WARNING LETTER

OriGen Biomedical, Inc.

MARCS-CMS 569074 — 20/12/2018

Delivery Method:

United Parcel Service

Product:

Medical Devices

Recipient:

Richard L. Martin
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Issuing Office:

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WARNING LETTER
CMS# 569074

UNITED PARCEL SERVICE
OVERNIGHT DELIVERY

December 20, 2018

Richard L. Martin, President
OriGen Biomedical, Inc.
7000 Burleson Rd., Bldg. D
Austin, TX 78744

Dear Mr. Martin:

During an inspection of OriGen Biomedical, Inc., located in Austin, TX, conducted from June 11 to July 5, 2018, an investigator from the United States Food and Drug Administration (FDA) determined that your firm is a manufacturer of duel lumen catheters including the Reinforced Dual Lumen ECMO Catheter. 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 any function of the body.

This inspection revealed that your 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. You may find the Act and FDA's regulations through links in FDA's home page at http://www.fda.gov/.

Our investigator issued a Form FDA-483, Inspectional Observations, to you on July 5, 2018. We acknowledge our meeting of August 3, 2018 and your written responses dated July 19, September 17, and October 15, 2018 concerning our investigator's observations noted on the form FDA 483 that was issued to your firm. We address these responses below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. Failure to establish procedures to control product that does not conform to specified requirements as required by 21 CFR 820.90(a) and documentation of rework and reevaluation activities does not include a determination of whether there has been any adverse effect from rework upon the product as required by 21 CFR 820.90(b)(2). For example, VV13F Dual Lumen Catheter, lot N18687 was reworked in 2015. The catheters failed endotoxin testing but were released and distributed. The

rework also included a second EO sterilization and there is no documentation demonstrating that this additional sterilization did not adversely affect the catheters.

Your responses fail to provide the specific steps you are taking to assure that only product that has met acceptance criteria are distributed. In addition, your response fails to provide documentation that you have verified the corrective actions have been effective. We acknowledge your voluntary recall of lot N18687.

2. Failure to establish and maintain procedures to control all documents that are required by 21 CFR 820.40. For example:

a. Your production drawings for all catheter sizes did not include the requirement to include **(b)(4)** in the resin used to manufacture the catheters.
b. Drawing **(b)(4)** had incorrect dimensional markings on the catheter tip.

Your response fails to provide documentation that you have verified the corrective actions have been effective. We acknowledge your voluntary recall of the implicated catheter.

Our inspection also revealed that your firm's Reinforced Dual Lumen ECMO catheter and components 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 respecting the device 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:

1. Failure to submit a report to FDA 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 may have caused or contributed to a death or serious injury, as required by 21 CFR 803.50(a)(1). For example,

a. The information included from Complaint PCR-No. **(b)(4)** describes a patient's death following the use of your firm's catheter. There is no information included in your firm's complaint file that justifies that the device may not have caused or contributed to the death. As such, the complaint meets the criteria for reportability. Your firm became aware of the event on August 1, 2016 but didn't submit an MDR for the referenced event.

b. The information included from Complaint **(b)(4)** reasonably suggests that patients experienced serious injury (e.g. atrial perforation) following the use of your firm's catheter that necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. There is no information included in your firm's complaint files that justifies that the device may not have caused or contributed to the referenced serious injuries. Your firm became aware of the event referenced for **(b)(4)** on September 12, 2014 and on May 30, 2017 for the event referenced for **(b)(4)**. An MDR for each referenced event was not submitted.

Your firm's response dated July 19, 2018 is not adequate. In your firm's response it noted that it plans to develop its complaint process to better define MDR reporting requirements. However, it did not provide evidence of the adequate corrective actions, including a retrospective review of relevant adverse events in accordance with its revised MDR process.

Your firm's response dated September 17, 2018 is not adequate. In your firm's response it noted that it plans to develop a separate MDR procedure, QP65 and that the corresponding MDRs were submitted to FDA via registered mail on August 15, 2018. Your firm did not provide evidence of the adequate corrective actions, including a retrospective review of relevant adverse events in accordance with its revised MDR process, and electronic reports for the corresponding reportable events. Please note that per the eMDR rule dated 2014 (https://www.gpo.gov/fdsys/pkg/FR-2014-02-14/pdf/2014-03279.pdf) manufacturers are required to submit MDRs electronically to FDA.

Your firm's response dated October 15, 2018 is not adequate. Your firm indicated that its consultant was unaware of the electronic submission requirements and plans to submit the referenced MDRs electronically by October 30, 2018. However, your firm did not provide evidence of the relevant corrective actions, including a retrospective review of all adverse events in accordance with its revised MDR process.

2. Failure to submit a report to FDA 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 ora similar device that it 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 Complaint **(b)(4)** reasonably suggests your firm's catheter malfunctioned (e.g. tube disconnection) while in use. Per the 1995 Preamble, a malfunction is reportable if the manufacturer takes, or would be required to take, an action under section 518 or 519(g) of the FD&C as a result of the malfunction of the device or other similar devices. (Refer to 1995 Federal Register Volume 60, Number 237, Page 63585. Please note that the preamble reference is section 519(f), but the appropriate designation for the section is now section 519(g) due to amendments to the FD&C Act). FDA determined that your firm's field action Z-1456-2015 conducted for its same catheter device met the criteria under the 1995 Preamble. There is no information included for the complaint that justifies that the malfunction would not be likely to cause or contribute to a death or serious injury, if it were to recur. Your firm became aware of the event on April 2, 2015 but didn't submit an MDR for the referenced event.

Your firm's response dated July 19, 2018 is not adequate. Your firm planned to develop its complaint process to better define MDR reporting requirements. However, your firm did not provide evidence of the adequate corrective actions, including a retrospective review of relevant adverse events in accordance with its revised MDR process.

Your firm's response dated September 17, 2018 is not adequate. Your firm stated that it planned to develop a separate MDR procedure QP65 and the corresponding MDRs were submitted to FDA via registered mail on August 15, 2018. However, your firm did not provide evidence of the adequate corrective actions, including a retrospective review of relevant adverse events in accordance with its revised MDR process. Additionally, please note that manufacturers are required to submit MDRs electronically to FDA, unless they have received a waiver or exemption from FDA that allows them to continue to use the paper form for a specific period of time.

Your firm's response dated October 15, 2018 is not adequate. Your firm indicated that its consultant was unaware of the electronic submission requirements and planned to re-submit the referenced MDRs electronically by October 30, 2018. However, your firm did not provide evidence of the adequate corrective actions, including a retrospective review of relevant adverse events in accordance with its revised MDR process and evidence that it implemented a process for electronic submission of MDR reportable events to FDA.

3. Failure to adequately develop,maintain and implement written MDR procedures, as required by 21 CFR 803.17. For example, after reviewing your firm's MDR procedure titled **(b)(4)** QP64", Version 1, undated, the following deficiencies were noted:

a. There is no evidence that QP64, Rev. 1 has been implemented. For example, there is no effective date for your firm's MDR procedure.

b. QP64, Rev. 1 does not establish internal systems that provide for timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements, as required by 21 CFR 803.17(a)(1). For example, the procedure omits the definition of the term "reasonably suggests," found in 21 CFR 803.20(c)(1). The exclusion of the definitions for this term from the procedure may lead your firm to make an incorrect reportability decision when evaluating a complaint that may meet the criteria for reporting under 21 CFR 803.50(a).

c. QP64, Rev. 1 does not establish internal systems that provide for timely transmission of complete medical device reports, as required by 21 CFR 803.17(a)(3). Specifically, the following are not addressed:

1. Although the procedure includes references to 30 day reporting, it does not specify calendar days.

2. The procedure does not 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. 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/Postmarke...

d. QP64, Rev. 1 does not describe how your firm will address documentation and record- keeping requirements, as required by 21 CFR 803.17(b), including:

1. 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.

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

Your firm's responses dated July 19, 2018, September 17, 2018, and October 15, 2018 did not address the deficiencies noted above.

In addition, our inspection revealed that the dual lumen catheters 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 respecting the device that is required by or under section 519 of the Act, 21 U.S.C. § 360i, and 21 CFR Part 806 – Medical Devices; Reports of Corrections and Removals. Significant violations include, but are not limited to, the following:

1. Failure to submit a written report to FDA of any correction or removal of a device initiated by such manufacturer if the correction or removal was initiated to reduce a risk to health posed by the device or remedy a violation of the act caused by the device which may present a risk to health within 10-working days of initiating such correction or removal, as required by 21 CFR 806.10. For example,

a. The Medical Device Market Withdrawal dated April 1, 2015, recommends to discontinue the use of all OriGen VV19F Reinforced Dual Lumen ECMO Catheters for Lot N18394. The document indicates that "serious injuries could occur due to the failure mode associated with this recall." As such, the Medical Device Market Withdrawal meets the criteria for a correction or removal, and your firm initiated the recall on April 1, 2015, but didn't submit an 21 CFR 806 report for this recall until August 2, 2018.

b. You sent Technical Bulletin, 1411, in July 2015, notifying customers that specific lots of the Reinforced Dual Lumen ECMO catheters in different sizes were not manufactured with barium sulfate additive, as intended per your specifications. Technical Bulletin 1411 meets the criteria for a correction or a removal as defined in 21 CFR 806. However, this recall was not reported to FDA until August 2, 2018. While the 2018 recall included additional sizes and lots that were not included on the Technical Bulletin 1411, the 2018 recall does not appear to include VV19F Lot N18447-1B.

c. In January 2017, you sent Technical Bulletin, 17.01, notifying customers that you identified a potential mechanism that may cause damage to the OriGen Reinforced Dual Lumen catheter affecting all lots. The bulletin indicated that forcefully rotating the clamp while it is in place may potentially cause an immediate disconnect of the clear tube or lead to a later fatigue failure of the adhesive bond, with subsequent clear tube disconnect from the hub. You notified FDA of the recalls of VV13F Lot N18549 on April 14, 2015, VV28F Lots N18487 and N18487-1 on August 14, 2017, and VV19F Lot N18394 on August 2, 2018. However, you have not reported this recall for the VV16F, VV23F, and VV32F Reinforced Dual Lumen Catheters.

Your firm's responses dated July 19, 2018, September 17, 2018, and October 15, 2018, are not adequate. In your firm's responses, it noted that you have recalled all items mentioned in Observation 1. While you submitted a recall (Z-0179-2019 – Z-0184-2019) for lack of barium sulfate on August 11, 2018, this recall did not include Lot N18447-1B for lack of barium sulfate, which was referenced in Technical Bulletin 1411. In addition, you submitted 3 recalls (Z-1456-2015, Z-0021-2018, Z-0269-2019) regarding the potential for the clear extension tube to separate from the hub for VV13F Lot N18549 on April 14, 2015, VV28F Lots N18487 and N18487-1 on August 14, 2017, and VV19F Lot N18394. However, Technical Bulletin 17.01 indicates that all OriGen Reinforced Dual Lumen catheters are affected, and a recall has not been submitted for your VV16F, VV23F, and VV32F catheters. In addition, you revised your procedures, but the revised procedures do not indicate to report corrections or removals to FDA within 10 days of initiating such action. In addition, the responses did not provide evidence of the adequate corrective actions, including a retrospective review of relevant technical bulletins and customer communications to determine reportability in accordance with 21 CFR 806.

Your firm should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction, and civil money penalties. Also, 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 violations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

Please notify this office in writing within fifteen (15) business days from the date you receive this letter of the specific steps your firm has taken to correct the noted violations, as well as 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 actions (including any systemic corrective actions) 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. Your firm's response should be comprehensive and address all violations included in this Warning Letter.

Your written response should be sent to the Office of Medical Devices and Radiological Health Division 3 via E-mail correspondence to ORADevices3FirmResponse@fda.hhs.gov. Refer to the Unique Identification Number (CMS Case # 569074) when replying. If you have any questions about the content of this letter, please contact Compliance Officer, Russell A. Campbell via email at russella.campbell@fda.hhs.gov or by phone at (510) 337-6861.

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,
/S/

Shari J. Shambaugh
Program Division Director
Office of Medical Device and Radiological Health
Division 3

Content current as of:
06/04/2019

Regulated Product(s)
Medical Devices

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