Inspections, Compliance, Enforcement, and Criminal Investigations

Alexion Pharmaceuticals, Inc. 3/22/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New England District Office
One Montvale Avenue, 4th floor
Stoneham, MA 02180
Phone 781.587.7500
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WARNING LETTER
CMS # 352798

VIA United Parcel Service
Overnight Delivery

March 22, 2013

Mr. Leonard Bell, M.D.
Chief Executive Officer
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410

Dear Dr. Bell:

During our July 12, 2012, through August 6, 2012, inspection of your pharmaceutical manufacturing facility, Alexion Pharmaceuticals, Inc., located at 100 Technology Way, Smithfield, RI, an investigator from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practices (CGMP) in the manufacture of licensed therapeutic drug substances (also known as "active pharmaceutical ingredients"(APIs)). These violations cause your API to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the 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; and the requirements of your biologics license application approved under 351 of the Public Health Service Act (PHS ACT).

We have conducted a detailed review of your firm's response and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated September 28, 2012, as well as the information provided during the status update meeting of December 21, 2012.

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

1. Inadequate investigation of critical deviations or a failure of a batch to meet its specifications or quality standards.

For example, your firm manufactured **(b)(4)** lots of Soliris API between April 2011 and August 2012. Six of these lots (**(b)(4)**, and **(b)(4)**) were found to be contaminated with too numerous to count (TNTC)/10 mL *Bacillus thuringiensis* **(b)(4)** of all lots manufactured) at the concentrated **(b)(4)** step. The contamination exceeded your established action limit of **(b)(4)** CFU/10 mL. Your firm did not conduct a thorough investigation of the multiple, microbiological contamination events to determine possible root cause. The microorganism, *Acinetobacter radioresistens* was also identified in Soliris lot **(b)(4)**. In addition, you failed to conduct an adequate assessment of the impact of this contamination on your final product, including the potential for non-host cell particle contamination, and you did not evaluate the ability of your manufacturing process to clear non-host cell impurities.

Your firm's corrective action at the time was to increase the use of a sporicidal agent in your clean rooms (*Bacillus thuringiensis* is a spore-forming organism). Nevertheless, your firm failed to verify the effectiveness of your cleaning procedure after the contamination event before further production.

Your firm later performed additional testing (**(b)(4)**. Although the additional testing does not provide the assurance of the absence of other impurities, you relied on those test results to justify releasing the API lot **(b)(4)** for further processing. Moreover, you failed to identify the underlying root cause to correct and prevent recurrence.

Please note that during the inspection we observed residues in already-cleaned equipment. You based your "Worst Case Calculations" section in your response on clearance of host cell protein (mammalian origin) in contrast to the non-host cell contamination (bacterial origin) identified during the **(b)(4)** step. However, your response did not provide the scientific rationale used to determine that the comparison for clearance of host cell protein (mammalian origin) to the non-host cell contamination (bacterial origin) is adequate.

We also note that you based your "Toxicology Assessment of Calculated Impurities" section in your response on a **(b)(4)** human. However, Soliris is indicated for pediatric use. Please explain how your toxicology assessment is valid in light of the product's intended use.

2. Failure of your quality unit to exercise its responsibility to ensure APIs are manufactured in compliance with CGMP and meet established specifications for quality and purity.

For example, two Soliris API lots, lots **(b)(4)** and **(b)(4)**, failed your firm's action limit of **(b)(4)** CFU/10mL with results of TNTC/10mL at the **(b)(4)** step. However, your quality unit released them for further manufacturing without adequate scientific justification. On July 24, 2011, you used lot **(b)(4)** to manufacture drug product lot **(b)(4)**. Lot **(b)(4)** had not yet been processed into Soliris drug product at the time of the inspection.

In your response, you did not clearly explain why you released one lot for further processing and placed the other on hold. In your response, explain the scientific justification for the two different actions.

Furthermore, we note that you have repeated bioreactor cleaning at least several times in one recent eighteen month period. Please verify that the bioreactor cleaning cycle is designed and functioning appropriately to handle expected conditions.

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

It appears that you have not implemented a robust quality system at your firm. Several of the CGMP deficiencies that our investigators observed during this inspection were also observed

during our inspection in February 18, 2011. We recommend that you implement a comprehensive quality system at your firm to encompass all manufacturing operations. Repeat citations from prior inspections could indicate that your quality control unit is not exercising its responsibilities or may not have the appropriate authority to carry out its responsibilities. Due to continuing CGMP issues at your firm, we recommend you engage a third party consultant with appropriate CGMP expertise to assess your firm's facility, procedures, processes, and systems to ensure that the drug products you manufacture have their appropriate identity, strength, quality, and purity.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or 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. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this warning letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

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 violations, 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 Soliris, provide the date and reason(s) you ceased production. Please identify your response with FEI # 3006568549.

Please send your reply to the following address: Amber G. Wardwell, Director of Compliance, New England District, Food and Drug Administration, One Montvale Avenue, 4th Floor, Stoneham, Massachusetts 02180. Ms. Wardwell can be reached by telephone at 781-587-7484.

Sincerely,
/S/
Mutahar S. Shamsi
District Director
New England District

cc: Mr. Scott C. Nickerson
Vice President Quality Assurance Quality Control
100 Technology Way
Smithfield, RI 02917

Page Last Updated: 04/08/2013
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