CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-626

CHEMISTRY REVIEW(S)

NDA 21–626

Radiogardase (Prussian Blue) Capsules 500 mg

Heyl Chemisch–pharmazeutische Fabrik GmbH& Co. KG

Eldon E. Leutzinger, PhD

Division of New Drug Chemistry II – HFD-820

Table of Contents

Chemistry Review Data Sheet

1. **NDA** 21–626

2. **REVIEW #** 2

3. **REVIEW DATE:** 9/30/2003

4. **REVIEWER:** Eldon E. Leutzinger PhD, HFD-820

5. **PREVIOUS DOCUMENTS:**

Submission(s) Reviewed	Letter Date	FDA Received
Original	10–MAR–2003	13-MAR-2003
Amendment N–000–BC	22–APR–2003	25-APR-2003
Amendment N–000–BC	28–APR–2003	02-MAY-2003
Amendment N–000–C	05–MAY–2003	07-MAY-2003
Amendment N–000–BC	05–MAY–2003	07-MAY-2003
Amendment N–000–BC	13–MAY–2003	15-MAY-2003
Correspondence N-000-C	25-JUL-2003	05-AUG-2003
Correspondence N-000-C	29-JUL-2003	04-AUG-2003
Amendment N-000-BC	30-JUL-2003	04-AUG-2003
Amendment N-000-BC	13-AUG-2003	19-AUG-2003

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

Submission(s) Reviewed	Letter Date	FDA Received
Amendment N-000-AC	28-AUG-2003	03-SEP-2003
Amendment N-000-BC	28-AUG-2003	02-SEP-2003
Amendment N-000-AC	01-SEP-2003	03-SEP-2003
Amendment N-000-BC	05-SEP-2003	09-SEP-2003
Amendment N-000-BC	10-SEP-2003	12-SEP-2003
Amendment N-000-BC	11-SEP-2003	12-SEP-2003
Amendment N-000-BC	12-SEP-2003	15-SEP-2003
Amendment N-000-BC	18-SEP-2003	23-SEP-2003

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

Name:	Heyl Chemisch–pharmazeutische Fabrik GmbH& Co. KG
Address:	Goerzallee 253, D–14167, Berlin, Germany
Representative:	Robert Z. Martin, Vice–President Operations, Heyltex Corp.
Telephone:	(281) 395–7040

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

a) Proprietary Name: Radiogardase–Cs

b) Non-Proprietary Names: Application to USAN (August 27, 2003) pending (applicant proposes "insoluble Prussian blue"

c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Not Applicable to NDAs

10. PHARMACOLOLGICAL CATEGORY/INDICATION: Radiocesium and thallium decorporation

11. DOSAGE FORM: Gelatin capsules, 500 mg.

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

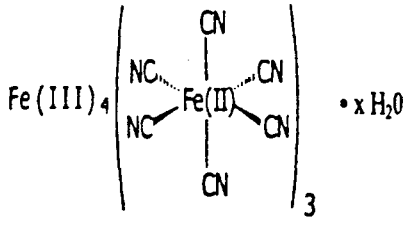
14. R_x/OTC DISPENSED: __X__ R_x ____ OTC

15. SPOTS (Special Products On–Line Tracking System)

_____SPOTS product – Form Completed __X__Not a SPOTS product

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

Chemical Name(s): Ferric hexacyanoferrate (II)
CAS Registry No. 170729–80–3
Molecular Formula: $Fe_4[Fe(CN)_6]_3 \cdot xH_2O$
Molecular Weight: 859.3 (anhydrous)
Molecular Structure: Face-centered cubic lattice with 14 – 16 molecules of water of crystallization and a variable amount surface water (adsorbed)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE a	STATUS b	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	10-FEB-2003	See Section P.2.4, review page 39

a Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

US Patent (Expires): None in USA or Germany

Exclusivity: Five years for NME, and 7 years of orphan exclusivity

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable (all sites)	9/11/03	
Pharm/Tox	Acceptable	8/26/03	A. Laniyonu, Ph.D
Biopharm	Labeling changes	8/30/02	Alfredo Sancho, Ph.D
LNC	USAN requested	8/27/03	
Methods Validation	To be requested		
DMETS	"Radiogardase" Acceptable	5/09/03	DMETS Staff
EA	Categorical Exclusion Satisfactory	3/11/03	Eldon E. Leutzinger
Microbiology	Approval	5/29/03	John Metcalfe

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): *Not Applicable*

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 21–626

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Review 1 identified three issues for which information needed to be submitted in order to complete the review of the NDA. The requests for this information was communicated to Heyl in a meeting between the Division of Medical Imaging and Radiopharmaceutical Drug Products on August 27, 2003 and included the following:

a. Data linking product manufactured currently with product manufactured in 1987 that was used in the Goiana accident.
b. Data on the Goiana drug product regarding the amount of water bound in the molecule (water of hydration) and the amount of surface water, the analytical procedures used to measure water (e.g., Loss on Drying or Karl Fischer). This information is necessary to express the amount of active moiety that is contained in "500 mg" of drug product used in the Goiana accident.
c. A more detailed description of the equations used to calculate cyanide dissociation in mcg free CN/gram of anhydrous Prussian blue.

In amendments submitted on September 1, 2003 and September 3, 2003, Heyl provided the required information which fully addressed these three issues. There was also information requested for six items for which a commitment was obtained from Heyl (amendment on September 5, 2003) to provide that information post-approval. Additionally, there were four other items that included (a) revision of the heavy metals acceptance criteria for drug substance, (b) revision of the specification sheet for drug product for cesium and thallium binding to 75 mg Cs/capsule and 125 mg Tl/capsule and (c) formal submission of certificates of analysis to the NDA for two batches of drug product sent to REAC/TS, as well as to provide samples of two extra batches of Prussian blue drug substance for interbatch variability testing. Heyl provided the certificates of analysis of the two batches in amendment September 11, 2003, and provided as well the complete specifications sheet reflecting the revision of specifications for heavy metal acceptance criteria (——— ——————————— for the drug substance. In the original submission, there were numerous references to Ph. Eur in the release specification sheets for drug substance and drug product. Heyl has revised and provided these specification sheets to include the USP.

Heyl's cesium and thallium binding specifications for drug substance (amendment September 11, 2003) are the following: ——————————————— They have added cesium and thallium binding specifications for drug product (amendment September 12, 2003) as follows: ——————————— Heyl submitted an application to USAN on August 27, 2003 for the established name; this can be handled post-approval. Based on what is known about Prussian blue in the literature, it is very stable, and this is supported by the data collected in formal stability studies discussed in the application. Evaluation by Pharm/Tox indicates that there are no safety issues (Memorandum dated September 29, 2003 from Adebayo

Laniyonu, Supervisory Pharmacologist, Division of Medical Imaging and Radiopharmaceutical Drug Products). Finally, the current GMP status for the Haupt and Apolda, Germany manufacturing facilities were found acceptable on August 26, 2003. **Based on the requested information submitted and its acceptability, as well as the written commitments for information post-approval, there remain no further issues for chemistry, manufacturing and controls. Hence, from the standpoint of CMC it is recommended that NDA 21-626 be approved.**

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

1.

2.

3.

4.

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6.

7.

II. Summary of Chemistry Assessments

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

The drug product consists of a hard gelatin capsule containing 500 mg of insoluble Prussian Blue and 0 to 38 mg of microcrystalline cellulose.

The drug substance is $Fe_4[Fe(CN)_6]_3 \cdot (14 - 16)\ H_2O$, and exists in a face-centered cubic lattice structure with Fe(II), Fe(III) atoms occupying the corners of the cube, and the C≡N groups positioned on the sides. The crystal lattice is an infinite 3-dimensional solid based on repetition of the type Fe(III)-N≡C-Fe(II)-C≡N-Fe(III). In aqueous media, this cubic structure is maintained because of the strong thermodynamic stability of the 3-dimensional structure and accounts for its insolubility.

Not all of the above atomic positions in the unit cube are occupied. There are "holes" in the crystal lattice. About one quarter of the $Fe(CN)_6$ positions are either vacant or filled with water (water of crystallization). These holes are distributed randomly to more orderly depending on the conditions in which the crystals are prepared [H. Buser, et.al., The Crystal Structure of Prussian Blue: $Fe_4[Fe(CN)_6]_3 \cdot x\ H_2O$, Inorganic Chemistry, 1977, 16(11), p. 2704]. The mechanism of uptake of cesium and thallium is not fully understood, but these "holes" are believed to play an important role. Nielsen, et.al. [in InVitro Study of ^{137}Cs Sorption of Hexacyanoferrate(II), Z. Naturforsch, 1987, 42b, 1451-1460] indicates that the mechanism of uptake is a combination of chemical ion-exchange and physical adsorption. Ion-exchange occurs with hydronium ion from water molecules entrapped in the crystal. According to Nielsen, the evidence for this is the reduction in the pH when cesium exchanges for hydronium ion. In ONDC's literature investigation and evaluation, it is found that the decrease in pH does not account for all of the cesium uptake, it is thought that the remainder is by absorption into the vacant "holes" of the crystal lattice where cesium is held electrostatically or mechanically.

Prussian Blue drug substance is very stable at room temperature as demonstrated in formal stability studies (12 months), and appears to be stable out to 5 years of storage, based on the collective experience of Heyl. Cesium and thallium binding capacities are maintained over the 12 months for drug substance and at least 6 months for drug product. As an indicator of long term stability, retained samples of drug product tested by Heyl after 12 years of storage had cesium and thallium binding capacities meeting the limits of

The general trend in the binding kinetics is similar between current manufactured batches (# 0719N0104 and # 1926M0110) and the 1987 batch (# 8712532), a steep incline over the first 4 hours and then leveling off after 6 hours. Cesium binding is somewhat less for the 1987 batch than the current ones at all time points beyond 6 hours, but all 3 batches approach close together at 36 hours. In conclusion, cesium binding kinetics for the current manufactured batches are very similar to that for the 1987 batch. At 24 hours, the cesium binding capacity for # 0719N0104 (year 2003) is 0.2825 g Cs/g PB, that for # 1926M0110 (year 2002) is 0.2700 g Cs/ g PB, as compared to # 8712532 (year 1987) with 0.2605 g Cs/g PB.

At low pH (acidic conditions) and high pH (basic conditions), some cyanide dissociation occurs. Heyl has provided cyanide (CN) dissociation data for two batches (# 0726N0205 and # 8712532, the latter the 1987 batch) over a pH range of 0 to 3 at contact times of 30 min and 60 min. Batch # 8712532, although not the actual batch used in the Goiana accident of 1987, is a batch manufactured in the same year with the same manufacturing process, and represents product having similar characteristics of that used in Goiana. The data for CN dissociation for both # 0726N0205 (2002) and # 8712532 (1987) are similar at 30 min and 60 min contact times. Secondly, CN dissociation appears to increase as pH drops from pH 1 to pH 0 for contact time of 60 min (15.4 to 36.7 ppm, 9.1 to 33.4 ppm, respectively). These apparent high values of CN dissociation at low pH have raised concerns, particularly at pH 1 and below because of the risk for patients with disorders associated with hypersecretory states (e.g., Zollinger-Ellison Syndrome, gastrinemia in which patients may have extremely low gastric pH levels for extended periods of time). Heyl has provided samples of current manufactured batches of Prussian Blue to the FDA, and DPQR laboratories have completed testing of these batches for both cyanide dissociation and cesium binding. Confirmatory studies by DPQR for cesium binding are complete. In a final study, DPQR performed a set of experiments to determine free cyanide in samples from 5 batches of Prussian blue drug substance and 2 batches of drug product at pH 1 and pH 5.5 with incubation time of 60 min. From the data provided in the DPQR report, it is concluded that the 10 ppm limit for free cyanide is satisfactory, and that there is no need for setting a new criteria at pH 1 for 60 min and justified in the review.

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

The drug product will be put into a national stockpile and be available for use in an event causing contamination of an area of population with Cs-137. In the case of Cs-137 contamination, a patient may be given orally up to 9 grams (18 capsules, 3 grams 3 times a day) per day over a minimum period of 30 days. Patients would be assessed for the amount of residual whole body radioactivity. Duration of treatment beyond 30 days would be determined by the level of radioactivity remaining. Dosage and administration is defined in the package insert, and includes adults and adolescents, and pediatrics (2 – 12 years).

C. Basis for Approvability or Not-Approval Recommendation
Not applicable.

III. Administrative

A. Reviewer's Signature

Chemist Eldon E. Leutzinger, PhD Date 9/02/2003

B. Endorsement Block Same date as draft review

Deputy Director, ONDC	Charles Hoiberg, PhD	_____	Date:
Project Manager	Lynn Panholzer	_____	Date:

cc: Orig. NDA 21–626
HFD–160/Division File
HFD–800/Deputy Dir ONDC/Hoiberg
HFD–160/MO/Yaes
HFD–160/Pharm/Laniyonu
HFD–160/DivDir/Loewke

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

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

/s/

Eldon Leutzinger
10/1/03 11:12:17 AM
CHEMIST

Charles Hoiberg
10/1/03 11:25:08 AM
CHEMIST

NDA 21–626

Radiogardase (Prussian Blue) Capsules 500 mg

Heyl Chemisch–pharmazeutische Fabrik GmbH& Co. KG

Eldon E. Leutzinger, PhD
Division of New Drug Chemistry II – HFD-820

Table of Contents

Chemistry Review Data Sheet

1. **NDA** 21–626

2. **REVIEW #** 1

3. **REVIEW DATE:** 9/16/2003

4. **REVIEWER:** Eldon E. Leutzinger PhD, HFD-820

5. **PREVIOUS DOCUMENTS:**

Submission(s) Reviewed	Letter Date	FDA Received

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

Submission(s) Reviewed	Letter Date	FDA Received
Original	10–MAR–2003	13-MAR-2003
Amendment N–000–BC	22–APR–2003	25-APR-2003
Amendment N–000–BC	28–APR–2003	02-MAY-2003
Amendment N–000–C	05–MAY–2003	07-MAY-2003
Amendment N–000–BC	05–MAY–2003	07-MAY-2003
Amendment N–000–BC	13–MAY–2003	15-MAY-2003
Correspondence N-000-C	25-JUL-2003	05-AUG-2003
Correspondence N-000-C	29-JUL-2003	04-AUG-2003
Amendment N-000-BC	30-JUL-2003	04-AUG-2003
Amendment N-000-BC	13-AUG-2003	19-AUG-2003

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

Name:	Heyl Chemisch–pharmazeutische Fabrik GmbH& Co. KG
Address:	Goerzallee 253, D–14167, Berlin, Germany
Representative:	Robert Z. Martin, Vice–President Operations, Heyltex Corp.
Telephone:	(281) 395–7040

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

a) Proprietary Name: Radiogardase–Cs
b) Non-Proprietary Names: Prussian Blue, PB, Berlin Blue, Berliner Blau
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: P

9. **LEGAL BASIS FOR SUBMISSION:** Not Applicable to NDAs

10. **PHARMACOLOLGICAL CATEGORY/INDICATION:** Radiocesium and thallium decorporation

11. DOSAGE FORM: Gelatin capsules, 500 mg.

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

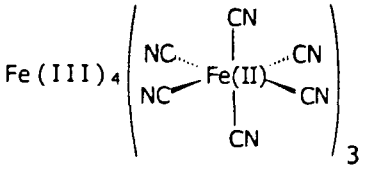
14. R_x/OTC DISPENSED: __X__ R_x ____ OTC

15. SPOTS (Special Products On–Line Tracking System)

_____SPOTS product – Form Completed __X__ Not a SPOTS product

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

Chemical Name(s): Ferric hexacyanoferrate (II)
CAS Registry No. 170729–80–3
Molecular Formula: $Fe_4[Fe(CN)_6]_3 \cdot xH_2O$
Molecular Weight: 859.3 (anhydrous)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [a]	STATUS [b]	DATE REVIEW COMPLETED	COMMENTS
[redacted]				3	Adequate	10-FEB-2003	See Section P.2.4, review page 39

a Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	51,700	Prussian Blue [redacted]

US Patent (Expires): None in USA or Germany

Exclusivity: Seven years requested subject to orphan drug designation

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable (all sites)	9/11/03	
Pharm/Tox	Acceptable	8/26/03	A. Laniyonu, Ph.D
Biopharm	Labeling changes	8/30/02	Alfredo Sancho, Ph.D
LNC	USAN requested	8/27/03	
Methods Validation	To be requested		
DMETS	"Radiogardase" Acceptable	5/09/03	DMETS Staff
EA	Categorical Exclusion Satisfactory	3/11/03	Eldon E. Leutzinger
Microbiology	Approval	5/29/03	John Metcalfe

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): *Not Applicable*

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review for NDA 21–626

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Pending review of the information in the forthcoming amendments to address remaining issues
See Deficiency Letter to Applicant

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

The sponsor should commit to address those items identified in the Deficiency Letter to Applicant in a timely fashion.

II. Summary of Chemistry Assessments

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

The drug product consists of a hard gelatin capsule containing 500 mg of insoluble Prussian Blue and 0 to 38 mg of microcrystalline cellulose.

The drug substance is $Fe_4[Fe(CN)_6]_3 \cdot (14 - 16)\ H_2O$, and exists in a face-centered cubic lattice structure with Fe(II), Fe(III) atoms occupying the corners of the cube, and the C≡N groups positioned on the sides. The crystal lattice is an infinite 3-dimensional solid based on repetition of the type Fe(III)-N≡C-Fe(II)-C≡N-Fe(III). In aqueous media, this cubic structure is maintained because of the strong thermodynamic stability of the 3-dimensional structure and accounts for its insolubility.

Not all of the above atomic positions in the unit cube are occupied. There are "holes" in the crystal lattice. About one quarter of the $Fe(CN)_6$ positions are either vacant or filled with water (water of crystallization). These holes are distributed randomly to more orderly depending on the conditions in which the crystals are prepared [H. Buser, et.al., The Crystal Structure of Prussian Blue: $Fe_4[Fe(CN)_6]_3 \cdot x\ H_2O$, Inorganic Chemistry, 1977, 16(11), p. 2704]. The mechanism of uptake of cesium and thallium is not fully understood, but these "holes" are believed to play an important role. Nielsen, et.al. [in InVitro Study of ^{137}Cs Sorption of Hexacyanoferrate(II), Z. Naturforsch, 1987, 42b, 1451-1460] indicates that the mechanism of uptake is a combination of chemical ion-exchange and physical adsorption. Ion-exchange occurs with hydronium ion from water molecules entrapped in the crystal. According to Nielsen, the evidence for this is the reduction in the pH when cesium exchanges for hydronium ion. In ONDC's literature investigation and evaluation, it is found that the decrease in pH does not account for all of the cesium uptake, the remainder is by absorption into the vacant "holes" of the crystal lattice where cesium is held electrostatically or mechanically.

Prussian Blue drug substance is very stable at room temperature as demonstrated in formal stability studies (12 months), and appears to be stable out to 5 years of storage, based on the collective experience of Heyl. Cesium and thallium binding capacities are maintained over the 12 months for drug substance and at least 6 months for drug product. As an indicator of long term stability, retained samples of drug product tested by Heyl after 12 years of storage had cesium and thallium binding capacities meeting the limits of

The general trend in the binding kinetics is similar between current manufactured batches (# 0719N0104 and # 1926M0110) and the 1987 batch (# 8712532), a steep incline over the first 4 hours and then leveling off after 6 hours. Cesium binding is somewhat less for the 1987 batch than the current ones at all time points beyond 6 hours, but all 3 batches approach close together at 36 hours. In conclusion, cesium binding kinetics for the current manufactured batches are very similar to that for the 1987 batch. At 24 hours, the cesium binding capacity for # 0719N0104 (year 2003) is 0.2825 g Cs/g PB, that for # 1926M0110 (year 2002) is 0.2700 g Cs/ g PB, as compared to # 8712532 (year 1987) with 0.2605 g Cs/g PB.

At low pH (acidic conditions) and high pH (basic conditions), some cyanide dissociation occurs. Heyl has provided cyanide (CN) dissociation data for two batches (# 0726N0205 and # 8712532, the latter the 1987 batch) over a pH range of 0 to 3 at contact times of 30 min and 60 min. The data for CN dissociation for both # 0726N0205 (2002) and # 8712532 (1987) are similar at 30 min and 60 min contact times. Secondly, CN dissociation appears to increase as pH drops from pH 1 to pH 0 for contact time of 60 min (15.4 to 36.7 ppm, 9.1 to 33.4 ppm, respectively). These apparent high values of CN dissociation at low pH have raised concerns, particularly at pH 1 and below because of the risk for patients with disorders associated with hypersecretory states (e.g., Zollinger-Ellison Syndrome, gastrinemia). Such patients may have extremely low gastric pH levels for extended periods of time. Heyl has provided samples of current manufactured batches of Prussian Blue to the FDA, and DPQR laboratories are testing these batches for both cyanide dissociation and cesium binding. Confirmatory studies by DPQR of cyanide dissociation and cesium binding are complete.

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

The drug product will be put into a national stockpile and be available for use in an event causing contamination of an area of population with Cs-137. In the case of Cs-137 contamination, a patient may be given orally up to 9 grams (18 capsules, 3 grams 3 times a day) per day over a minimum period of 30 days. Patients would be assessed for the amount of residual whole body radioactivity. Duration of treatment beyond 30 days would be determined by the level of radioactivity remaining. Dosage and administration is defined in the package insert, and includes adults and adolescents, and pediatrics (2 – 12 years).

C. Basis for Approvability or Not-Approval Recommendation

The final decision on approvability is pending the review of forthcoming amendments to address the remaining issues (list of deficiencies at the end of this review). Summarizing, the major issues are to establish a safety profile for current manufactured Prussian Blue and determine the safety impact of the known cyanide dissociation at low pH, composition per capsule for how much active ingredient is contained in 500 mg of Prussian Blue, and establish a linkage between product manufactured currently and product used in the Goiana accident. A number of requests for information are asked in the list of deficiencies in order to address these issues. There are also a number of lesser important issues dealing with controls for the drug substance, and information to address these issues are listed in the letter.

III. Administrative

A. Reviewer's Signature

Chemist Eldon E. Leutzinger, PhD Date 9/02/2003

B. Endorsement Block Same date as draft review

Deputy Director, ONDC Charles Hoiberg, PhD _____ Date:
Project Manager Lynn Panholzer _____ Date:

cc: Orig. NDA 21–626
HFD–160/Division File
HFD–800/Deputy Dir ONDC/Hoiberg
HFD–160/MO/Yaes
HFD–160/Pharm/Laniyonu
HFD–160/DivDir/Loewke

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

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21626/000
Org Code : 160
Priority : 1P
Stamp Date : 13-MAR-2003
PDUFA Date : 13-SEP-2003
Action Goal :
District Goal: 15-JUL-2003

Sponsor: HEYL CHEMISCH PHARMAZEUTISCHE
NO CITY, , XX

Brand Name : RADIOGARDASE (PRUSSIAN BLUE)
500MG CAPS
Estab. Name:
Generic Name: PRUSSIAN BLUE
Dosage Form: (CAPSULE)
Strength : 500 MG

FDA Contacts: L. PANHOLZER Project Manager (HFD-160) 301-827-7510

Overall Recommendation: ACCEPTABLE on 11-SEP-2003by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : FEI :
HAUPT PHARMA AG
GRADESTRASSE 13
BERLIN, , GM D-12347

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : CHG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-SEP-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-SEP-03		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		
