Biotronik SE & Co. KG 9/1/16

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
White Oak Building 66
Silver Spring, MD 20993

WARNING LETTER
SEP 1, 2016

VIA UNITED PARCEL SERVICE

Lothar Krings
Managing Director
Biotronik SE & Co. KG
Woermannkehre
12359 Berlin
Germany

Dear Mr. Krings:

During an inspection of your firm located in Berlin, Germanyon March 7, 2016, through March 10, 2016, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures Selectra percutaneous catheters, Galeo coronary guide wires, implantable pace makers, and implantable cardioverter defibrillators. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of

the body.

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.

We received a response from you dated March 30, 2016, concerning our investigator's observations noted on the Form FDA 483 (FDA 483), List of Inspectional Observations, which was issued to your firm. We address this response below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. Failure to ensure that when the results of a process cannot be fully verified by subsequent inspection and test that the process shall be validated with a high degree of assurance and approved according to established procedure, as required by 21 CFR 820.75(a). For example,

a. Your firm's validation of the **(b)(4)** process used to manufacture the coated Selectra Catheter lead introducer system lacked statistical rationale to justify using **(b)(4)** to demonstrate the consistency and reliability of the coating process.
b. The **(b)(4)** coating process validation did not include the testing of coating integrity, coating adhesion, or thickness.
c. The **(b)(4)** coating process validation did not determine the process limit boundaries (upper and lower limits) for the process parameters of **(b)(4)**.

We reviewed your firm's response and conclude that it is not adequate. Your firm's response did not include a revised validation procedure which specifies the number of units to be included in process validations with the appropriate criteria and rationale.

2. Failure to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements, as required by 21 CFR 820.50(a)(1). Specifically, your firm's "Select Supplier" procedure, GPV-101-200.010, requires supplier evaluation to be documented on form FOR-101-197 prior to becoming an approved supplier. However, your firm did not document the component supplier evaluations for the Selectra Catheter, including for the critical suppliers.

The adequacy of your firm's response cannot be determined at this time because corrective actions are still in progress.

3. Failure to ensure that where environmental conditions could reasonably be

expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures to adequately control these environmental conditions, as required by 21 CFR 820.70(c). For example, your firm does not monitor environmental parameters such as **(b)(4)** manufacturing area, to ensure that the environmental conditions do not have an adverse impact on the **(b)(4)** coating.

We reviewed your firm's response and conclude that it is not adequate. Your firm's response did not evaluate the potential impact of the lack of environmental controls on previously distributed product.

4. Failure to establish and maintain procedures to ensure that sampling methods are adequate for their intended use, as required by 21 CFR 820.250(b). For example, your firm did not provide any statistical rationale to justify the sampling method for incoming raw material inspection.

We reviewed your firm's response and conclude that it is not adequate. Your firm's response did not address whether failure to utilize statistically valid sampling plans resulted in the distribution of nonconforming product.

Our inspection also revealed that the Selectra Percutaneous Catheter and Galeo Coronary Guide Wire are misbranded under Section 502(t)(2) of the Act, 21 U.S.C. § 352(t)(2), in that your firm failed or refused to furnish material or information regarding the devices that is required by or under Section 519 of the Act, 21 U.S.C. § 360i, and 21 CFR Part 803 - Medical Device Reporting. Significant deviations include, but are not limited to:

5. Failure to report to us no later than 30 calendar days after the day that your firm received or otherwise became aware of information, from any source, that reasonably suggests that a device that your firm markets has malfunctioned and this device or a similar device that your firm markets would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur, as required by 21 CFR 803.50(a)(2). For example, the information included for Complaints 1540001682576, 140613085055, 140613102123 and 140611133257 references events in which your firm's device malfunctioned. Based on your firm's "Urgent Field Safety Notice, Product: Galeo Coronary Guide Wire" to its customers dated December, 2013, your firm noted that the malfunctions in the referenced complaints (i.e. delamination) would be likely to cause or contribute to a serious injury.Therefore, your firm needs to submit a MDR report for each of the above referenced complaints.

6. Failure to adequately develop, maintain and implement written MDR procedures, as required by 21 CFR 803.17. For example, after collectively reviewing your firm's MDR Procedural documents titled "Handle Complaints," GPV-101-190.010, Rev O, dated 03/13/2016 and "Guideline for Complaint Handling," GER-101-098, Rev H, dated 10/07/2015, the following issues were noted:

a. The procedure does not establish internal systems that provide for timely transmission of complete medical device reports. Specifically, the circumstances under which your firm must submit initial 30 day, supplemental or follow-up reports and the requirements for such reports, are not addressed.

b. The procedure does not describe how your firm will address documentation and record-keeping requirements, including:

i. Documentation of adverse event related information maintained as MDR event files.

ii. Information that was evaluated to determine if an event was reportable.

iii. Documentation of the deliberations and decision-making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable.

iv. Systems that ensure access to information that facilitates timely follow-up and inspection by FDA.

Please adjust your MDR procedures accordingly to include a process for submitting MDRs electronically in accordance with the Final Rule for electronic Medical Device Reporting (eMDR) published in the Federal Register on February 14, 2014. In addition, your firm will need to establish an eMDR account in order to submit MDRs electronically. Information about the Final Rule for eMDR and the eMDR set-up process can be found on the FDA website at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/Repo

If your firm wishes to discuss MDR reportability criteria or to schedule further communications, it may contact the Reportability Review Team by email at ReportabilityReviewTeam@fda.hhs.gov.

Given the serious nature of the violations of the Act, devicesmanufactured by your firm are subject to refusal of admission under section 801(a) of the Act, 21 U.S.C. § 381(a), in that they appear to be adulterated. As a result, FDA is taking steps to refuse entry of these devices into the United States, known as “detention without physical examination,” until these violations are corrected. In order to remove the devices from detention, your firm should provide a written response to this Warning Letter as described below and correct the violation(s) described in this letter. We will notify you regarding the adequacy of your firm’s response(s) and the need to re-inspect your firm’s facility to verify that the appropriate corrections and/or corrective actions have been made.

Also, U.S. federal agencies may be advised of the issuance of Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected.

Please notify this office in writing, within fifteen business days from the date you receive this letter, of the specific steps your firm has taken to correct the noted violations, including an explanation of how your firm plans to prevent these violations, or similar violations, from occurring again. Include documentation of the corrections and/or corrective action (which must address systemic problems) that your firm has taken. If your firm's planned corrections and/or corrective actions will occur over time, please include a timetable for implementation of those activities. If corrections and/or corrective actions cannot be completed within fifteen business days, state the reason for the delay and the time within which these activities will be completed. Please provide a translation of documentation not in English to facilitate our review. We will notify you regarding the adequacy of your firm's response(s) and the need to re-inspect your firm's facility to verify that the appropriate corrections and/or corrective actions have been made.

Your firm's response should be sent to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Field Inspections Support Branch, White Oak Building 66, Rm 3540, 10903 New Hampshire Ave., Silver Spring, MD 20993. Refer to CMS Case No. 500732 when replying. If you have any questions about the contents of this letter, please contact Daniel Walter, Chief, Foreign Enforcement Branch, at feb@fda.hhs.gov (email), or +1(240) 402-4020 (telephone).

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your firm's facility. It is your firm's responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, FDA 483, issued at the close of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality management systems. Your firm should investigate and determine the causes of the violations, and take prompt actions to correct the violations and bring the products into compliance.

Sincerely yours,
/S/
CAPT Sean M. Boyd, MPH, USPHS
Deputy Director for Regulatory Affairs
Office of Compliance
Center for Devices and Radiological Health

Cc.
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