U.S. FOOD & DRUG ADMINISTRATION

PHARMACEUTICAL QUALITY INVESTIGATION BRANCH
19701 Fairchild
IRVINE, CA 92612
949-608-3519

www.fda.gov

Via UPS
Return Receipt Requested

09/26/2018

[redacted]
PHAST GmbH
Kardinal-Wendel-Str. 16
66424 Homburg, Germany

Dear [redacted]

The U.S. Food and Drug Administration (FDA) conducted an inspection at PHAST GmbH, FEI:3005909718, located at Kardinal-Wendel-Str. 16, Homburg, 66424 DE from 07/16/2018 - 07/17/2018. FDA has determined that the inspection classification of this facility is "no action indicated" ('NAI')[1]. Based on this inspection, this facility is considered to be in an acceptable state of compliance with regards to current good manufacturing practice (CGMP).

This letter is not intended as an endorsement or certification of the facility. It remains your responsibility to ensure continued compliance with CGMP.

An inspection classification of NAI for CGMP compliance will not directly negatively impact FDA's assessment of any pending marketing application referencing this facility. Please note, however, that application approval will depend on a product- and application-specific facility assessment conducted by CDER's Office of Pharmaceutical Quality. This letter does not address or reflect FDA's decision making with respect to any potential non-CGMP compliance issues.

FDA has concluded that this inspection is "closed" under 21 CFR 20.64(d)(3), and we are enclosing a copy of the narrative portion of the Establishment Inspection Report (EIR). It may reflect redactions made by FDA in accordance with the Freedom of Information Act (FOIA) and 21 CFR part 20. This, however, does not preclude you from requesting additional information under FOIA.

If you have any questions regarding this letter, you may contact me at [redacted] or email at [redacted].

Sincerely,

[redacted]

[1] See Inspection Classification Definitions, at https://www.fda.gov/ICECI/Inspections/ucm223231.htm.

Establishment Inspection Report	FEI:	**3005909718**
PHAST GmbH	EI Start:	7/16/2018
Homburg, Saarland, 66424 Germany	EI End:	7/17/2018

TABLE OF CONTENTS

SUMMARY

This surveillance inspection of a control testing laboratory was performed according to eNSpect Operation ID 93616. The inspection was conducted in accordance with Compliance Program 7356.002, Drug Manufacturing Inspections, and Trip 2018-274D. The firm operates as a contract testing facility for various dosage forms marketed in the U.S. including dabigatran etexilate mesylate capsules and etanercept injectable. The Quality and Laboratory Control Systems were selected for coverage during the inspection. Profile classes for the laboratory are LBI and LCP.

The previous U.S. FDA inspection occurred 04/26-30/2013. The previous inspection was a surveillance and preapproval inspection for the laboratory testing of one NDA and two ANDA products. At the conclusion of the inspection no Form FDA 483, Inspectional Observations, was issued.

The current inspection also resulted in no FDA 483 being issued. Two items were verbally discussed with the firm. The firm was cautioned that they have the responsibility to detect and correct any GMP issues whether or not they are discussed during an inspection. During the inspection, it was noted that the firm has new ownership since the last inspection. On 05/08/2018, Eurofins Biopharma Services Holding Germany GmbH signed an exclusive agreement to acquire 100% of PHAST shares.

There were no refusals and no samples were collected during the course of the inspection.

ADMINISTRATIVE DATA

Inspected firm:	PHAST GmbH
Location:	Kardinal-Wendel-Str. 16 Homburg, Saarland, 66424 Germany
Phone:	+49 68419242
FAX:	0 4 7493 8794
Mailing address:	Kardinal-Wendel-Str. 16 Homburg, Saarland, 66424 Germany
Dates of inspection:	7/16/2018-7/17/2018
Days in the facility:	2
Participants:	**Alan P Kurtzberg, Investigator**

On 07/16/2018, I displayed my credentials to CEO, Pascal Van De Veire. Mr. Van De Veire identified himself as the most responsible person on-site. No Form FDA 482, Notice of Inspection, was issued due to the nature of a foreign inspection.

The firm provided a professional translator to facilitate communication during the inspection. Mike Morandin of Language Professionals Partnerschaft (Heildelberg) was present for both days of the inspection. During the inspection, I was introduced to Eurofins Quality Manager Europe, Alice Hoffmann. Ms. Hoffmann was present for the closing meeting with the firm.

No FDA 483 was issued at the close of the inspection on 07/17/2018.

HISTORY

PHAST was founded in 2002 by Johannes Krämer, PhD. In 2018, PHAST was acquired by Eurofins. Dr. Krämer remains with PHAST/Eurofins as a Senior Scientific Director. The firm continues to operate using the PHAST name. PHAST also has three wholly-owned affiliates. See pages 5 and 7 of **Exhibit 1** for a listing of the PHAST affiliates.

The firm was previously inspected by U.S. FDA in 2013 with a final classification of NAI and in 2009 with a VAI classification. The facility is currently registered as a drug establishment for the purpose of analysis.

The U.S. agent for the firm is:
mdiConsultants, Inc.

55 Northern Blvd.
Great Neck, NY 11021
tel: 516-482-9001

The firm employs 250 people. Office hours are 8am-5pm, Monday to Friday. The laboratory hours are 6am-8pm, Monday to Friday.

FMD 145 and other correspondence should be addressed to:
Pascal Van De Veire
PHAST GmbH
Kardinal-Wendel-Str. 16
66424 Homburg, Germany

INTERSTATE (I.S.) COMMERCE/JURIDICTION
The firm does product testing (release and stability) for a number of products that are distributed in the U.S. Total volume for the lab in 2017 was about 11,000 samples. Although the country that the product is marketed is not always known, products tested that are known to be marketed in the U.S. are given on page 2 of **Exhibit 2**. All products listed are considered human drugs subject to the Federal Food, Drug, and Cosmetic Act.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED
For more information on reporting relationships, see the organizational chart on page 10 of **Exhibit 1**.

CEO Pascal Van De Veire has been with the firm since 2009. In 2017, he assumed global responsibilities. Mr. Van De Veire also oversees the quality organization with the heads of the quality system and quality operations reporting directly to him. He was present for both the opening and closing meetings.

Compliance Manager Verena Müller has been with the firm since 2008. She assumed her current position in 2009. Dr. Müller acted as my host during the inspection. She provided answers to questions asked, requested documents, and arranged for subject matter experts to answer certain questions. Dr. Müller reports to CEO Pascal Van De Veire.

Head of Operational Quality Christoph Pfahler has been with the firm since 2014 and in his current position since 2016. Dr. Pfahler was present for most of the inspection to answer questions. He

reports to CEO Pascal Van De Veire.

FIRM'S TRAINING PROGRAM

I reviewed SOP ABEP00118, GMP Training System, effective 03/29/2018. New employees are given an initial training which includes a GMP component. They are also given a training assessment which may be written, oral, or a practical. Individual employees are put into training groups based on training needs. Training records are kept electronically. QA signs to approve trainers based on their experience.

I looked at the training record for Analyst Laura Mathieu. Ms. Mathieu started with the firm on 09/02/2015. I found introductory GMP training given on 09/04/2015. I found evidence of training which qualified her to do the type of testing (size exclusion chromatography) she did. She also had recent (12/19/2017) GMP training recorded. There were no issues noted.

MANUFACTURING/DESIGN OPERATIONS

QUALITY SYSTEM

Samples are received in the sample management area. The samples are first given a visual inspection. Information including product name, strength, dosage form, and batch number are entered into the firm's LIMS system, a customized system purchased from MAQSIMA GmbH. The system assigns each sample a LIMS ID number. If a sample requires cold storage, the firm has one hour after receipt to transfer the sample to the proper storage condition. Samples without a storage requirement are kept in a controlled room temperature environment.

I reviewed SOP QK-A01407, OOS Procedure for Test Results, effective 05/07/2018. The scope of this procedure also includes OOT (out of trend) and OOE (out of customer limits. An obvious error is defined. In the case of obvious error, the analysis is stopped and no results are generated. The use of statistical tests is not permitted. The SOP did allow for an unlimited number of retests if lab error was continually assigned. See **Discussion Item 1**.

LABORATORY CONTROL SYSTEM

I examined storage of a USP standard, tadalafil lot number F0L003. The standard represented the current USP lot and was stored consistent with information on the label. I looked at three logs in the lab, a daily balance check log, a GC column logbook, and a Karl Fischer auto titrator use log. There were no issues noted.

The firm uses controlled blank forms to record laboratory analyses. I was told that most of the

methods used are customer supplied and blank forms allow flexibility during testing.

The firm's HPLCs use the Empower 3 software data system. The system requires a unique ID/password for users. The password is required to be changed every 90 days. The system features an audit trail which cannot be turned off. A system audit trail review by QA is performed on a monthly basis. In addition, the firm is piloting a process audit trail review by a data reviewer. This review is expected to be implemented within the next three months. An IT administrator can add, delete, or edit users. There are seven pre-defined user roles in the system. The role assigned is based on signed training.

I looked at the results from two Erelzi (etanercept) stability samples. The samples were for a nine-month pull from batches ST913 (50 mg) and ST912 (25 mg). A Sandoz (customer) SOP being used for these samples defines an allowed pull window. For nine-month samples, they must be pulled within seven calendar days of their due date. Testing must start within 14 calendar days of the pull and be completed within 30 calendar days. I examined raw data for the size exclusion chromatography test per method QKU51313. The test date is recorded as 06/28/2018. The test method was received from Sandoz as SOP AP 83.179. The procedure calls for the sampling rate of the HPLC's UV detector to be set to 0.86 Hz. The actual setting was 1.25 Hz. When I asked about the discrepancy, I was shown a deviation, approved 06/07/2018, which allowed and justified the use of the 1.25 Hz sampling rate. I told the firm that the deviation needs to be referenced in their original data in order to show that the deviation was permitted. Also, a minimum 3-hour column equilibration was not documented. See **Discussion Item 2**.

I looked at the testing for Pradaxa (dabigatran etexilate) 150 mg capsules batch 803796. The packet included assay, purity, ID, uniformity of dosage, appearance, and loss on drying (contents and capsules). There were no issues noted with the testing.

The firm also uses qualified contract laboratories for certain testing services. See the list in **Exhibit 3**.

REFUSALS
No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT

On 07/17/2018, a meeting was held with members of the firm's management. Representing the firm at this meeting were:

- Christoph Pfahler, PhD, Head of Operational Quality
- Verena Müller, PhD, Compliance Manager GMP
- Elke Bügler, Operational Planning Administrator
- Pascal Van De Veire, CEO
- Alice Hoffmann, Quality Manager Europe (Eurofins BioPharma Product Testing)

Also in attendance was Professional Interpreter Mike Morandin of Language Professionals Partnerschaft.

The following **Discussion Items** were presented during this meeting.

1. The OOS procedure needs to be strengthened. In the current procedure, if a lab error is identified, the result is invalidated and testing cycle repeated. There is no limit as to how many times this cycle can be repeated. A limit of retesting needs to be established to avoid the potential of testing into compliance.
2. Testing write-ups need to be more detailed. In the write-up for stability testing of Erelzi batches ST913 and ST912, the analyst deviated from the approved procedure. Although the firm produced an approved deviation, ABW_0043_2018, it was not referenced in the testing write-up. In the same testing write-up, a required three-hour column equilibration was not documented.

No FDA 483 was issued to the firm. The firm was cautioned that the inspection is not all-inclusive. Firm management is ultimately responsible to detect and correct any deviations from good manufacturing practice.

ADDITIONAL INFORMATION

During the inspection, I stayed at the Schlossberg Hotel in Homburg. Free Wi-fi and a breakfast buffet were included with the room. The restaurant is open for dinner. The hotel is not within easy walking distance into town. I arrived into town by train. I took a taxi from the train station to my hotel. The firm provided transportation to the Frankfurt airport after the inspection. Travel time from the hotel to the Frankfurt airport is about an hour and a half. The firm provided a car to the translator during the inspection as he was also staying at the Schlossberg. We rode together in this car to and from the hotel and the inspection site. A one-way trip from the hotel to the firm is about 15 minutes.

SAMPLES COLLECTED
No samples were collected during the course of the inspection.

EXHIBITS COLLECTED
1 Opening Presentation, 22 pages
2 Factory Profile Information, submitted by the firm, 2 pages
3 List of Qualified Contract Manufacturers and Contract Laboratories of PHAST GmbH (Annex to Site Master File), approved 04/28/2017, 3 pages

Alan P. Kurtzberg -S

Digitally signed by Alan P. Kurtzberg -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001403102, cn=Alan P. Kurtzberg -S
Date: 2018.08.15 14:39:55 -06'00'