package which includes the two vials of Hydroxocobalamin, two transfer spikes, and one sterile IV infusion set. Thus the principal display panel should indicate all components contained in the carton. Therefore, the established name, Hydroxocobalamin, should not appear in conjunction with this name. Conversely, the established name should be the only name that appears on the container label of active drug. In summary, the proprietary name, Cyanokit, should only be used on the carton and insert labeling with no established name associated with it. The active drug substance should be labeled only with its established name.

2. DMETS questions why the unit contains two vials of 2.5 g rather than one vial of 5 g, which provides the usual dose. The directions describe administering 2.5 g in 100 mL of diluent over 7.5 minutes, which is then repeated to make the initial dose of 5 g. Providing two vials to comprise one dose of 5 g may be confusing to practitioners and may lead to dosing errors. Practitioners may assume that each vial comprises one dose resulting in half the recommended dose being administered. Additionally, in an emergency setting, it may not be feasible for a health care professional to stay with the patient the entire time. They may need to triage and assess other patients while the first 2.5 g is being administered and forget to administer the second 2.5 g vial when they return to the patient. To decrease the potential for confusion, it seems practical to provide one 5 g vial, as the recommended initial dose is 5 g, diluted with 200 mL of diluent, which is administered over 15 minutes.

3. The proper names for the diluents should be used in all labels and labeling (e.g., 0.9% Sodium Chloride for Injection, not "[redacted] Saline (0.9% NaCl) and 5% Dextrose for Injection, not "5% dextrose (D5W)."

4. DMETS is concerned with the number of drugs and blood products that are considered incompatible with Cyanokit, thereby necessitating a separate intravenous line for administration. Cyanokit may be administered in a stressful and busy emergency setting or in the field where intravenous access is limited to a single line. Thus, these recommendations for incompatibility should be featured prominently on all labels, labeling, and packaging to remind practitioners to avoid co-adminstration of Cyanokit with the other drugs in the same intravenous line.

5. The letter 'C' in Cyanokit is shaped like a wrench or a cellular receptor which is distracting and makes the proprietary name more difficult to read. DMETS recommends that a regular letter 'C' be used for the font in the proprietary name. Additionally, the same graphic is included as a large symbol on the carton labeling. Please remove the graphic as it distracts away from the important information.

6. For the storage directions, please add the text "at temperatures not exceeding 40°C (104°F)," so the statement reads "Stable up to 6 hours after reconstitution *at temperatures not exceeding 40°C (104°F).*" Also add the statement, "*Discard the unused portion.*"

7. DMETS recommends that the sponsor consider including the diluent within the Cyanokit packaging due to the incompatibility issues and also so that everything needed for mixing and administering Cyanokit is contained in the one unit.

B. CONTAINER LABEL (2.5 g Hydroxocobalamin Vial)

1. Refer to General Comments A1-A2 and A4-A6.

2. The established name for this product should read "Hydroxocobalamin for Injection". The route of administration statement "for Intravenous Use" should be relocated to appear below the established name. Additionally, please increase the prominence of this statement.

3. The prominence of the strength (2.5 g/vial) should be increased. Furthermore, DMETS recommends expressing the strength as "2.5 g per vial". On all labels and labeling, it should be apparent that each vial contains 2.5 g of hydroxocobalamin, whereas each Cyanokit unit contains 5 g of drug (two 2.5 g vials) to decrease the potential for confusion and possible error.

4. DMETS questions whether the "fill line" on the vial is labeled as such. DMETS would recommend that text be placed on or adjacent to the fill line so that it is easily identifiable to the person reconstituting the vial, especially if it is only an indented line or bump on the vial.

5. Ensure that when the bottle is hung, the label is oriented so it can still be read. The sponsor may wish to provide an arrow on the bottle to demonstrate the orientation of how the bottle is hung. DMETS questions whether there is a hanger on the bottle to facilitate hanging in the proper position?

C. CARTON LABELING (2.5 g Hydroxocobalamin Vial Carton)

Refer to General Comments A1-A3 and A4-A6.

D. CARTON LABELING (Outer Carton Labeling for Cyanokit Unit)

Refer to General Comments A1-A3 and A4-A6.

E. Instructions For Use Card

1. Refer to General Comments A1-A5.

2. The contents of each Cyanokit unit should be listed on the card, such as "each unit contains 2 vials of 2.5 g Hydroxocobalamin..."

3. DMETS questions the wording "Repeat for Adult", specifically the use of the word "adult". Cyanokit is not indicated or intended for use in children, but this wording implies otherwise. We recommend removing the word "adult" as the total initial recommended dose is 5 g in adults.

4. DMETS recommends that important safety information also be included on this card. Specifically, bulleted statements reminding practitioners of topics such as:

   a. Guidance on appropriate patient selection for use of Cyanokit.

   b. Physical and chemical incompatibilities that may necessitate the use of a separate intravenous line for administration.

   c. A list of compatible diluents and intravenous solutions.

   d. Other monitoring requirements such as blood pressure monitoring and monitoring for hypersensitivity, and interventions that may be required to manage these events.

F. PACKAGE INSERT LABELING

1. HIGHLIGHTS OF PRESCRIBING INFORMATION
DOSAGE AND ADMINISTRATION section

   DMETS recommends that a statement reminding the practitioner of important incompatibilites with Cyanokit be placed in the HIGHLIGHTS OF PRESCRIBING INFORMATION [e.g., There are a number of drugs and blood products that are incompatible with Cyanokit, thus Cyanokit may require a separate intravenous line for administration (2.3)]

2. DOSAGE AND ADMINISTRATION section

   a. Directions for Reconstitution sub-section

      The complete directions on preparation and administration of Cyanokit need to be included in the PI. This information should be consistent with the "Instructions for Use" card. Specifically, this section should state that the complete dose of 5 g should be comprised of two 2.5 g vials that are reconstituted and prepared as directed.

b. Incompatibility sub-section

In the chemical incompatibility paragraph, we recommend that you define the term as you did in the physical incompatibility paragraph (e.g., particle formation). Additionally, this sub-section follows the Use With Other Cyanide Antidotes section where it may be overlooked by the reader. DMETS recommends that a statement regarding the number of important incompatibilities with Cyanokit be prominently featured within the first three paragraphs of the DOSAGE AND ADMINISTRATION section.

c. Rate of Infusion sub-section

The complete recommendations of the rate of infusion for Cyanokit need to be included in the PI. This information should be consistent with the "Instructions For Use" card. Specifically, this section should state that one reconstituted vial (2.5 g) should be infused over 7.5 minutes and then followed by the second reconstituted vial (2.5 g) which should be infused over 7.5 minutes, for a total initial dose of 5 g administered over 15 minutes. This section should also include rate of infusion information for the optional second dose which ranges from 15 minutes (for patients in extremis) to 2 hours.

3. PATIENT COUNSELING INFORMATION section

This section should note that Cyanokit may cause the patient's urine to turn red. Revise accordingly. As currently written, the FDA Patient Approved Labeling section contains this side effect but it should also be in the PATIENT COUNSELING INFORMATION section for the prescriber.

NDA # 22-041
OSE Consult 06-0207

Appendix A: Cyanokit

Requisition 1	Voice	Requisition 2
Cyanokit	ciatel kit	Cyantect
Cyanokit	Cyanokit	Cyanovert
Cyanokit	Cyanokit	cyclosert
Cyanokit	Cyanokit	Cyanokot
Cyanokit	Cyanolkit	Cyanket
CYANOKIT	Cyanokit	Cyanokit
Cyanokit	CyanoKit	Cyanvert
Cyanokit	Cyanokit	Cyannpct
CyanoKit	Cyano kit	Cyankit
Cyanokit	Cyanokit	Cyanotest
Cyanokit	Cyanokit	Cyanert
Cyanokit	Cyanokit	Cyambit
Cyanokit		Cyankit
Cyanokit		Cyanokit
Cyanokit		Cyanavert
Cyanobit		Cyanrit
Cyanokit		Cyanpet
Cyanokit		

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

/s/

Laura Pincock
11/13/2006 04:32:06 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/13/2006 04:46:52 PM
DRUG SAFETY OFFICE REVIEWER

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, October 25, 2006 5:07 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Subject: FW: Cyanokit CMC comments

Elliott –

Regarding the infusion set/transfer spike system provide the following data:

- Physicochemical and Biological testing using the drug product (reconstituted Cyanokit® Injection) as the vehicle and extracting medium to verify the extraction characteristics for this system. Provide physicochemical data according to current USP conditions listed in <381> Elastomeric Closures and <661> Containers. The Biological testing data performed according to the current USP recommendations in <87> Biological Reactivity Tests, In-vitro and <88> Biological Reactivity Tests, In-vivo.

Thanks
Matt

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Thursday, October 19, 2006 4:18 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: CMC comment / N22041

Elliott –

Couldn't let a day go by without one:

Provide a revised hydroxocobalamin assay value in Table 3.2.S.4.1-1 Hydroxocobalamin Release Specifications, which includes the current USP/NF compendial requirement of 95 to 102%.

Thanks
Matt

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, October 18, 2006 4:59 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: 10/18 IR

Elliott –

The death reports for many patients indicate "soot in the lower airways." Some of these patients were clearly not intubated at the time (Fortin patient 19856). Please describe what the phrase is referring to and how the evaluation was made.

Thanks
Matt

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, October 18, 2006 4:06 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: RE: NDA 22-041 - CYANOKIT - Response to Info Request on Impurities in Non-clinical Batches

Sorry, we did get it on the 12th. We just overlooked it.

However, we do need some follow-up on this point. Our contention is that this is not a traditional cause of death, and therefore we need more information for how it was utilized.

So, please do one of the following:
1) Provide another, more specific, cause of death for these patients
2) Assuming that the terms refers to patients with brain death, provide the specific criteria utilized to determine this.

If we need to clarify our needs over the phone (with Dr Simone), please let me know and I'm sure we can do that.

Matt

From: elliott.berger@emdpharmaceuticals.com [mailto:elliott.berger@emdpharmaceuticals.com]
Sent: Wednesday, October 18, 2006 3:06 PM
To: Sullivan, Matthew
Cc: cindy.marshall@emdpharmaceuticals.com
Subject: RE: NDA 22-041 - CYANOKIT - Response to Info Request on Impurities in Non-clinical Batches

Dear Matt

On October 12 I sent an e-mail which included responses to several of Dr. Simone's requests. Included was the following:

Question 5 (E-mail 2 of 10 October)
Many deaths were attributed to "decerebration." Please define what is meant by the term and how the determination was
made. Generally, decerebration is used to describe a patient's condition and is not a cause of death per se. If the term was
used to describe brain death, what criteria were used to make the determination and to stop further therapy.

Response
"Decerebration" was used to describe a neurological status including a deep coma (unresponsive to painful stimulation and
absence of pupillary reflex), refractory to treatment, in patients with documented initial cardiorespiratory arrest. In the majority of
patients, this neurological status was associated with multiple organ failure.

Please let me know if you require any additional information.

Elliott T. Berger, Ph.D.

Vice President, Regulatory Affairs & Quality Assurance
EMD Pharmaceuticals, Inc.
(919) 401-7107 Phone
(919) 401-7191 Fax

"Sullivan, Matthew" <Matthew.Sullivan@fda.hhs.gov>

10/18/2006 12:51 PM

To elliott.berger@emdpharmaceuticals.com

cc

Subject RE: NDA 22-041 - CYANOKIT - Response to Info Request on Impuritie clinical Batches

Thanks.

Any clarification on the deceberation issue (ie as a cause of death)?

Matt

From: elliott.berger@emdpharmaceuticals.com [mailto:elliott.berger@emdpharmaceuticals.com]
Sent: Wednesday, October 18, 2006 12:35 PM
To: Sullivan, Matthew
Cc: cindy.marshall@emdpharmaceuticals.com
Subject: NDA 22-041 - CYANOKIT - Response to Info Request on Impurities in Non-clinical Batches

Dear Matt

The attached table is in response to your request of October 11 regarding impurity levels in the batches used in non-clinical studies.

Elliott T. Berger, Ph.D.
Vice President, Regulatory Affairs & Quality Assurance
EMD Pharmaceuticals, Inc.
(919) 401-7107 Phone
(919) 401-7191 Fax

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, October 17, 2006 4:36 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: Chemistry IR request

Here is an information request from our chemistry reviewers:

1. DMF — for hydroxocobalamin was deemed inadequate to support the NDA. A letter of deficiency was sent to ——— .. on August 31, 2006.

2. Provide following additional information on the reference standards:
   a. A clear discussion of how secondary reference standards are established for hydroxocobalamin and and how they are traced to the respective primary reference standards.
   b. A description of the periodic qualification, mentioned in section 3.2.P.6., including testing and acceptance criteria.

3. With reference to the description of the manufacturing process for the drug product, clarify whether ——— before being processed further. If so, submit holding time(s) and provide justification.

4. Provide updated long-term stability data and statistical analysis for all stability-indicating quality attributes including hydroxocobalamin assay, individual and total impurities for batches 2079, 2080, and 2081. The data should be submitted in SAS transport format.

5. There appears to be a near — increase in the free cobalt content in the drug product batches within 12 months. This indicates that free cobalt content is a ——— attribute of the drug product. Therefore, provide a specification for its control and revise the stability protocol for its monitoring. The acceptance limit should be based on safety considerations. Also ensure that the updated stability data includes this information.

6. Provide a revised comparability protocol to include solution stability of reconstituted Cyanokit at various intervals, e.g. 0, 2, 4, and 6 hours post-reconstitution.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration

Phone 301-796-1245
Fax 301-796-9722 / 9723

10/17/2006

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 22-041

10/12/06

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 June 16, 2006, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Cyanokit (hydroxocobalamin).

We are reviewing the content and format of your prescribing information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

HIGHLIGHTS

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to CONTENTS and the FULL PRESCRIBING INFORMATION (FPI). Refer to 21 CFR 201.57(d)(6) and the Implementation Guidance.

2. The HIGHLIGHTS must be limited in length to one-half page, in 8 point type, two-column format. Refer to 21 CFR 201.57(d)(6) and (d)(8).

3. Bold the HIGHLIGHTS statement. Refer to 21 CFR 201.57(d)(5) and http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

4. Remove the space between HIGHLIGHTS OF PRESCRIBING INFORMATION and the highlights limitation statement. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

5. The preferred format for presenting the drug names is without all capital letters and without trademark or other symbol.

6. The drug name must be followed by the drug's dosage form and route of administration. Refer to 21 CFR 201.57(a)(2).

7. Remove the space between the drug name and the initial U.S. approval. Refer to 21 CFR 201.57(a)(3).

8. All headings must be presented in the center of a horizontal line. Refer to 21 CFR 201.57(d)(2).

9. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

   "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

   Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the HIGHLIGHTS.

10. Under DOSAGE AND ADMINISTRATION, you indicate that the initial dose of Cyanokit for adults is "5.0 g." Do not use trailing zeros for doses expressed in whole numbers throughout the labeling. Refer to the Institute for Safe Medication Practices website at http://www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations. This applies to the entire label.

11. Under DOSAGE AND ADMINISTRATION and CONTRAINDICATIONS, add cross-references. Refer to 21 CFR 201.56 (d)(3).

12. Under DOSAGE AND ADMINISTRATION, include the poison control center information stated in the FPI since this is critical information that belongs in HIGHLIGHTS.

13. Under CONTRAINDICATIONS, "theoretical" possibilities must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. This applies to both the HIGHLIGHTS and the FPI. Refer to 21 CFR 201.57(a)(9).

14. Regarding the adverse reactions reporting statement, you list a company website "emdpharmaceuticals.com." Note that a general link to a company website or an email address cannot be used to meet the requirement to have adverse reactions reporting contact information in HIGHLIGHTS. It would not provide a structured format for reporting. Please delete. Also delete the word "phone" since it is not included in the required statement. Refer to 21 CFR 201.57 (a)(11).

15. Under the ADVERSE REACTIONS heading, include the most frequently occurring adverse reactions along with the criteria used to determine inclusion (e.g., incidence rate). The same applies to the FPI. Refer to 21 CFR 201.57(a)(11) and (c)(7).

16. A revision date must appear at the end of HIGHLIGHTS. For a new NDA this will be month/year of approval. Refer to 21 CFR 201.57(a)(15).

17. A horizontal line must separate the HIGHLIGHTS, CONTENTS and FULL PRESCRIBING INFORMATION. Refer to 21 CFR 201.57(d)(2).

FULL PRESCRIBING INFORMATION: CONTENTS

18. The FPI:CONTENTS (table of contents) is not written in the new labeling format. Refer to 21 CFR 201.57(b) and http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format and revise accordingly.

19. Add the required statement "*Sections or subsections omitted from the full prescribing information are not listed" at the end of FPI:CONTENTS. Refer to 21 CFR 201.57(b).

FULL PRESCRIBING INFORMATION

20. The paragraphs throughout the FPI under the sections and subsections are not indented and aligned left. Indent each paragraph. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

21. The preferred presentation of cross-references in the FPI is in brackets, not parentheses. For example, [see Dosage and Administration (2)], not (see Dosage and Administration (2)). Correct your cross-references throughout the labeling.

22. Regular text should be used when referring to tables in the text of the label, not italics.

23. Only section or subsection headings can be numbered. Subheadings under subsections do not have numbers, e.g. under Dosage and Administration 2.1.1 Smoke Inhalation should not be numbered. Just use the subheading Smoke Inhalation. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

24. Your adverse reactions lists are lengthy. Refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance. Revise your ADVERSE REACTIONS section accordingly.

25. Under NON-CLINICAL TOXICOLOGY delete "and" in the subheading title 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility." Refer to 21 CFR 201.57(c)(14).

26. Delete section 15 (REFERENCES) from the labeling since it is not applicable. Refer to 21 CFR 201.56(d)(4).

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

Sincerely,

{See appended electronic signature page}

Sara Stradley
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
10/12/2006 09:19:20 AM

Date: October 5, 2006

From: Robin Anderson, RN, MBA
Label Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

Through: Laurie B. Burke, RPh, MPH
Director, SEALD

To: Matthew Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

Subject: Proposed Labeling Format Review
NDA 22-041 Cyanokit (hydroxocobalamin) for Intravenous Use

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant. Please contact me at 796-0534 with questions or concerns.

Comments to convey to the applicant:

These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Highlights:

- Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(6) and (d)(8)]

- The Highlights statement needs to be bolded. [See 21 CFR 201.57(d)(5) and http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- There is no space between Highlights of prescribing information and the Highlights limitation statement. Please correct.
[See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- The preferred format for presenting the drug names is without all capital letters and without trademark or other symbol.

- The drug name must be followed by the drug's dosage form and route of administration. Please include the dosage form. [See 21 CFR 201.57(a)(2)]

- There is no space between the drug name and the initial U.S. approval. Please correct. [See 21 CFR 201.57(a)(3)]

- All headings must be presented in the center of a horizontal line. [See 21 CFR 201.57(d)(2)]

- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

  "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

  Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

- Under Dosage and Administration, you indicate that the initial dose of Cyanokit for adults is "5.0 g." Do not use trailing zeros for doses expressed in whole numbers throughout the labeling. Please refer to the Institute for Safe Medication Practices website at http:www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations. This applies to the entire label.

- Under Dosage and Administration and Contraindications, there are no cross-references cited for those statements. Please add. [See 21 CFR 201.56 (d)(3)]

- Under Dosage and Administration, include the poison control center information stated in the FPI since this is critical information that belongs in Highlights.

- Under Contraindications, "theoretical" possibilities must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. This applies to both the Highlights and the FPI. [See 21 CFR 201.57(a)(9)]

- Regarding the adverse reactions reporting statement, you list a company website "emdpharmaceuticals.com." Note that a general link to a company website or an email address cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. Please delete. Also delete the word "phone" since it is not included in the required statement. [See 21 CFR 201.57 (a)(11)].

- Under the Adverse Reactions heading, you must include the most frequently occurring adverse reactions along with the criteria used to determine inclusion (e.g., incidence rate). The same applies to the FPI.
[See 21 CFR 201.57(a)(11) and (c)(7)].

- A revision date must appear at the end of Highlights. For a new NDA this will be month/year of approval. [See 21 CFR 201.57(a)(15)]

- A horizontal line must separate the Highlights, Contents and Full Prescribing Information. [See 21 CFR 201.57(d)(2)]

Full Prescribing Information: Contents:

- The FPI:Contents (table of contents) is not written in the new labeling format. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format and revise accordingly. [See 21 CFR 201.57(b)]

- Also note that the required statement "*Sections or subsections omitted from the full prescribing information are not listed" is missing at the end of Contents. [See 21 CFR 201.57(b)]

Full Prescribing Information (FPI):

- The paragraphs throughout the FPI under the sections and subsections are not indented and aligned left. Indent each paragraph. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

- The preferred presentation of cross-references in the FPI is in brackets, not parentheses. For example, *[see Dosage and Administration (2)]*, not (*see Dosage and Administration (2)*). Please correct your cross-references throughout the labeling. [Implementation Guidance]

- When referring to tables in the text of the label, do not italicize, e.g. *(Table 5-1)* Use regular text.

- Only section or subsection headings can be numbered. However, subheadings under subsections do not have numbers, e.g. under Dosage and Administration 2.1.1 Smoke Inhalation should not be numbered. Just use the subheading Smoke Inhalation. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

- Your adverse reactions lists appear lengthy. Refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise your Adverse Reactions section accordingly.

- Under Non-clinical Toxicology delete "and" in the subheading title 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility."
[See 21 CFR 201.57(c)(14)]

- Delete 15 References from the labeling since it is not applicable.
[See 21 CFR 201.56(d)(4)]

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/s/

Robin E Anderson
10/6/2006 09:38:42 AM
CSO

Laurie Burke
10/11/2006 07:36:16 PM
INTERDISCIPLINARY

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, October 10, 2006 4:39 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Subject: NDA 22-041 CYANOKIT -Information Request

Elliott –

As we spoke about on the phone, here are two items that were requested in terms of the Risk Management Plan.

1) Provide additional information regarding the training that will be provided for those who will be administering the kit. For example, will it be via a web module, an in-service, etc? Will competency be assessed in any way?
2) Provide your draft distribution plan.

Thanks
matt

Sullivan, Matthew

From: Simone, Arthur
Sent: Tuesday, October 10, 2006 1:04 PM
To: Sullivan, Matthew
Subject: OH-Co questions for Sponsor

Matt,

Still more questions. At least they know we're working on it.

1. Many deaths were attributed to "decerebration." Please define what is meant by the term and how the determination was made. Generally, decerebration is used to describe a patient's condition and is not a cause of death per se. If the term was used to describe brain death, what criteria were used to make the determination and to stop further therapy.
2. Can you provide further information on USUBJID Baud1-9 who had diffuse bleeding with major hepatic cytolysis, in particular, what was meant by the terms used, i.e., can you describe the condition in more detail.

Thanks.

Art

Arthur Simone, M.D., Ph.D.

Medical Officer, Anesthesia Products

Division of Anesthesia, Analgesia and Rheumatology Products

Center for Drug Evaluation and Research

Food and Drug Administration

Telephone: (301) 796-1294

Facsimile: (301) 796-9723

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, October 10, 2006 8:50 AM
To: 'elliott.berger@emdpharmaceuticals.com'
Subject: NDA 22-041 CYANOKIT -Information Request

Elliott – Another clinical IR for you.

Thanks
Matt

1. Please review the submission for medications other than Cyanokit that were administered to patients and identify and describe those drugs which are not approved in the US. For example, tetracosactide - a synthetic analogue of the naturally-occurring hormone, adrenocorticotrophic hormone (ACTH).
2. Create an adverse event table for each individual study: healthy volunteers, Baud 1, Baud 2, Baud 3 and Fortin as well as a table for the combined studies that provides the following information:

- Adverse events by each system organ class (SOC) with preferred-term (PT) subcategories
- use total dose of hydroxocobalamin administered
- if a subject has more than one episode of a specific adverse event, count that subject only once (i.e., the table is to show the number of subjects who experienced each adverse event, not the number of times each adverse event occurred).
- for each adverse event and total dose, identify the number of patients who experienced the adverse event and indicate the percentage that number is for all patients who received that total dose.
- for each SOC indicate the total number of patients and the percentage of all patients receiving that dose who experienced any AE for that class. If only half the subjects experienced any AE, then the percentage for that dose group would be 50%, no matter how many AEs those individuals experienced for that category

For the healthy subject study the table may appear as below (the numbers have been fabricated)

Adverse Events	n (%)				
	Placebo (all doses) [N=50]	Hydroxocobalamin			
		2.5 g [N=25]	5 g [N=50]	7.5 g [N=25]	10 g [N=10]
Skin and Subcutaneous Tissue					
Total	10 (20)	0	50 (100)	5 (20)	10 (100)
Erythema			50 (100)	5 (20)	10 (100)
exanthema					2 (20)
Face edema	1 (2)		1 (2)		
Generalized erythema	2 (4)		1(2)		
hyperhydrosis				1 (5)	
Pruritis	9 (18)		1(2)	3 (15)	3 (30)

Stradley, Sara

From: Stradley, Sara
Sent: Tuesday, August 29, 2006 8:13 AM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: Sullivan, Matthew; Stradley, Sara
Subject: info request for NDA 22-041

Hi Elliott

I am covering for Matt while he is on vacation. I have the following request from the CMC reviewer:

- Provide a Letter of Authorization for DMF [redacted] b(4)

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
email: Sara.Stradley@fda.hhs.gov

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/s/

Sara Stradley
8/29/2006 08:24:00 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-041

FILING COMMUNICATION

8/18/06

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 June 16, 2006, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Cyanokit (hydroxocobalamin).

We also refer to your submission dated July 28, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 18, 2006, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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

Sincerely,

{See appended electronic signature page}

Sara Stradley
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Sara Stradley
8/18/2006 12:42:13 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22041 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Cyanokit
Established Name: Hydroxocobalamin
Strengths: 2.5 grams per vial (2 vials per carton)

Applicant: EMD Pharmaceuticals, Inc.
Agent for Applicant (if applicable):

Date of Application: June 16, 2006
Date of Receipt: June 19, 2006
Date clock started after UN:
Date of Filing Meeting: July 19, 2006
Filing Date: August 18, 2006
Action Goal Date (optional): December 15, 2006 User Fee Goal Date: December 19, 2006

Indication(s) requested: Treatment of known or suspected cyanide poisoning

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P ☒
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) orphan

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☐ Exempt (orphan, government) ☒
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☒ NO ☐

  Keystone Pharmaceuticals received orphan designation on June 16, 2006, for *treatment of cyanide poisoning* with sodium thiosulfate.

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☒
   This application is: All electronic ☐ Combined paper + eNDA ☒
   This application is in: NDA format ☐ CTD format ☒
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Electronic data sets for each of the clinical studies as well as the Integrated Tabulation of Clinical Experience.

   Additional comments:

3. This application is an eCTD NDA. YES ☐

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, 7 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO ☒
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: PIND 67, 151
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) February 10, 2006 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 19, 2006

NDA #: 22-041

DRUG NAMES: Cyanokit (hydroxocobalamin)

APPLICANT: EMD Pharmaceuticals, Inc.

BACKGROUND: Hydroxocobalamin, also known as vitamin B_{12a}, was initially approved by the FDA on August 16, 1978. EMD established a PIND file in 2003, and has had numerous meetings with the Division since that time. EMD was granted Orphan drug status for hydroxocobalamin on November 25, 2003. The PIND was granted fast track status on March 24, 2006.

The Sponsor began a rolling NDA submission in April of 2006, and completed their submission on June 19, 2006.

ATTENDEES: In addition to the assigned reviewers listed below, the following CDER personnel were in attendance:

Ali Al Hakim, PhD, Pharmaceutical Assessment Lead, ONDQA Branch V.
Su Yang, MSN, RN, Regulatory Project Manager, Division of Counter-Terrorism
Rosemary Roberts, MD, Director, Division of Counter-Terrorism
Dan Mellon, PhD, Pharmacology/Toxicology Supervisor, DAARP
Sharon Hertz, MD, Deputy Director, DAARP
Dionne Price, PhD, Statistics Team Leader (Acting)
Sara Stradley, MS, Chief, Project Management Staff, DAARP

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization	Reviewer
Medical:	Arthur Simone, MD, PhD
Secondary Medical:	
Statistical:	James Gebert, PhD
Pharmacology:	Lawrence Leshin, DVM, PhD
Statistical Pharmacology:	
Chemistry:	Milagros Salazar-Driver, PhD
Environmental Assessment (if needed):	
Biopharmaceutical:	David Lee, PhD
Microbiology, sterility:	Brian Riley, PhD
Microbiology, clinical (for antimicrobial products only):	Jim McVey, PhD
DSI:	
OPS:	
Regulatory Project Management:	Matthew Sullivan, MS

Other Consults:

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain: No clinical sites to audit – application has no clinical data.
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☒ NO ☐

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☒ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments: Stability data, line listing of Biopharmaceutical subjects and labeling submitted electronically, and loaded in EDR.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

All filing issues have already been addressed by an Information Request submitted t the Sponsor on July 25, 2006.

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

M. W. Sullivan
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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/s/

Matthew Sullivan
8/17/2006 11:22:38 AM
CSO

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, August 09, 2006 5:19 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: N22041 Information request 8/9/06

Elliott –

Here is another information request. Again, please respond via email and in hardcopy as well.

Please provide the following information, revisions and data:

1. Revision of the Cyanokit® shelf life specification for the Hydroxocobalamin assay that assures at least a — % of the label amount. The amount of Hydroxocobalamin proposed in the shelf life of Cyanokit® is equivalent to — % of label amount (— g/vial of a 2.50 g/vial target label). The manufacturing data you have provided also supports — of label claim.

2. Additional stability data for all primary batches. Due to the priority status of this application, the availability of at least 12 months data of stability data for batches 9499, 9507, 9525 manufactured on Mar, Apr, and Jun of 2005 respectively should be provided as soon as possible to support a viable expiry for the to-be-marketed product. The file format for stability data previously sent would be adequate.

3. Files for the SAS statistical analysis of clinical batches, 2067 and 2070 with all available time points.

4. Analytical data on Free Cobalt assay for batches 9499, 9507, and 9525 (for all available storage conditions tested). Also, include equivalent data for clinical batches 2067 and 2070.

b(4)

5. Structural identification data or information on the individual main impurities, — and —].

6. Any toxicology (Gene/Tox) data or information on the individual main impurity, [—

7. An explanation for the acceptance limits for the Assay (Recovery —%) and Related Substances by HPLC (Recovery —%) tests in the reconstituted Hydroxocobalamin product. How are these criteria related to the target label and the actual content of Hydroxocobalamin in the final product at different times from zero to 6 hours post-reconstitution? We recommend you express the acceptance limits for the assay and the related substances in mass units and percent per gram respectively.

8. An explanation as to why reconstituted Hydroxocobalamin product which is made from same batch of Cyanokit® vials freshly made and from vials stored for 12 months

show a different pH value (up to 1.1 pH unit) immediately after reconstitution? (Table 2.3.P-89)

9. Revised specifications of Hydroxocobalamin for Injection product, reconstituted product to include an acceptance limit for the pH test to comply with compendial requirements.

10. Data showing the analytical data of the reconstituted product prepared with lyophilized product stored at 36 month of storage conditions (i.e., from supportive stability batches).

11. Two mock-up samples of the Cyanokit® product, including the proposed label and carton.

Thanks,
Matt

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/s/

Matthew Sullivan
8/15/2006 03:49:41 PM
CSO

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, July 25, 2006 1:10 PM
To: 'elliott.berger@emdpharmaceuticals.com'
Cc: 'cindy.marshall@emdpharmaceuticals.com'
Subject: N22041 Information request 7/25/06

Elliott –

As I mentioned to Cindy last week, we have a couple of information requests that we'd like addressed.

1. Please confirm that all facilities are ready for GMP inspection.
2. Please confirm that your NDA application does not rely upon the Agency's previous findings of safety or efficacy of any other drug product, and that no proprietary products were utilized in the literature that you have referenced. If you are relying upon data that is not your own or is not within the public domain, you may need to file your NDA as a 505(b)(2) submission.

Thanks
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Bldg 22 Rm 3167
10903 New Hampshire Ave
Silver Spring MD 20903-0002

Phone 301-796-1245
Fax 301-796-9722 / 9723

matthew.sullivan@fda.hhs.gov

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/s/

Matthew Sullivan
8/15/2006 03:47:27 PM
CSO

7/31/06

FDA, Center for Drug Evaluation and Research,
Division of Anesthesia, Analgesia and Rheumatology Products
HFD-170, 10903 New Hampshire Ave., White Oak, MD 20993-0002

Clinical Review and Evaluation for Filing of New NDA

NDA# (serial):	22-041(N-000)
Drug Name (generic):	Cyanokit (hydroxocobalamin)
Sponsor:	EMD Pharmaceuticals, Inc.
Indication:	treatment of known or suspected acute cyanide poisoning
Type of Submission:	new NDA
Date of Submission:	June 16, 2006 (rolling submission completed)
Date of Receipt:	June 19, 2006(CDER-stamp date)
PDUFA Filing Date:	August 18, 2006
Project Manager:	Matthew Sullivan
Reviewer:	Arthur Simone, MD, PhD

Clinical Filing Questions and Responses:

(1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?

Yes. Review of the contents of the clinical section reveals it to be complete in terms of content and organization.

(2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?

Yes. The NDA is submitted in paper with some material in electronic format. All the submissions are in the Common Technical Document format. The tables of contents, as well

as the hyperlinks in the electronic submissions, allow for appropriate navigation of the document and access to the various sections.

(3) On its face, is the clinical section of the NDA legible so that substantive review can begin?

Yes. Text and tables are legible.

(4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?

A study was conducted to evaluate safety, tolerability and PK of 2.5, 5, 7.5 and 10-gram doses of Cyanokit in healthy volunteers. Animal studies assessed efficacy in dogs comparing survival with placebo, 75 and 150 mg/kg doses of Cyanokit. Based on this information and the human-use data accumulated in Europe, the sponsor has determined a 5-gm dose to be the appropriate starting dose for adults.

(5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?

Yes. Human and animal studies were conducted as initially required by the Division with input from OCTAP. During product development, additional trials were conducted as indicated. The Division and sponsor also discussed conducting a clinical study evaluating the effects of hydroxocobalamin on cyanide levels in heavy smokers in terms of reducing cyanide levels and assessing tolerability of potentially high cyanocobalamin levels. This trial is planned as a Phase-4 commitment by the sponsor as indicated in the meeting minutes of April 5, 2005.

(6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?

Yes. The efficacy studies provide placebo-controlled, randomized, animal trials that meet the approvability requirements for the proposed labeling and appear to satisfy the written request of the Division.

(7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?

Yes. The animal efficacy study data sets appear to be complete for the indication requested, both in the pivotal trials and the supporting trials.

(8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?

On the basis of the proposed labeling, the efficacy studies appear adequate and well controlled.

(9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?

Line listings of patient data are in a format suitable for review, and which appear to be used to fill the table provided by the Division for organizing safety data gathered from human experience based on studies in France and in the literature.

(10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?

This is not applicable for the animal studies; however, the human tolerability-PK trial and the actual use safety data come from European volunteers. It is expected that the European patients and volunteer subjects will adequately reflect the U.S. population in terms of responses to both cyanide poisoning and hydroxocobalamin therapy.

(11) Has the application submitted all additional required case records forms (beyond deaths and drop-outs) previously requested by the Division?

Not applicable.

(12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?

Yes.

(13) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?

Current safety data is presented for use of the product on European poisoning victims and for the subjects in the tolerability trial. The sponsor was asked to search the literature for information related to the effects of hypercyanocobalaminemia. The literature in the submission includes at least two articles that may have information on this topic. A PubMed search turned up two articles, only one of which was relevant and was included in the submission. This is not an issue that would be expected to affect fileability.

(14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?

A draft label along with proposed carton and container labels were submitted with the application. They are appear to be consistent with the requirements of 21 CFR §201.56 and 201.57.

(15) Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?

The Sponsor has addressed the issues raised by the division during pre-submission discussions and has completed the proposed table of safety and responded to the efficacy issues generated by the Division.

(16) From a clinical perspective, is this NDA fileable? If "no," please state below why it is not?

This NDA is fileable.

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/s/

Arthur Simone
7/31/2006 04:56:37 PM
MEDICAL OFFICER

This has been previously reviewed by you.

Sharon Hertz
7/31/2006 05:11:43 PM
MEDICAL OFFICER
i concur.

7/20/06

45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:

On initial overview of the NDA application:

STATISTICAL:

(1) On its face, is the statistical section of the NDA organized in a manner to allow substantive review to begin? Yes.

(2) Is the statistical section of the NDA indexed and paginated in a manner to allow substantive review to begin? Yes.

(3) On its face, is the statistical section of the NDA legible so that substantive review can being? Yes.

(4) On its face, do there appear to be at least two adequate and well-controlled studies in the application? No, but the one animal efficacy study is sufficient because it is highly significant, the dog is an appropriate species, the mechanism of action is the same in humans and beagle dogs, and the mechanism of action is demonstrated in the study

(5) Are the pivotal efficacy studies of appropriate design to meet the basic requirements for approvability of this product based on proposed draft labeling? Yes

(6) Are all the data sets for pivotal efficacy studies 'complete for all indications (infections) requested? Yes where appropriate.

(a) Line listings by Center

(b) Intermediate analysis summary tables

(c) Pathogen listing

(d) Adverse events listing by Center

(e) Lost subject/patient tables by reason, time of loss, and center

(7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? Yes

(8) From a statistical perspective, is this NDA fileable? If "no", please state below why it is not.
Yes

James Gebert — July 19, 2006

Reviewing Statistician — Date

Dionne L. Price — July 20, 2006

Supervisory Statistician — Date

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/s/

James Gebert
7/20/2006 09:32:39 AM
BIOMETRICS

Dionne Price
7/20/2006 04:53:27 PM
BIOMETRICS
Concur.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: **22-041** Applicant: **EMD Pharmaceuticals, Inc.** Stamp Date: **June 16, 2006**
Drug Name: **Cyanokit® (Hydroxocobalamin)**

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? Yes [X] No [ ]

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review begin?	X		
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	X		The Sponsor stated the following topics were not applicable and no studies were submitted: Safety Pharmacology (but a safety pharmacology study was included in the Other section # 4.2.3.7.7) Pharmacodynamic Drug Interactions. Absorption, Distribution, Metabolism, and Excretion Pharmacokinetic Drug Interactions (Nonclinical) Other Pharmacokinetic Studies Carcinogenicity Reproductive and Developmental Toxicity, (but a rat and a rabbit embryofetal study were included in the Other section # 4.2.3.7.7) Other Toxicity Studies Local Tolerance Antigenicity Immunotoxicity
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	X		Formulation is the same, but manufacturing process differed with product used previously in France (some clinical information) and the current product in France (some clinical information) and the Animal Efficacy study
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?		X	Quantitative animal to human toxicity comparisons are not provided
7	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	X		
8	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X		
9	Has the sponsor submitted a statement(s) that all of the	X		Within each study

	pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			
10	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	X		Within each study
11	From a pharmacology perspective, is this NDA fileable?	X		

Note:
This application's efficacy will be determined under the Animal Efficacy Regulation 21CFR 314 subpart H "Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible."

Reviewing Pharmacologist: L. Steven Leshin July 17, 2006
Date:

Team Leader:
Date:

cc:
Original NDA
HFD-170/Division File
HFD-170/Pharm-Tox/
HFD-170/Pharm-ToxTL/
HFD-170/MO
HFD-170/PM

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/s/

Lawrence Leshin
7/19/2006 03:13:07 PM
PHARMACOLOGIST

R. Daniel Mellon
7/19/2006 10:52:13 PM
PHARMACOLOGIST
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-041

NDA ACKNOWLEDGMENT

6/29/06

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:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Cyanokit (hydroxocobalamin)
Review Priority Classification:	Priority (P)
Date of Application:	June 16, 2006
Date of Receipt:	June 19, 2006
Our Reference Number:	NDA 22-041

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 18, 2006 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be December 19, 2006.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at 301-796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Matthew Sullivan
6/29/2006 03:35:30 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

EMD PHARMACEUTICALS INC
Cindy Marshall
3211 Shannon Road Suite 500
Durham NC 27707
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-041

2. TELEPHONE NUMBER
919-401 7136

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[ ] YES [X] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.
IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[ ] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Cyanokit(R) (Hydroxocobalamin)

6. USER FEE I.D. NUMBER
PD3006577

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[X] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Elliott H. Berger	Vice President, Regulatory Affairs	07 June 2006

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

4/10/06

NDA 22-041

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Cyanokit (hydroxocobalamin).

We also refer to our March 24, 2006 letter granting fast track designation for Cyanokit (hydroxocobalamin) for the treatment of known or suspected cyanide poisoning and to your April 3, 2006, request for step-wise submission of sections of the New Drug Application (NDA) for this product.

We have reviewed your request and have concluded that the proposed plan for step-wise submission of sections of the NDA is acceptable.

If you pursue a clinical development program that does not support use of Cyanokit (hydroxocobalamin) for the treatment of known or suspected cyanide poisoning, the application will not be reviewed under the fast track drug development program and submission of sections of the NDA will not be permitted under this program.

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

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
4/10/2006 04:43:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Pre-NDA Meeting

PIND 67,151

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 Pre-Investigational New Drug Application (PIND) file for Cyanokit (hydroxocobalamin).

We also refer to the meeting between representatives of your firm and the FDA on February 10, 2006. The purpose of the meeting was to discuss the development of your product and your forthcoming NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Meeting Date: February 10, 2005 11:30 – 1:00 pm

Location: White Oak Conference Room 1415

Application PIND 67, 151

Drug Name: Cyanokit (hydroxocobalamin)

Indication: Treatment of acute cyanide poisoning

Sponsor: EMD Pharmaceuticals, Inc.

Type of Meeting: Pre-NDA, Type B

Meeting Chair: Arthur Simone, M.D., Ph.D.
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

Minutes Recorder: Matthew Sullivan, M.S., Regulatory Project Manager

EMD Pharmaceuticals Inc.	Title
Elliott Berger, Ph.D.	Regulatory Affairs
Cindy Marshall	Regulatory Affairs
Wolfgang Uhl, M.D.	Clinical Pharmacology
Arno Nolting, M.D.	Clinical Pharmacokinetics
Brigitte Le Bealle, M.D.	Clinical Research
Dieter Galleman, Ph.D.	Pharmacokinetics
Friedrich von Landenberg, Ph.D.	Toxicology
Stephen Borron, M.D.	Clinical Toxicology Consultant
Juergen Zieschang	Biostatistics
Marie-Helene Joffre, Pharm.D.	Pharmaceutical Development
FDA - DAARP	**Title**
Bob Rappaport, M.D.	Director
Arthur Simone, M.D., Ph.D.	Medical Officer
Ravi Harapanhalli, Ph.D.	Chief, CMC Branch V, Office of New Drug Quality Assessment (ONDQA)
Ali Al Hakim, Ph.D.	CMC Reviewer, ONDQA
Dan Mellon, Ph.D.	Supervisor, Pharmacology/Toxicology
David Lee, Ph.D.	Clinical Pharmacology Reviewer
Thomas Permutt, Ph.D.	Team Leader, Statistics
Matthew Sullivan, M.S.	Regulatory Project Manager
Narayan Nair, M.D.	Medical Officer, Division of Counter-Terrorism (DCT)
Su Yang, MSN, RN	Regulatory Health Project Manager, DCT

Meeting Objective(s): To discuss questions related to the format and structure of a New Drug Application for Cyanokit (hydroxocobalamin).

Opening Discussion: Following introductions, the discussion focused on EMD Pharmaceuticals, Inc.'s questions that were included in the January 6, 2006 meeting package. The questions and Division responses are presented below in *italicized* text in the order in which they were addressed at the meeting. Discussion is presented in normal text. The slides containing the Division's responses were sent to the sponsor on February 9, 2006.

Question 1: In accordance with 21 CFR 314, we plan to submit a representative executed production record (translated) with the NDA. We believe that one of the current commercial batches would be most appropriate for submission, because the current commercial batches are representative of the batches used in the clinical safety study (H101) and they support production information. Does the Agency agree that the executed production record for one of the current commercial batches is appropriate for submission in the NDA?

FDA RESPONSE: Yes, however, all the CMC information related to this batch should be provided in the NDA. Please refer to FDA and ICH guidelines regarding submitting CMC information for NDA. However, primary stability data on three batches should be submitted in the NDA.

Discussion: The Sponsor requested clarification on which batches they could utilize for stability testing for submission with their NDA. The Division replied that it was acceptable to use the commercial batches for stability testing purposes, given that all other requirements were met.

Question 2: The Dog Efficacy Study, conducted under GLP [Good Laboratory Practices] conditions, will be accompanied by the usual data listings as part of the study report. Does the Agency agree with this proposal?

FDA RESPONSE
Yes

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 3: A number of toxicology studies that are planned for submission in the NDA were conducted in the 1970s under non-GLP conditions. Information from these studies will be placed in section 4.2.3.7.7 (Other). Does the Agency agree with the placement of the information collected from these studies?

FDA RESPONSE
Yes

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 4: The development of Cyanokit has spanned over 10 years. During the course of the development of Cyanokit, Merck KGaA has instituted an electronic document management system. Some of the older "legacy" documents have been scanned into the document management system and therefore include scanned images of the handwritten signatures on the approval page of the reports. Newer reports, however, have been generated within the electronic document management system and therefore do not include handwritten signature pages, but retain blank signature pages. For the newer reports, the handwritten signatures are maintained in a separate paper file in the GLP archives. All GLP reports submitted with the NDA will be approved reports. Is it acceptable to submit some GLP reports with signatures and some without signatures?

FDA RESPONSE:
All GLP reports should have been audited and signed in some fashion. If the signature page is blank and not signed, include a link to the document containing the signatures.

Discussion: There was no additional discussion beyond the information presented in the slides.

Additional Nonclinical Comments: The adequacy of the referenced nonclinical data to support your NDA application can only be determined following submission of the studies for review. For the NDA, you should provide your summary of the existing data, your evaluation of how such data impacts the safety of the proposed drug product and copies of the referenced literature. Key publications necessary to support the NDA application should be specifically discussed in terms of the information about the study design and methodology.

The exposure margins established in the completed nonclinical efficacy study should be based upon pharmacokinetic [PK] data (Cmax and AUC values) rather than body weight or body surface area comparison.

Provide your rationale for proposed clinical dosing to be included in the labeling for hydroxocobalamin based upon the data obtained in the nonclinical efficacy study and the safety margin's obtained in this study.

Submit the toxicokinetic data for cyanocobalamin that were obtained in the nonclinical efficacy study and comparison of the exposures obtained in the toxicology study of cyanocobalamin already completed.

The submission supplement does not contain your rationale for the relevance of the rabbit mechanism data to your drug product safety profile. Provide your rationale why the mechanism studies provided support the safety of the drug product.

Determine whether there is a dose-response relationship between the adverse events [AE's] of hypertension and skin reaction/rash in the dog as was observed in the human.

Provide the NOAEL for these AE's and discuss how it relates to the effective dose as determined from the pivotal dog efficacy study.

Discussion: The Division emphasized that the references cited will not be evaluated until the NDA is submitted. Furthermore, assurances are needed that nonclinical studies will provide adequate toxicological coverage.

The Sponsor stated that they have PK data available from healthy volunteers. The Division reminded the Sponsor to address the issue of patients unexposed to cyanide but intentionally or unintentionally treated with hydroxocobalamin.

The Division encouraged the Sponsor to provide their rationale for differences observed between the rabbit model and the dog model. Specifically, the Sponsor should address the interpretability of animal data given that hypertension and skin reaction/rash were not a consistent finding in all animal models. The Sponsor replied that the dog model might not be appropriate for detecting a skin reaction/rash.

Question 5: We plan to provide data listings and SAS data sets (electronically) to accompany the Phase I safety study that was conducted in healthy volunteers. The clinical study report will include narratives for any subject deaths and serious adverse events as well as for certain other significant adverse events. We will provide paper copies of Case Report Forms for any subject who died or discontinued the study due to an Adverse Event. Does the Agency agree with our proposal to provide the above data sets, listings, narratives and CRFs?

FDA RESPONSE:
This is acceptable.

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 6: As expected, there have been a number of patient deaths observed in the French Clinical Experience with marketed Cyanokit® (Data from Dr. Baud (I, II, and ingestion) and Dr.Fortin).

BAUD I
We will have an updated study report and limited electronic datasets for the Baud I (n=69) cohort. There are 19 patient deaths. No narratives have been written, as the data available is minimal.

BAUD CARDIOVASCULAR SAFETY REPORT
We will have a study report and electronic data sets.

BAUD II
We will have a study report for the Baud II (n=61) cohort. There are 23 patient deaths. We will provide an electronic data set with the available information. No narratives are planned for this group.

FORTIN – PARIS FIRE BRIGADE
We will have a study report for the Fortin – Paris Fire Brigade (n=101) cohort. We will provide an electronic data set with the available information. There are a total of 42 patient deaths (17 deaths at the scene of the fire and 25 deaths at the hospital). No narratives are planned for this group.

FORTIN CARDIOVASCULAR SAFETY REPORT
We will have a study report and electronic data sets.

BAUD INGESTION AND SMOKE INHALATION
We will have a study report and electronic data sets.

This plan was previously discussed with the Agency at our meeting on April 8, 2004. We want to confirm the acceptability of this proposal.

FDA RESPONSE:
Narratives should be provided, to the extent possible, for each death.

Discussion: The Division reiterated that they understand the nature of some of the studies does not lend itself to precise clinical narratives. However, narratives are required by regulation and should be as detailed as possible even if only to document that no information is available.

Question 7: We plan to place the reports listed in question #11 above in section 5.3.5.2 of the NDA (Study Reports of Uncontrolled Clinical Studies). Does the Agency agree with the proposed placement of these reports?

FDA RESPONSE:
This is acceptable.

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 8: Due to the small amount of clinical data in this NDA, we plan to fulfill the requirement for the ISE/ISS in the Clinical Overview (Module 2.5) and Clinical Summary (Module 2.7). Does the Agency agree that separate ISE and ISS documents are not required?

FDA RESPONSE:
The data and their analyses should be described in detail for each individual study. The findings should then be integrated to the extent possible in the ISE and ISS. It is imperative that a coherent and detailed argument be presented in the NDA to justify Agency findings of safety and efficacy, support a favorable outcome for the benefit-risk assessment, and warrant approval for the indication(s) sought.

Module 2 is for true summaries, module 5 is for analyses across studies such as the ISS & ISE.

Discussion: The Sponsor explained that they did not anticipate including an ISS and ISE section in their NDA application. The Division replied that both of the sections are required even if the same, or similar, documents were located in each place.

Question 9: We plan to submit the table requested by FDA at the May 23, 2005 meeting. This table will be included in section 5.3.5.3 (Reports of Analyses of Data From More Than One Study). Does the Agency agree with the proposed placement of this table?

FDA RESPONSE:
This is acceptable. The integrated summary of safety should also be included in this section.

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 10: We plan to collect any post-marketing adverse events that are provided to us and promptly submit any reports to the Agency meeting expedited report criteria. All others will be submitted in Periodic Safety Update Reports. No formal post-marketing surveillance program is planned for Cyanokit. Does the Agency agree with the proposed Risk Management Plan?

FDA RESPONSE:
As previously indicated, a formal post-marketing surveillance plan will be required.

Discussion: The Division reiterated that a post-marketing surveillance plan must be included with the NDA submission, as this is required for products seeking approval under the animal efficacy rule.

Question 11: Since Cyanokit is intended for use in either the pre-hospital or the hospital setting, we do not intend to prepare a patient package insert. Does the Agency agree that a patient package insert is not required?

FDA RESPONSE:
We agree that a patient package insert is not required.

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 12: During the December 2, 2005 teleconference, the Agency suggested a fill line to facilitate rapid reconstitution in the field. We agree that a fill line would be helpful for the user and would like to hold additional discussion regarding the fill line. Does the Agency agree that it would be acceptable to have additional discussions at the Pre-NDA meeting regarding the fill line?

FDA RESPONSE:
Further discussions are acceptable as this is an important safety issue that will need to be resolved before submission of the NDA.

Discussion: The Sponsor indicated their desire to have a fill line placed at the — ml level of the vial. The Division inquired why the fill line would be placed at this level, since 100 ml of saline is used in the reconstitution process and the active drug product would only occupy 4 ml of volume. The Sponsor replied that during a mass casualty setting, a hurried medical provider might mistakenly under fill, and therefore over concentrate, the hydroxocobalamin. The Sponsor contended that this possible over concentration was more worrisome than under concentration, and could be averted by simply raising the fill line slightly. The Division inquired as to whether any safety or efficacy studies had been done with this concentration, to which the Sponsor replied that no such studies had been pursued. The Division expressed concern that the fill line would encourage dilution to a level that had not been studied. b(4)

The Division inquired about the lack of co-packaged saline in the proposed Cyanokit product. The Sponsor stated that they were unable to locate a saline package with a suitable expiry. The Division stated that they could perform stability analyses themselves. The Sponsor replied that they didn't think they would pursue that option at this time.

Post-Meeting Note: Further discussions between the Sponsor and the Division after the meeting led to an agreement to place the fill line at the 104 ml level, equal to the level of 100 ml of saline plus 4 ml occupied by the drug substance.

Question 13: Does the Agency have any comments on the proposed TOC, provided in Appendix 1 of this submission, for the NDA? (Please note that the TOC has been revised since it was originally submitted in the Pre-NDA Meeting Request. The revisions consist primarily of changing the order of information presented in Sections 2.3.A, 2.3.R, 3.2.A, and 3.2.R, as well as moving study T 15096 from Other Pharmacokinetics (4.2.2.7) to Single-Dose Toxicity (4.2.3.1).

FDA RESPONSE:
Guidance for Industry documents pertaining to electronic submissions, as well as updates to these documents, are available at (www.fda.gov/cder/regulatory/ersr).

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 14: We plan to provide Module 1 information in the same order as presented in Form FDA 356h. Does the Agency agree with this proposal?

FDA RESPONSE:
Guidance for Industry documents pertaining to electronic submissions, as well as updates to these documents, are available at (www.fda.gov/cder/regulatory/ersr).

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 15: We plan to provide in-text cross-references using Section Number and short title, e.g., "Section 2.7.2 Summary of Clin. Pharm." We intend to provide only the section number on the tabs, e.g., "2.7.2". Does the Agency agree with this proposal?

FDA RESPONSE:
Guidance for Industry documents pertaining to electronic submissions, as well as updates to these documents, are available at (www.fda.gov/cder/regulatory/ersr).

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 16: We propose to provide review copies as described in Table 1 below:

Discipline	Module 1	Module 2	Module 3	Module 4	Module 5
Quality (Red)	X	X	X	---	---
Nonclinical (Yellow)	X	X	---	X	---
Biopharmaceutics (Orange)	X	X	---	---	X
Mircobiology (White)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Clinical (Tan)	X	X	---	---	X
Statistical (Green)	X	X	---	---	X
Field Copy (Maroon)	X	X	X	---	---

A complete Archive Copy, containing all Modules, will be included in blue archive binders. Does the Agency agree with this proposal?

FDA RESPONSE:
Guidance for Industry documents pertaining to electronic submissions, as well as updates to these documents, are available at (www.fda.gov/cder/regulatory/ersr).

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 17: As indicated in previous questions, we plan to provide electronic data for the clinical studies as described in question numbers 10 and 11 below, as well as electronic listings for the healthy volunteer study. The electronic data will be submitted on either CD or DVD. We

intend to place one copy of the CD or DVD in Module 5 of the Archive Copy. Does the Agency agree with this proposal?

FDA RESPONSE:
Guidance for Industry documents pertaining to electronic submissions, as well as updates to these documents, are available at (www.fda.gov/cder/regulatory/ersr).

Discussion: The Sponsor informed the Division that they will be submitting the NDA as a paper application, not electronic. The Division replied that there are guidelines for electronic submission which include guidance on the physical media used.

Question 18: We expect that no new data will come available after the submission of the NDA since there are no ongoing studies with Cyanokit. There is the possibility of one or two post-marketing events from use of Cyanokit in France. Since it is likely that there will be no new data, we propose that no 120-day safety update be required. Does the Agency agree with this proposal?

FDA RESPONSE:
This proposal is not acceptable. Submission of a 120-day safety update is a regulatory requirement, even if only to state that no new data have become available.

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 19: Cyanokit will be manufactured in France by Merck Sante and imported into the United States for distribution by EMD Pharmaceuticals. We intend to submit the Certified Field Copy Module 3 as well as Module 1 and Section 2.3 to the International Office at FDA Headquarters. Does the Agency agree that this is the appropriate place to forward the Field Copy?

FDA RESPONSE:
This is acceptable, however, an additional certified copy should be submitted to the foreign inspection team of the Division of Manufacturing and Product Quality - Office of Compliance.

Discussion: There was no additional discussion beyond the information presented in the slides.

Question 20: On July 01, 2004, we submitted a Request for Trade Name Review for Cyanokit. At the time of the request, we intended to supply saline for reconstitution and an intravenous delivery system along with the drug. Since the original Request for Trade Name Review, we have determined that it will not be feasible to include the saline for reconstitution. We still intend to include the intravenous delivery system and transfer spike along with the drug.
Does the Agency agree that Cyanokit is an acceptable tradename?

FDA RESPONSE:
The proposed trade name will be evaluated during the NDA review process.

Discussion: There was no additional discussion beyond the information presented in the slides.

General Discussion: The Sponsor clarified that they plan to submit the NDA for rolling review, and inquired if fast-track status was required to achieve this. The Division had no immediate comments on this at the meeting, but promised to get back to the Sponsor.

The Division reminded the Sponsor that 36 months of stability data are required from their three drug lots. Additionally, updates in SAS transport file format are also required. The Sponsor acknowledged this requirement.

Post-Meeting Note: In further discussions with the Sponsor after the meeting, the Division confirmed that a fast-track designation application would be required to be eligible for a rolling NDA review.

Action Items:
None

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

/s/

Matthew Sullivan
3/9/2006 09:17:50 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 67,151

Chesapeake Regulatory Group
6574 River Clyde Drive
Highland, MD 20777

SPA Meeting for dog study

Attention: David Zuchero, MS, JD
Agent for EMD Pharmaceuticals, Inc.

Dear Mr. Zuchero:

Please refer to the meeting between representatives of your firm and FDA on April 8, 2004. The purpose of the meeting was to discuss the special protocol assessment letters dated December 11 and 19, 2003.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPA Mtg for Dog Study

Industry Meeting Minutes

Date/Time: April 8, 2004 / 1:30 pm

Location: Chesapeake Conference Room

Application: PIND 67,151

Sponsor: EMD Pharmaceuticals, Inc.

Drug/Dosage Form/Doses: Cyanokit (hydroxocobalamin) Injection

Indication: treatment of cyanide toxicity

Type of Meeting: Guidance

Meeting Chair: Bob Rappaport, M.D., Director, Division of Anesthetic, Critical Care, and Addiction Drug Products

Minutes Recorder: Sara Stradley, M.S., Regulatory Project Manager

EMD Pharmaceuticals	Title
Elliott Berger, PhD	VP, Regulatory Affairs and Quality Assurance, EMD
Michelle Rose, PhD	Regulatory Affairs, EMD
Kevin Judge, MD	VP, Medical Affairs and Medical Director, EMD
Liddy Chen, MB, MS	Statistics, EMD
Brigitte LeBealle	Clinical Research, Merck France
Marie-Helene Joffre, PhD	CMC, Merck France
Dieter Gallemann, PhD	Pharmacokinetics, Merck Germany
Friedrich vonLandenberg, PhD	Toxicology, Merck Germany
[redacted]	Clinical Toxicology Consultant, [redacted]
[redacted]	Regulatory Affairs Consultant, [redacted]

b(4)

DAGCADP	Title
Bob Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Dan Mellon, PhD	Supervisor Pharmacology/Toxicology
Eric Duffy, PhD	Director, ONDC/DNDC II
Thomas J. Permutt, PhD	Team Leader, Statistics
Ravi Harapanhalli, PhD	Team Leader, Chemistry
Jila Boal, PhD	Chemistry Reviewer
Arthur Simone, MD, PhD	Medical Reviewer
David Lee, PhD	Biopharmaceutics Reviewer
Mamata De, PhD	Pharmacology/Toxicology Reviewer

Division of Counter-Terrorism/OCTAP/CDER	Title
Brad Leissa, MD	Deputy Division Director
Mitchell Mathis, MD	Medical Team Leader
Narayan Nair, MD	Medical Officer
Su Yang, MSN, RN	Regulatory Health Project Manager
Frank Pelsor, Pharm.D.	Clinical Pharmacologist (OPS/DPEIII)

Meeting Objective(s): To discuss the special protocol assessment letters dated December 11 and 19, 2004.

General Discussion: Following introductions, the discussion focused on the Sponsor's questions that were included in the March 1, 2004, meeting package. In addition, chemistry questions from the December 23, 2003 submission were addressed as well as one clinical issue that was raised in the March 24, 2004 submission. The Sponsor's questions and the Agency's responses are presented below in italicized text. Any additional discussion is presented in normal text.

CMC Questions

Question 1: Does the Agency have any comments on the Compatibility Protocol and two USP-related questions submitted to PIND 67,151 on 23DEC2003 that EMD Pharmaceuticals, Inc. should take into consideration

FDA RESPONSE
Yes. Please see the comments on the following slides.

Question 1:
Cobalamin Radiotracer Assay: In the USP monograph for hydroxocobalamin, both the "Limit of Cyanocobalamin" and "Assay" tests employ a unique and outdated Cobalamin Radiotracer Assay <371>. We have contacted the USP and a current U.S. manufacturer of hydroxocobalamin and neither could recommend a laboratory to perform this test. Because this assay cannot be performed by our laboratories and we cannot find an alternative laboratory, we are proposing to use an alternative HPLC method. Because of the difficulty in running the out-dated Cobalamin Radiotracer Assay method, we propose to submit a more modem, fully-validated HPCL method, without demonstrating equivalence to the USP method. Is this acceptable?

FDA RESPONSE
If the HPLC method cannot be validated against the USP method <371>, the HPLC method should be validated on its own merit. The method should be specific and stability indicating.

Full validation of the HPLC method is needed for the NDA.

Question 2:
USP pH Dependant Cobalamin Test: The pH dependant cobalamin test described in the USP monograph for hydroxocobalamin will be performed on 3 batches to compare the data with that obtained from our HPLC method. Because the pH dependent cobalamin test serves no useful function in light of the more accurate HPLC assay, we propose to replace it by the new validated HPLC method. Is this acceptable?

FDA RESPONSE
Yes, the HPLC method could conceivably be a more accurate method. Perform the test on three batches to compare the data with that obtained from the HPLC method.

Based on the results, the USP pH dependant test maybe deleted.

Question 3:
Bacterial Endotoxin Levels: The USP monograph for Hydroxocobalamin Injection imposes a bacterial endotoxin limit of not more than 0.4 USP Endotoxin Unit (EU) per µg of hydroxocobalamin. Based upon the proposed Cyanokit administration rate of 70mg/kg/15min, the specification for bacterial endotoxins should be less than — U/mg. According to the drug substance manufacturer (——) the available data on six batches show that one batch in six does not meet this limit. Based on their data, —— has determined that a bacterial endotoxin limit of — mg would be possible. Is this acceptable? b(4)

FDA RESPONSE
The proposed limit of — EU/mg is acceptable.

General CMC Comments

The compatibility protocol (physical test and chemical compatibility tests) is adequate.

Suitable analytical methods should be used to assess the drug compatibility.

Discussion
The Sponsor stated they omitted the blood compatibility studies in the protocol because of their concern about the color interference between human blood and hydroxocobalamin. The Division stated that, if color interference is an issue with blood and hydroxocobalamin, any of the several alternative approaches described in the literature may be used. Either a new protocol should be submitted for the blood compatibility studies or the existing protocol should be revised. The Sponsor agreed to submit a new compatibility protocol for these studies.

Preclinical Questions

Question 2: For technical reasons, it is not feasible to administer the antidote/placebo to dogs in a blinded fashion. Does the Agency concur with EMD Pharmaceuticals' proposal to have a blinded assessor for the neurological assessments and decisions on whether the animals should be euthanized, the only subjective assessments in the study.

FDA RESPONSE
This response is acceptable.

Question 3: Does the Agency concur with EMD Pharmaceutical's revised proposal for anesthetic and/or sedative procedures in the study.

FDA RESPONSE
The proposed use of propofol and fentanyl are acceptable.

Discussion
The Division requested that the Sponsor incorporate procedures for adjusting the dose/infusion rate of each of these agents into the protocol. Parameters for adjusting each agent as well as the amount by which the dose or infusion should be adjusted should be specified. The Sponsor agreed to do so.

Question 4: Does the Agency concur with EMD Pharmaceuticals' proposal for cycling ventilatory weaning (the procedure the Agency referred to as rescue ventilation in Response 1f of the Division's response to the Special Protocol Assessment request) during the study?

FDA RESPONSE
The proposal is for use of mechanical ventilation from first apnea until the end of treatment followed by 6 cycles of artificial ventilation (tidal volume 4 ml/kg), 30 sec each with an intermediate weaning of 30 sec, if the dog fails to resume spontaneous ventilation. If the dog has not resumed spontaneous ventilation after the 6th attempted weaning, the treatment will be considered as a failure.

This proposal is acceptable.

Question 5: Does the Agency concur with EMD Pharmaceuticals' proposal for other treatment protocols during the study?

FDA RESPONSE
The intent of the Division was to assess the drug product in a setting which mimicked, as closely as possible, that of the anticipated clinical use. The proposed study allows for clearer delineation of the drug's effect and is acceptable. However, depending on findings from both studies, further assessment may be necessary to determine the role of hydroxycobalamin in multicomponent therapy.

Discussion
The Division clarified that multicomponent therapy included efforts to support victims' cardiovascular and respiratory status. Such efforts could be expected to include drugs routinely utilized in resuscitation as well as other cyanide antidotes. The Sponsor stated that their intent is to seek approval of Cyanokit as a stand-alone antidote. The Sponsor requested that the Division consider that, if any additional assessments are deemed necessary, the assessments be performed as post-marketing commitments. The Division stated that such a proposal would be considered.

Question 6: Does the Agency concur with EMD Pharmaceuticals' revised proposal for primary and secondary effectiveness endpoints?

FDA RESPONSE:
The primary and secondary endpoints are acceptable.

For the NDA, the potential toxicity of the high levels of cyanocobalamin will have to be addressed either via literature references or via a 28-day repeat-dose toxicology study.

Since, the present protocol uses the combination of cyanide and hydroxycobalamin; it is recommended that the surviving animals be maintained for (preferably) 30 days to obtain additional safety data. In particular, full histopathological assessment will address some of the concerns for human safety related to the combination of cyanide, hydroxycobalamin and cyanocobalamin exposures.

The kidney, heart, lung, spleen, adrenal along with the brain tissue should be analyzed histopathologically. Brain tissue should also be analyzed with special staining for neuronal as well as glial cell abnormalities.

Discussion
The Division stated that the proposed 7-day observation period is acceptable for the efficacy study. However, the Division advised the Sponsor to continue the evaluation period if evidence of a lack of full recovery is noted during clinical observations and that they provide additional safety data in this case. The Division also stated that a 14-day or 28-day safety study could be done as a post-marketing commitment.

The Sponsor questioned the importance of histopathology data in this study as the number of control-treated animals is likely be low and, therefore, the hydroxocobalamin-treated animals that survive will not have an adequate control for comparison. The Division agreed that the data obtained would not be definitive. However, this study may be the only study in which the effects of endogenously generated cyanocobalamin are present. Obtaining the blood levels of cyanocobalamin in this study may help to determine dosing for the repeat-dose cyanocobalamin studies that will be required to establish the safety of the high levels of cyanocobalamin that would be produced in an actual cyanide exposure. In addition, the results from the repeat-dose toxicology study for cyanocobalamin alone could be compared to those obtained from cyanide-exposed, hydroxocobalamin-treated animals. The Division advised the Sponsor to measure cyanide, cyanocobalamin, and hydroxocobalamin. Examining all three would provide valuable safety information and all three would be obtainable in the proposed study. The Division recommended that the Sponsor seriously consider obtaining all possible toxicology data from this study, since this may be the only study that will examine the histopathology in animals that were exposed to hydroxocobalamin and cyanide, thus mimicking the actual clinical use.

The Sponsor asked, if no histological differences are seen between the three treatment groups in this study, would they have to conduct the repeat-dose toxicology study on cyanocobalamin alone. The Division stated the strength of any conclusions derived from the data in this efficacy study would ultimately be dependent upon the number of animals that are available for analysis and the consistency of the findings. However, if a question arises from the data that would require tissue comparisons, it would be easier to examine existing tissue samples than to repeat the study.

Question 7: Does the Agency concur with EMD Pharmaceuticals' proposal regarding comparison of dosing groups in terms of efficacy and safety findings?

FDA RESPONSE
The initial proposal was for 17 male dogs /group. The Agency then recommended the additional of female animals in the study groups. In the current protocol, the proposal is to use 9 males and 9 females/group.

The use of dogs of both sexes is appropriate and acceptable with the understanding that the studies will not be powered to analyze differences based on gender.

Discussion
The Division asked if the Sponsor was aware that the study will not be powered adequately to detect statistically significant differences based on gender. The Sponsor stated they were aware of this concern. The Division noted that inclusion of both sexes is essential in order to detect any potential trends suggesting differences between males and females. If the study suggests a difference, further studies could then be conducted to explore the finding.

The Division noted that pharmacokinetic (PK) sampling should be collected up to 80-90% of total AUC or least 3-4 times the half-life of the drug. The Division stated that the 4-hour sampling point may not be adequate. The Sponsor expressed concern about additional sampling due to the amount of blood needed to be drawn from the animals. The Division suggested that the Sponsor provide a proposal based on the number of sampling points needed to provide the necessary data. The Division stated that, ultimately, the data obtained in this animal efficacy study will be used to establish the recommended clinical dose for the label. As such, consideration of the data required to complete that task should be evaluated prior to initiation of the study and possibly linked to the clinical data (PK-PD modeling), thereby providing additional information for the package insert. The Sponsor stated that they will send a proposal to the Division for review.

Clinical Questions

Question 8: Does the Agency concur with EMD Pharmaceuticals' revised proposal for assessing the tolerance of the rapid infusion?

FDA RESPONSE
The proposed method for assessing tolerability of the rapid infusion and plan for reducing individual flows, abandoning rapid infusions of individual dose groups, and repeating trials for dose groups that fail to tolerate the rapid infusion are acceptable.

Question 9: Does the Agency concur with EMD Pharmaceuticals' revised proposal for neurological testing?

FDA RESPONSE
The proposal is acceptable.

Question 10: Does the Agency concur with EMD Pharmaceuticals' rational for dose selection and dosing schedule?

FDA RESPONSE
The need for studies of repeat dosing may be addressed in the future, based on findings of the currently planned trials. The findings from animal studies to date and the rationale provided from human experience with the drug support abandoning the 15g dose. The new doses to be tested in humans are acceptable.

Question 11: In the revised study design, 150 subjects will receive Cyanokit in the following dose groups:

Dose	2.5g	5.0g	7.5g	10g
# Subjects	9	66	9	66

Does the Agency concur with EMD Pharmaceuticals' proposal for number of subjects receiving Cyanokit per dose group?

FDA RESPONSE
It was not clear what the basis was for selecting subject numbers for each group. It would be preferable to increase the number of subjects in the 7.5 g dose group at the expense of the 5.0 g group.

Discussion
The Sponsor stated that the 5.0 g and 10.0 g doses are the essential doses for the study and that the 2.5 g and the 7.5 g doses would provide only exposure and safety information. The Division agreed with this plan and with the proposal that the number of subjects per group will remain as stated on the table above.

The Sponsor also clarified that each vial contains one 2.5 g dose.

Question 12: Does the Agency concur with EMD Pharmaceuticals' proposal for blinding the study drug administration to the subjects and investigator?

FDA RESPONSE
The proposal for blinding the study is acceptable.

Discussion
The Division concurred with the proposal to blind the study by using different investigators to administer the drug and assess subjects post-administration. However, the Division questioned the technique of wrapping the i.v. bag and tubing to provide additional blinding. The Division asked if such a method had actually been attempted. The Sponsor stated that they will evaluate this method to determine its usefulness. It was agreed that the involvement of two separate investigators would maximize the blinding process.

Question 13: Does the Agency concur with EMD Pharmaceuticals' rationale regarding the safety of cyanocobalamin?

FDA RESPONSE
The anticipated, and indeed, previously measured level of cyanocobalamin are many times greater than levels for which any safety data is available. The results of the animal study may serve as a basis for determining the need for additional human studies.

Discussion
The Division stated that the lack of data on the effects of cyanocobalamin in humans at serum levels orders of magnitude above that seen in typical clinical situations may be addressed, in part, by the histopathology findings of the animal studies; especially if those studies indicate no pathology beyond what has previously been identified with exposure to either cyanide or hydroxocobalamin alone. The Division stated that the concern regarding cyanocobalamin is two-fold. First, at high doses, the compound may be toxic. Such toxicity would be an important consideration in performing an overall benefit risk analysis of hydroxocobalamin. Second, cyanocobalamin at levels expected with treating cyanide poisoning may adversely affect the hemodynamic, neurologic or respiratory stability of victims at a time when the stability of these systems are being significantly affected by both cyanide and hydroxocobalamin. There is concern that an additional challenge to these systems posed by cyanocobalamin may be

sufficient to negatively affect both the antidote's safety and efficacy. Therefore, further evaluation of the effects of cyanocobalamin will be necessary for approval of Cyanokit.

Question 14: Hydroxocobalamin appears to be significantly unstable in native human urine at 37^{0}C and this stability seems to be dependent on the hydroxocobalamin concentration and the individual composition of the urine. In addition, individual variations in bladder emptying intervals will lead to variations in the extent of decomposition rendering the reliability of urinary excretion data uncertain. Therefore we propose to remove the measurement of urinary levels of hydroxocobalamin from this human safety study. Does the Agency concur with this proposal?

FDA RESPONSE

- *No.*
- *The Sponsor's urine stability draft report is acknowledged.*

Although OH-Co may be unstable, urine OH-Co information is needed. Therefore, it is recommended that the Sponsor collect the urine samples:

- *Stability of OH-Co in urine at room temperature (25°C)*
- *Chill urine samples ASAP*
- *Collect urine samples frequently*
  - *Proposal :*
  - *0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24, 24-48, 48-72 hours*
- *Mass balance: account "all peaks" observed in urine profile*
- *Exclusion of Vitamin C in Inclusion/Exclusion Criteria*

Discussion

The Division acknowledged the draft report on hydroxocobalamin's stability in urine. However, the Division noted that further data on the stability of hydroxocobalamin in urine is important for the overall drug description, and therefore proposed the urine collection time points. The Division stated that the Sponsor should submit a proposal if they do not agree with the urine collection time points. The Division advised that mass balance data should also be included. The Division stated that this is routinely done in drug development. All peaks, those identified and unidentified (some peaks may not be identified in the urine sample), should be accounted for in the mass balance and compared with the total drug input. The Sponsor stated that it would not be easy to analyze the urine samples with the current method, due to the endogenous co-eluting peaks. The Division asked if the Sponsor had explored an alternative approach. The Sponsor stated that they will explore this option. The Division stated that the Sponsor should consider excluding Vitamin C in Inclusion/Exclusion Criteria, since Vitamin C may further degrade hydroxocobalamin in urine. The Division also reminded the Sponsor of the other topics (e.g., special populations, renal impairment, etc.) discussed previously, and that they should be addressed at the time of the NDA filing.

Clinical Pharmacology / Biopharmaceutical Comments

- *PK blood sampling :*
  - *adequate for all groups.*

- *PK analysis should include:*
  - *Cyanocobalamin*
  - *Cyanide*

Discussion
Regarding the current protocol, the Division stated that cyanocobalamin and endogenous cyanide levels should be assayed, in addition to hydroxocobalamin. The Division added that smokers may have endogenous cyanide levels 2-3 times higher than non-smokers. The Sponsor noted that smokers were removed from the study for logistical reasons (i.e., to deal with their anxiety to have a smoke in the middle of the study). The Division stated that analyses of all three entities, hydroxocobalamin, cyanocobalamin, and endogenous cyanide would help to develop PK/PD modeling, and this information could be linked to animal PK/PD information. The Sponsor stated that they will include a subgroup of heavy smokers.

Additional Question

March 24, 2004 Submission Question: We proposed to submit the database containing Dr. Fortin's data in the NDA and no raw data (i.e., data collection forms in French). Does the FDA agree with this proposal?

FDA RESPONSE
Submitting the database instead of the raw data (in French) is acceptable

The database needs to be more comprehensive than proposed. It should contain data to be collected in the proposed human and animal studies.

- *Include all laboratory data (full ABG results and all ECG and radiography readings)*
- *Include all medications administered from initiation of treatment to discharge/death*
- *Include AE data*
- *Each patient should be provided with a unique identification code*

Discussion
The Division reminded the Sponsor that the raw data should be available for inspection. The Sponsor clarified that the data were collected under appropriate ethical guidelines.

The Sponsor stated that additional French data will be available for the NDA.

Additional Issues Discussed

The Sponsor clarified that the following information would be provided at the time of the NDA filing.

- Animal efficacy data
- Human safety data
- Data from two French studies
- Clinical and preclinical supporting literature

The Division stated that the following information could be provided as post marketing commitments

- Repeat dose study
- Special population studies
- Pediatrics
- Other studies may be required based on agreements at the time of the NDA approval.

Dr. Mellon reminded the Sponsor that the animal efficacy rule specifically states that products evaluated for efficacy under that rule will be evaluated for safety under preexisting requirements for establishing the safety of new drug and biological products. Dr. Mellon indicated that he would review the previous discussions regarding preclinical data required for an IND/NDA and provide additional information in the meeting minutes to clarify what will be required for an NDA.

> **Post Meeting Note:** Based upon review of the previous discussions with the Sponsor and the requirements for an NDA, the following non-clinical studies will be required for an NDA and/or to support proposed clinical studies. Specifically, an IND will be required prior to conducting clinical studies. The standard battery of genetic toxicology studies should be submitted with the IND as described in ICH M3 Guidance Document. Specific requirements for the NDA will depend in part on the available nonclinical data obtained from Lipha. The requirements and concerns raised in the April 29, 2004 meeting, as described in the meeting minutes, should be addressed in the NDA. The Division encourages the Sponsor to submit an outline of the planned non-clinical pharmacology and toxicology sections of the proposed NDA for comment.

The Sponsor asked for clarification of the process for their tradename review. The Sponsor stated that they will be submitting "Cyanokit" as their tradename. The Division responded that the Sponsor should submit a request for a tradename review and advised the Sponsor to include additional names because of the concern about the word "kit" in the name. The Division reminded the Sponsor that any tradename found to be acceptable would be reviewed again 60 days prior to the PDUFA due date for the NDA.

The Division requested clarification on the shelf-life of the Cyanokit. The Sponsor responded that Cyanokit has a shelf life of 30 months. It is approved in France and sold on an emergency basis in other European countries. The Sponsor stated that they have a 36-month stability study underway.

The Sponsor expressed concern about obtaining the necessary pharmaceutical-grade cyanocobalamin to conduct an animal study and asked whether nonpharmaceutical-grade product might be used. The Division agreed to consider this option, and recommended that the Sponsor examine the impurity profile of the available products to determine the potential utility of their drug substances. Ultimately, dosing should be based on actual cyanocobalamin content. If studies with an impure drug product produce a toxicity profile that is adequate, the presence of the impurities may not be of concern. The Sponsor may provide justification for the use of the non-pharmaceutical grade material to the Division for comment prior to use in the animal study.

The Division asked if the Sponsor has had any interaction with the US Army Institute of Defense as this Institute may be able to provide useful information. The Sponsor responded that they just signed a CRADA with the Institute.

Action Items

1. The Sponsor agreed to submit a new compatibility protocol.

2. The Sponsor agreed to incorporate procedures for adjusting the dose/infusion rate of propofol and fentanyl into the protocol. Parameters for adjusting each agent, as well as the amount by which the dose or infusion should be adjusted should be specified in the protocol.

3. The Division suggested that the Sponsor provide a proposal for the number of sampling points needed to provide the necessary data for PK sampling.

4. The Sponsor stated that they will evaluate the technique of wrapping the i.v. bag and tubing to provide additional blinding.

5. The Sponsor stated that they will include a subgroup of smokers in the current protocol.

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

/s/

Sara Stradley
4/29/04 09:15:53 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

November 25, 2003

[redacted]

Attention: [redacted] b(4)

Re: Designation Request # 03-1774

Dear Mr. [redacted]

Reference is made to your request for orphan-drug designation dated August 22, 2003, of hydroxocobalamin for the treatment of acute cyanide poisoning, submitted on behalf of EMD Pharmaceuticals, Inc. Reference is also made to our acknowledgement letter dated September 9, 2003, and your amendment dated September 24, 2003.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bb), your request for orphan drug designation of hydroxocobalamin is granted for the treatment of acute cyanide poisoning.

Please note that if the above product receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. § 360cc). Therefore, prior to final marketing approval, we request that you compare the product's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. § 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the product's designated use.

If you need further assistance in the clinical development of your product, please feel free to contact James Bona, RPh, MPH, at (301) 827-3666. Please refer to this letter as official notification and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Pre-IND Meeting

[redacted]

Attention: [redacted]

b(4)

Dear Mr [redacted]

Please refer to the meeting between representatives of your firm and FDA on April 29, 2003. The purpose of the meeting was for EMD Pharmaceuticals, Inc., as represented by Chesapeake Regulatory Group, to obtain FDA's feedback on its clinical development program for Cyanokit® (hydroxocobalamin).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-827-7430.

Sincerely,

Sara Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: April 29, 2003 **Time:** 3:30pm-5:00pm

Location: Parklawn Building,

Sponsor: EMD Pharmaceuticals, Inc.

Drug Name: Cyanokit® (hydroxocobalamin)

Type of Meeting: Pre-IND Meeting

Meeting Chair: Nancy Chang, M.D., Medical Team Leader

Minutes Recorder: Victoria Kao, Regulatory Project Manager

EMD Pharmaceuticals, Inc.	Title
Elliot Berger, Ph.D.	Vice President Regulatory Affairs
	Clinical Toxicologist
Thierry Hulot	Project Leader, Merck Sante
	Managing Director of
Friedrich von Landenberg, Ph.D.	Toxicology
	Regulatory Affairs Consultant,
FDA	**Title**
Bob Rappaport, M.D.	Acting DivisionDirector
Nancy Chang, M.D.	Medical Team Leader
Art Simone, M.D.	Medical Reviewer
Tim McGovern, Ph.D.	Supervisor, Pharmacology and Toxicology
Tom Permutt, Ph.D.	Statistics Team Leader
Suresh Doddapaneni, Ph.D.	Office of Clinical Pharmacology and Biopharmaceutics Team Leader
David Lee, Ph.D.	Office of Clinical Pharmacology and Biopharmaceutics Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Jila Boal, Ph.D.	Chemistry Reviewer
Victoria Kao, B.S.	Regulatory Project Manager
CDER Division of Counter-Terrorism	**Title**
Dianne Murphy, M.D.	Director, Office of Counter-Terrorism and Pediatrics,
Mary Purucker, M.D., Ph.D.	Director, Division of Counter-Terrorism
Su Yang	Project Manager, Division of Counter-Terrorism,
Cheryl Turner	Regulatory Project Manager, Division of Counter-Terrorism
Joanne Holmes	Special Assistant, Office of Counter-Terrorism and Pediatrics

Background:
Cyanokit (hydroxocobalamin), owned by Lipha s.a., was approved in France in 1996. In March 2001, Lipha s.a., as represented by Orphan Medical, Inc. met with the Agency to discuss the requirements for a successful procedural review of an NDA in order to obtain marketing licensing rights for Cyanokit in US. This current meeting, which took place on April 29, 2003, directly between the Agency and Merck-Sante s.a.s. (formerly Lipha s.a.), was a follow up discussion to that original meeting in 2001 and was guided by specific questions submitted in the Sponsor's March 31, 2003, meeting background package. Merck-Sante s.a.s. proposes to pursue Cyanokit® in US as an antidote for the treatment for cyanide toxicity.

Note: The slides presented at the meeting are in italics and any discussion that followed is summarized below each slide.

Chemistry, Manufacturing, Controls (CMC)

Question 1:
Are the analytical methods and specification proposed for the drug substance acceptable?

Agency Response:

a. *The analytical methods and specifications should comply with the USP monograph*
b. *Justify lack of an infra-red test for identity*
c. *Clarify the acceptance criteria to be used with the HPLC assay method*
d. *Provide a numerical acceptance criteria for Bacterial Endotoxins*
e. *The limit of quantitation for the impurities test should be expressed as % of the drug substance. LOQ should be less than 0.1%*
f. *Acceptance criteria should be provided for each individual specified impurity at 0.1% or above as a % of the drug substance (not of the total chromatogram integration)*
g. *A specification of NMT 0.1% for individual unspecified impurities should be provided*
h. *The related substances should be structurally identified if possible. The agency recognizes that total characterization could be difficult. At a minimum, the sponsor is asked to identify only the major structural configurations of the related substances, i.e.: open/closed, core ring, etc.*

Question 2:
Based on the fact that hydroxocobalamin is a fermentation product, does FDA agree with our proposed drug substance specification for related substances?

Agency Response:
See Agency's Response to CMC Question 3.

Question 3:
Does FDA agree with our plan for the safety qualification of related substances?

Agency Response:
Safety qualification of related substances is deferred to Pharm/Tox and Medical review teams; although it was noted that normal ICH safety qualification threshold is 0.05%, for the dose proposed.

Question 4:
Does FDA agree with diluent and drug compatibility proposal?

Agency Response:
Response to this question is deferred to the Medical Review Team.

Question 5:
Does FDA have a standardized protocol for diluent and drug compatibility studies?

Agency Response:
No. Please provide a protocol, and we will respond with comments.

Additional Agency CMC Comments:

The following comments pertain to the drug product:

1) *Provide and justify an acceptance criteria for Bacterial Endotoxins which should comply with the USP monograph* b(4)
2) *The proposed acceptance criteria for degradation products on stability (—%) is not acceptable.*
3) *We note that the ICH identification/specification threshold for degradation products is 0.2%.*
4) *Provide a test for free cobalt or justify why it is not provided.*

Chemistry Discussion

The Agency expressed concern regarding the level of impurities for both drug substance and drug product; an acceptance criteria of —% would not be acceptable. However, the Sponsor noted that data generated to date indicate that such a large limit would not be needed.

Physical and chemical compatibility studies designed for actual use under realistic conditions will need to be performed. Such studies would help to provide useful instructions for labeling. The Agency will work with the Sponsor to establish the list of drugs and diluents to be studied.

The drug substance is a USP item and should therefore meet USP specifications. However, if the Sponsor can meet alternative equivalent specifications plus any additional ones as required by the Agency, such an approach may be acceptable.

There were concerns regarding the validity of the USP Cyanocobalamin Radiotracer assay. The Sponsor was encouraged to submit data from an alternative test. b(4)

Dr. Berger noted that based upon the current technology and information received from the supplier of the API (—— , the API would not meet the specifications proposed by the

Agency. Dr. Koble indicated that the Agency would review the data submitted in support of specifications proposed by EMD, in conjunction with the safety qualification data on the related substances to determine what the appropriate specifications should be. He also suggested that EMD consider refrigerating the product or propose shorter expiration dating.

Pharmacology/Toxicology

Question 1:
Are the Lipha Sante pharmacology study reports and a complete review of the scientific literature sufficient to support the Nonclinical Pharmacology section of the NDA, based on the fact that the ability of hydroxocobalamin to reduce blood cyanide levels is well established?

Agency Response:

- *Once the study reports and literature references are submitted, they can be reviewed by the Agency for adequacy.*
- *Complete study reports, including methodology and animal data line listings, are generally needed especially in regards to efficacy studies.*
- *An efficacy parameter of interest in animals is decreased lethality as well as reduced blood cyanide levels.*
- *Studies to support human efficacy are subject to GLP practices*
- *If the available Lipha Sante reports do not meet the above criteria, data should be generated in a new nonclinical study on efficacy.*
- *You are encouraged to submit study protocols with supporting rationale to the Agency for comment* prior to initiating the study.

Question 2:
Based on the pilot toxicology study results and exposure data, are the doses (75, 150 and 300 mg/kg) selected for the 28-day intravenous dog study appropriate, from a human exposure perspective?

Agency Response:

- *Based on the submitted comparative kinetic exposure data for dog and man, it is unlikely that exposures at the proposed high dose 300 mg/kg in dogs will achieve the expected exposure in humans at 5 g/day.*
- *Exposure in dogs at 300 mg/kg is likely to be significantly below the expected maximum human exposure at a dose of 15 g/day.*
- *The Agency recommends dosing up to MTD/MFD in the proposed 28-day dog study to fully characterize the potential toxicity profile*

Question 3:
Is the design and dose selection in the proposed 28-day Intravenous Dog Study acceptable?

Agency Response:
The design appears to be adequate for a toxicologic assessment.

Regarding dose selection, the proposed high dose of ___ mg/kg does not appear to adequately characterize the potential toxicity in animals when compared to the expected human exposures at doses of 5-15 g.

b(4)

Question 4:
What is the Agency's rationale for requesting the Segment II teratogenicity study in this particular setting (emergency use involving exposure to highly toxic compounds) and is it a requirement for approval?

Agency Response:

Rationale for request:

- *Adequately inform medical personnel/ patients of the potential reproductive risk with the use of this product*
- *The requested reproductive Segment II study is not a requirement for approval.*
- *The study may be performed as a Phase 4 commitment should the Lipha Sante reports not adequately address reproductive toxicity potential.*
- *Should a review of the Lipha Sante studies or the new Segment II study identify findings of concern, additional studies could be requested.*

Question 5:
Is the toxicology information described in this briefing document sufficient for the filing and approval of an NDA for Cyanokit?

Agency Response:
The Agency will need to review the referenced Lipha Sante studies and published literature prior to determining the adequacy for approval.

However, outstanding concerns remain regarding safety and efficacy evaluations in animals

Efficacy:
It is likely that at least one efficacy study in an appropriate animal model and performed under GLP conditions will be needed to support approval.

This study, along with previously generated animal data and human experience, will assist in determining appropriate dosing in humans.

You are strongly encouraged to submit a protocol for Agency review and feedback prior to initiating the study.

Safety:
Dosing in the proposed 28-day dog study should achieve the MTD/MFD to provide an adequate characterization of the toxicity profile.

Ideally, systemic exposure (based on AUC) will equal or exceed that expected in humans.

A segment II reproductive toxicity study should be conducted as a Phase 4 commitment should the Lipha Sante studies be deemed inadequate to address this issue.

Question 6:
Does the Agency agree with our plan for the safety qualification of related substances?

Agency Response:
Your plan for safety qualification is adequate under the following conditions:

- *The levels of substance impurities are identified in the drug batches used for the proposed 28-day dog study and genetic toxicology studies*

- *The overall exposure in dogs at the NOAEL dose for the 28-day study provides a 10-fold safety margin compared to the maximum expected human exposure based on body surface area*

Pharmacology/Toxicology Discussion

Pivotal animal studies conducted as basis for establishing efficacy must be conducted under GLP.

Based upon current human exposure information, the proposed 28-day study in dogs will not produce exposure greater than that expected with a 5-gram human dose. The Agency recommended that doses of 600 mg/kg/day be studied. Dr. vonLandenberg pointed out that in a pilot study in which animals were dosed up to 600 mg/kg/day, there was a non-specific toxicity observed which he believed was due to product overload. Even at a dose of 300 mg/kg/day there were clinical signs present 24 hours following dosing. Given that this product would be administered as a single dose, the Sponsor stipulated that 300 mg/kg/day should be the highest dose for the study. Dr. McGovern responded that the maximum dose chosen must be justified as MTD/MFD and found comparable to a human administration of 15 g of hydroxocobalamin. Dr. Chang added that the Sponsor would need to explain toxicity that is not drug specific, i.e., provide evidence that the toxicity is not drug specific and provide a rationale as to why the Agency should not be concerned about the same toxicity in humans.

Dr. McGovern reiterated that comparable exposure between human and animals must be shown. A possibility may be a one week trial at a higher dose than 300 mg. Further discussion on this topic will be necessary.

The Sponsor asked whether there could be leeway on the 10-fold safety margin for a 4-week study. The Agency responded that more discussion will be necessary; however, the indication will be taken into account.

With respect to the qualification of related substances, the 28-day dog study may be adequate to qualify related substances if the level of related substances in the 28-day study material are equal

to or greater than what one would expect in a commercial batch, if they are identified, and depending upon the toxicities observed in the study.

Clinical Pharmacology

Question:
Is the proposed pharmacokinetic package sufficient to support the Human Pharmacokinetics and Bioavailability requirements of an NDA for Cyanokit?

Agency Response:

- *The proposal of submitting the literature information is acceptable.*

- *However, depending on the overall information, Clinical Pharmacology studies (e.g., renal, pediatric, multiple-dose if necessary, dose-ranging if necessary, etc.) may be needed (performed as a Phase 4 commitment).*

Clinical Pharmacology and Pharmacokinetics Discussion

Dr. Lee indicated that the EMD proposal for using literature supported by source data is acceptable. However, the adequacy of this package will be data dependent. Data on other populations, e.g., renally impaired subjects, pediatric subjects, may be needed as a Phase IV commitment.

Clinical

Question 1:
Is the proposed effectiveness and safety package sufficient for the filing and approval of an NDA for Cyanokit in the treatment of cyanide toxicity?

Agency Response:
Usual Standards

- *Replicated randomized controlled studies of efficacy in humans*
- *Prospective safety database of at least 1000*
  - *all studies reasonably applicable*
  - *special populations*
  - *safety of highest dose*
- *Original GCP data*
- *Dose response studies*

Because of the potential public health impact of this product, we are open to alternative means of establishing safety and efficacy. However, our current assessment of available information reveals important gaps.

Current Gaps

- *Justification for a general indication*

- *Data supporting the proposed dose range and particularly, the highest dose*
- *Prospective assessment of the effects, if any, that hydroxocobalamin has on laboratory and clinical measurements, e.g., pulse oximetry*
- *Physical compatibility with fluids and medications reasonably expected to be coadministered – (updated FDA proposal to be provided)*
- *Electrolytes, CBC, urine, Ca^{+}, PO_4^{-}, BUN, ECG, ABG, pulse oximetry*
- *Long term safety*
- *Size of the literature safety database is unclear; identify subjects/patients whose data are presented in more than one study*
- *Individual data/complete ranges versus median values and quartiles*
- *Pediatric and special populations*

Safety Concerns

- *Hepatic toxicity?*
- *Hematology (platelets)*
- *HTN*

Proposal to Fill Clinical Gaps

- *Multi-dose, controlled, human stud(ies) for safety*
- *Safety database*
  - *150 subjects with 50 exposed to the highest dose*
  - *long term follow-up (4-6 weeks) with physical exam and laboratory studies*

- *Hemodynamics, cardiac rhythm, 12-lead ECGs*
- *Respiratory: ABGs, pulse oximetry, ausculation*
- *Laboratory: hematology, chemistries, coagulation profiles*
- *Neurologic*
- *Urologic: Urinalysis, urine output*
- *Musculoskeletal/integument: Injection sites*

You are encouraged to submit all protocols for review and comment.

Post-Approval Studies

- *Post-marketing safety and efficacy data*
- *Pediatric*
- *Prophylactic use*

Clinical Response Cont'd – Efficacy; Baud's Data

- *Historical control (1991 paper):*
  - 43 deaths/109
  - 36 found dead
  - 7/73 = 9.6% deaths

- *Baud Study (counting only patients with CN levels)*

- *69 patients in all; 6 had either no measurable or recorded cyanide levels*
- *17 deaths/63*
- *12 in initial arrest*
- *5/51 = 9.8% deaths*

Clinical Response Cont'd – Efficacy Issues

- *Animal studies will serve as the primary basis for establishing antidote efficacy (endpoint = survival) and dosing guidelines.*
- *Supportive efficacy data from human subject studies is expected to be based on randomized, placebo-controlled, double-blinded studies using a surrogate endpoint (lowering of blood cyanide levels) in subjects with nontoxic blood cyanide levels, e.g., smokers, patient receiving SNP.*
- *Published human subject studies submitted to date might be sufficient for NDA review, with respect to efficacy, if the animal data submitted provides strong evidence of efficacy and safety. More complete data will strengthen the application.*
- *Animal dosing studies will have to be related to the proposed human dosing schedule.*

Clinical Discussion

Because of the potential public health impact of the product, the Agency is open to alternative means of establishing the safety and efficacy of the product. The Agency has identified, and presented to the Sponsor during this industry meeting a number of "gaps" that will need to be addressed before an application can be approved. As a means to address those gaps, the Agency proposed that a study be conducted in 150 subjects (healthy volunteers are acceptable) in which subjects are treated with doses representative of the proposed range, and with at least 50 subjects treated with the highest proposed dose. (All subjects should be followed for at least 4-6 weeks with physical exam and laboratory studies.)

Dr. Boron noted that the proposal for a generalized cyanide toxicity indication is linked to the pathophysiology of the condition and the mechanism of the product. Dr. Chang indicated that the Agency is willing to accept a scientific rationale describing why the mechanism of action for the product is the same in all cyanide toxicity situations in conjunction with the requested animal efficacy study.

Regulatory

Question:
Will priority review be available for this NDA?

Agency Response:
The priority review option will be available, but this decision is usually made at the time of submission.

Meeting Adjourned

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/s/

Sara Stradley
9/12/03 12:30:25 PM