Tubilux Pharma Spa 7/6/17

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS

Warning Letter 320-17-41

July 6, 2017

Mr. Emilio Fedeli
President and CEO
Tubilux Pharma S.p.A.
Via Costarica 20/22
00071 Pomezia
Rome, Italy

Dear Mr. Fedeli:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Tubilux Pharma S.p.A. at Via Costarica 20/22, 00071 Pomezia, Rome, from December 1 to 9, 2016.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products 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 December 30, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

During the inspection, our investigator reviewed and noted turbulent airflow in the September 2015 smoke studies (airflow visualization studies) conducted on your aseptic processing line in room **(b)(4)** where you manufacture **(b)(4)** and **(b)(4)** for the U.S. market. This turbulent airflow poses a significant contamination hazard to your product.

In your response, you submitted additional smoke studies conducted in December 2016. Like your September 2015 studies, the December 2016 smoke studies show turbulent airflow in multiple locations on the aseptic filling line.

You have not established that unidirectional airflow exists at the station where the cap is applied to the container. Additionally, your dynamic smoke study videos show turbulent airflow when operators manually **(b)(4)** the sterile container-closure components into **(b)(4)** bowls, which are located outside of the filling and sealing enclosure. Operators reach over the **(b)(4)** bowls while loading sterile container-closure components to overcome a limitation in your current equipment and process design. The ergonomics of these manual manipulations pose a significant hazard in your aseptic processing operation.

Our investigator also observed operators performing these manually intensive aseptic activities during our inspection. For instance, the investigator noted many significant routine and non-routine interventions during production of **(b)(4)** lot **(b)(4)** on December 2, 2016.

In response to this letter:

- Identify all contamination hazards, including with respect to your aseptic processes, equipment, and facilities. This should cover, among other things, analyses of all interactions with the ISO 5 area, facility layout, personnel and material flow, air systems, ISO 5 area protection, and equipment ergonomics.
- Complete and submit a formal risk assessment of these process, equipment, and facility hazards. The risk assessment should fully evaluate the microbiological contamination risks throughout your operation and describe risk mitigations and remediations.
- Prepare and submit a comprehensive corrective action and preventive action (CAPA) plan that details and tracks your planned remediation. Note that a sustainable CAPA includes a combination of improvements in both design and control.

2. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

You do not require your **(b)(4)** products to be tested for particulates prior to release. Notably, our investigator observed repeated instances of high particle count alarms during production of **(b)(4)** lot **(b)(4)** on December 2, 2016.

An addendum to your change control document (CC-QA_006-16), signed December 9, 2016, addresses the need for particle testing of finished products, and references USP 39. The addendum states that you "will need to implement this testing and make it a part of the product specification." However, your response did not describe actual implementation of particulate testing. Particulate contamination can pose a hazard to the **(b)(4)**.

In response to this letter, provide your implementation plan to test for particulate matter in **(b)(4)** drug products. Include your revised drug product specifications and your written procedure regarding in-process inspection of units for visible particles.

Additional CGMP Issues

We also note the following deficiencies related to your facility's sterility assurance program.

Sterility testing
You use a **(b)(4)** to transfer samples into the microbiology laboratory. When **(b)(4)** into the **(b)(4)**, you disinfect sample surfaces with **(b)(4)**. You also disinfect sample surfaces with **(b)(4)** when you **(b)(4)** from the **(b)(4)**. In addition to these two appropriate sample decontamination steps, you subject sterility test samples to **(b)(4)** exposure in the **(b)(4)**. Use of this **(b)(4)** cycle may kill or injure organisms that the sterility test could otherwise detect.

In response to this letter, provide a CAPA that fully remediates this issue and ensures that sterility samples are disinfected in a manner that does not potentially compromise their validity.

***(b)(4)** Clogging*
Your firm has experienced recurring instances in which **(b)(4)** were found to be clogged during batch manufacture. You have attributed the clogging to a **(b)(4)** impurity. These clogs required **(b)(4)** changes during aseptic processing.

In response to this letter, summarize all **(b)(4)** clogging incidents since December, 2015. Also describe the status and effectiveness of your CAPA implementation.

Guidance on Aseptic Processing

See FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, at **https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf (https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf)**.

Conclusion

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

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 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 may also result in FDA refusing admission of articles manufactured at Tubilux Pharma S.p.A., Via Costarica 20/22, 00071 Pomezia, Rome, 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 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

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

Catherine Gould
Compliance 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 3003854110.

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

More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)