product used in the Goiana accident."

Discussion:

- The Division stated that it accepts the use of a batch manufactured at about the same time and by the same process as the product used in the Goiana accident to generate the needed data.
- In response to the applicant's request for clarification, the Division confirmed that the objective of this request by the Division is to standardize the amount of active moiety from batch to batch rather than the amount of cyanide. The applicant noted that, in a submission dated August 28, 2003, it proposed an alternative to the measurement of water content as the best way to determine the amount of active moiety that is contained in "500mg" of drug product, and asked if the Division had rejected this proposal. After further deliberation, the Division notified the applicant that it accepts the applicant's August 28, 2003 proposal to calculate the amount of active moiety based on iron content, and stated that all future data should be expressed in terms of anhydrous Prussian blue.

Item #3: "Cyanide dissociation data at pH's 7 and 9 at 24 and 48 hours. Express the data in mcg free CN/g anhydrous Prussian Blue. Provide details of your calculations."

Discussion: The applicant stated that this data would be in an upcoming amendment.

Item #4: "Send samples of 100 grams each of API batches and drug product currently being held from shipment to REAC/TS pending testing by FDA. Send samples of 100 grams each of two additional API batches for inter-batch variability evaluation."

Discussion:

- The applicant stated that it is unaware of any shipment currently being held pending testing by FDA, but that here isa pending order that has not yet been shipped to REAC/TS. The Division subsequently confirmed with Dr. Robert Ricks of REAC/TS that there is no shipment on hold, and notified the applicant that this was a misunderstanding on the part of the Division.
- The Division stated that the 25gm samples of each of three API batches (0899N0105, 0457N0103, 0929N0205) sent by the applicant to the FDA for interbatch variability evaluation were not sufficient, and that the applicant should send additional quantities of these batches to provide a total of 100gm each. The applicant stated that, due to German requirements for retained samples, it had only limited quantities available to send to the Division, which would not be sufficient to fulfill the Division's request. The Division agreed to accept the quantities available. The Division also asked that the applicant send samples of two drug product batches, made from API batch numbers 0899N0105 and 0719N0104, which are part of the pending order that will be shipped to REAC/TS. The applicant agreed to send 7 packages from each of these lots. The applicant also stated that it will send Certificates of Analysis for the API and product samples.

Item #5: "Formal submission of the Certificates of Analysis for the 2 recent batches sent to REAC/TS."

Discussion: The applicant stated that these would be submitted in a September 1, 2003 amendment.

Item #6: "In accordance to the certificate of analysis for 3 batches of Prussian Blue drug substance (amendment dated August 13, 2003), your results for heavy metals by [redacted] However, the acceptance criteria is indicated to be [redacted] The limit in the CFR for Prussian Blue is [redacted] Revise the acceptance criteria for heavy metals to be consistent with the CFR."

Discussion:

- The Division confirmed that the applicant should submit the pages that were revised.
- The applicant referred to the Certificates of Analysis and asked whether the Division was asking for revision of the acceptance criteria for "Extractable heavy metals" or for "Heavy metals (according to USP)". In a telephone conversation that also included Eldon Leutzinger, Ph.D, Chemistry Team Leader for the Division, the Division responded that it was referring to the acceptance criteria for Heavy metals (as lead), as is listed in the CFR, which should replace Heavy metals (according to USP).

Items #1 through 6 under section beginning with "We also have the following items for which we need a commitment to provide information:"

Discussion: The Division confirmed that a letter containing a statement of commitment by the applicant to the 6 items followed by a verbatim list of the six items as they are stated in the fax is an acceptable response. The applicant can provide the information listed at a later date.

/S/

Lynn Panholzer
Regulatory Project Manager

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/s/

Lynn Panholzer
9/29/03 10:16:45 AM

MEMORANDUM OF TELECON

APPLICATION: NDA 21,626

DRUG: Radiogardase (Prussian blue)

DATE: August 28, 2003

BETWEEN:

Name: Eduard Heyl, M.D., Managing Director
Wolfgang Parr, Ph.D., Managing Director
Andreas Kramer, Qualified Chemist & Laboratory Manager
Brigitte Simons-Wirth, Ph.D., Head of Quality Assurance

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG
Phone: 202-737-7542

AND:

Name: Eldon Leutzinger, Ph.D., Chemistry Team Leader for DMIRDP, DNDC II
Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

BACKGROUND/AGENDA: This teleconference was requested by the applicant to discuss the Division's request during an August 27, 2003 face-to-face meeting with the applicant's regulatory consultant for 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 Division stated in the August 27, 2003 meeting that this information is necessary in order to express the amount of active moiety that was contained in "500mg" of drug product used in the Goiana accident, to ensure consistency of dose/efficacy (and not just weight) from batch to batch. The Division asked that the applicant specify the analytical procedure(s) used to measure the water (e.g., Loss on Drying or the Karl Fischer method). The applicant requested this meeting to propose an alternate method.

The following issues were discussed:

- The applicant stated that measuring the water content in the drug product by either the Loss on Drying or the Karl Fischer method may not provide a standardized measure of the amount of anhydrous Prussian blue in the product because there are different amounts of water in each capsule, especially if the capsule contains cellulose. The applicant proposed instead to use iron content to standardize the weight of anhydrous Prussian blue per capsule, as it believes this method would produce a more reliable result.

  The Division asked that the sponsor submit a formal proposal with rationale to the FDA, and stated that the Division would provide the applicant with a formal response to the proposal after internal discussion.

- The applicant referred to the Division's August 27, 2003 request for samples of two additional batches for inter-batch testing. The applicant stated that it can send samples of API from 3 different batches, but that no drug product produced from these batches is currently available. The applicant asked if these API samples would satisfy the Division's request. The Division stated that it would take what the applicant had.

- The applicant stated that there are no longer any samples available of the actual batch of Prussian blue used in the Goiana accident, but that it has submitted samples to the FDA of product that was manufactured around the same time and by the same manufacturing process as the batch used in the Goiana event. A formal statement will be provided by the applicant in a future amendment.

- The applicant stated that it will submit to the Division an amendment containing all remaining action items as of this date during the week ending September 5, 2003.

ACTION ITEMS:

1. The applicant will fax, then mail, to the Division its proposal for measuring the amount of anhydrous Prussian blue per capsule.
2. The Division will provide the applicant with a formal response to the proposal identified in Action Item #1.
3. The applicant will send to the FDA samples of API from three different batches for inter-batch testing.
4. The applicant will submit a formal statement regarding the availability of drug product used in the Goiana accident and the relationship of samples already submitted to the FDA to the Goiana batch in a forthcoming amendment.
5. The applicant will submit an amendment containing all remaining action items as of this date during the week ending September 5, 2003.

Meeting minutes prepared by Lynn Panholzer, Pharm.D., Project Manager, HFD-160.

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/s/

Lynn Panholzer
9/29/03 10:22:21 AM

MEMORANDUM OF TELECON

DATE: August 28, 2003

APPLICATION NUMBER: NDA 21-626, Radiogardase (Prussian blue)

BETWEEN:

Name: [redacted]
Phone: [redacted]
Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND

Name: Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Request for Safety Update

The Division notified the regulatory consultant that the applicant needs to submit a safety update for this NDA as per 21 CFR 314.50(d)(5)(vi)(b).

/S/

Lynn Panholzer
Regulatory Project Manager

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/s/

Lynn Panholzer
9/2/03 09:52:26 AM
CSO

MEMORANDUM OF TELECON

DATE: August 11, 2003

APPLICATION NUMBER: NDA 21-626, Radiogardase (Prussian blue)

BETWEEN:

Name:
Phone:
Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND

Name: Lynn Panholzer, Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Submission of batches to NDA

The Division contacted the applicant's regulatory consultant to request that Heyl amend the NDA with the two recent batches Heyl sent to REAC/TS. The Division stated that the applicant needs to submit release data on the drug substance and drug product for these batches, which could be in the form of Certificates of Analysis. The regulatory consultant stated that it was already Heyl's understanding that it was to submit these batches to the NDA based on the discussion during the August 8, 2003 teleconference between the Division and the applicant, and that the applicant would comply.

/S/

Lynn Panholzer
Regulatory Project Manager

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/s/

Lynn Panholzer
9/2/03 09:03:06 AM
CSO

MEMORANDUM OF TELECON

APPLICATION: NDA 21,626

DRUG: Radiogardase (Prussian blue)

DATE: August 8, 2003

BETWEEN:

Name: Eduard Heyl, M.D., Managing Director
Wolfgang Parr, Ph.D., Managing Director
Andreas Kramer, Qualified Chemist & Laboratory Manager
Brigitte Simons-Wirth, Ph.D., Head of Quality Assurance

[redacted]

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG
Phone: 800-216-3907,

AND:

Name: Florence Houn, M.D., M.P.H., Director, ODE III
Sally Loewke, M.D., Division Director, DMIRDP
Charles Hoiberg, Ph.D., Deputy Director, ONDC
Eric Duffy, Ph.D., Division Director, DNDC II
Eldon Leutzinger, Ph.D., Chemistry Team Leader for DMIRDP, DNDC II
David Place, Ph.D., Chemistry Reviewer for DMIRDP, DNDC II
Patricia A. Stewart, Acting Chief, Project Management Staff
Lynn Panholzer, Pharm.D., Regulatory Project Manager

Representing: Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

BACKGROUND/AGENDA: This teleconference was held to identify the information required by the FDA to complete its review of the sponsor's NDA.

The meeting began with the introduction of meeting participants. The Division then stated that it required further information from the sponsor in order to complete its review

of the applicant's NDA. The following discussion regarding this information took place during the meeting:

- The applicant verified that Laborchemie Apolda GmbH is the manufacturer of the API for the batches of Prussian blue submitted in the NDA. The July 29, 2003 e-mail to the Division from [redacted] naming [redacted] as the source of the API was in error. A written correction will be submitted to the FDA in response to the August 4, 2003 Information Request letter from the FDA asking for clarification.

- The Division requested that the applicant measure cyanide dissociation of its Prussian blue product at pHs 7 and 9, in ppm, at 24 and 48 hours. The applicant agreed. The Division identified this as a minor, non-approvability issue. [See ADDENDUM below.]

- The Division requested that the applicant provide a more detailed description of the equations it uses to calculate cyanide dissociation than is currently included in the NDA. The applicant agreed.

- Reference was made to two batches of Prussian blue recently sent to REAC/TS. The applicant confirmed the following regarding those 2 batches:

  - They are not included in the NDA.
  - They were manufactured using the processes detailed in the NDA.
  - All release tests were performed on them as indicated in the NDA.

  The applicant agreed to submit Certificates of Analysis for the drug substance and drug product for these 2 batches, as well as the cyanide level in the drug substance used in the production of the batches, as soon as possible. The applicant will amend the NDA to include the two batches. The applicant noted that cyanide level in the drug substance is included in the COA for the drug substance, but it has no cyanide level data for the drug product. The applicant also stated that no pH testing was performed on these batches.

- The Division stated that it is performing its own tests to confirm Heyl's data. The FDA may be able to share the results of its own testing with the applicant when the tests are completed. The Division noted that with regard to cyanide dissociation, preliminary data from tests performed in FDA labs differ from data provided by Heyl's labs.

- The Division stated that the review clock for NDA 21,626 would be extended 90 days in order to review new data being submitted and to determine possible changes in labeling. The Division will provide Heyl with the updated labeling once all of the data is taken into consideration. Heyl may submit the current labeling for its product in the meantime.

- The applicant reviewed its timeline for the submission of amendments to the NDA containing information previously requested by the FDA. The applicant gave the following details about the amendments:

  - Amendment #1- already received by FDA, contains elucidation of structure information, revised cyanide testing method, cesium binding kinetics at multiple time points (one batch), and translated certificates of all reagents and starting materials used in Pb production.
  - Amendment #2- due mid-August, will contain heavy metal testing data, the post-approval stability testing program, translated terms and data, and a draft package insert and container labels.
  - Amendment #3- expected to be dated August 31, 2003, will contain data comparing cesium binding of new product with Goiana product, and cesium binding at multiple time points of two additional batches.

- The Division noted tha[redacted] s for the drug product [redacted] in the NDA: [redacted] The Division stated that stability testing should be done on both formulations. For criteria, a batch should be chosen that contains a large amount of excipient. The applicant agreed.

ACTION ITEMS:

1. The applicant will submit a written correction regarding the manufacturer of the API to the FDA.
2. The applicant will perform the specified cyanide dissociation tests and submit the data to the FDA.
3. The applicant will provide a detailed description of the equations it uses to calculate cyanide dissociation to the FDA.
4. The applicant will submit to the FDA COAs for the drug substance (which will also contain the cyanide level) and drug product for 2 recent batches sent to REAC/TS. The NDA will be amended to include these two batches.
5. The Division will send a formal letter of notification to the applicant before September 13, 2003 regarding extension of the review clock.
6. The Project Manager will prepare minutes of the meeting and fax them to the applicant by September 7, 2003.

Meeting minutes prepared by Lynn Panholzer, Pharm.D., Project Manager, HFD-160.

ADDENDUM: In a telephone conversation that took place August 21, 2003 between [redacted] for the applicant, and Lynn Panholzer, Pharm.D.,

Project Manager for the Division of Medical Imaging and Radiopharmaceutical Drug Products, the Division made known that it no longer considers its request for cyanide dissociation measurements at pHs 7 and 9, in ppm, at 24 and 48 hours to be a minor, non-approvability issue. The Division now considers this a major issue. Mr ——— stated that Heyl had already committed to performing these measurements, and that he would notify the applicant of this change.

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/s/

Lynn Panholzer

9/4/03 02:56:10 PM

MEMORANDUM OF TELECON

DATE: August 4, 2003

APPLICATION NUMBER: NDA 21-626, Radiogardase (Prussian blue)

BETWEEN:

Name:
Phone:
Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND:

Name: Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: United States Adopted Name (USAN)

The Division notified the regulatory consultant that the applicant needs to obtain a USAN for this drug. The regulatory consultant was also told that the NDA can be approved without a USAN, but that if this occurred, a USAN should be obtained as soon as possible, and the approved labeling will be considered provisional and may have to be re-done if the USAN is different than the name used in the approved labeling.

/S/

Lynn Panholzer
Regulatory Project Manager

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/s/

Lynn Panholzer

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CSO

MEMORANDUM OF TELECON

DATE: July 17, 2003

APPLICATION NUMBER: NDA 21-626, Radiogardase (Prussian blue)

BETWEEN:

Name: [redacted]

Phone: [redacted]

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

AND

Name: Sally Loewke, M.D., Acting Division Director
Patricia A. Stewart, R.T.N., Acting Chief, Project Management Staff
Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: German regulations regarding Prussian blue and/or cyanide release into the environment.

In order to evaluate the environmental impact of the manufacturing of Prussian blue, the Division contacted the sponsor's U.S. regulatory consultants to request the following information:

1. What are the German requirements regarding the release of Prussian blue and/or cyanide into the environment during manufacturing?
2. Is Heyl in compliance with these requirements?

The sponsor's regulatory consultants stated that Heyl has indicated it is in compliance with all German regulations, but they will contact Heyl to provide a specific response regarding the Division's questions.

In reference to a July 8, 2003 teleconference between the Division and the sponsor during which the sponsor agreed to perform further cesium binding tests, the sponsor's regulatory consultants stated that the sponsor will complete cesium binding tests on one batch of its Prussian blue by July 28, 2003, and on 2 other batches by the end of August, 2003.

Lynn Panholzer
Regulatory Project Manager

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/s/

Lynn Panholzer
8/26/03 08:17:56 AM

MEMORANDUM OF TELECON

APPLICATION: NDA 21-626

DRUG: Radiogardase (Prussian blue)

DATE: July 8, 2003

BETWEEN:

Name: Eduard Heyl, M.D., Managing Director
Wolfgang Parr, Ph.D., Managing Director

Representing: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG
Phone: 800-216-3907

AND:

Name: Florence Houn, M.D., M.P.H., Acting Division Director
Sally Loewke, M.D., Deputy Division Director
Eric Duffy, Ph.D., Division Director, DNDC II
Eldon Leutzinger, Ph.D., Chemistry Team Leader
David Place, Ph.D., Chemistry Reviewer
Patricia A. Stewart, R.T.N., Acting Chief, Project Management Staff
Lynn Panholzer, Pharm.D., Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

BACKGROUND/AGENDA: This teleconference was requested by the sponsor to clarify deficiencies identified by the Division in an e-mail to the sponsor dated June 3, 2003.

The meeting began with the introduction of Division and sponsor participants. The sponsor confirmed that its meeting participants had received copies of two literature articles faxed to the sponsor's U.S. representative by the Division the morning of the meeting [Nielsen P, Dresow B, et al. *In vitro* Study of ^{137}Cs Sorption by Hexacyanoferrates (II). Z. Naturforsch 1987; 42b:1451-1680; Buser HJ, Schwarzenbach

D, et al. The Crystal Structure of Prussian Blue: $Fe_4[Fe(CN)_6]_3 \times H_20$. Inorganic Chemistry 1977; 16(11):2704-2710]. Discussion of the deficiencies listed in the June 3, 2003 e-mail followed.

1. Elucidation of structure, which is a basic requirement for NDA approval.

   Discussion:
   - The Division and the sponsor agreed that the literature, particularly the articles identified above, has provided a satisfactory understanding of the structure of Prussian blue.
   - The sponsor agreed to send any additional information that it has collected on the structure of its Prussian blue product, including other literature articles and x-ray defraction data, to the Division.

2. Performance evaluation- Cesium uptake should be measured over time to ascertain the kinetics of Cs+ exchange.

   Discussion:
   - The sponsor stated that the kinetics of Prussian blue were well-described in the Nielsen paper, and refers to the drug's mixed mechanism of action detailed in this paper as physical adsorption with chemical ion exchange.
   - The Division stated that it is unsure whether "physical adsorption" adequately describes the mechanism of action. This issue will be addressed when labeling is discussed.
   - The sponsor agreed to perform cesium binding determinations at 2, 4, 6, 8, 12, 24, and 36 hours to characterize the changes in cesium kinetics over time, and the Division found this to be acceptable.
   - The sponsor agreed to compare the cesium binding of the "to be manufactured" product with that of the 1987 product used in the Goiana event (the manufacturing process of the current product is different than the 1987 product).
   - The Heyl chemist will tell the Division Project Manager how long it will take Heyl to complete cesium binding testing on July 9, 2003.

3. Heavy metal tests should be performed on the full sample, not just aqueous washes.

   Discussion:
   - The sponsor agreed.

4. Certificates of Analysis, in both German and English, should be supplied for all reagents and starting materials used in PB production.

   Discussion:
   - The sponsor agreed.

[Points 5 and 6 were discussed together.]

5. A post-approval stability program needs to be designed and Heyl needs to commit to performing it.

6. Long term capsule stability should be monitored.

Discussion:

- The sponsor agreed to these points.
- The sponsor stated that stability testing will be completed in August, 2003 and data will be provided to the FDA at that time.
- The Division stated that the specific methods for post-approval stability testing can be determined by Heyl, but must include tests for capsule integrity as well as capsule disintegration.
- The Division stated that further communications with the sponsor regarding the [redacted] to be assigned to the product will occur. If the sponsor wants a [redacted] it will need to provide data to the FDA to support this.

The Division stated that it has additional comments for the sponsor, and may have future comments as the NDA review continues. Completion of the review is targeted for the end of July. The Division identified the following issues:

1. The definition of cesium "bonding" is unclear. The sponsor clarified that "bonding" is the same as "binding".
2. The appendices need to be presented more clearly and completely, and should be translated completely into English. Volume 1.2, Pages 116-120 and 132-138a (especially page 134) were specifically identified.
3. The sponsor references DIN Analytical Methods in the NDA without identifying the specific steps that it is performing. The test for cyanide was used as an example of the way tests for all impurities were presented in the NDA. The sponsor must identify the specific section of the DIN Analytical Methods that it is using, and must provide validation data that compares the sponsor's results with known standards. The sponsor stated that is has submitted a revised version of the cyanide method with detailed procedures to Dr. Patrick Faustino of the FDA, and that the revised version could be described as an analyst's SOP. The Division instructed the sponsor to submit the revision formally to the NDA. In response to an inquiry by the sponsor, the Division stated that it was acceptable for the sponsor to use USP methods, but that validation of the methods must still be performed.

ACTION ITEMS:

1. The Heyl chemist will tell the Division's Project Manager on July 9, 2003 how long it will take the sponsor to complete cesium binding tests.
2. The FDA chemistry team will review the sponsor's cyanide test method revision and will provide comments to the sponsor.
3. The Project Manager will complete meeting minutes and fax them to the sponsor by August 7, 2003.

Meeting minutes recorded by Lynn Panholzer, Pharm.D., Project Manager, HFD-160.

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/s/

Lynn Panholzer
7/29/03 12:55:39 PM

MEMORANDUM OF TELECONFERENCE

DATE: June 30, 2003

APPLICATION NUMBER: IND 51,700; Radiogardase™ ferric hexacyanoferrate (II) (insoluble Prussian blue); also NDA 21-262

BETWEEN:

Name: [redacted]

AND:

Name: Florence Houn,M.D., Acting Division Director
Sally Loewke, M.D., Deputy Director
Kyong Kang, PharmD, Chief, Project Management Staff
Eric Duffy, Ph.D, Director, DNDC II
Eldon Leutzinger, Ph.D., Chemistry Team Leader
David Place, Ph.D., Chemistry Reviewer
Patricia A. Stewart, Acting Chief, Project Management Staff
Division of Medical Imaging and Radiopharmaceutical Drug Products

SUBJECT: Follow-up to issues raised at the June 18, 2003 meeting regarding concerns with supplying the Strategic National Stockpile (SNS) through REAC/TS IND 51,700 and changes in labeling requested by REAC/TS.

DISCUSSION:

After brief introductions the teleconference began with the Heyl consultant explaining that they did not want to make any changes to the IND drug labeling before the NDA (21-626) was approved. The Agency said that a teleconference had been held with REAC/TS and FDA informed them that the regulation 21 CFR 312.6(a) requires labeling on the immediate package that states "Caution: New Drug--Limited by federal law to investigational use" (i.e. cartons and bottles). The Agency said new labels are not required and they did not want the shipments delayed. The regulation can be complied with by adding a "sticky" label with the statement to the existing bottles and cartons. The current status of the shipments for REAC/TS: 1) 1700 units received, and 2) 2500 units prepared to ship.

The Heyl consultant raised an issue of concern that the regulations require an investigator to be informed by the sponsor through an investigator's brochure. Heyl is concerned that they may be held liable if there is not an investigator's brochure alerting to problems such as the cyanide disassociation if the drug is being sent to the Strategic National Stockpile

(SNS) under the IND. The Agency suggested that they discuss their concerns with REAC/TS, the IND holder.

The FDA explained that the current labeling is acceptable for the IND, but unacceptable for the NDA application. The following deficiencies have been noted in the labeling:

The FDA said the focus of the next upcoming teleconference with Heyl (Germany) will be on the technical/scientific deficiencies in the NDA and will also address the labeling. Heyl will provide a revised label for the teleconference. The FDA chemist said they want to focus on the structure of PB (the manner of the presence of the —ion) explore how the Cesium is bound, characterization of the drug, and how the drug works. Heyl indicated that the —is an impurity. The Agency asked whether Heyl had any more information on the cyanide disassociation and the consultant replied that they did not.

The Heyl consultant said that as an interim measure until the NDA is approved, they will provide the required IND caution statement on labels for the 2500 units to be shipped.

Patricia A. Stewart

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/s/

Patricia Stewart
9/30/03 05:02:17 PM
CSO

MEMORANDUM OF TELECONFERENCE

DATE: April 15, 2003

APPLICATION NUMBER: NDA 21-626; Radiogardase™ ferric hexacyanoferrate (II) (insoluble Prussian blue)

BETWEEN:

Name: Eduard Heyl, M.D. President
Wolfgang Parr, Ph.D., Managing Director
Brigette Simons-Horvath, Ph.D, Head of Quality Assurance and Regulatory Affairs
Andreas Kramer, Qualified Chemist, Laboratory Manager

Representing: Heyl Chemisch
Number: 800-216-3907 Conf # 110618

AND:

Name: Eldon Leutzinger, Ph.D., Chemistry Team Leader
David Place, Ph.D., Chemistry Reviewer
Patricia A. Stewart, Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products

SUBJECT: To discuss/clarify with Heyl additional filing deficiencies that were faxed to the sponsor on April 11, 2003 and must be resolved by May 13, 2003.

DISCUSSION:

After brief introductions the teleconference began with discussion/clarification of the following deficiencies identified in a faxed April 11, 2003:

1. Actual and translated batch records for one lot each of drug substance and product. The records we would like to receive are those for the PB that required the addition of microcrystalline cellulose in the formulation before encapsulation.

The Agency explained that the translations provided are not "true" translations. There was a translation code provided which is not adequate. Heyl asked if the FDA wanted records from a particular batch. The Agency responded that the FDA labs will do some in-house testing and would like to bridge the data from the current NDA batches manufacturing method to the manufacturing method used for the lots used in the Goiana incident upon which the clinical efficacy is based. Heyl agreed to provide the API batch records and samples from a current lot and one from around the time of the Goiana

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- The environmental assessment and facility registration issues will be resolved by the lawyers.

Patricia A. Stewart

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/s/

Patricia Stewart
9/30/03 05:00:21 PM
CSO

MEMORANDUM OF TELECONFERENCE

DATE: March 31, 2003

APPLICATION NUMBER: NDA 21-626; Radiogardase® **ferric hexacyanoferrate (II) (insoluble Prussian blue)**

BETWEEN:

Representing: Heyl Chemisch
Number: 202-737-7542

AND:

Name: Florence Houn,M.D., Acting Division Director
Sally Loewke, M.D., Deputy Director
Brenda Gierhart, M.D., Acting Medical Team Leader
Kyong Kang, PharmD, Chief, Project Management Staff
Eric Duffy, Ph.D, Director, DNDC II
Eldon Leutzinger, Ph.D., Chemistry Team Leader
Patricia A. Stewart, Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products

SUBJECT: To discuss filing deficiencies and preliminary review issues with the sponsor.

DISCUSSION:

After brief introductions the teleconference began with the Agency outlining the deficiencies that were noted during the NDA filing meeting. The US representative was informed that the following data must be submitted by May 13, 2003, to make the application fileable:

1) Register all facilities with the FDA
2) Environmental assessment report or categorical exclusion request
3) Stability data to support the requested expiration on the to be marketed product
4) German translation of pages 222 to 227

The FDA stated that the following review issues were identified thus far:

1) Need for cyanide dissociation pH curves for labeling. Dissociation at a physiologic pH may be unsafe
2) Characterization of the drug substance is lacking (various salts are not identified and quantified)
3) More information on controls for drug product is needed
4) More information on methods validation is needed

5) Data needs to be expressed in "real" numbers, rather than "less than" a specification limit.
6) The manufacture procedures for the drug product may be improved to ensure reproducibility. A timeline should be provided for plans to replace the —— manufacturing process with an — process.
7) Stability data was only provided for the drug substance, but is also needed for the drug product

The US representative was asked to QC the future submissions of this company. He was pleased the Agency had called and transmitted this information early and will work to get the data in.

/S/

Patricia A. Stewart

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/s/

Patricia Stewart
5/19/03 03:40:36 PM

MEMORANDUM

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

DATE: September 11, 2003

SUBJECT: Chemistry Determinations- Prussian Blues

CC: NDA 21-626, [redacted] IND 51,700,

This memorandum supercedes the memorandum of David A. Place, Ph.D dated July 11, 2003.

Introduction:

Prussian Blue is a blue industrial and artist pigment first synthesized by Diesbach in 1704. The common name 'Prussian Blue' has been used for several different but related ferric(III) hexacyanoferrate(II) compounds; specifically potassium ferric(III) hexacyanoferrate(II), $KFe[Fe(CN)_6]$ or $KFeFe(CN)_6$[i, 5] and ferric hexacyanoferrate, $Fe^{III}_4[Fe^{II}(CN)_6]_3$[ii,iii]. The compound most commonly associated with the common name 'Prussian Blue' is $Fe^{III}_4[Fe^{II}(CN)_6]_3$ with chemical names iron (III) ferrocyanide, ferric ferrocyanide, iron (III) hexacyanoferrate (II), and ferric hexacyanoferrate. This Prussian Blue is also commonly called 'Insoluble Prussian Blue' while potassium ferric(III) hexacyanoferrate(II), $KFe[Fe(CN)_6]$, is commonly named 'Soluble Prussian Blue'. Prussian Blue and related compounds, including ammonium iron(III) hexacyanoferrate(II), $NH_4Fe[Fe(CN)_6]$, have a very high affinity for cesium and thallium and have been investigated and used as a treatment for radiocesium contamination[iv] and thallium poisoning[v]. On February 4, 2003, FDA published a Federal Register notice announcing that the Agency has determined that Prussian Blue can be found to be safe and effective for the treatment of internal contamination with radioactive thallium, nonradioactive thallium, and radioactive cesium (68 FR 5645) and the availability of Guidance on submit ing a new drug application.

The question:

There has been much discussion regarding whether the different ferric(III) hexacyanoferrate(II) compounds, specifically $Fe^{III}_4[Fe^{II}(CN)_6]_3$, $KFe[Fe(CN)_6]$, and $NH_4Fe[Fe(CN)_6]$, are all different active moieties and, therefore, 'New Molecular Entities' or are all different salts of the same active moiety. The reason for the difficulty in making this determination is that the information on the structure and mechanism of action for all three forms of Prussian Blue is incomplete, and in some cases conflicting.

Definitions:

Before addressing this question, it is helpful to keep in mind the following definitions for a 'molecular entity', an 'active moiety', and a salt. A new molecular entity (NME) is defined as an active moiety that has not been previously approved or legally marketed as the active moiety in the United States in any drug product, either as a single ingredient, as part of a combination product, or as part of a mixture of stereoisomers.

Active moiety is defined in the Code of Federal Regulations (21 CFR 314.108(a)) as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

There is no regulatory definition of salts. Chemically, a salt is a molecule that contains two or more oppositely charged ions that are bound together by electrostatic attraction. These electrostatic attractions that bind the oppositely charged ions are called "ionic bonds".

Discussion:

For the purposes of this discussion, ferric(III) hexacyanoferrate(II) compounds are divided into two groups, insoluble ferric(III) hexacyanoferrate(II) with the empirical formula $Fe^{III}_4[Fe^{II}(CN)_6]_3$ and those with the generalized empirical formula $M_AFe^{(III)}[Fe^{(II)}(CN)_6]\bullet xH_2O$. All of the ferric(III) hexacyanoferrate(II) compounds are practically insoluble in water with a solubility constant of 10^{-40}g/L. Potassium ferric(III) hexacyanoferrate(II), $KFe[Fe(CN)_6]$, forms a colloidal suspension in water, despite its very low ionic dissociation, and for this reason is commonly called "Soluble Prussian Blue". Ferric hexacyanoferrate, $Fe^{III}_4[Fe^{II}(CN)_6]_3$, however, does not readily form a colloidal suspension in water and therefore, is commonly called 'insoluble Prussian Blue'. As stated in the introduction section, although the common name 'Prussian Blue' has been used for both of these compounds, for consistency with the published Federal Register Notice and Guidance, the common name 'Prussian Blue' will refer only to ferric(III) hexacyanoferrate(II) with the empirical formula $Fe^{III}_4[Fe^{II}(CN)_6]_3$.

It is accepted in the literature that the crystal structure of Prussian Blue, $Fe^{III}_4[Fe^{II}(CN)_6]_3$, is a cubic lattice with the Fe^{II} and Fe^{III} atoms occupying the corners of the cube and the $C\equiv N^-$ groups positioned on the sides (Figure 1[vi]). The Fe^{II} atoms are always bonded to the carbon atom in the cyano group and the Fe^{III} atoms are bonded to the nitrogen atom of the cyano group. Therefore, the crystal matrix is an infinite 3-dimensional solid based on repeat units of the type $Fe^{(III)}$-N≡C-$Fe^{(II)}$-C≡N-$Fe^{(III)}$ with the ratio of Fe(III), Fe(II) atoms and cyano groups in the crystal structure of 4:3:18. In aqueous media, this cubic structure is maintained because of the strong thermodynamic stability of the 3-dimensional structural architecture, a fact that accounts for the insolubility of the ferric(III) hexacyanoferrate(II).

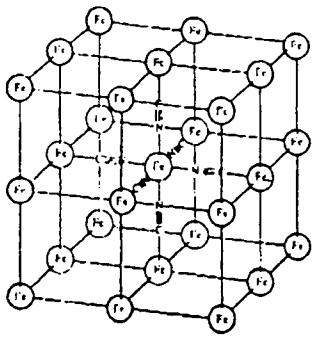

Figure 1: Portion of the basic crystal structure of ferric(III) hexacyanoferrate(II) compounds illustrating bridging by ambidentate cyanide ions. For clarity, any charge neutralizing cations, waters of crystalization, and most of the cyanide groups have been omitted

An important characteristic of the crystal structure of Prussian Blue is that not all of the atomic positions in the unit structure are completely occupied. Rather, the crystal lattice has "holes" in it with about one-quarter of the $Fe^{(II)}(CN)_6$ positions, particularly in the internal positions, either vacant or filled with water molecule. The distribution of these vacancies (or "holes") within the crystal lattice range from random to more ordered depending upon the conditions in which the crystals were prepared[vii].

Although the mechanism of cesium (Cs^+) or thallium (Tl^+) uptake by Prussian Blue is not fully understood, it is believed that these "holes" play an important role in Prussian Blue's ability to strongly bind Cs^+. Literature reports indicate the mechanisms for cesium (Cs^+) and thallium (Tl^+) uptake are the combination of chemical ion-exchange and physical adsorption (physisorption). For Prussian Blue, the ion-exchange occurs with the hydrogen (hydronium ion) from the water molecules in the crystal. Evidence for this mechanism is the reduction in pH when Cs^+ exchange is performed and hydronium ions are released as observed by Neilsen et al.[viii] In solutions containing $Fe^{III}_4[Fe^{II}(CN)_6]_3$, a decrease of pH from 5.54 for $Fe^{III}_4[Fe^{II}(CN)_6]_3$ in water to pH 2.82 when CsCl was added. However, through mass balance calculations, this decrease in pH alone does not account for all the Cs^+ uptake. It is believed that remainder of uptake of Cs^+ is absorption into the crystal lattice with the Cs^+ cation being mechanically or electrostatically trapped in the unoccupied cavities and "holes" within the crystal lattice. This is similar in concept to trapping balls in a box with a few holes in it. The larger the cation, the more difficult it is for the cation, once inside the interstices of the crystal, to diffuse out of the structure (a kinetic issue), i.e., it is "held more tightly" within the crystal lattice.

If the ferric(III) hexacyanoferrate(II) compound contains a monovalent alkali metal or ammonium cation, then the generalized empirical formula is of the general type $M_AFe^{(III)}[Fe^{(II)}(CN)_6]\bullet xH_2O$ where M_A represents the charge neutralizing cation (e.g., K^+, Na^+, NH_4^+, Cs^+) and x represents the number of water of crystallization (i.e., water molecules within the crystal lattice). Similar to Prussian Blue, the crystal structure of ferric(III) hexacyanoferrate(II) salts consists of a cubic lattice with the Fe^{II} and Fe^{III} atoms occupying the corners of the cube and the $C\equiv N^-$ groups positioned on the sides. Unlike the transition metal $Fe^{(III)}$ ions which are directly bonded to the nitrogen end of the cyanide ligand with a degree of covalency to the bonding, however, the alkali metal ions (e.g., K^+, Na^+, Cs^+, Tl^+) or ammonium

(NH_4^+) ions are held in place electrostatically by ionic bonds in the "holes" within the crystal framework (as "defects" in the perfect face-centered cubic unit cell) and within the cubic lattice (as charge neutralizing counterions). The presence of these cations contributes to the increased tendency of these compounds to form colloidal suspensions. The ratio of Fe(III), Fe(II) atoms and cyanide groups in the crystal structure for ferric(III) hexacyanoferrate(II) salts is 1:1:6.

Literature reports also indicate that the mechanism of cesium (Cs^+) and thallium (Tl^+) uptake by ferric(III) hexacyanoferrate(II) salts is a combination of ion-exchange and physical adsorption. However, unlike "pure" ferric(III) hexacyanoferrate(II), the ion-exchange for ferric(III) hexacyanoferrate(II) salts is primarily cation exchange with the monovalent cations. For these monovalent cations, the relative binding affinity is largely determined by the size of the cations. According to Neilsen *et al.*[8], the binding affinity (i.e., stability) of the cations with the ferric hexacyanoferrate(II) anion increases in the order of $Na^+ < K^+$, $NH_4^+ < Cs^+ < Tl^+$. The ionic nature of these cations was observed by Nielsen et.al. In that paper, it was reported that in artificial gastric juice, at a pH of 1.2, and artificial duodenal juice, at a pH of 6.8, where there are relatively large amounts of sodium ions, the sodium ion exchanges with the potassium cation. However, because the affinity for Cs^+ is so high, the competing sodium ions do not appreciably interfere with Cs^+ exchange. In contrast to Prussian Blue, there was no significant decrease in pH associated with the uptake of Cs^+ by ferric(III) hexacyanoferrate(II) salts suggesting that ion-exchange with the hydrogen (hydronium ion) from the waters of crystallization do not contribute appreciably to the mechanism of uptake for Cs^+.

Regulatory Chemical Classification Determination

Determination of the chemical classification for new drugs, in particular the differentiation between a new molecular entity and a new salt, requires the determination of the active moiety. In the case of drugs containing metal ions, the active moiety may be a coordination complex or chelate, rather than a metal ion itself, when the metal-ligand complex is sufficiently stable in-vivo to be responsible for its physiologic-pharmacologic action. In such cases, the metal-ligand complex usually needs to be of a clearly defined stoichiometry and contain coordinate bonds with bond strengths comparable to covalent bonds.

For Prussian Blue, $Fe^{III}_4[Fe^{II}(CN)_6]_3$, all of the atoms are incorporated into the frame work of the cubic crystal structure in an infinite 3-dimensional matrix of $Fe^{(III)}$-N≡C-$Fe^{(II)}$-C≡N-$Fe^{(III)}$ repeat units with a $Fe^{(III)}$:$Fe^{(II)}$:CN ratio of 4:3:18. All of the atoms that make up the crystal structure of Prussian Blue are tightly bound and the whole structure, represented by the empirical formula of the molecular solid $Fe^{III}_4[Fe^{II}(CN)_6]_3$, remains intact in aqueous media, and participates in the uptake of Cs^+. Therefore, the active moiety for ferric(III) hexacyanoferrate(II), or Prussian Blue, is the whole molecule (i.e., $Fe^{III}_4[Fe^{II}(CN)_6]_3$).

In contrast, in the ferric(III) hexacyanoferrate(II) compounds that contain alkali metal or ammonium cations, the monovalent cations are electrostatically held in place (i.e., ionic bonds) within the crystal structure and are available for cation exchange with the Cs^+ ion. For ion-exchange resins, the function of the resin is determined by the chemical composition of the resin, excluding the ion to be exchanged, and the structure of the resin determines its performance. The "active moiety" could be thought of as a traditional ion-exchange resin excluding the ion being exchanged. Because of the relative insolubility of ferric(III) hexacyanoferrate(II)

compounds, the 3-dimensional cubic colloidal suspension based on $[Fe(II)\text{-}C\equiv N\text{-}Fe(III)]^{-1}$ units acts as an ion-exchange resin. Therefore, the $(Fe^{III}[Fe^{II}(CN)_6])^{-1}$ anion that makes up the framework of the crystal structure is the "active moiety". Further, although the crystal structures for both Prussian Blue and ferric(III) hexacyanoferrate(II) salts are very similar, the ratio of atoms that make up the crystal framework of ferric(III) hexacyanoferrate(II) salts is different with a $Fe^{(III)}$:$Fe^{(II)}$:CN ratio of 1:1:6. Finally, because of the ionic nature of the monovalent alkali metal and other similar cations, and the fact that the crystal structures of the ferric(III) hexacyanoferrate(II) salts do not change with different monovalent alkali metal cations, all ferric(III) hexacyanoferrate(II) compounds containing different monovalent alkali metal cations should be considered salts of the same active moiety.

In summary, one can say that the Fe(III) is an integral part of a molecular solid of Prussian Blue, $(Fe^{III}_4[Fe^{II}(CN)_6]_3)$ where the Fe(III) ions are held by covalent bonding (chemical interactions) that are not merely electrostatic, whereas the alkali metal and ammonium ions in the ferric(III) hexacyanoferrate(II) compounds are physisorbed due to weak interactions with an anionic framework.

Conclusion

After review of the current information available in the literature and careful consideration, based on the current understanding of the structure and mechanism of sorption of the ferric(III) hexacyanoferrate(II) compounds, we have concluded that Prussian Blue with the empirical formula $Fe^{III}_4[Fe^{II}(CN)_6]_3 \bullet xH_2O$, also known as "Insoluble Prussian Blue," should be considered a different active moiety than ferric(III) hexacyanoferrate(II) salts that contain monovalent cations. Thus, Potassium ferric(III) hexacyanoferrate(II) and Ammonium ferric(III) hexacyanoferrate(II) should not be considered as different salts of Prussian Blue. Table 1 summarizes the difference between Prussian Blue and ferric(III) hexacyanoferrate(II) salts.

Table 1: summary of differences between "pure" ferric hexacyanoferrate and salts of ferric hexacyanoferrate

Compound(s)	Empirical formula	Mechanism of Cs uptake	Active Moiety
Ferric(III) hexacyanoferrate(II) (a.k.a., Prussian Blue or Insoluble Prussian Blue)	$Fe^{III}_4[Fe^{II}(CN)_6]_3 \bullet xH_2O$	(1) Ion-exchange with the hydronium ion of the waters of crystallization. (2) Adsorption/mechanical trapping of the Cs^+ cation within the crystal structure.	The crystal structure incorporating the whole molecule, including the waters of crystallization, with a $Fe^{(III)}$:$Fe^{(II)}$:CN ratio of 4:3:18.
Potassium ferric(III) hexacyanoferrate(II) & Ammonium ferric(III) hexacyanoferrate(II)	$M_4Fe^{(III)}[Fe^{(II)}(CN)_6] \bullet x H_2O$	(1) Cation-exchange with the ionically bound monovalent cation. (2) Adsorption/mechanical trapping of the Cs^+ cation within the crystal structure.	The crystal structure defined with the $Fe^{(III)}[Fe^{(II)}(CN)_6]^{-1}$ anion with a $Fe^{(III)}$:$Fe^{(II)}$:CN ratio of 1:1:6.

[i] A.F.Wells, *Structural Inorganic Chemistry*, Third Edition, Oxford, 1962, pg. 739

[ii] H.J.Buser, D.Schwarzenbach, W.Petter, and A.Ludi. The Crystal Structure of Prussian Blue: $Fe_4[Fe(CN)_6]_3$-xH_2O. *Inorganic Chemistry*, **16**, 2704-2710 (1977)

[iii] Bernd Dresow, Peter Nielsen, Roland Fischer, Alexander A. Pfau, Hellmuth H. Heinrich, In vivo Binding of Radiocesium by two forms of Prussian Blue and by ammonium iron hexacyanoferrate (II), *Clinical Toxicology*, 1993, **31**(4), pg. 563-569

[iv] Jaroslaw Rachubik and Bogdan Kowalski. Ammonium Ferric Hexacyanoferrate (AFCF) as a countermeasure for reducing the Radiocaesium Transfer to Muscles and Inner Edible Organs of Broiler Chickens, *Bull. Vet. Inst. Pulawy*, **45**, 57-61 (2001)

[v] Pau PW., Management of thallium poisoning, 2000, *Hong Kong Med. J.*, **6**(3), pg. 316-318

[vi] James E. Huheey, *Inorganic Chemistry, Principles of structure and reactivity*, Harper & Row Publishers, New York, 1972, pg. 413-415

[vii] H.J. Buser, D. Schwarzenbach, W. Petter, and A. Ludi, The Crystal Structure of Prussian Blue: $Fe_4[Fe(CN)_6]_3 \bullet xH2O$, *Inorganic Chemistry*, 1977, **16**(11), pg. 2704

[viii] Peter Nielsen, Bernd Dresow, and Hellmuth C. Heinrich. In vitro Study of ^{137}Cs Sorption by Hexacyanoferrates(II), *Z.Naturforsch*, 1987, **42b**, 1451-1460

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/s/

Lynn Panholzer
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CHEMIST

MEMORANDUM

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

DATE: July 11, 2003

FROM: David A. Place, Ph.D.
Reviewing Chemist, DNDCII

SUBJECT: Chemistry Determinations – Prussian Blues

TO: Eric Duffy, Ph.D.
Director, DNDCII

AND: Florence Houn, MD
Acting Director, HFD–160

CC: NDA 21–626, [redacted] IND 51,700, [redacted]

After examining and discussing the chemical literature[1] concerning various ferric ferrocyanide forms, we have concluded that the different forms are different salts, not sufficiently different in their structure and function to be considered distinct new chemical entities.

The Prussian blues encompass a range of compounds that are based on a cubic array of insoluble ferric ferrocyanide. Many variants are known. The material marketed in Europe, Radiogardase, is primarily $Fe_4[Fe(CN)_6]_3$, with [redacted] as impurities. The material takes up cesium (Cs^+) or thallium (Tl^+) ions by three possible mechanisms:

1. Exchange of hydrogen (or hydronium ion) from water that is present in the crystal lattice)
2. Exchange of smaller, less tightly bound alkali metal ion impurity [redacted]
3. Sorption into cavities in the cubic ferric ferrocyanide crystal lattice.

[redacted]

Laboratory investigations are being conducted by [redacted] labs on various samples of Prussian blue to validate industrial results on Cs^+ binding capacity and kinetics of the sorption process.

[redacted]

[1] e.g. In vitro Study of ^{137}Cs Sorption by Hexacyanoferrates(II), P. Nielsen, B. Dresow, H. C. Heinrich, *Z. Naturforsch,* **42b,** 1451 (1987) and references therein.

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/s/

David Place
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CHEMIST

Eric Duffy
7/11/03 12:36:00 PM
CHEMIST

NDA: 21,626
Product: Radiogardase™ (insoluble Prussian blue) 0.5gm capsules
Applicant: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG

Administrative Summary

NDA 21,626 for Radiogardase™ (insoluble Prussian blue) 0.5gm capsules, letter date March 10, 2003, was received by the Food and Drug Administration (FDA) March 13, 2003. The product was classified as a new molecular entity and given priority review status. Insoluble Prussian blue is indicated for treatment of patients with known or suspected internal contamination with radioactive cesium and/or radioactive or non-radioactive thallium, to increase their rates of elimination. At the time of submission, a user fee goal date of September 13, 2003 was assigned. The user fee goal date was extended to December 13, 2003 due to the submission of major chemistry amendments within 3 months of the goal date.

The FDA announced in a Federal Register (FR) notice dated February 4, 2003 (Volume 68, Number 23) that it had concluded that Prussian blue, when produced under conditions specified in approved new drug applications (NDAs), can be found to be safe and effective for the treatment of internal contamination with radioactive thallium, non-radioactive thallium or radioactive cesium. In this same FR notice, the FDA encouraged the submission of NDAs for Prussian blue drug products, and announced the availability of a guidance for industry entitled "Prussian Blue Drug Products—Submitting a New Drug Application". In accordance with the guidance, the applicant submitted a 505(b)(2) application and cited the FR notice and the literature references upon which the FDA relied in making its determination of safety and effectiveness listed therein for the clinical sections of the NDA. Therefore, also in accordance with the guidance, this NDA included chemistry, manufacturing and controls information, labeling, and patent information.

Following submission, the FDA identified filing deficiencies and preliminary review issues that were discussed with the applicant within 3 weeks of receipt of the NDA. The applicant submitted information addressing the filing deficiencies before the filing date. During the review period, the FDA chemistry team continued to identify deficiencies and potential safety issues, and FDA laboratories supported the efforts of the chemistry team by conducting tests and providing data. Throughout the review process, the FDA initiated numerous teleconferences to notify the applicant of issues as they arose and helped the applicant resolve them.

Since Radiogardase™ is the first insoluble Prussian blue product to be approved by the FDA, it has been given —— marketing exclusivity, as well as orphan drug exclusivity. The applicant has agreed or committed to perform Phase 4 studies as described in the approval letter.

Lynn Panholzer, Pharm.D.
Regulatory Project Manager

MEMORANDUM

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

DATE: August 7, 2003

FROM: Ruyi He, M.D.
Acting Medical Team Leader, GI Team II
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

TO: Sally Loewke, M.D.
Acting Director
Division of Medical Imaging and Radiopharmaceutial Drug Products, HFD-160

THROUGH: Robert Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: A high priority consultation from HFD-160

NDA: 21,626

Type of Document: CMC amendment

Sponsor: HEYL

Drug Name: Prussian blue

Consult sent: July 31, 2003

Indication: Treatment of patients with known or suspected internal contamination with radioactive cesium and/or radioactive or non-radioactive thallium to increase their rates of elimination

1. BACKGROUND

NDA 21,626 for Prussian blue was submitted to the Division of Medical Imaging and Radiopharmaceutial Drug Products (HFD-160) on March 13, 2003. Prussian blue acts as an ion-

exchange medium. Prussian blue has a very high affinity for radioactive and non-radioactive cesium and thallium. The proposed indication is treatment of patients with known or suspected internal contamination with radioactive cesium and/or radioactive or non-radioactive thallium to increase their rates of elimination. Cesium-137 is an element that can be used in terrorist weapons and thus this NDA is receiving high priority.

In our previous consultation, we provided data, comments and recommendations regarding Gastric Emptying Time, Intragastric Acidity and Public Health Concern on the pH-cyanide Dissociation Curve. Please see consultation review dated May 28, 2003 for details.

2. THE PURPOSE OF CONSULTATION

FDA OTR testing of the Heyl Prussian blue product and literature data from the Environmental Protection Agency, suggest that Prussian blue dissociates to free Cyanide in extreme pHs, both low and high pHs. HFD-160 is asking for our advice on how to construct testing situations for high pH-cyanide release. Specifically, HFD-160 is asking: 1) what is the range of high pHs in normal and disease conditions; 2) what is the maximum transit or dwell time ingested Prussian blue will be in contact with high pHs; 3) any other considerations in constructing a meaningful in vitro model.

The goal is to obtain cyanide information to properly assess safety and to properly label any findings for patients in whom the risk of cyanide release may be increased relative to disease conditions of pH in their gastrointestinal tract.

3. COMMENTS AND RECOMMENDATIONS

In order to help to develop a model for FDA labs to characterize the pH-cyanide dissociation curve of Prussian blue that simulates patient use, I provide the following clinically relevant information, as well as comments and recommendations.

3.1 The range of High pHs in Normal and Disease Conditions

For the range of high pHs, we need to check secretion of intestinal juices. From the table below (A. Guyton et al. Textbook of Medical Physiology. 9th ed. W.B. Saunders Company 1996; 64: 817), it is clearly shown that pancreatic secretions and Brunner's gland (also called duodenal gland) secretions have higher pH values from 8.0 to 8.9.

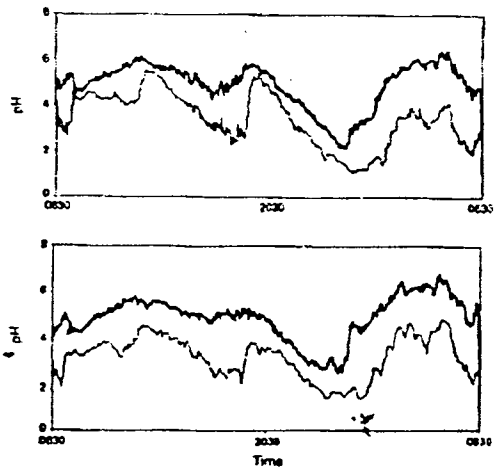
It is very unlikely, if not impossible, that Prussian blue can be exposed to body fluid with pH higher than 9.0 to 9.5 in both normal and disease conditions, according to the data provided in the table below. Of course, we do not discuss here the situation in which persons drink a solution with higher pH for some reason, such as, suicide attempt.

Table 64-1 DAILY SECRETION OF INTESTINAL JUICES

	Daily Volume (ml)	pH
Saliva	1000	6.0–7.0
Gastric secretion	1500	1.0–3.5
Pancreatic secretion	1000	8.0–8.3
Bile	1000	7.8
Small intestine secretion	1800	7.5–8.0
Brunner's gland secretion	200	8.0–8.9
Large intestinal secretion	200	7.5–8.0
Total	6700	

There are a few conditions which may cause higher pH values in the stomach. The commonest situation will be administration of anti-acid medication, such as a Proton Pump Inhibitor (PPI). Other situations include achlorhydria and alkaline reflux gastritis. Concomitant anti-acids may not increase pH values further in patients with achlorhydria or alkaline reflux gastritis; however, concomitant anti-acids should be avoided.

One study (Verdu etal, Gut 1995; 36: 539-543) evaluated intragastric pH during treatment with omeprazole in 18 H pylori positive and 14 H pylori negative subjects. The results are shown below.



The highest pH value was about 7 in late night-time for Omeprazole treated subjects with H pylori positive. The pH value in control group (placebo) was about 4 at same time (not shown in this Fig.).

Another situation which may cause high pH in stomach is achlorhydria. One recent study (Annibale et al, Gut 2003; 52: 496-501) tested 30 iron deficiency anemia patients with gastric body atrophy and found that pHs were between 6.5 and 8.2.

The worst situation which may cause high pH in stomach would be alkaline reflux gastritis and highest pH would be 8.9 from duodenal gland's secretion, according to the study shown in the table above.

3.2 The Maximum Transit or Dwell Time

Longer exposure times are known to release larger amounts of cyanide as indicated in the pH-cyanide dissociation curve of Prussian blue. Gastric residence time is an important parameter to evaluate the release of cyanide at lower pH which has been discussed in the previous consultation.

In order to answer what is the maximum transit or dwell time ingested Prussian blue will be in contact with high pHs, we should focus intestinal residence time. If Prussian blue is not absorbable through intestinal tract, we can assume that the maximum transit or dwell time ingested Prussian blue in contact with high pHs is similar to constipation time that can last up to a week or more. However, constipation can be managed through many methods.

As I mentioned in my previous consultation, I fully agree with the approach by the Division of Medical Imaging and Radiopharmaceutial Drug Products to develop a model for FDA labs to further characterize the pH-cyanide dissociation curve of this drug to determine safety and for labeling purposes.

Benefit/risk assessment should consider this unique indication for the treatment of patients with internal contamination with radioactive cesium and/or thallium and no available therapy for this indication currently.

4. CONCLUSION

In conclusion, I have following information and recommendations for you:

- Pancreatic secretions and Brunner's gland (also called duodenal gland) secretions have higher pH values from 8.0 to 8.9.

- It is very unlikely, if not impossible, that Prussian blue can be exposed to body fluid with pH higher than 9.0 to 9.5 in both normal and disease conditions. Of course, this does not include the situation in which persons drink a solution with higher pH for some reason, such as a suicide attempt.

- The highest pH value was about 7 in late night-time for Omeprazole treated subjects with H pylori positive. The pH value in placebo group was about 4 at same time.

- The pHs were between 6.5 and 8.2 in 30 iron deficiency anemia patients with gastric body atrophy (achlorhydria).

- If Prussian blue is not absorbable through intestinal tract, the maximum transit or dwell time ingested Prussian blue in contact with high pHs will be similar to constipation time that can last up to a week or more. However, constipation can be managed through many methods.

I hope that the information above are helpful to you in the development of a model for FDA labs to characterize the pH-cyanide dissociation curve of Prussian blue to determine safety and for labeling purposes. For any questions related to this consultation, I can be reached at 301-827-7456.

CC:
NDA: 21-626 Consultation #2
HFD-180/Div. Files
HFD-180/R. Justice
HFD-180/J. Korvick
HFD-180/F. Houn
HFD-160/S. Loewke
HFD-160/E. Duffy
HFD-180/R. He
HFD-180/J. DuBeau
HFD-160/L. Panholzer
f/t 08/7/03 rh
N21-262/consultation #2.RH

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/s/

Ruyi He
8/7/03 02:16:28 PM
MEDICAL OFFICER

Robert Justice
8/7/03 02:56:50 PM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: May 28, 2003

FROM: Ruyi He, M.D.
Medical Officer
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

TO: Florence Houn, M.D.
Acting Director
Division of Medical Imaging and Radiopharmaceutial Drug Products, HFD-160

THROUGH: Robert Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

And

Hugo Gallo-Torres, M.D., Ph.D., P.N.S.
Medical Team Leader, GI
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: A high priority consultation from HFD-160

NDA: 21,626

Type of Document: CMC amendment

Sponsor: HEYL

Drug Name: Prussian blue

Consult sent: May 19, 2003

Indication: Treatment of patients with known or suspected internal contamination with radioactive cesium and/or radioactive or non-radioactive thallium to increase their rates of elimination

1. BACKGROUND

NDA 21,626 for Prussian blue was submitted to the Division of Medical Imaging and Radiopharmaceutial Drug Products (HFD-160) on March 13, 2003. Prussian blue acts as an ion-exchange medium. Prussian blue has a very high affinity for radioactive and non-radioactive cesium and thallium. The proposed indication is treatment of patients with known or suspected internal contamination with radioactive cesium and/or radioactive or non-radioactive thallium to increase their rates of elimination. Cesium-137 is an element that can be used in terrorist weapons and thus this NDA is receiving high priority.

2. THE PURPOSE OF CONSULTATION

Prussian blue dissociates and becomes inactive in very acidic environments (e.g., pH of 0 to 1). The Prussian blue dissociation phenomenon involves release of cyanide. HFD-160 is asking us to provide advice on developing a model for FDA labs to characterize the pH-cyanide dissociation curve of this drug to determine safety and for labeling purposes.

Two specific requests are: 1) advice on the length of time for drug (Prussian blue) staying in a pH level to emulate gastric residence time (normal case and worst case scenario, say in gastroparetic individuals); and 2) advice on when you receive the pH-cyanide dissociation curve, if the data pose a public health concern.

3. COMMENTS AND RECOMMENDATIONS

The active drug substance of Prussian blue, ferric hexacyanoferrate is known to dissociate at low pH, releasing cyanide, with obvious safety implications.

The sponsor tested two different batches of Prussian blue at different acidic pH-levels. After 30 and 60 minutes respectively the cyanide was measured and results shown in Fig. 1 (p220, the sponsor's CMC amendment submission dated April 22, 2003).

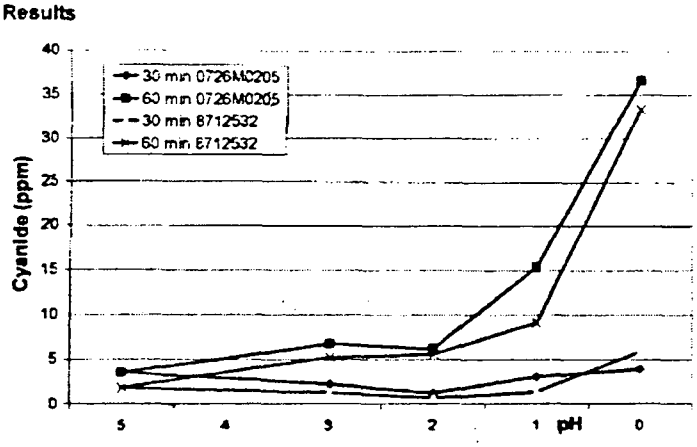


Fig. 1: pH-cyanide dissociation curve of Prussian blue

The results indicated that after a contact time of 30 minutes the release of cyanide in both batches was lower than 10 ppm, even in the strong acidic medium at pH less than 1. However, after the contact time of 60 minutes both tested batches showed a significant increase in the release of cyanide especially in a very acidic medium ($pH \leq 1$). The safety window period is short, about 30 minutes, especially in a very acidic condition ($pH < 1$).

Two factors, low pH and exposure time in low pH, play major roles in the release of cyanide. In order to help to develop a model for FDA labs to characterize the pH-cyanide dissociation curve of Prussian blue that simulates patient use, I provide the following clinically relevant information, as well as comments and recommendations.

3.1 Gastric Emptying Time

Longer exposure times are known to release larger amounts of cyanide as indicated in the pH-cyanide dissociation curve of Prussian blue (Fig. 1). Gastric residence time is an important parameter to evaluate the release of cyanide. In order to estimate the minimum and the maximum gastric emptying time as required in the consultation, I provide the following published study results to you.

Gastric emptying times were monitored in 7 healthy male subjects using 300 ml radiolabelled beef consomme with and without 60 g margarine (Houghton LA et al, Gut 1990; 31:1226-1229).

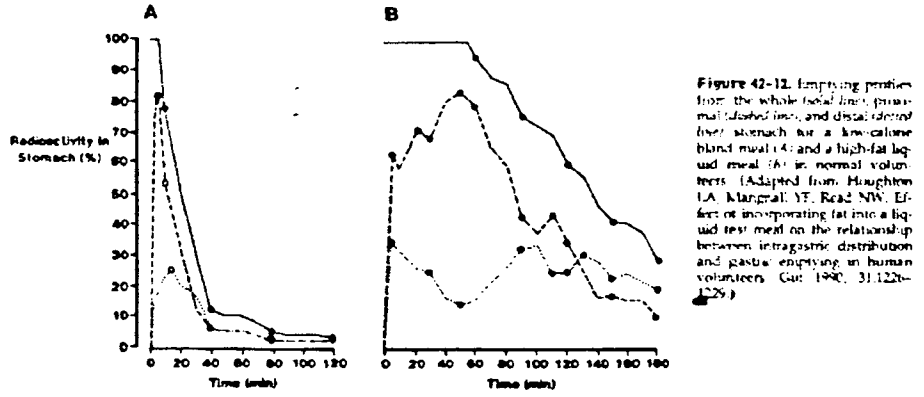


Fig. 2: Gastric emptying time in normal volunteers by different meals.
Emptying profiles from the whole (solid line), proximal (dashed line), and distal (dotted line) stomach for a low-calorie bland meal (A) and a high-fat liquid meal (B) in normal volunteers.

The rate of gastric emptying in normal subjects is influenced by many factors, such as, different meals shown in this study. This study indicated that for normal subjects, average gastric emptying time (80% of content) is approximately 30 minutes for a low-calorie bland meal, and 3.5 hours for a high-fat liquid meal. Normally, the gastric emptying time for liquid meals may be lower than for solid meals.

There is no standardized definition of gastroparesis, but in this condition, the gastric emptying times vary significantly from one patient to another and may be up to days dependent on severity. In addition, nausea and vomiting may often occur in patients with gastroparesis that may further complicate the evaluation of gastric emptying time. Patients with gastroparesis should be evaluated on case by case basis and provided proper treatment that is based on the results of the evaluation (e.g. prokinetic drugs and PPI's). However, the dissociation curves should be followed out long enough to determine maximum dissociation of cyanide.

3.2 Intragastric Acidity

Using continuous intraluminal pH-metry, 24-hour intragastric acidity was monitored in 19 normal volunteers and 37 patients with active and endoscopically proven duodenal ulcer and results are shown below (Savarino et al, Dig Dis Sci 1988: 33; 1077-1080).

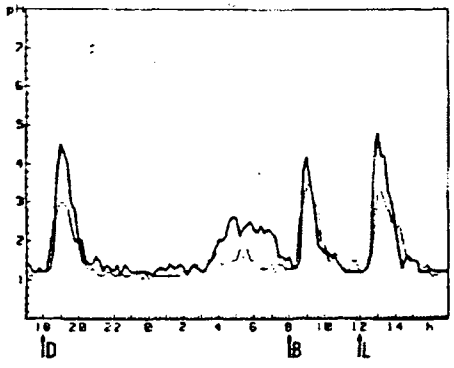


Fig 1. The 24-hr profiles obtained by calculating the medians of 12-min pH values. Solid line = normal subjects; dotted line = duodenal ulcer patients. D = dinner; B = breakfast; L = lunch.

Fig. 2: 24-hour intragastric acidity

The study showed that the baseline pH values in both normal subjects and patients with duodenal ulcer are between 1 and 2, and meals could raise pH up to 3 to 4 for a period of 1 to 2 hours. Therefore, to avoid exposure in low pH medium, I agree and strongly recommend that Prussian blue be taken with meals. It may be necessary to mention that meal, not a small piece of food, is necessary to raise the intragastric pH. A small piece of food may stimulate acid secretion and may worse the situation.

The Table below shows the median nighttime pH values in both groups.

	9 pm – 12 pm		12 pm – 4 Am		4 Am – 8 Am	
	NS	DU	NS	DU	NS	DU
Median pH value	1.38	1.19	1.54	1.51	2.17	1.81

NS + normal subjects; DU = duodenal ulcer

For patients with Zollinger-Ellison syndrome and these who are hypersecretors, baseline pH and nocturnal pH values will be lower than most of patients with duodenal ulcer. I do not recommend using the scenario which simulates patients with Zollinger-Ellison syndrome or hypersecretors in a model for FDA labs to characterize the pH-cyanide dissociation curve of Prussian blue to determine safety. It is to be noted that the incidence of Zollinger-Ellison syndrome is rare, only 0.1 to 1% of patients with duodenal ulcer and patients with Zollinger-Ellison syndrome need to be treated by PPI medication which will raise intragastric pH values. Only patients with Zollinger-Ellison syndrome receiving treatment with a PPI should received Prussian blue.

3.3 Public Health Concern on the pH-cyanide Dissociation Curve

For this consultation, HFD-160 specifically asked for "your advice on when you receive the pH-cyanide dissociation curve, if the data pose a public health concern".

Responses
The simple answer is yes. The pH-cyanide dissociation curve in this submission does pose a public health concern, because safety window period is short (about 30 minutes) and cyanide is released in low pH condition. However, the data from this pH-cyanide dissociation curve is incomplete for adequate evaluation of safety. Only two time points (30 and 60 min.) were provided in this pH-cyanide dissociation curve. More time points beyond 60 minutes are needed. An additional time point between 30 and 60 minutes should be added too. Data for accumulative amount of cyanide are not provided in the submission. The accumulative amount of cyanide should be estimated for up to 30 days and 60 days for the safety assessment. The risk of cyanide toxicity should be estimated based on the in vitro treatment.

I fully agree with the approach by the Division of Medical Imaging and Radiopharmaceutial Drug Products to develop a model for FDA labs to further characterize the pH-cyanide dissociation curve of this drug to determine safety and for labeling purposes.

Benefit/risk assessment should consider this unique indication for the treatment of patients with internal contamination with radioactive cesium and/or thallium and no available therapy for this indication currently. Public health concern regarding cyanide release in low pH condition is manageable. The role of factors, such as taking a meal with the drug and taking PPI medications for special populations should be explored.

4. CONCLUSION

In conclusion, I have following information and recommendations to you:

- The rate of gastric emptying is influenced by many factors. Average gastric emptying time (80% of content) in normal subjects is approximately 30 minutes for a low-calorie bland meal and 3.5 hours for a high-fat liquid meal.

- The gastric emptying times in patients with gastroparesis vary significantly from one patient to another and may be up to days dependent on severity. Because of lack of standardization or even agreed upon definition of gastroparesis, the scenario that simulates patients with gastroparesis is not recommended as a model for FDA labs to characterize the pH-cyanide dissociation curve of Prussian blue to determine safety. However, the dissociation curves should be followed out long enough to determine maximum dissociation of cyanide.

- The baseline pH values in both normal subjects and patients with duodenal ulcer are between 1 and 2, and meals could raise pH up to 3 to 4 for a period of 1 to 2 hours.

- Taking Prussian blue with three meals (not just food as current proposed labeling) are strongly recommend.

- The scenario that simulates patients with Zollinger-Ellison syndrome and/or gastric acid hypersecretors is not recommended in a model for FDA labs to characterize the pH-cyanide dissociation curve of Prussian blue to determine safety. Only patients with Zollinger-Ellison syndrome receiving treatment with a PPI should received Prussian blue.

- Current data from the pH-cyanide dissociation curve of Prussian blue are inadequate to properly evaluate safety. More time points are needed.

- Accumulative amount of cyanide should be estimated for up to 30 days or 60 days for the safety assessment. The risk of cyanide toxicity should be estimated based on the in vitro treatment.

- The current pH-cyanide dissociation curve does pose a public health concern. However, safety concern regarding cyanide release in low pH condition may be manageable. The role of certain factors such as taking a meal with the drug or taking PPIs especially in hypersecretory conditions is worth exploring.

I hope that the recommendations and information above are helpful to you in the development of a model for FDA labs to characterize the pH-cyanide dissociation curve of Prussian blue to determine safety and for labeling purposes. For any questions related to this consultation, I can be reached at 301-827-7456.

CC:
NDA: 21-626 Consultation
HFD-180/Div. Files
HFD-180/R. Justice
HFD-180/J. Korvick
HFD-180/H. Gallo-Torres
HFD-160/F. Houn
HFD-160/E. Duffy
HFD-180/R. He
HFD-180/J. DuBeau
HFD-160/P. Stewart
f/t 05/28/03 rh
N21-262/consultation.RH

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

/s/

Ruyi He
5/28/03 05:47:30 PM
MEDICAL OFFICER

Hugo Gallo Torres
5/28/03 05:49:58 PM
MEDICAL OFFICER

Robert Justice
5/28/03 06:20:02 PM
MEDICAL OFFICER

In a September 1, 2003 submission, the applicant reported that it is unaware of any new safety information.

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: March 27, 2003	**DUE DATE:** May 9, 2003	**ODS CONSULT #:** 03-0115

TO: Flourence Houn, M.D.
Acting Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

THROUGH: Patricia Stewart
Project Manager
HFD-160

PRODUCT NAME:	**NDA SPONSOR:**
Radiogardase (Insoluble Prussian Blue Capsules) 500 mg **NDA: 21-528**	Heyl Chemisch-pharmazeutische Fabrik Gmbh & Co. **U.S. AGENT:** Robert Martin, Heyltex Corporation

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), the Division of Medication Errors and Technical Support (DMETS) conducted a review of he proposed proprietary name "Radiogardase" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Radiogardase.

   This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. DMETS also recommends implementation of the labeling revisions outlined in Section III of this review.

3. DDMAC does not recommend use of the proprietary name Radiogardase from a promotional perspective for the following reason: "the name implies that the drug will guard against radiation when in fact it is an ion exchange medium for patients internally contaminated with radioactive or non-radioactive thallium or cesium."

/S/

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 6, 2003

NDA # 21-626

NAME OF DRUG: Radiogardase
(Insoluble Prussian Blue Capsules)
500 mg

NDA HOLDER: Heyl Chemisch-pharmazeutische Fabrik Gmbh & Co..

I. INTRODUCTION:

This consult was written in response to a request from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), to review the proprietary name Radiogardase regarding potential name confusion with other proprietary/established drug names. The draft container labels, carton and package insert labeling were reviewed for possible interventions to minimize medication errors.

PRODUCT INFORMATION

Radiogardase (Insoluble Prussian Blue) Capsules contain insoluble ferric hexacyanoferrate (II). Radiogardase is indicated for the treatment of patients with known or suspected internal contamination with radioactive and/or non-radioactive cesium or thallium to increase the rate of elimination. Prussian Blue acts as an ion-exchange medium that has a high affinity for radioactive and non-radioactive cesium and thallium. Clearance from the body of Prussian Blue is dependent upon gastrointestinal tract transit time. Radiogardase is not absorbed through the intact gastrointestinal wall after oral ingestion. The recommended dose for pediatric patients older than 12 years of age and adults is 3 grams orally three times a day. The recommended dose for pediatric patients between the ages of two and twelve years of age is one gram orally three times a day. Insoluble Prussian Blues are supplied in 500 mg capsules for oral administration. The product will be marketed in bottles of thirty capsules.

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] for existing drug names which sound-alike or look-alike to "Radiogardase" 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.[4] The Saegis[5] 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 consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Radiogardase." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The members of this panel include 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. The Expert Panel identified the proprietary names — and Periogard as having potential for confusion with Radiogardase. These products are listed in Table 1 (see Page 4), along with the dosage forms available and usual dosage.

2. The panel also noted that the medical term 'radiopaque' had look-alike similarities to Radiogardase.

3. DDMAC does not recommend use of the proprietary name Radiogardase from a promotional perspective for the following reason: "the name implies that the drug will guard against radiation when in fact it is an ion exchange medium for patients internally contaminated with radioactive or non-radioactive thallium or cesium."

---

[1] MICROMEDEX Integrated Index, 2003, 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 98-03, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/main/trademarks.htm

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

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel			
Product Name	**Dosage form(s), Established name**	**Usual adult dose***	**Other****
Radiogardase	Insoluble Prussian Blue 500 mg Capsules Bottles containing 30 capsules	Children > 12 years of age and adults three grams orally three times a day Children 2 – 12 years of age one gram orally three times a day	N/A
	NAME WITHDRAWN BY SPONSOR		
Periogard	Chlorhexidine Gluconate Oral Rinse 0.12% 16 ounce Bottle	Use 15 mL two times a day as a oral rinse	S/A
* Frequently used, not all-inclusive. ** L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Radiogardase with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 128 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Radiogardase (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were 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 prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

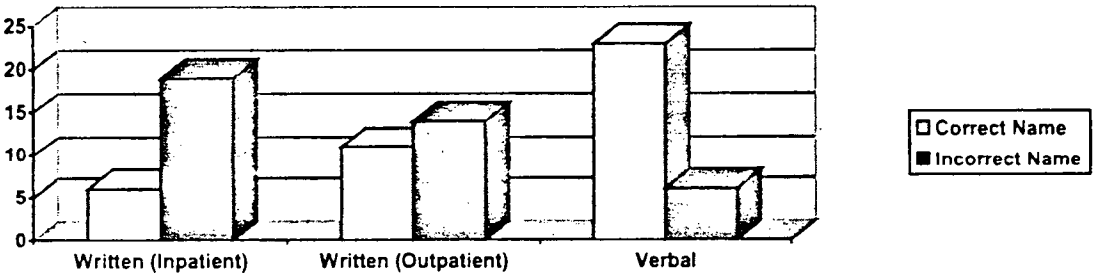
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX Radiogardase 6 cap TID # 90	The first prescription is for Radiogardase. She's to take six capsules three times a day. Dispense 90.
Inpatient RX: Radiogardase #6 caps) tid #200	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	43	25 (58%)	6 (24%)	19 (76%)
Written Outpatient	42	29 (69%)	23 (79%)	6 (21%)
Verbal	43	25 (58%)	11 (44%)	14 (56%)
Total	128	79 (62%)	40 (51%)	39 (49%)



In the written inpatient study 6 (24%) of the 25 participants interpreted Radiogardase correctly. The misinterpretations were misspelled variations of Radiogardase. The misinterpretations included . None of the misinterpreted names represented a currently marketed product.

In the written outpatient study 23 of 29 (69%) participants interpreted Radiogardase correctly. The majority of the incorrect name interpretations were phonetic variations of "Radiogardase." The misinterpretations included . None of the misinterpreted names represented a currently marketed product.

In the verbal prescription study 11 of the 25 (58%) participants interpreted Radiogardase correctly. The misinterpretations were misspelled variations of Radiogardase. The majority of the misinterpretations include (1). None of the misinterpreted names represented a currently marketed product.

3. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Radiogardase, the primary concerns raised were related to Periogard a sound-alike name that currently exists in the U.S. market and to the medical term, radiopaque.

DMETS conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Radiogardase could be confused with Periogard or the medical term radiopaque. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of interpretations from the verbal and written prescription studies were phonetic or spelling misinterpretations of the drug name Radiogardase.

There is potential for look-alike confusion between Radiogardase and Periogard. Periogard is a topical antimicrobial agent that is used as an oral rinse for the treatment of gingivitis. The beginning letters (R vs. P) of each name may look alike depending upon how they are scripted. The names also share similar letters (iogard) which increases the look-alike characteristics. Additionally, if the ending of Radiogardase is not scripted clearly (e.g., the letters 'ase' trail off), then the prescriptions may look similar. However, there are differences between the two products that may decrease name confusion. The products have different dosage forms (tablets vs. liquid), dosing intervals (three times a day vs. two times a day), and indications of use. Radiogardase is indicated for an unusual indication of use (i.e., increasing elimination of internal radioactive and/or non-radioactive cesium or thallium.) The unusual indication of use for Radiogardase will help to differentiate the two products since it will not likely be a frequently prescribed medication. The quantity prescribed will also help to differentiate the two products. Periogard is supplied as a sixteen-ounce bottle, which may be prescribed in quantities of one (#1), 16 ounces, or 473 mL. However, the number of capsules required will need to be indicated on Radiogardase prescriptions (e.g., 63 for a week's supply). Although Radiogardase and Periogard may look similar, the product differences, and the different context of use will help to minimize the potential for name confusion between these two products.

The medical term radiopaque and Radiogardase start with the same five letters which, contributes to the sound-alike characteristics. However, the endings of both names are phonetically different when pronounced thus minimizing the potential for medication errors between radiopaque and Radiogardase.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Radiogardase, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL AND CARTON LABELING

1. The established name should be used in lieu of the active substance. DMETS suggests that the sponsor contact USAN to apply for an established name for Radiogardase.

2. The strength of the product (i.e., 0.5 grams) should be expressed in milligrams and relocated so that it appears immediately following the established name. For example:

RADIOGARDASE
(Established Name)
500 mg

Additionally, increase the prominence of the proprietary name, established name, and strength.

3. [redacted]

4. [redacted]

5. [redacted]

B. PACKAGE INSERT LABELING

1. PRECAUTIONS SECTION

a. Information for Patients Subsection

[redacted]

b. Pediatric Use Subsection

The abbreviation 'PB' is used to represent prussian blue. However, the abbreviation PB is also commonly used to represent phenobarbital. DMETS recommends that PB not be used in the labeling of Radiogardase. Revise accordingly.

2. DOSAGE AND ADMINISTRATION SECTION

a. [redacted]

b. [redacted]

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Radiogardase.

   This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. DMETS also recommends implementation of the labeling revisions outlined in Section III of this review.

3. [redacted]

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 Sammie Beam, project manager, at 301-827-3242.

S

Denise P. Toyer, Pharm.D.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support

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

/s/

Denise Toyer
5/9/03 08:47:10 AM
PHARMACIST

Carol Holquist
5/9/03 03:37:13 PM
PHARMACIST

Jerry Phillips
5/9/03 04:32:12 PM
DIRECTOR

DIVISION OF MEDICAL IMAGING AND
RADIOPHARMCEUTICAL DRUG PRODUCTS

Chemistry comments for the sponsor:

The following items are missing from the NDA 21-626 submission:

1. Actual and translated batch records for one lot each of drug substance and product. The records we would like to receive are those for the PB that required the addition of microcrystalline cellulose in the formulation before encapsulation.

2. For Drug Master File # , — the DMF holder (———— should provide the FDA with authorization to review their DMF in connection with this NDA application.

3. The sponsor continues to use European Pharmacopoeia methods almost exclusively, despite the fact that they were told in August 2002 that the FDA requires USP methods or an analysis that shows that the EP method is equivalent or superior.

3a. Since the firm cannot go back and do the work over using USP methods, an analysis of each EP test, comparing it to EP, should be carried out and submitted for review.

3b. A commitment is required from the firm to transition from EP to USP methods.

3c. They need to use consistent decimal point symbols "." on all future documents submitted. The European "," is used sometimes, and interchangeably with the preferred "." even on the same page.

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

/s/

Patricia Stewart
10/1/03 06:22:48 PM
CSO

Panholzer, Lynn

om: Stewart, Patricia A
nt: Monday, September 29, 2003 2:08 PM
o: Panholzer, Lynn
Subject: FW: Prussian blue Phase 4 studies

Lynn,

This email should go in the Action package.

Pat

Patricia A. Stewart
Acting Chief, Project Management Staff

FDA/CDER/DMIRDP (HFD-160)
5600 Fishers Lane
Rockville, Maryland 20857
(voice) 301-827-7496
(fax) 301-480-6036

-----Original Message-----
From: Stewart, Patricia A
Sent: Friday, May 16, 2003 5:38 PM
To: 'Paul L. Ferrari'
Subject: Prussian blue Phase 4 studies

ul,

The following Phase 4 studies will be required for any NDA applicant for Prussian blue:

· Longitudinal studies involving follow up on case report forms and placement of data into a database for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness.

· Pediatric studies to investigate safety tolerability of dosing for neonates to 2 years of age.

There may be additional Phase 4 commitments determined upon review of individual applications. If you have any questions please call.

Regards,
Pat

Patricia A. Stewart
Regulatory Project Manager

FDA/CDER/DMIRDP (HFD-160)
5600 Fishers Lane
Rockville, Maryland 20857
(voice) 301-827-7496
fax) 301-480-6036

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

Heyl Chemisch-pharmazeutische Fabrik
GmbH & Co. KG
Goerzallee 253
D-14167 Berlin (Germany)

2. TELEPHONE NUMBER *(Include Area Code)*

(+49) 308169629

3. PRODUCT NAME

Radiogardase (capsules)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-626

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☒ 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:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

J.

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 *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☒ YES ☐ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Wolfgang Parr	Dr. W. Parr Managing Director	March 10, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: September 26, 2003

To: Robert Martin	**From:** Lynn Panholzer, Pharm.D.
Company: Heyltex Corporation	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 281-395-7040	**Fax number:** 301-480-6036
Phone number: 281-395-7040	**Phone number:** 301-827-3132

Subject: NDA 21-626 Radiogardase (Prussian blue): additional suggested data collection

Total no. of pages including cover: 5

Comments: In the revised package insert faxed earlier today, the following statement appears in the "Patient Treatment Data" section: "Please see the following website SPONSOR TO FILL IN OR PROVIDE OTHER CONTACT INFORMATION for additional suggested data collection." The data that we suggest should be collected is attached as a revised case report form. If you agree to these revisions, please submit revised labeling by September 30, 2003.

Document to be mailed: YES X NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: September 26, 2003

To: Paul Ferrari	**From:** Lynn Panholzer, Pharm.D.
Company: Hyman, Phelps & McNamara, P.C.	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 202-737-9329	**Fax number:** 301-480-6036
Phone number: 202-737-7542	**Phone number:** 301-827-3132

Subject: NDA 21-626 Radiogardase (Prussian blue): additional suggested data collection

Total no. of pages including cover: 5

Comments: In the revised package insert faxed earlier today, the following statement appears in the "Patient Treatment Data" section: "Please see the following website SPONSOR TO FILL IN OR PROVIDE OTHER CONTACT INFORMATION for additional suggested data collection." The data that we suggest should be collected is attached as a revised case report form. If you agree to these revisions, please submit revised labeling by September 30, 2003.

Document to be mailed: YES X NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: September 26, 2003

To: Robert Martin	**From:** Lynn Panholzer, Pharm.D.
Company: Heyltex Corporation	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 281-395-7040	**Fax number:** 301-480-6036
Phone number: 281-395-7040	**Phone number:** 301-827-3132

Subject: NDA 21-626 Radiogardase (Prussian blue): Request for revised labeling

Total no. of pages including cover: 13

Comments: The attached package insert (PI) includes our changes (additions underlined, deletions marked by strikethrough) to your proposed labeling submitted August 13, 2003. If you agree to these changes, please submit revised labeling by September 30, 2003. Please note: (1) We have revised your case report form (CRF), submitted March 10, 2003, with our recommendations for types of information that may be collected; and (2) under "Patient Treatment Data" in the revised PI appears the statement "Please see the following website SPONSOR TO FILL IN OR PROVIDE OTHER CONTACT INFORMATION for additional suggested data collection." The data which we suggest should be collected will be sent in a separate fax.

Document to be mailed: YES X NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: September 26, 2003

To: Paul Ferrari	**From:** Lynn Panholzer, Pharm.D.
Company: Hyman, Phelps & McNamara, P.C.	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 202-737-9329	**Fax number:** 301-480-6036
Phone number: 202-737-7542	**Phone number:** 301-827-3132

Subject: NDA 21-626 Radiogardase (Prussian blue): Request for revised labeling

Total no. of pages including cover: 13

Comments: The attached package insert (PI) includes our changes (additions underlined, deletions marked by strikethrough) to your proposed labeling submitted August 13, 2003. If you agree to these changes, please submit revised labeling by September 30, 2003. Please note: (1) We have revised your case report form (CRF), submitted March 10, 2003, with our recommendations for types of information that may be collected; and (2) under "Patient Treatment Data" in the revised PI appears the statement "Please see the following website SPONSOR TO FILL IN OR PROVIDE OTHER CONTACT INFORMATION for additional suggested data collection." The data which we suggest should be collected will be sent in a separate fax.

Document to be mailed: YES X NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: July 18, 2003

To: Robert Martin	**From:** Lynn Panholzer, Pharm.D.
Company: Heyltex Corporation	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 281-395-7040	**Fax number:** 301-480-6036
Phone number: 832-646-0176	**Phone number:** 301-827-3247

Subject: Information requests, NDA 21-626 (prussian blue)

Total no. of pages including cover: 4

Comments: As per our telephone conversation, attached are a memo and letter with requests for information and samples, respectively. The letter will also be mailed to you. Thank you.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: July 18, 2003

To: Paul L. Ferrari	**From:** Lynn Panholzer, Pharm.D.
Company: Hyman, Phelps & McNamara, P.C., representing Heyl Chemisch-pharmazeutische	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: 202-737-9329	**Fax number:** 301-480-6036
Phone number: 202-737-7542	**Phone number:** 301-827-3247

Subject: Information requests, NDA 21-626 (prussian blue)

Total no. of pages including cover: 4

Comments: As per our telephone conversation, attached are the memo and letter that were faxed to Robert Martin of Heyltex earlier. Thank you.

Document to be mailed: ☐ YES ☑ NO

FACSIMILE TRANSMISSION RECORD
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-08
5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet) **Date**: April 11, 2003

To: Paul Ferrari

Fax Number: 202-737-9329 **Voice Number**: 202-737-7542

From: Patricia Stewart
Regulatory Project Manager

Fax Number: (301) 480-6036 **Voice Number**: (301) 827-77496

Message: Chemistry comments for Heyl, NDA 21-626 Prussian Blue

Please note that we do not consider this a formal communication.
NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.
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