

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-626**

**CORRESPONDENCE**



HEYL · Goerzallee 253 · D-14167 Berlin (Zehlendorf)

**NDA 21-626  
Amendment  
September 29 , 2003**

**147**

Sally Loewke, M.D.

Acting Director

Div. of Medical Imaging and Radiopharmaceutical Drug Products

Center for Drug Evaluation and Research

Food and Drug Administration, HFD-160

5600 Fishers Lane, Room 18B-45

Rockville, MD 20857

September 29, 2003  
dr.s-/hm

**NDA no. 21-626  
Post-Approval Commitments**

Dear Dr. Loewke,

Reference is made to our NDA No. 21-626 for Radiogardase™ [insoluble Prussian Blue (capsules)] and to a facsimile sent to Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG ("Heyl") from Lynn Panholzer in FDA's Division of Medical Imaging and Radiopharmaceutical Drug Products ("Division") on September 25, 2003. The facsimile identifies two items that Heyl must address once NDA No. 21-626 is approved. This letter is Heyl's formal commitment to provide the post-approval Phase IV study items identified by FDA within the timeframes specified below. Heyl commits to provide FDA the following:

1. Longitudinal studies involving follow-up of case report forms and placement of data into a registry for periodic analyses to determine length of treatment, safety profile, and other factors related to drug effectiveness, within the following periods of time:
  - a. Protocol submission: Within six months of the date of the action letter.
  - b. Study start (i.e., the date the database will be ready to accept patient data, should it be necessary): Within six months of agreement to the protocol.
  - c. Annual reports of ongoing study beginning one year from study initiation.

Telefon: 030/816 96-0    Telefax: 030/817 40 49    E-mail: info@hey-berlin.de

KG, Sitz Berlin, Registergericht AG Charlottenburg, HRA 4138 · Komplementärin: Heyl Chemische Erzeugnisse GmbH, Sitz Hamburg, Registergericht AG Hamburg, HRB 5300  
Geschäftsführer: Dr. med. Eduard Heyl, Dipl.-Chem. Dr. Wolfgang Parr

HEYL · Goerzallee 253 · D-14167 Berlin (Zehlendorf)

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The Division proposed that the protocol be submitted within — months of the date of the action letter. However, Heyl intends to collaborate with an outside party familiar with establishing such studies in the United States. Identifying, retaining, and working with such a party to design the study will take some time, which is why Heyl is proposing that the time to protocol submission deadline be extended by — months to six months.

Heyl also intends to use as the basis for its longitudinal study the ICH Harmonized Tripartite Guideline Draft, titled Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting, Recommended for Adoption at Step 2 of the ICH Process on July 18, 2003 by the ICH Steering Committee (available at <http://www.fda.gov/cber/gdlns/ichexrep.pdf>).

## 2. Pediatric studies:

- a. Develop appropriate dosage form for use in younger children:
  - i. Submission of plan to develop a pediatric formulation: Within six months of the date of the action letter.
  - ii. Begin development: Within six months of agreement to the plan.
  - iii. Completion of formulation development: Within eighteen months of initiation of development.
  
- b. Studies to determine dosing for neonates to 2 years of age (based on human extrapolation and/or animal models).
  - i. Protocol submission: Within six months of the date of the action letter.
  - ii. Study start: Within six months of agreement to the protocol.
  - iii. Final study report submission: Within twelve months of initiation of the study.

HEYL · Goerzallee 253 · D-14167 Berlin (Zehlendorf)

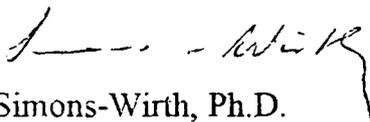
**NDA 21-626**  
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The Division proposed that the pediatric formulation development be completed within          months from the start of the development effort. Heyl does not believe that          months is sufficient time, for example, to generate adequate stability data, which is why Heyl is proposing that the time to completion of formulation development deadline be extended by six months to eighteen months.

Sincerely,

**HEYL Chemisch-pharmazeutische Fabrik**  
**GmbH & Co. KG**

A handwritten signature in black ink, appearing to read 'B. Simons-Wirth'.

B. Simons-Wirth, Ph.D.  
Head of Quality Assurance



NDA 21-626

Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG  
c/o Heyltex Corporation  
Attention: Robert Martin, Vice President of Operations  
925 South Mason Road  
PMB # 242  
Katy, TX 77450

Dear Mr. Martin:

Please refer to your March 10, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Radiogardase (Prussian blue-insoluble).

We received your July 30, 2003 major amendment to this application on August 4, 2003, your August 13, 2003 major amendment on August 19, 2003, and your August 28, 2003 major amendment on September 3, 2003. The receipt dates are within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submissions. The extended user fee goal date is December 13, 2003.

If you have any questions, call Lynn Panholzer, Pharm.D., Regulatory Project Manager, at 301-827-3247.

Sincerely,

{See appended electronic signature page}

Patricia A. Stewart  
Acting Chief, Project Management Staff  
Division of Medical Imaging and  
Radiopharmaceutical Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Patricia Stewart  
9/5/03 02:43:30 PM



NDA 21-626

**INFORMATION REQUEST LETTER**

Heyltex Corporation  
Attention: Robert Martin  
Vice President of Operations  
925 South Mason Road  
PMB # 242  
Katy, TX 77450

Dear Mr. Martin:

Please refer to your March 10, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Radiogardase (Prussian blue).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

We refer to the e-mail from Kurt R. Karst, Regulatory Consultant, Hyman, Phelps & McNamara, P.C., dated July 29, 2003, regarding environmental release of Prussian blue and cyanide during the manufacture of Prussian blue. The following statement appears at the end of the e-mail:

— the manufacturer of the API, is an independent German company and Heyl has informed us that they do not have access to their documentation on production quantities and waste disposal.” However, Volume 1.1, page 55 of your NDA states that —  
— the API source for the to-be-marketed product. Please identify the source(s) of the API.

If you have any questions, call Lynn Panholzer, Pharm.D., Regulatory Project Manager, at 301-827-3247.

Sincerely,

*{See appended electronic signature page}*

Eldon E. Leutzinger, Ph.D.  
Chemistry Team Leader for the  
Division of Medical Imaging and  
Radiopharmaceutical Drug Products, HFD-160  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Eldon Leutzinger  
8/4/03 12:17:22 PM



NDA 21-626

**INFORMATION REQUEST LETTER**

Heyltex Corporation  
Attention: Robert Martin  
Vice President of Operations  
925 South Mason Road  
PMB # 242  
Katy, TX 77450

Dear Mr. Martin:

Please refer to your March 10, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Radiogardase (prussian blue).

We are reviewing your submission and have the following requests. We request a prompt response in order to continue our evaluation of your NDA.

Please provide approximately 100 grams of each sample of the batches for which Heyl provided data (batch numbers 8712532 and 0726M0205), as well as five (5) additional Spectroquant kits.

If you have any questions, call Lynn Panholzer, Pharm.D., Regulatory Project Manager, at 301-827-3247.

Sincerely,

A handwritten signature in black ink, appearing to be "E. Leutzinger", written over a horizontal line.

Eldon E. Leutzinger, Ph.D.  
Chemistry Team Leader for the  
Division of Medical Imaging and  
Radiopharmaceutical Drug Products, HFD-160  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Eldon Leutzinger  
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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

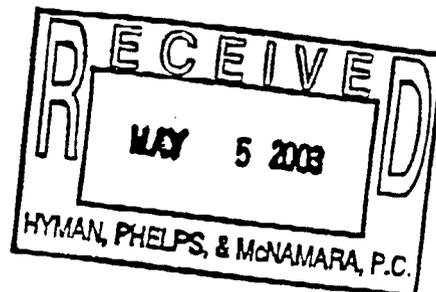
## Public Health Service

Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

May 01, 2003

Hyman, Phelps & McNamara, P.C.  
700 Thirteenth Street, NW, Suite 1200  
Washington, DC 20005

Attention: Frank J. Sasinowski, Esq.  
US Agent



Re: Designation Request # 03-1692

Dear Mr. Sasinowski: *Frank*

Reference is made to your request for orphan-drug designation dated March 5, 2003, of iron (III)-hexacyanoferrate(II) for the treatment of patients with known or suspected internal contamination with radioactive or non-radioactive cesium or thallium, submitted on behalf of HEYL Chemisch-Pharmazeutische Fabrik GmbH & Co. Please also refer to our acknowledgement letter dated March 24, 2003.

We have completed the review of the information submitted in your original request and we have determined that iron (III)-hexacyanoferrate(II) qualifies for orphan-drug designation for the *treatment of patients with known or suspected internal contamination with radioactive cesium (cesium-137), radioactive thallium (thallium-201), or nonradioactive thallium*. Please note that it is iron (III)-hexacyanoferrate(II) and not its formulation that has received orphan-drug designation. You have notified us that you are currently developing iron (III)-hexacyanoferrate(II) under the trade name Radiogardase<sup>®</sup>.

Please be advised that if iron (III)-hexacyanoferrate(II) is approved for an indication broader than the orphan-drug designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 USC 360cc). Therefore, prior to final marketing approval, we request that you compare the designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of iron (III)-hexacyanoferrate(II) as designated. Also an annual progress

report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact Tan Nguyen, MD, PhD, at (301) 827-3666.

Please refer to this letter as official notification and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

/s/

Marlene E. Haffner, MD, MPH  
Rear Admiral, United States Public Health Service  
Director, Office of Orphan Products Development

**Not Applicable:** No clinical studies were conducted in support of this NDA.



NDA 21,626

Heyl Chemisch-pharmazeutische Fafrik GmbH & Co. KG  
Dr. Wolfgang Parr  
C/O Robert Z. Martin  
Vice President of Operations  
Heyltex Corporation  
925 South Mason Road  
Katy, Texas 77450

Dear Dr. Parr:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Radiogardase (insoluble Prussian blue)

Review Priority Classification: Priority (P)

Date of Application: March 13, 2003

Date of Receipt: March 14, 2003

Our Reference Number: NDA 21-626

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 14, 2003, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be September 14, 2003.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-626

Page 2

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)  
Attention: Division Document Room, 8B45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call Patricia A. Stewart, Regulatory Project Manager, at (301 827-7496).

Sincerely,

*{See appended electronic signature page}*

Kyong Kang, PharmD  
Chief, Project Management Staff  
Division of Division of Medical Imaging  
and Radiopharmaceutical Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Kyong Kang

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FEB 25 2003

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Robert Z. Martin  
U.S. Agent, Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG  
Heyltex Corporation  
925 South Mason Road PMB #242  
Katy, TX 77042

**RE: Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG, Small Business Waiver Request 2003.041 for Prussian Blue Capsules**

Dear Sir:

This responds to the February 6, 2003, letter from Dr. Wolfgang Parr of Heyl Chemisch-pharmazeutische Fabrik GmbH & Co. KG (Heyl) requesting a waiver of the human drug application fee for new drug application (NDA) 21-626 for prussian blue capsules under the small business waiver provision of section 736(d)(1)(D)<sup>1</sup> of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2003.041). For the reasons described below, the Food and Drug Administration (FDA) grants the urgent request from Heyl for a small business waiver of the application fee for NDA 21-626 for prussian blue capsules.

According to your waiver request, Heyl is a small, family-owned pharmaceutical business with 85 employees worldwide and an annual revenue of approximately \_\_\_\_\_ (USD). You intend to submit an NDA for prussian blue capsules within the next 2 weeks under Section 505(b)(2) of the Act as outlined in the FDA guidance for industry on *Prussian Blue Drug Products — Submitting a New Drug Application*.<sup>2</sup>

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate<sup>3</sup> submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

<sup>1</sup> 21 U.S.C. 379h(d)(1)(D).

<sup>2</sup> FDA announced its conclusions regarding prussian blue in the *Federal Register* of February 4, 2003 (68 FR 5645). The guidance is available on the Internet at [www.fda.gov/cder/guidance](http://www.fda.gov/cder/guidance).

<sup>3</sup> "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

FDA's decision to grant Heyl's request for a small business waiver for the NDA for prussian blue capsules is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated February 21, 2003, that Heyl has fewer than 500 employees including its affiliates:

Heyl Chemisch Erzeugnisse GmbH; Laborchemie Apolda GmbH; Heyl Verwaltungs GmbH; Heyl Japan K.K. Ltd. Co.; Heyl GmbH Berlin; Heyltx Corporation; Heyl Teltow GmbH Marketing and Pharmaservices; Heyl Beteiligungs und Vertriebs GmbH Iserlohn; Heyl Vertriebs GmbH & Co. KG Iserlohn

Second, according to FDA records, the marketing application for prussian blue capsules, NDA 21-626, is the first human drug application, within the meaning of the Act, to be submitted to FDA by Heyl or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 21-626 for prussian blue capsules is granted, provided that FDA receives the marketing application for prussian blue capsules no later than February 21, 2004, 1 year after the effective date of the size determination made by SBA. Please include a copy of this letter with the application when it is submitted.

If FDA refuses to file the application or Heyl withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Heyl should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for NDA 21-626.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman, Michael Jones, or Tawni Schwemer at 301-594-2041.

Sincerely,

  
Jane A. Axelrad  
Associate Director for Policy  
Center for Drug Evaluation and Research