# VUAB Pharma a.s. 5/27/15

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

**Warning Letter**

**WL: 320-15-10**

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

May 27, 2015

Mr. Jan Mengler
General Manager
VUAB Pharma a.s.
Vltayska 53
Roztoky 25263
Czech Republic

Dear Mr. Mengler:

During our inspection of your pharmaceutical manufacturing facility VUAB Pharma a.s., Vltayska 53, Roztoky, Czech Republic, from June 09, 2014, through June 13, 2014, an investigator from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). These deviations cause your human and veterinary APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or

administered in conformity with, CGMP.

After a detailed review of your firm's response dated July 01, 2014, we note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated December 18, 2014, and May 07, 2015.

Our investigator observed specific violations during the inspection, including, but not limited to, the following.

1. Failure to adequately investigate and resolve all quality-related customer complaints, and to investigate other batches that may have been associated with specific failures.

Your quality unit released API with objectionable microbial contamination into distribution. For example,

a. In January 2014, your firm received a customer complaint regarding microbial contamination of **(b)(4)**, API lot **(b)(4)**. Your customer tested samples of this lot produced by your firm and identified *Clostridium sphenoides*. During your customer complaint investigation, you were unable to detect the contamination in the samples your customer returned. Your customer's May, 2014, on-site audit of your firm revealed differences in microbiological test methods: your test method was inadequate to detect *Clostridium sphenoides* growth. Once you modified the test method per your customer's recommendation, your firm confirmed *Clostridium sphenoides* contamination in your retain sample. However, you failed to identify the source of the contamination or to implement meaningful corrective actions to prevent future microbial contamination.

Test results exhibiting objectionable microbial contamination represent a significant deficiency in the safety and quality of your APIs. Since microbial contamination is typically non-uniform, the risk of patient exposure to a contaminated drug is exacerbated by low detectability of a test of limited sample size. In addition, your customers may not perform any additional microbiological testing upon receipt of your API. Furthermore, objectionable microbiological contamination in your API, which is intended for **(b)(4)** and **(b)(4)** suspensions, indicates a significant failure in your capability to prevent microbiological contamination in your operation.

And although a non-U.S. customer made this complaint, the Agency is concerned about your firm's poor investigation because you manufacture **(b)(4)**, API, using common equipment, materials and personnel in the operation, regardless of the destination of a given batch.

Your response states that you will retroactively test **(b)(4)** batch per **(b)(4)** to cover January, 2013, to June, 2014, when you implemented the modified test method. However, your rationale for testing **(b)(4)** batch per **(b)(4)** is not scientifically sound. This approach does not evaluate all batches that could be contaminated with objectionable organisms. It relies on the false assumption that retroactively testing a limited number of API batches will assure that all batches distributed to customers were of acceptable quality. Your investigation did not sufficiently pursue or determine root causes. Corrections you have described are insufficient.

In addition, you do not mention any improvements to your procedure for deviation and corrective action and preventive action (CAPA) management. Please note that your senior management is responsible for ensuring the quality and safety of your APIs. Additionally, your senior management is responsible for assuring quality defects are thoroughly investigated and resolved quickly as well as for preventing the distribution of defective APIs.

In response to this letter, provide an accelerated timeline for completing retroactive testing of all potentially affected batches and a commitment to respond with all results promptly. Also provide a detailed update on whether your firm has determined root cause of this contamination problem and implemented any further risk controls. Provide your improved deviation and CAPA management procedure, as well as a review of all microbial test methods to ensure they are suitable for their intended use. Finally, provide documentation of all changes implemented as a result of your review and remediation of these issues.

b. In April 2014, your firm received a customer complaint concerning *Bacillus spp.* contamination of **(b)(4)**, API lot **(b)(4)**. Your tests of the returned customer samples confirmed microbial contamination, including both high levels of bioburden and *Bacillus spp.* contamination. During your investigation, your firm did not extend the investigation to any other batches potentially affected. In addition, deficient sampling procedures compromised your firm's ability to detect the contamination your customer found. Your firm sampled **(b)(4)** per batch and had no statistical justification that this sample was representative of the entire batch.

While your response focuses on detecting future contaminations prior to release, it fails to adequately identify the potential root causes of the contamination. Your response states that you have updated your Final Product Adjustment SOP and Product Homogenization SOP to add a step: **(b)(4)**, API. However, you have no data to support this will adequately remediate the contamination issues.

Your response states that you will now sample from **(b)(4)** those samples before testing. While your response proposes using **(b)(4)** samples, your customer complaint shows that **(b)(4)** samples are not representative. For example, the returned sample from lot **(b)(4)** container number **(b)(4)** had gross contamination of 4,800 cfu/g; while returned samples from the other **(b)(4)** containers ranged from **(b)(4)** to **(b)(4)** cfu/g, within specification. We are concerned that testing a **(b)(4)** sample could mask an out-of-specification (OOS) result for a single container.

In response to this letter, provide data and information from a detailed root cause investigation into the source of this contamination. In addition, provide a summary of your investigation into other batches potentially affected by this contamination, including testing of retain samples of all potentially affected batches. Furthermore, revise your sampling plans to ensure they are statistically appropriate and non-uniform contamination can be detected. The revisions should encompass finished API testing, in-process testing, and raw material acceptance testing.

2. Failure to prevent unauthorized access or changes to data and to provide adequate controls preventing data omissions.

Our inspection noted that your firm did not retain complete raw data from testing performed to assure the quality of **(b)(4)**, API. Specifically, our inspection revealed your firm did not properly maintain a back-up of HPLC chromatograms that form the basis of your product release decisions. Our inspection revealed discrepancies between the printed chromatograms and the operational qualification protocol for the High Performance Liquid Chromatography (HPLC) system, which is intended to demonstrate correct operation of the HPLC. These discrepancies included injection sequences and values to calculate relative standard deviation (RSD).

While investigating these discrepancies, our investigator requested the original electronic raw data. Your quality unit, after consulting with the Information Technology (IT) department, stated they were unable to retrieve the original electronic raw data because back-up discs were unreadable. Your quality unit then stated that back-up disks have been unreadable since at least 2013. Your HPLC system is used to test **(b)(4)**, API for batch release. However, without complete, accurate, reliable, or retrievable raw data about the HPLC system's qualification, you lacked complete assurance that the system was operating as intended.

You also failed to have proper controls in place to prevent unauthorized manipulation of your laboratory's raw electronic data. Our inspection revealed your HPLC system did not have access controls to prevent alteration or deletion of data. Your HPLC software lacked an audit trail recording any changes to the data, including: previous entries, who made changes, and when changes were made. During the inspection,

we also noted that all laboratory employees shared a common log-in and password to access the system.

This lack of control over the integrity of your data raises questions about your analytical data's authenticity and reliability, and about the quality of your APIs. We note that the September 2008 FDA inspection uncovered concerns over your handling of raw analytical data, including discrepancies between laboratory notebooks and printed chromatograms.

Your response states you are qualifying a new HPLC system which allows operator-specific passwords and has audit trial and back-up functions. Your response also states you will implement a new electronic back-up system in your QC chemistry department.
However, your response lacks sufficient detail about systems and controls you will implement. Simply activating audit trail functions and instituting password controls is inadequate. In addition, you failed to review historical data to ensure the quality of your products distributed to the US market.

In your response to this letter, provide a comprehensive corrective action plan for computer system controls over all laboratory and manufacturing instrumentation and equipment. This response should include but not be limited to:

- Information regarding changes in the reliability of your information technology infrastructure, including but not limited to improved computer systems, systems validation, revised procedures, and appropriate retraining of employees that will be implemented immediately to ensure your firm creates and retains complete and accurate electronic raw data.
- Your firm's procedure for the establishment, issuance, and control of passwords used to access your analytical instrumentation. All access levels for computerized systems should be clearly defined and documented in a written procedure.
- A detailed summary of the steps taken to train your personnel on the proper use of computerized systems.

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations.

Please note that a guidance document entitled "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (ICH CGMP guidance), prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use,

describes current good manufacturing practice (CGMP) for the manufacture of APIs. The guidance is intended to help ensure that all APIs meet the standards for quality and purity they purport or are represented to possess. FDA considers the expectations outlined in ICH Q7, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under section 501(a)(2)(B) [21 USC 351(a)(2)(B)] of the Act. To obtain the ICH CGMP guidance document for your reference, please refer to the following page of FDA's website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM0

If, as a result of receiving this warning letter, or for other reasons, you are considering a decision that could reduce the number of active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Similarly, if you are considering a decision that could reduce the supply of veterinary active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CVM immediately, at AskCVM@fda.hhs.gov.

Until all corrections have been completed and FDA has confirmed corrections of the deviations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as an API manufacturer. In addition, your failure to correct these violations may result in FDA continuing to refuse admission of articles manufactured at VUAB Pharma a.s. into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of deviations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the APIs at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3003002370.

Please send your reply to:
David S. Jones, Compliance Officer
White Oak 51 Room 4220
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
USA

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

**More in 2015**

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.



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Contact FDA