CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-041

CHEMISTRY REVIEW(S)

NDA 22-041

CYANOKIT® 5 g
(Hydroxocobalamin for Injection)
(2.5 g per vial)
-For intravenous Use -

Each carton contains:

2 vials, each containing Hydroxocobalamin for Injection, 2.5 g
2 Transfer Spikes
1 Intravenous Administration set
1 Quick Use Reference Guide
1 Package Insert

(Diluent not included)

EMD Pharmaceuticals, Inc.

Milagros Salazar, Ph.D.
ONDQA-DPAIII & MS, Branch V,
For
The Division Anesthesia, Analgesia, Rheumatology Products (DAARP)

Table of Contents

Chemistry Review Data Sheet

1. **NDA Number: 22-041**

2. **REVIEW #: 1**

3. **REVIEW DATE:** 14-Dec-2006

4. **REVIEWER:** Milagros Salazar Driver, Ph.D.

5. **PREVIOUS DOCUMENTS:** N/A

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Quality reviewable unit[1]	30-MAY-2006
Original (N-000)	16-JUN-2006
IR-1 communication[3]	09-AUG-2006
Amendment[2] BC (response to IR-1)	08-SEP-2006
Amendment[2] BC (response to IR-1)	05-OCT-2006
IR-2 communication[3]	16-OCT-2006
Amendment[2] BC (response to IR-2,email 27-Oct-06)	30-OCT-2006
IR-3 communication[3]	25-OCT-2006
T-con and email responses	08-NOV-2006
Amendment[2] BC (response to IR-3)	09-NOV-2006
FDA Communication	14-NOV-2006
Minutes of 8-Nov-06 T-con from firm	15-NOV-2006
Amendment BC, email (17-Nov-06)	20-NOV-2006
[a]Amendment BC	06-DEC-2006
T-cons	08,11 &12-DEC-2006
[b]Amendment BC (Compatibility study & resp. to 8-Dec-06 Tcon)	11-DEC-2006
[c]Amendment BC (response to 11 & 12-Dec-06 T-cons)	13-DEC-2006
Amendment BZ ([a, b, c] Amendments consolidated plus labeling)	14-DEC-2006

[1] Chronology of previous CMC communications between CDER and the firm and/or reviews
[2] Applicant's letter date or date of review and/or communication with applicant
[3] For ONDQA– IR letter or action letter

7. **NAME & ADDRESS OF APPLICANT:**

Name:	EMD Pharmaceuticals, Inc.
Address:	3211 Shannon Road, Suite 500 Durham, NC 27707
Representative:	Elliott T. Berger, Ph.D., VP Regulatory Affairs and Quality Assurance
Telephone:	919-401-7107
Facsimile:	919-401-7166

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name:	CYANOKIT ®, 5.0 g
b) Non-Proprietary Name (USAN):	Hydroxocobalamin for Injection
c) Code Name#:	705
d) Chem.Type/Subm.Priority:	3,5,6 / P (new strength, manufacturer & indication)

9. **LEGAL BASIS FOR SUBMISSION:** NDA 22-041, 505(b)(1)

10. PHARMACOL. CATEGORY: Analog of Vitamin B12;
Therap. Class: Hematopoietic vitamin

11. DOSAGE FORM: Lyophilized Powder for Injection

12. STRENGTH/POTENCY: 5.0 per kit or 2.5 g per vial or
25 mg/mL after reconstitution

DOSE: 5.0 g initial and up to 10.0 g (15 min. Initial dose and 15min.- 2 hrs second dose)

13. ROUTE OF ADMINISTRATION: i.v. infusion

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
***(If applicable, fill out the form for special products and deliver to the team leader).

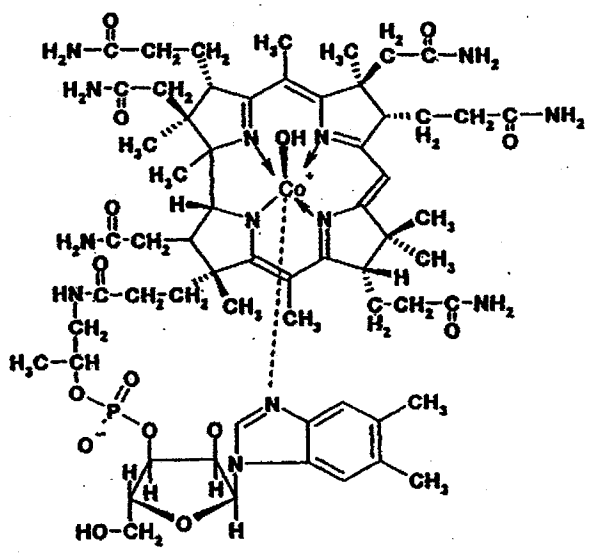
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CHEMICAL NAME: Cobinamide hydroxide phosphate 3'-ester with 5,6-dimethyl -1-α-D-ribofuranosylbenzimidazole inner salt

OTHER NAMES: Vitamin B_{12a}, Hydroxy vitamin B12, Hydroxycobalamin, b(4)

CAS No: 13422-51-0 EINECS No.: 236-533-2
Molec. Formula: $C_{62}H_{89}CoN_{13}O_{15}P$ M.W. 1346.36

STRUCTURAL FORMULA:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
b(4)	II		Hydroxo-cobalamin	1	Adequate	12-Dec-2006 LOA : 13-Feb-06	API Manufacturer
	II			1	Adequate	19-Oct-2006 LOA : 30-Aug-2006	
	III			4	Adequate	LOA: 9-Apr-2004	
	III			1	Adequate	1-Nov-2006 LOA: 3-Jan-2006	

Code 1 – DMF Reviewed. 2 –Type 1 DMF 3 – Reviewed previously and no revision since last review 4 – Sufficient information in application

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,151	Cyanokit®
b(4) 510k		
Patent # (Merck Patent GmbH) Issued: 11/10/1998 Expiry: 11/14/2016	5,834,448	The patent claims the drug product in this NDA as a product-by-process. The patent claims 15 methods of use, one of them is the use proposed in this NDA: Treatment of known or suspected cyanide poisoning. [Section 1.4 of the NDA16-Jun-2006 submission.]

18. STATUS: The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION / COMMENTS	DATE	REVIEWER
Biostatistics	—mo. Expiry.	14-Nov-2006 13-Dec-2006	Jim Gebert. Ph.D. (for clinical) Roswitha Kelly, MS (for CMC)
EES **(printed record attached at the end of this review)**	Overall CGMP status: Acceptable (DS & DP Manufacturers, Packagers and Testers)	13-Dec-06	Inspector: Mark Mcclain Insp. Date: 4-12 Dec-06 DP manufacturer. CGMP Status: recommended for approval by inspector and OC (Mr. Dietrick).
b(4) Pharm/Tox	X Free Co limits of — adequate for DP Inadequate qualification of impurity levels for DP. Agreed to include a post-marketing commitment.	30-Oct-06 6-Nov-06 12-Dec-06 (T-con)	Steve Leshin, Ph.D. Dan Mellon, Ph.D., TL
Biopharm	Not consulted. However, approval recommended.		

LNC	X- Agreed and advised on established name and on CMC–DMETS labeling.	3-AUG-2006 15-NOV-2006 8-DEC-2006	Guirag Poochikian, Ph.D.
Methods Validation	x N/A- DP analytical methods do not qualify for any of the ONDQA seven criteria for requesting MV.	25-Oct-2006	Milagros Salazar, Ph.D.
DMETS/ODS	X Comments were appropriately rolled over into CMC comments.	19-Oct-2006	Laura Pincock, Pharm. D.
EA	x- adequate EIC less than 1 ppb.	25-OCT-2006	Milagros Salazar, Ph.D.
Microbiology	Not consulted. However, approval recommended.	2-NOV-2006	Bryan Riley, Ph.D.
OCTEC	X Not consulted. However, AP recommendation was made		

19. ORDER OF REVIEW (OGD Only): N/A

APPEARS THIS WAY
ON ORIGINAL

Chemistry Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

All outstanding issues have been resolved. The firm has revised the specifications satisfactorily and on December 13, 2006, the Office of Compliance has deemed all facilities acceptable for cGMP compliance. From the CMC perspective, the NDA for Cyanokit® is recommended for approval.

The expiration dating period grantable for the lyophilized Cyanokit® product is 30 months with storage conditions of 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. This should be included in the action letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant has agreed to provide the following data by June 30, 2007. This should be reminded in the approval letter

b(4)

i. Available data supporting the identity of all impurities exceeding the identification threshold of —% in the drug substance.
ii. Data supporting the safety of all impurities exceeding the qualification threshold of —% in the drug substance.
iii. Available data supporting the identity of all impurities exceeding the identification threshold of —% in the drug product.
iv. Data supporting the safety of all impurities exceeding the qualification threshold of — % in the drug product.

II. Summary of Chemistry Assessments

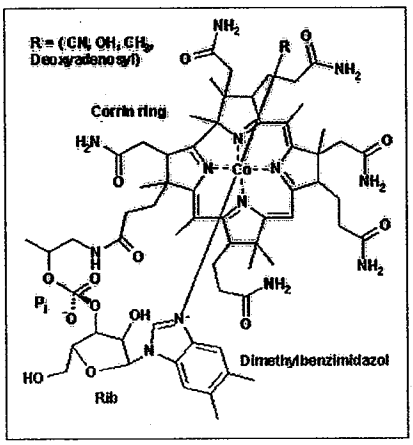
A. Description of the Drug Product(s) and Drug Substance(s)

Cyanokit® (hydroxocobalamin for injection) 5 g total, for intravenous use, is indicated for the treatment of known or suspected cyanide poisoning. Cyanokit® (NDC ———) carton contains two 250 mL glass vials, each vial containing 2.5 grams of lyophilized Hydroxocobalamin dark red crystalline powder; two sterile transfer spikes and one sterile IV infusion set. Each vial is recommended for reconstitution with 100 mL of 0.9% Sodium chloride. The diluent is not provided as part of the kit. The strength of the reconstituted hydroxocobalamin injection is 25mg/mL and it must be used within 6 hours after reconstitution. The reconstituted product has a pH between 3.5 to — immediately after reconstitution and up to pH=6.0 at 6 hours post reconstitution. Cyanokit® is a single-dose, sterile, ——— product manufactured aseptically. The treatment dosing range is 5 to 10 grams of one single 5 g dose, intravenous infusion over 15 minutes or two sequential 5g doses. The rate of infusion for the second dose ranges from 15 minutes to 2 hours based on patient condition.

b(4)

The drug substance in Cyanokit® is Hydroxocobalamin (OHCo) or Vitamin B12a, CAS No. 13422-51-0 and molecular formula $C_{62}H_{89}CoN_{13}O_{15}P$. The chemical name of hydroxocobalamin is Cobinamide dihydroxide dihydrogen phosphate (ester), mono(inner

salt), 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosyl-1*H*-benzimidazole. This drug substance is the hydroxylated active form of vitamin B12 with a molecular weight of 1346.36 amu, in which a trivalent cobalt ion is coordinated by a tetrapyrol (or corrin) ring. The corrin ring is a macrocycle similar to the porphyrin ring found in heme, chlorophyll and cytochrome, has two of the pyrrole rings directly bonded, while the others are linked by methylene bridges. In Hydroxocobalamin, the central metal ion Cobalt has four coordinations provided by the nitrogens in the corrin ring, the fifth by the dimethylbenzimidazole group and the sixth coordination is the hydroxyl group. See diagram below:



Hydroxocobalamin is a hygroscopic, odorless, dark red crystalline powder which is freely soluble in water and ethanol, and practically insoluble in acetone and diethyl ether. A 0.2% aqueous solution of OHCo has pH values from 8.0 to 10.0.

b(4)

In consultation with the Pharm/Tox

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

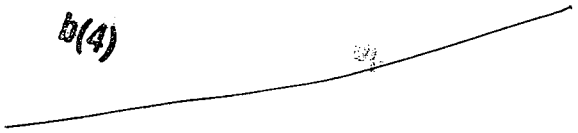
_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

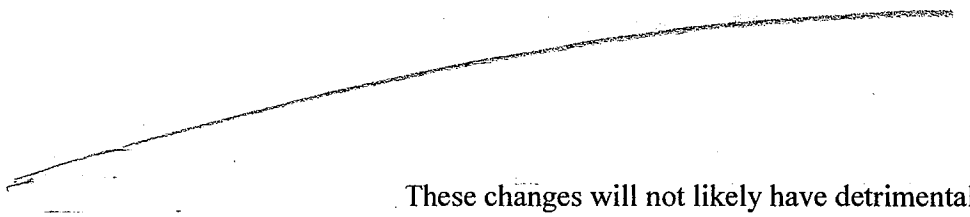
[redacted]

b(4)



These limits were derived from recommendations under ICH Q3B for the reporting, identification and qualification levels, manufacturing/stability data , and a risk assessment regarding the nature of the related substances. For example, all UV spectra of the unidentified

b(4)



These changes will not likely have detrimental effects on the efficacy or safety of the drug product. Therefore, although many impurities seem to have exceeded the qualification thresholds and minimal data was provided supporting their safety, the above chemical basis for the safety and efficacy led us to accept the above limits with a post-marketing commitment from the firm to provide additional data on identification and qualification within six months from the date of approval of this NDA. The formulations of Cyanokit® during pre-clinical /clinical studies were not significantly different from the proposed drug product for approval. Therefore, no comparability studies were necessary.

The estimated expiration dating period of 30 months was based on the statistical analysis of Impurity at [redacted], the main impurity at the qualification level of [redacted]%. b(4)

B. Description of How the Drug Product is Intended to be Used

Cyanokit carton, NDC [redacted], contains two 250 mL glass vial with 2.5 g of Hydroxocobalamin each. Two sterile transfer spikes to deliver the diluent solution to the vial, and one sterile infusion set to administer the reconstituted injectable solution to the patient intravenously. Diluent is not included. Cyanokit is formulated as lyophilized powder for injection, single-dose sterile, [redacted] and aseptically manufactured product. b(4)

The initial dose of Cyanokit® for adults is 5 g, (2 vials) administered by intravenous (IV) infusion over 15 minutes. A second dose of 5 g may be administered by IV infusion for up to a total maximum dose of 10 g. The rate of infusion for the second dose may range from 15 minutes to 2 hours based on patient condition.

Each vial of Cyanokit® is recommended for reconstitution with 100 mL of 0.9% sodium chloride Injection. Other diluents, such as Lactated Ringers Injection and 5% Dextrose Injection are also compatible with Hydroxocobalamin for its reconstitution.
Physical incompatibility (with particle formation) was observed with the mixture of Cyanokit® in solution and the following drugs: diazepam, dobutamine, dopamine, fentanyl, nitroglycerin, pentobarbital, phenytoin sodium, propofol and thiopental. These drugs should not be administered simultaneously through the same IV line as OHCo. Chemical incompatibility (with hydroxycobalamin degradation) was also observed with sodium thiosulfate, sodium nitrite and ascorbic acid. These drugs should not be

administered simultaneously through the same IV line as OHCo. Simultaneous administration of Hydroxocobalamin and blood products (whole blood, packed red cells, platelet concentrate and plasma) through the same IV line is not recommended. However, blood products and Hydroxocobalamin can be administered simultaneously using separate IV lines (preferably on contralateral extremities).

Cyanokit® injection for intravenous administration is indicated for the treatment of known or suspected cyanide poisoning. Its mechanism of action is straight forward, the hydroxo ligand, in Hydroxocobalamin is displaced by the toxic cyanide ion which is linked to the trivalent cobalt ion, and results in the stable Cyanocobalamin (Vitamin B12) compound that is excreted in the urine.

The expiration dating period recommended is 30 months for the lyophilized product with storage conditions of 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Cyanokit® injection product should be used within 6 hours after reconstitution at storage conditions not exceeding 40°C (104°F). Do not freeze.

C. Basis for Approvability or Not-Approval Recommendation

The application has provided sufficient information and data to fulfill the requirements under section 505(b)(1) of the Act to support the identity, purity, strength and quality of the Cyanokit® product for its intended use as a cyanide poisoning antidote.

The post-approval commitments on identification and qualification of related Substances are justified based on the following consideration:

- All related substances specification limits have been tightened to reflect the batch analysis, stability data, and to be very close to the levels used in the limited toxicology studies in the NDA.
- All impurities

b(4)

These changes will not likely have detrimental effects on the efficacy or safety of the drug product.

- Commitment from the applicant to revise, if necessary, the current tentative impurity limits after toxicology qualification studies are presented in June 2007.
- The nature of the indication and the urgency for an approved cyanide antidote was also considered into this risk management step.

III. Administrative

A. Reviewer's Signature: Milagros Salazar (For ONDQA, signatures are electronic in DFS.)

B. Endorsement Block

- ONDQA Branch Chief: Ravi S. Harapanhalli (electronic signature in DFS.)

C. CC Block

- ONDQA: cc: Salazar; Al-Hakim; Harapanhalli
  cc: Original NDA 22-041
  cc: DAARP-Div. File/NDA 22-041

131 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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

/s/

Milagros Salazar
12/14/2006 05:12:22 PM
CHEMIST
CMC recommendation: Approval
PDUFA Date: 19-Dec-2006

Ravi Harapanhalli
12/14/2006 05:29:14 PM
CHEMIST

7/18/06

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)
NDA:	22-041
Applicant:	EMD Pharmaceutical, Inc.
Stamp date:	June 16, 2006
PDUFA Date:	April 19, 2007
Trademark:	Cyanokit®
Established Name:	Hydroxocobalamin
Dosage Form:	Lyophilized powder
Route of Administration:	Intravenous (IV) infusion
Indication:	Treatment of known or suspected cyanide poisoning
Pharmaceutical Assessment Lead:	Ali Al-Hakim, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

Hydroxocobalamin, can be considered as a new type of emerging antiterrorism drug product; it is the hydroxolated active from of vitamin B_{12} (see structures below). It is a large molecule in which a cobalt ion is coordinated in the 4 position by a tetrapyrol ring. The drug product, Cyanokit® formulated as a lyophilized powder for intravenous injection, it is a hydroscopic, odorless, dark red powder that is freely soluble in water and methanol. Excipients used in the drug product formulation include [redacted] b(4)

Cyanokit® was approved in France in 1996.

The unit quantity of hydroxocobalamin per vial is 2.5g; however, the initial recommended dose is 5 g, requiring the administration of 2 vials. Each vial is recommended to be constituted with 100 mL of sterile saline. The drug product powder is also compatible with Lactated Ringers, and 5% dextrose. The rationale for administering hydroxocobalamin (OHCo) drug product as an antidote to cyanide poisoning is based on the high affinity of the cyanide ion for cobalt compounds as depicted in the following equation:

$$OHCo + HCN \rightleftharpoons CNCo + H_2O$$

Mechanism of action/Cyanide poisoning

Following absorption, the Cyanide ion enters the cells and binds ferric iron in mitochondrial cytochrome oxidase to form a reversible complex. Cyanide inhibits electron transport chains, oxidative phosphorylation, and reduces

the cellular redox potential. This leads to cytotoxic anoxia, which shifts the cell to anaerobic metabolism, resulting in lactic acid production.

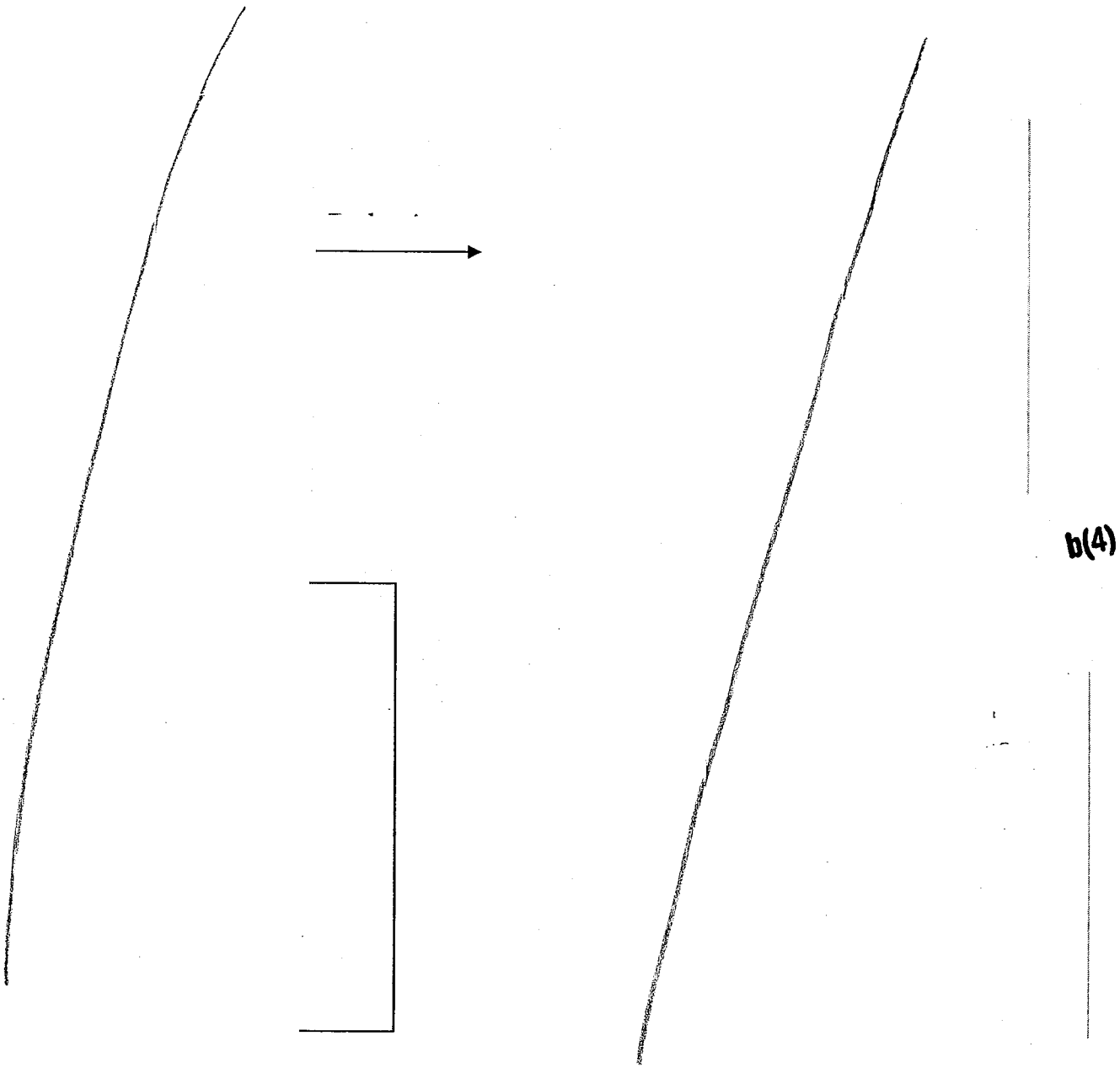
Mechanism of action/cyanide intoxication

Hydroxocobalamin, is an antagonist of cyanide intoxication that binds cyanide directly which results in the displacement of the hydroxo ligand by the cyanide ion to form cyanocobalamin (CNCo), another form of vitamin B12.

B. Review, Comments and Recommendations

Drug Substance

The drug substance manufacturing process is described in DMF [redacted] (LOA is included). Therefore, this DMF should be reviewed and evaluated accordingly. As indicated above, the drug substance,



Due to the nature of the dosage form of the final product (reconstitution solution for injection), related process controls for these steps need to be evaluated with respect to adequacy of the followings:

- Bioburden testing and filter integrity
- Sterilization Process of bulk solution, vials and stoppers (time, temperature, etc.)
- Lyophilization procedure and any differences between cycle for that may impact the drug product.

b(4)

Evaluation and assessment of the comparability protocol regarding the manufacturing process using the lyophilizer and cycling of the lyophilization procedure. This manufacturing change was introduced during the end of phase 2 meeting based on the sponsor's proposal for scale-up.

b(4)

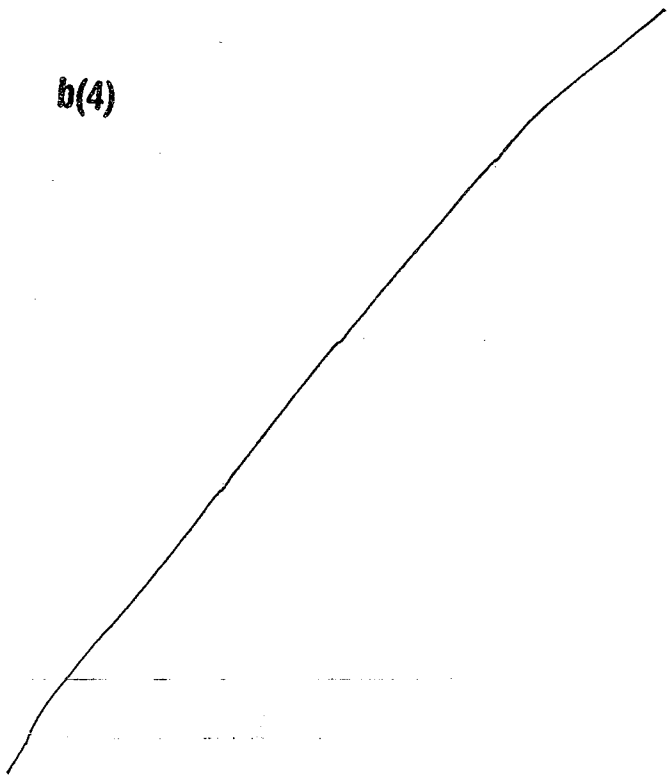
Stability

This section contains stability data obtained from studies performed on the Cynokit drug product powder and the reconstituted solution. Cycling temperature studies were conducted with respect to temperature zones variation and transport. The reviewer needs to evaluate the data and draw a conclusion regarding the above data with respect to the proposed expiry dating and the appropriate commitment regarding post-approval stability protocol.

Labeling

Labeling information on the primary, secondary and label insert should be assessed with respect to CMC related information and reconstitution use. Due to the unique nature of the drug product as a cyanide antidote, the drug product contains instruction card (see below) for reconstitution as shown below. The information needs to be assessed with respect to ease of use, instructions and subsequent administration of the drug product taking into consideration that such drug will be administered on the field during mass cyanide poisoning.

b(4)



Instruction Card

C. Critical issues for review and recommendation

During the assessment process, it is important to evaluate and assess the critical issues important parameters of the drug substance and the drug product. These issues may include, but are not limited to the following items:

- Reviewing of the DMFs for the drug substances manufacturing process with main emphasis on the [redacted]
- Proposed specifications and limits for the drug substance based on the test data obtained from NDA stability batches
- Assessment of the analytical metrology for identification, quantification and characterizing the related substances taking into consideration the [redacted] the impurities compared to [redacted], etc). b(4)
- Overview and critique of the manufacturing process capability and the impact of any changes between the clinical batches and the subsequent scale up leading to the validation/commercial NDA validation batches.
- Holding/storage time for the bulk solution
- Process controls during the manufacturing process for the drug product (e.g. [redacted] etc.)
- Validation of the lypholization step.
- Evaluating the release and shelf life proposed specifications, with respect to biological tests (particulate matter, Sterility test, and bacterial endotoxins) and related substances.
- Analytical procedures, validation, qualification of impurities, and the justification for not including free Cobalt test.
- Container/closure for this injectable solution. Reconstitution procedure and of the container/closure system compatibility with three recommended diluents (compliance with USP particulates tests).
- Comparability protocol of the manufacturing process using the [redacted] lyophilizer instead of the [redacted] lyophilizer, [redacted] cycling [redacted] of the lyophilization step, co-packaging issue with saline, and scale up proposal. These issues were discussed during the end of phase 2 and pre-NDA meetings with sponsor. It is recommended that the reviewer review the meeting minutes in the DFS for IND 67,151.
- Stability issues with respect to the proposed expiry dating and the appropriate commitments regarding post-approval stability protocol.
- Due to the nature of the dug product solution, it is recommended that the reviewer communicates with the microbiology reviewer regarding any issue related to sterilization aspects and microbiological testing of the drug product which include:
    - Bioburden testing and filter integrity
    - Sterilization Process of bulk solution, vials and stoppers (time, temperature, etc)
    - Lyophilization procedure and any differences between cycle [redacted] that may impact the drug product.
- Assessment of the pharmaceutical development report with respect to:
    - Formulation development and the final formulation used in clinical studies
    - Development of the manufacturing process with main emphasis on lyophilization process which afforded the final drug product.
    - Differences in manufacturing processes including equipment and any subsequent impact on the clinical and stability batches.

D. **Comments for 74-day Letter:** Confirmation that all sites are ready for inspection.

E. **Recommendation for fileability:** The NDA is fileable because it contains a considerable amount of CMC information and data with respect to drug substance and drug product which are suitable for evaluation and assessment based on the FDA and related ICH guidelines for submitting CMC information for New Drug Application. See also fileability template on next page.

Recommendation for Team Review: It is recommended that the NDA be reviewed by a single reviewer due to short synthetic scheme for the drug substance and nature of the drug product as a lyophilized powder dosage form reconstituted for intravenous injection which does not contain any novel excipients.

Consults

The reviewer, in conjunction with project manager, should initiate the following consults/requests as early as possible (see fileability template below).

Ali Al-Hakim, Ph.D. — 07/07/2006
Pharmaceutical Assessment Lead — Date

Ravi Harapanhalli, Ph.D. — 07/07/2006
Branch Chief — Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?		√	Office of compliance entered the sites that do not have CFN numbers.
5	Is a statement provided that all facilities are ready for GMP inspection?		√	This will be requested din the 45 day letter.
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated?	√ √ √ √	 √ 	Biopharm Statistics LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included	Status
[redacted]		Drug Substance	Yes	Pending
[redacted]	[redacted]	[redacted]	Yes	pending
[redacted]	[redacted]	[redacted]	Yes	pending
[redacted]	[redacted]	[redacted]	Yes	pending

b(4)

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

/s/

Ali Al-Hakim
7/18/2006 10:47:08 AM
CHEMIST

Ravi Harapanhalli
7/18/2006 03:05:18 PM
CHEMIST