DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

UPS EXPRESS MAIL

Dr. Rolf Vornhagen
Division R & D Manager/Site Manager
Bio-Rad Medical Diagnostics GmbH
Industriestrasse 1
63303 Dreieich, Germany

Dear Dr. Vornhagen:

The Food and Drug Administration (FDA) conducted an inspection of Bio-Rad Medical Diagnostics GmbH located in Dreieich, Germany, between March 16 and March 24, 2015. During the inspection, an FDA investigator documented violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act (FD &C Act) and deviations from applicable standards and requirements of your biologics license application approved under Section 351 of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Part 820. At the close of the inspection, our investigator issued a Form 483, Inspectional Observations which described a number of significant deviations relating to your facility's compliance with current good manufacturing practice (CGMP). Your manufacture of Reagent Red Blood Cells, Blood Grouping Reagents, and Anti-Human Globulin products fails to conform to the applicable standards established in your license and in the above-cited regulatory provisions, all of which are designed to ensure the continued safety, purity, and potency of your Reagent Red Blood Cells, Blood Grouping Reagents, and Anti-Human Globulin.

The significant deviations observed during the inspection include, but are not limited to, the following:

1) You failed to establish and maintain procedures for implementing corrective and preventive actions, including procedures that include requirements for identifying the actions needed to correct and prevent the recurrence of nonconforming products and other quality problems [21 CFR 820.100 (a)(3)]. For example:

    a) CAPA 005-13 was opened on June 26, 2013, due to complaints about leaking vials. The CAPA has been open for 604 days and remained opened as of the date of the close of this inspection. The problems with leaking vials continue to occur. From December 2012 through May 2015, thirty Biological Product Deviation Reports regarding leaking vial complaints were submitted to the agency.

    b) CAPA 004-10 dated April 20, 2010, has been open for over 1785 days due to four complaints of turbidity in Blood Grouping Reagents Seraclone Anti-A, B and remained opened as of the date of the close of this inspection. Eighteen additional complaints of turbidity in Blood Grouping Reagents Seraclone Anti-A, B have been received since the initiation of CAPA 004-10.

c) CAPA 032-09 was opened on November 4, 2009, due to false negative reactions with Blood Grouping Reagent Anti Jk (a) and remained open as of the date of the close of this inspection. The CAPA has been open for over 1932 days. Twenty four additional complaints of false negative reactions with Blood Grouping Reagent Anti Jk (a) have been received since the initiation of the CAPA 032-09. Additionally, fifteen Medical Device Reports have been reported to the agency regarding this issue.

d) CAPA 007-12 was opened on October 18, 2012, for false positive or questionable reactions for antibody screening and identification of group B with Blood Grouping Reagent Anti-A. CAPA 007-12 was noted to be ineffective and was closed on January 28, 2013, after 102 days, and CAPA 006-13 was opened on August 12, 2013, for the same issue and remained open for 557 days.

2. You failed to establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mix-ups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed [21CFR 820.150(a)]. For example:

a. The storage of incoming, and outgoing components used in the manufacture of products is not controlled. The products under quarantine are stored in the same location as incoming and outgoing components. It was later noted through the Systems Applications and Products (SAP) system that these incoming and outgoing components have been stored in these locations ranging from twenty-six days to seventy-two days, thereby further increasing the likelihood of mix-ups between products under quarantine and those that were not under quarantine.

b. The SAP system is not updated as the products are moved from one location to another within your facility. In addition, the inspection of (b)(4) revealed that neither the stored products nor the shelves are labeled to assure that the wrong products are not selected by personnel. Expired materials are also stored in this fashion.

We acknowledge receipt of your written response dated April 13, 2015, which addresses the inspectional observations on the form FDA 483 issued at the close of the inspection. We also acknowledge your commitment to complete an assessment of the current CAPA system and develop a corrective action plan.

We have reviewed your response and have the following specific comments. The Items are numbered to correspond to the observations listed on the Form 483.

Observation 4B

We note that you are revising OOS SOP-D:A-020-00/09 “Handling Out of Specification-Test Results in Quality Controls” to receive regulatory agency approvals before release of the

products that fail to meet specifications. Please be advised that FDA would not be able to approve a supplement to release OOS products.

Neither the above deviations, nor the observations listed on the Form FDA 483 presented to your firm at the conclusion of the inspection, are intended to be an all-inclusive list of deviations at your establishment. It is your responsibility to ensure compliance with all requirements of the laws and regulations administered by FDA.

We request that you notify this office, in writing, of the specific steps you have taken or will take to address the noted violations, and to prevent their recurrence. Your response should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, 10903 New Hampshire Avenue, Bldg.71, Silver Spring, MD 20993. If you have any questions regarding this matter, you may contact Najma Khan at (240) 402-9156. Please be advised that only written communications are considered official.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc: Mr. Scott Dennis, Vice President RA/QA
6565 185th Ave. NE,
Redmond WA 98052
Firm name: Bio-Rad Médical Diagnostics GmbH.