Inspections, Compliance, Enforcement, and Criminal Investigations

Baxter Healthcare Corporation 5/31/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Atlanta District Office
60 Eighth Street N.E.
Atlanta, GA 30309
Telephone: 404-253-1161

May 31, 2013

VIA UNITED PARCEL SERVICE

WARNING LETTER
(13-ATL-17)

Robert L. Parkinson, Jr.
Chairman and Chief Executive Officer
Baxter International Inc.
One Baxter Parkway
Deerfield, IL 60015

Dear Mr. Parkinson:

During our November 7 to 16,2012, and March 13, 2013 to April 19, 2013, inspections of your pharmaceutical manufacturing facilities, Baxter Healthcare Corporation (Baxter) located at 65 Pitts Station Road, Marion, North Carolina, and Baxter Healthcare Corporation, located at No. 250 Road No. 144 Jayuya, Puerto Rico, investigators from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21 , Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products 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.

In addition, the inspection at Jayuya, Puerto Rico, identified your firm's failure to submit NDA Field Alert Reports (FARs) to the FDA as required by 21 C.F.R. § 314.81 (b)(1)(i) and (ii), and section 505(k) of the Act [21 U.S.C. § 355(k)].

We have conducted a detailed review of your firm's written response from your Marion, North Carolina facility and note that it lacks sufficient corrective actions.

Our investigators observed specific violations during the inspections, including, but not limited to, the following:

CGMP Violations

Baxter Healthcare Corporation, Marion, North Carolina Facility:

1. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

For example, FDA inspection of Fill Line **(b)(4)** on November 14,2012, revealed that numerous HEPA filters, HEPA filter supporting grid work, HEPA filter screens, and HEPA filter screen tracks contained varying amounts of discolored areas, chipping paint, multicolored coalescing droplets, and clumps of dark material that FDA testing later revealed was mold.

In your response, you state that you ceased production on large volume parenteral (LVP) Fill Line **(b)(4)** on November 14, 2012, and LVP Fill Line **(b)(4)**, on November 17, 2012. You state further that you suspended release of product "prior to those dates," and did not resume production until remediation and qualification activities were completed. However, your response is inadequate because you have not yet indicated how long the objectionable conditions described above persisted prior to intervention, nor have you identified the root causes that allowed these conditions to go uncorrected. We are especially concerned that you have not identified the root cause that allowed the mold to proliferate to a level of TNTC (Too Numerous to Count) in several environmental samples directly over your filling line. Without identifying, correcting, and preventing the root cause of the mold growth at your sterile fill lines, the contamination hazard to the products manufactured on those lines could continue and potentially pose risk to patients.

This is a repeat observation from the August 2012 inspection at the Marion, North Carolina facility.

2. 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).

For example, the inspection revealed that your maintenance personnel had documented evidence of visible discoloration and stains and "possible mold" on the "clean" side of the HEPA filters supplying air to LVP Lines **(b)(4)** at least as far back as July 6, 2010. You did not properly investigate and remediate this condition. No samples of the discoloration or stains were tested at the time to determine if mold was in fact present.

In your response, you state you will establish acceptance criteria for critical attributes, such as discoloration, stains, and particulates associated with the visual inspection of the HEPA filters. Your "acceptance criteria will include the requirement that any evidence of contamination (product, water or cleaning agents) or microbial growth will be investigated, the investigation documented, and the filter at issue will be replaced." The procedure regarding **(b)(4)** inspections of ceilings, walls, and floors (on all fill lines) will be updated to include the newly established acceptance criteria. These acceptance criteria will also be included in **(b)(4)** inspections of the HEPA filters (on all fill lines). These inspections will include representation from the Quality organization and any potential quality-related issue identified will be escalated into the environmental deviations process. However, your response is inadequate because you did not perform a risk assessment of all the products that were manufactured since July 6, 2010 and that are within expiration in the market.

This is a repeat observation from the August 2012 inspection at the Marion, North Carolina facility.

3. 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).

For example, there was no scientific justification for the sampling plans utilized for environmental monitoring in areas that your firm uses to manufacture terminally sterilized injectables. This included the frequency and locations of viable airborne particulate sampling activities, the locations of non-viable airborne particulate sampling activities, the frequency and locations of non-product contact surface monitoring, and the evaluation of microorganisms found through environmental monitoring activities. Your environmental monitoring program was insufficient to detect contamination of concern, including mold observed on the clean side of the air filters supplying air to the sterile filling areas. In addition, your environmental monitoring records do not identify the locations from which environmental monitoring samples were taken in each manufacturing area and room including, but not limited to: viable airborne particulate monitoring, non-viable airborne particulate monitoring, and large non-product contact surface area monitoring. Your incomplete records make evaluating the air quality of the filling area during the time prior to this inspection more difficult. In your response, you state that you use a formal risk assessment to justify the type, extent, frequency, and location of sampling and test procedures. Baxter also will create a procedure for periodic reassessment of that risk assessment to incorporate any relevant new or emerging information, and you will continue to conduct bioburden testing.

Although we acknowledge your use of formal risk assessments in implementing these revised environmental monitoring procedures and bioburden testing, your response is still deficient. In your response, you downplay the product quality and safety impacts posed by the mold observed on the clean side of HEPA filters supplying air to your sterile filling areas on the grounds that products made in these areas are terminally sterilized. Please note that sterile products should be protected from microbiological contamination during processing, even when terminally sterilized, in order to minimize sterilization challenge and byproducts of excessive bioburden.

The products covered during the inspection of the Marion facility are made using a parametric release approach instead of sterility testing. FDA permits the use of a properly qualified and adequately maintained parametric release program to meet the intent of the CGMP regulation for product sterility testing (see 21 CFR 211.165(a) and 211.167(a)). Further, FDA considers a properly qualified and maintained parametric release program to encompass multiple, integrated CGMP systems that are in a state of control, including 1) sterilization process validation and control, 2) verification by suitable load monitor(s), 3) a validated container/closure system, and 4) an effective Quality System. Failure to meet any one of these criteria could disqualify the parametric release program. For your bioburden-based sterilization process, basic environmental control is integral to ensuring continuing sterilization process control by preventing an excessive challenge to the sterilization process. We acknowledge that your firm has been performing sterility testing on your terminally sterilized products since December 2012 as part of your corrective action plan. We also urge you to evaluate all Baxter terminal sterilization operations to verify that the overall operation of your sterility assurance program meets CGMP and drug application requirements, including, but not limited to, application commitments pertaining to the use of parametric release. Please update all of your drug applications containing parametric release provisions to incorporate your newly enhanced environmental monitoring program as application commitments. FDA will evaluate the adequacy of your environmental control and monitoring program in a future inspection.

Baxter Healthcare Corporation, Jayuya, Puerto Rico Facility:

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).

For example,

a. On February 13, 2012, this site generated a nonconformance investigation report--number 81986--addressing a bag leak detected during routine microbiology testing. The investigation concluded that the root cause for bag leaking was weak membrane defects within the port component of the bag. According to the referenced investigation, the defective closure component resulted from machinery problems during the manufacturing process at the supplier **(b)(4)**. The investigation identified at least thirty-nine (39) lots of finished drug product affected by this defect that were released for distribution.

Upon identification of the defect you placed portions of the impacted lots remaining under your control on hold and you developed sampling/inspection protocols to evaluate the impact of the bag closure system defect on the referenced lots. According to the inspection protocol of the product lots tested did not meet the established acceptance criteria of **(b)(4)** Based on this result, you discarded the portions in stock of at least twenty five (25) product lots. Nonetheless, you did not take any actions to mitigate risks posed by affected product lot portions (pertaining to at least 27 product lots) that you had already distributed to the market. You based your decision not to intervene on a Medical Risk Assessment (MRA) in which you evaluated the product defect and determined that it presented a low risk to patient health. Your MRA concluded that product sterility was not compromised by the defective closure on the grounds that the closure assembly is sealed off from the environment by a blue cap. According to your evaluation, "if the membrane were to leak the cap will maintain sterility of the product until use."

However, your firm received several complaints reporting inadequate fitting of the blue cap. One complaint reports that in approximately 30% of the bags the blue cap was either unattached or barely attached to the port, often falling without being touched. Therefore, your assumption that the blue cap represents a reliable extra barrier to contamination and your dependent conclusion that product sterility and patient safety are not compromised by poorly fitting caps may be unfounded. Your evaluation of the membrane defect should have considered all common failure modes associated with container and closure integrity, including the loss of the blue cap. We note that you initiated recall of the impacted portion of these lots only after FDA brought the matter to your attention. In your response to this letter, please describe how your firm will be correcting the root causes of these defects, including describing any remediation plans to improve manufacturing robustness.

b. On June 201 1 to May 2012, your firm generated twenty (20) nonconformance reports or product retention records related to particulate matter such as paper fiber, cotton fibers, nylon fibers, PVC particles, cardboard, skin, polyester, polyethylene, human hair, rayon, and frangible material from the vial adapter found inside drug product solution during the manufacturing process. This defect has been detected in products within the Mini Bag Plus and Quads families of products. In-process and final inspection specifications for these products define "[s]olution and solution path not substantially free from particulate matter" as a "major defect." There is no assurance these specifications were adequate in preventing the production of defective units during your manufacturing process.

In addition to the inadequate investigations described above, on inspection, FDA observed that several investigations remained opened for three (3) months. Non Conformance Report NCR 55675 was generated on July 23, 2011 and remained opened until February 8, 2012 (over 6 months). These examples of lengthy, incomplete investigations are inconsistent with your firm's own procedures for handling such events. SOP JA-03-01-012 "Manejo de Nonconformance CAPA Tier I" ("Handling of Nonconformance establishes that a non-conformance is to be completed and approved in a maximum period of **(b)(4)** calendar days from its generation. Your quality system evaluated deviations from the referenced SOP; NCR 79184 documented that as of December 31, 2011 a total of sixty four (64) non-batch related investigation reports remained open for more than **(b)(4)** days. NCR 79184 (approved on February 2, 2012) also indicated

that for these lengthy incomplete investigation reports, no extension request was submitted as required by SOP JA-03-01-12.

This is a repeat violation cited in our Warning Letter 11-SJN-WL-04 dated January 20, 2011, issued to you corporation that discussed the Jayuya, Puerto Rico Facility.

2. Your firm failed to ensure your container closure system provided adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product (21 CFR 211.94(b)).

For example, you received consumer complaints identifying at least ten (10) membrane leaks and one hundred fifty-five (155) inadequately-fitting blue caps during the period of November 2011 to March 2013. These are critical defects that can impact the sterility and stability of your products.

This is a repeat violation cited in our Warning Letter 11-SJN-WL-04 dated January 20, 2011, issued to you corporation that discussed the Jayuya, Puerto Rico Facility.

Post Marketing Reports Violations:

Your firm failed to submit NDA Field Alert Reports (FARs) within three (3) working days of receipt of information concerning a product defect. This includes any bacteriological contamination, any significant chemical, physical, or other change, any deterioration in the distributed drug product, or any failure of one or more distributed batches of drug product to meet the specifications established for it in the application [21 C.F.R. §314.81(b)(1)(ii)].

For example, your firm submitted a final FAR dated March 21, 2012, regarding to the membrane leak defect investigation covered in your non-conformance investigation report number 81986. However, after submission of your final FAR, your firm identified additional lots impacted by the membrane component defect. No additional FAR was submitted to the FDA until FDA notified you of your failure to submit a FAR as required during the current inspection of the Jayuya facility. Further, on July 25, 2012, your firm received a consumer complaint reporting one unit of Potassium Chloride Injection 100 ml with no expiration date. The inspection of the returned complaint sample reported that the unit was also missing the product lot number. You did not submit a FAR to the FDA regarding this labeling error.

This is a repeat violation cited in our Warning Letter 11-SJN-WL-04 dated January 20, 2011, issued to you corporation that discussed the Jayuya, Puerto Rico Facility.

The CGMP violations described in this letter include similar violations to those cited in the January 20, 2011, Warning Letter issued to your Jayuya, Puerto Rico facility. FDA expects Baxter International to undertake a comprehensive and global assessment of your manufacturing operations to ensure that your systems and processes, and ultimately, the drug products you manufacture, have the quality they are represented to possess and conform to FDA requirements.

Further, be advised that a recent FDA inspection at another Baxter facility cited a pattern of inadequate corrections and interventions concerning sterile facility sanitization. While the response to that location's deficiencies appears adequate, we expect appropriate correction at all Baxter facilities in this critical area.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facilities. 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.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of fmished 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.

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.

Your written responses should be sent to Marie Mathews, Compliance Officer, at the address noted in the letterhead. If you have any questions about this letter, please contact Ms. Mathews at (404) 253-1279 or email at marie.mathews@fda.hhs.gov. Send a copy of your response to the Food and Drug Administration, Attention: Carlos A. Medina, Compliance Officer, 466 Fernandez Juncos A venue, San Juan, Puerto Rico 00901-3223.

Sincerely,

/S/

John R. Gridley, Director
Atlanta District

cc:
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