Inspections, Compliance, Enforcement, and Criminal Investigations

RPG Life Sciences Limited 5/28/13

Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-13-17

May 28, 2013

Mr. Ajit Singh Chouhan, Managing Director
RPG Life Sciences Limited
RPG House
463, Dr. Annie Besant Road,
Worli, Mumbai, 400 030, Maharashtra, India

Dear Mr. Chouhan:

The U.S. Food and Drug Administration (FDA) inspected the pharmaceutical manufacturing facilities of RPG Life Sciences Limited-Ankleshwar (hereinafter referred to as MS-Ankleshwar), located at 3102/A, GIDC Estate, Ankleshwar, District Bharuch, Gujarat, India, and RPG Life Sciences Limited-Navi Mumbai (hereinafter referred to as MS-Navi Mumbai), located at 25, MIDC Land, Thane-Belapur Road, Navi Mumbai, Maharashtra, India. During our November 20, 2012 through November 24, 2012 inspection of your pharmaceutical manufacturing facility, MS-Ankleshwar, investigator(s) from the FDA identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. Likewise, during our January 28, 2013 through January 31, 2013 inspection of your pharmaceutical manufacturing facility, MS-Navi Mumbai, investigator(s) from the FDA identified significant deviations from CGMP for the manufacture of active pharmaceutical ingredients (APIs). These violations cause your APIs and 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.

We have conducted a detailed review of your firm’s responses dated December 11, 2012 and February 19, 2013 and note that they lack sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondences dated January 14, 2013, February 6, 2013, March 18, 2013, and April 9, 2013.

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

MS-Ankleshwar

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, your firm did not identify, report, or investigate the following out-of-specification (OOS) results.

a. On May 06, 2012, the 12-month stability interval assay test for **(b)(4)** mg tablet batch **(b)(4)** failed to meet the established specifications with a result of **(b)(4)** (specifications: **(b)(4)**-**(b)(4)**).

b. On July 16, 2011, the assay for **(b)(4)** API batch **(b)(4)** failed to meet the established specification with a result of **(b)(4)** (specifications: **(b)(4)**- **(b)(4)**). This API batch was used in the manufacture of **(b)(4)** finished drug product batches.

c. On January 26, 2011, the related substance assays for three **(b)(4)** API raw material batches **(b)(4)**, **(b)(4)**, and **(b)(4)** exceeded the **(b)(4)** and **(b)(4)** impurity specifications (**(b)(4)**%). These API batches were used in the manufacture of **(b)(4)** finished drug product batches.

d. On October 10, 2012, the two-month stability assays for the **(b)(4)** USP batch **(b)(4)**-tablet presentation showed a significant unknown peak at approximately **(b)(4)** on the chromatograms.

For incidents 1(a)-(c), your firm repeated these assays, and selectively reported only the passing retest values in the final assay results, then disregarded the initial OOS data without conducting investigations. In incident 1(d), your firm disregarded the **(b)(4)** stability OOS data, and selectively used only the passing results from the other **(b)(4)** presentations.

In response to the FDA-483, you conducted retrospective investigations and hypothesized the causes of the OOS results as sample dilution error, HPLC auto-sampler injection error, use of aged sample solutions, and vial contamination, respectively. However, your response is inadequate because your retrospective investigations lacked documentation, raw data, or scientific evidence to support your hypotheses. As mentioned above, your firm did not retain documents associated with the sample weights, sample preparations and sample dilutions. You also acknowledged that without raw data it is difficult or impossible to definitively determine the root causes and the exact actions of the analyst when OOS results are encountered.

In response to this letter, please conduct a comprehensive review of the laboratory data for all finished drug products within expiry, and for the raw materials within retention period. Provide a summary report of all OOS results that your firm disregarded without conducting an investigation. Thoroughly investigate all OOS results, including testing of the reserve samples if necessary, and provide your conclusions in the report. Describe the corrective actions you will take against all batches for which a non-conforming result was obtained. You stated in your response that you revised your investigation procedure and implemented **(b)(4)** audit trails for each laboratory instrument. Your QC managers will review the **(b)(4)** audit trail printouts to ensure identification and investigation of OOS results. We will verify the effectiveness of these corrective and preventive actions during our next inspection.

2. Your firm failed to follow required laboratory control mechanisms and to record and justify any deviations from them (21 CFR 211.160(a)).

For example, your *Investigation of Out-of-Specification Results* procedure (SOP/F2/QCD/035-02) established sample retesting as part of an OOS investigation. This procedure required re-analysis of the original retained test solution to determine assignable causes prior to new sample retesting during the phase I laboratory investigation. It also required preservation of all samples, dilutions, and related printouts, as well as prompt initiation and documentation of OOS investigations on the specific *Annexure-I* form. Your firm performed related substance analyses of **(b)(4)**mg tablet batches **(b)(4)** and **(b)(4)** multiple times on May 10, 2012, and on May

12, 2012. Your firm then repeated the analysis again on May 13, 2012, using a new set of sample solutions, and reported only this test result on the certificates of analysis (COAs). Moreover, your firm used **(b)(4)** different HPLC processing methods to process the data for these analyses. Your firm did not investigate or document all these tests, and discarded raw data related to sample weights and preparations, in disregard of the SOP requirements.

In response to the FDA-483, you conducted a retrospective investigation and attributed the causes for the OOS to instrument communication error, lack of standard and blank injections, and peak splitting, respectively. However, you did not explain what caused the peak splitting. In addition, you did not record or provide justifications for not documenting these incidents on form *Annexure-I* as required by the procedure.

3. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

For example, your firm did not retain any raw data related to sample weights and sample solution preparations for the HPLC assays of **(b)(4)** tablet batches **(b)(4)** and **(b)(4)** that you conducted on July 18, 2012. In addition, you did not include those results in the calculation of the final assay values. Instead, you repeated the analysis the next day using a new set of sample solutions, and reported the retest results on the certificates of analysis (COAs). Other examples were also noted during the inspection (please refer to citations 1 and 2 of this letter).

In response to the FDA-483, you conducted a retrospective investigation and concluded that the analyst realized he recorded the initial data incorrectly in the HPLC "trial folder" instead of the regular folder. Thus, he repeated the test the next day using the same sample solutions. However, your QC manager stated during the inspection that the initial injections were trial runs, and that performing trial standard and sample analysis prior to official analysis is a standard practice in your QC laboratory. Moreover, our review of the final QC worksheet revealed that you prepared the new retest samples on July 19, 2012, the day after you performed the trial injections.

Our investigator also observed **(b)(4)** trial HPLC injections during the period of January 5, 2012 to November 16, 2012. Your response acknowledged that a number of these trial injections involved sample testing. However, you provided no evidence that your firm retained laboratory records and raw data associated with these sample tests.

Additionally, during an audit of the data submitted in support of the **(b)(4)** regarding **(b)(4)** tablets USP **(b)(4)** mg, our investigator requested to review the electronic analytical raw data to compare the values for **(b)(4)** assay and degradation products. However, your firm provided only the printed copies of the raw data because your firm did not have the software program available to view the electronic raw data.

In response to this letter, please perform a retrospective quality review of all retests conducted related to any unexpected or OOS results, and include a summary that identifies the test results that apply to product currently within expiration and distributed that are lacking supporting raw data. Include a corrective and preventive action (CAPA) plan to prevent recurrence that addresses this observation and that will ensure that all electronic analytical raw data will be readily available for review during the next inspection.

4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

For example, you analyzed **(b)(4)** API lot **(b)(4)** on February 14, 2011, at 2:55 a.m., and then retested it at 2:05 p.m. using a new sample solution. You did not maintain any raw data associated with the initial test.

In your response, you stated that the retest was performed due to data deletion of the original analysis. You concluded that the analyst misused the administrator password to delete and

overwrite the actual data logged in the audit trail. The ability of your analysts to alter and delete electronic analytical data raises serious concerns regarding laboratory controls in place at your facility.

During the inspection, our investigator also identified a backdated QC worksheet in the analytical report of **(b)(4)** API raw material batch **(b)(4)**. When your analyst affixed the related substance and IR weight printouts to the *Format for Blank Sheet for Printout* (Format No. F2/QCD/F/026-00), he signed and dated this worksheet as July 29, 2011. A second analyst, who reviewed this worksheet, also signed and dated it as July 29, 2011. However, your QA department did not issue this worksheet until July 31, 2011. Your analyst acknowledged during the inspection that he backdated this worksheet on July 31, 2011.

Your response stated that the analyst incorrectly dated the worksheet as July 29, 2011, instead of July 31, 2011, and that there was no intention to deliberately backdate the document. However, your response contradicted your analyst's backdating admittance during the inspection. In addition, your response did not explain the reviewer's signature which was also dated July 29, 2011. Backdating documents is an unacceptable practice and raises doubt about the validity of your firm's records.

Provide in your response the investigation conducted regarding the practice of deleting critical analytical data and backdating records. This practice is a clear breach in your quality system that raises serious concerns regarding the integrity and reliability of the laboratory data used to release drug products. As a corrective action, you revised your *Good Documentation Practices* procedure and provided training on your password policy procedure to prevent deletion and overwriting of electronic records. Provide a copy of your investigation into this matter, along with your risk assessment regarding the extent and impact of the missing data on the quality of all finished drug products released for distribution.

MS-Navi Mumbai

1. Your firm failed to investigate and document out-of-specification results according to a procedure.

For example, your nine-month stability assays of three **(b)(4)** batches **(b)(4)**, **(b)(4)**, and **(b)(4)**, conducted on April 2, 2012, exceeded the related substance specification for unknown impurities. Your firm failed to report and investigate these OOS results. Your firm subsequently repeated these analyses the next day using a new set of sample solutions, and reported only the passing retest results. Moreover, your firm discarded all raw data related to the OOS results including sample weights, sample solution preparations, and sample dilutions.

In response to the FDA-483, you conducted a retrospective investigation and attributed the cause of these OOS results to syringe contamination. However, your report, *"Justification for Unprocessed Runs on Waters HPLC,"* provided to our investigator during the inspection described the cause of these OOS results as vial or glassware contamination. Your investigation lacked scientific evidence to support your root cause hypothesis.

In response to this letter, provide a summary of OOS results for all API product batches within expiry that your firm disregarded without adequate investigations. Thoroughly investigate the OOS results, including testing of the reserve samples if necessary, and provide your conclusions. Describe corrective actions you will take for any non-conforming batches.

2. Your firm failed to adequately investigate all quality-related complaints.

For example,

a. Your firm received three complaints from December 2011 to August 2012 regarding **(b)(4)** particles found while **(b)(4)** four batches of your distributed **(b)(4)**, API. Your complaint report MC/11/13 acknowledged that you observed particles in the returned samples, yet your firm never determined the identity and cause of the **(b)(4)** particles. Rather, you discarded the samples. Your response stated that you could not evaluate the

samples because of their small quantities. However, you did not describe the quantity of the returned samples, nor did you request additional sample quantities from your customer.

In response to the FDA-483, you **(b)(4)** four returned **(b)(4)** batches through a **(b)(4)** and found no **(b)(4)** particles. However, according to your returned goods investigation report RG/12/006, you only visually inspected the **(b)(4)** material for the presence of foreign particles, and discarded the oversized material. There is no assurance that your firm thoroughly inspected all returned **(b)(4)** material for the presence of **(b)(4)** particles.

b. Your customer rejected **(b)(4)** batch **(b)(4)** on September 19, 2011 for exceeding the impurity limit for **(b)(4)** (**(b)(4)**) impurity. As part of your investigation, you randomly retested the reserve samples from **(b)(4)** batches distributed since May 2011, and found that another batch **(b)(4)** had exceeded the unknown and total impurity limits. Your firm subsequently tested the returned batches **(b)(4)** and **(b)(4)**, and confirmed that all **(b)(4)** drums of **(b)(4)** exceeded the **(b)(4)** and total impurity limits, and that all **(b)(4)** drums of **(b)(4)** exceeded unknown and total impurity limits. Yet, your investigation did not extend to other **(b)(4)** batches within expiry that may have been associated with these confirmed batch failures. Your decision to exclude testing of other **(b)(4)** batches was based on the fact that your customers accepted them. However, this is not a scientifically sound justification for not extending the investigation to other associated **(b)(4)** batches.

3. Your firm failed to establish and exercise adequate controls over computers to prevent unauthorized access or changes to electronic data.

For example, the computers that control your analytical laboratory instruments, including an HPLC, **(b)(4)** GCs, and an FTIR, lacked control mechanisms to prevent unauthorized access to, changes to, or omission of data files.

a. Your analysis of **(b)(4)** USP batch **(b)(4)** exceeded the **(b)(4)** residual solvent limit on February 29, 2012. Your firm did not report or investigate this OOS result, and deleted the related electronic records. During our inspection, your analyst admitted that he also deleted other uninvestigated failing and/or OOS electronic data from the laboratory database in January 2013 prior to our inspection. Your QC Senior Manager also acknowledged this laboratory-wide electronic data deletion practice.

b. During our inspection, your analysts demonstrated to our investigators that they could delete any electronic analytical data files from the laboratory computers and external backup hard drives.

Adequate controls prevent improper deletion of essential data. You stated in your response that you are procuring a centralized server and software, which will prevent electronic data deletion. Each analyst will have an individual user ID and password. You also trained your analysts not to delete electronic analytical data and report all laboratory incidences to managers. We will verify the effectiveness of these corrective actions during our next inspection.

You are responsible for the accuracy and integrity of the data generated by your firm. A firm must maintain all raw data generated during each test, including graphs, charts, and spectra from laboratory instrumentation. These records should be properly identified to demonstrate that each released batch was tested and met release specifications.

Our inspection revealed that your firm discarded OOS laboratory records and deleted OOS electronic analytical data. Your firm also disregarded OOS data without investigations, and selectively reported only passing results. The lack of reliability and integrity of data generated is a serious CGMP deficiency that raises concerns with all data generated by your firm.
The items listed above, as well as other deficiencies our investigator(s) found, lead us to question the effectiveness of your current quality system to achieve overall compliance with

CGMP at your facility. It is apparent that you have not implemented a robust quality system at your firm. Be advised that corporate management is responsible for ensuring the quality, safety, and integrity of drugs manufactured by RPG Life Sciences Limited. FDA strongly recommends that your corporate management immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP and CGMP regulations.

We highly recommend that you hire a third party auditor, with experience in detecting data integrity problems, to assist you with this evaluation and assist with your overall compliance with CGMP. It is your responsibility to ensure that data generated during operations are accurate and that the results reported are a true representation of the quality of your APIs and drug products.

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.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at MS–Ankleshwar and MS–Navi Mumbai, into the United States. The articles are 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 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 the drug product(s) at issue, provide the date(s) and reason(s) you ceased production.

Please send your reply to the following address:

Allison A. Aldridge, Ph.D.
Compliance Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

/Michael Smedley/
Michael D. Smedley
Acting Director
Office of Manufacturing and Product Quality
Office of Compliance

Page Last Updated: 06/17/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.