# Porton Biopharma Limited 1/17/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

**Via UPS**
**Return Receipt Requested**

**Warning Letter 320-17-19**

January 19, 2017

Dr. Roger J. Hinton
Managing Director
Porton Biopharma, Limited
Manor Farm Road
Porton Down
Salisbury, SP4 OJG, United Kingdom

Dear Dr. Hinton:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Porton Biopharma, Limited (formerly known as Public Health England), at Manor Farm Road, Porton Down, Salisbury, from March 7 to 18, 2016.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) for finished pharmaceuticals, 21 CFR parts 210 and 211, and significant deviations from CGMP for active pharmaceutical ingredients (API).

In a previous inspection of your facility from January 12 to 23, 2015, FDA cited similar CGMP violations. You proposed specific remediation for these violations in your February 12, 2015, response and during a regulatory meeting with FDA on November 24, 2015. These repeated failures demonstrate that management oversight and control over the manufacture of drugs at your facility is inadequate, and that your previous corrective actions did not address persistent contamination hazards and drug quality issues.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your April 8, 2016, and September 16, 2016, responses in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations and deviations including, but not limited to, the following.

**Finished Product Violations**

**1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).**

Your quality control unit identified particulate matter in several batches of Erwinaze® lyophilized powder for injection that exceeded established action limits.

You did not adequately investigate these particulate matter failures. For example, your investigation into visible particulate matter detected in 237 units of batch CAMR171 (nonconformance investigation CN16305, initiated on April 22, 2015) identified the stopper supplier's manufacturing process as the likely source of metal particles. However, the only correction implemented at that time was to update your standard operating procedure, *Inspection, Counting and Packaging of Erwinaze®* by adding foreign material as a subcategory in your reject criteria for finished drug product. Your firm's corrective action and preventive action (CAPA) plan was inadequate. You did not investigate how you manage incoming stoppers or your supplier's stopper manufacturing process until after the inspection, as described in your response to the Form FDA 483.

Your firm initiated nonconformance investigations for Erwinaze® finished drug product batches CAMR174, CAMR175, and CAMR176, and again identified the particulate matter as mostly **(b)(4)** metal particles, likely originating from the stopper manufacturing process. However, these investigations were incomplete and it was not until the inspection on March 7, 2016, that two additional CAPAs were initiated to investigate the root cause of the particulate matter in CAMR176.

Your firm also detected fibers in the lyophilized product of five finished units of lot CAMR171. The fibers were later identified as cardboard or paper. Your firm did not adequately investigate the potential sources of this unusual extrinsic contamination in your sterile drug product.

In addition, in October 2016, your firm submitted additional batch records for batch CAMR178, documenting that this batch contained visible particulate matter of **(b)(4)** origin. In December 2016, your firm submitted batch records for batch CAMR179, documenting that the batch contained visible particulate matter including that of proteinaceous nature. Your investigations indicated that these additional instances of contamination are likely from another source besides the stoppers and call into question your ability to prevent contamination.

Your response to the Form FDA 483, dated September 16, 2016, states that your stopper supplier has been upgrading their equipment and facilities to reduce

particulate matter on their stoppers, and that you have increased quality control sampling of stoppers to **(b)(4)** percent.

We also recognize your efforts to evaluate use of an alternate supplier for stoppers. However, based on your written response, you have not yet completed qualification to enable your use of stoppers from an alternate supplier. We encourage you to consider additional CAPA to mitigate risk until you have fully qualified an alternate supplier of stoppers.

Your firm has failed to implement prompt and sufficient corrective and preventive actions to resolve the hazard posed by foreign contaminants in your injectable products. The continuing presence of various types of visible particles in Erwinaze® batches is evidence of an insufficient assessment of all potential manufacturing failure modes and an overreliance on finished product visual inspection.

Additionally, your firm does not have appropriately strict action limits for certain individual defect categories, including but not limited to particles that are extrinsic to the process (e.g. fiber or cardboard).

**2. Your firm failed to establish and follow appropriate written procedures, designed to prevent microbiological contamination in drug products purporting to be sterile (21 CFR 211.113(b).**

During our January 2015 inspection, our investigators observed several deficiencies related to your aseptic manufacturing operation, including the following:

- a restricted access barrier system (RABS) **(b)(4)** which had fallen off the enclosure system;
- a lack of environmental monitoring within the RABS;
- no use of sporicidal disinfectant on surfaces inside aseptic filling room **(b)(4)**, although your environmental monitoring detected spore-forming organisms there; and
- a lack of traceability for media-filled vials.

We discussed these deficient manufacturing practices during a regulatory meeting with your firm on November 24, 2015.

During our March 2016 inspection, our investigators observed the following additional aseptic manufacturing issues:

- a floor exhaust vent, shown in smoke studies to remove air entering the filling room, blocked by ancillary equipment during media fill process simulations
- inadequate validation of the **(b)(4)** sterilization cycle used on equipment to be transferred into aseptic filling room **(b)(4)**

It is critical that your firm implement proper ongoing control over your aseptic processing operation to prevent microbial contamination of your injectable products.

We note that your firm did not conduct drug product batch manufacturing during our recent inspections. We will need to observe your manufacturing operation during the next inspection to determine whether corrective actions have been fully implemented.

**Drug Substance Deviations**

**1. Failure to establish and follow change controls to evaluate all changes that could affect the production and control of intermediates or API.**

Your firm failed to conduct adequate change controls prior to the use of each working cell bank. For example, your firm has used working cell banks **(b)(4)** for the production of drug substance and drug product batches of Erwinaze®.Your firm previously used only working cell banks **(b)(4)** for production of Erwinaze® drug substance and drug product batches. You failed to ensure sufficient change control oversight to assure the **(b)(4)** new working cell banks were acceptable for use in the commercial operation.

You manufacture Erwinaze® under contract on behalf of Jazz Pharmaceuticals, which holds the Biologics License Application for Erwinaze®. The process changes discussed above were not approved by FDA before you manufactured, or your customer, Jazz, distributed, Erwinaze®. Specifically, working cell banks **(b)(4)** were used in commercial production prior to approval. These working cell banks were not reviewed and approved by the Agency for their suitability for Erwinaze® manufacture, even though the changes in the source material or cell line have a substantial potential to adversely affect the identity, strength, quality, purity or potency of Erwinaze®.

**Quality Agreements**

Firms acting as contract manufacturers must comply with CGMP. FDA is aware that many pharmaceutical product manufacturers use independent contractors, such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

You and your customer, Jazz Pharmaceuticals, have a quality agreement regarding the manufacture of Erwinaze®. Regardless of this agreement, you and Jazz Pharmaceuticals are both responsible for the quality of drugs released and ultimately administered to patients. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act to ensure safety, identity, strength, quality, and purity. See FDA's guidance document, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf.

**Conclusion**

Violations and deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations and deviations, for determining the causes, for preventing their recurrence, and for preventing other violations and deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

Until you correct all violations and deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations and deviations may also result in FDA refusing admission of articles manufactured at Porton Biopharma, Limited, Manor Farm Road, Porton Down, Salisbury, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 business days. Specify what you have done since our inspection to correct your violations and deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 business days, state your reasons for delay and your schedule for completion.

Because these violations and deviations are significant and repeated, it is urgent that corrective action is taken as soon as possible. FDA will contact your firm to schedule a face-to-face regulatory meeting between your firm, your customer, and Agency officials. The purpose of this meeting is to ensure your firm is taking prompt actions to correct the violative conditions found during the 2015 and 2016 inspections discussed in this Warning Letter.

Send your electronic reply to CDER-CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Marisa Heayn
Consumer Safety Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3011691465.

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

Cc:
Russell Cox

Chief Operating Officer
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