WARNING LETTER

Hologic, Inc.

MARCS-CMS 698214 — DECEMBER 18, 2024

Delivery Method:
VIA Electronic Mail
Product:
Medical Devices

Recipient:
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Issuing Office:
Center for Devices and Radiological Health
United States

WARNING LETTER
CMS # 698214

December 18, 2024

Dear Mr. MacMillan:

During an inspection of your firm located in Marlborough, MA on July 30, 2024, through September 24, 2024, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures class II implantable radiographic markers, such as your BioZorb product line. 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 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 Adam Gorzeman, Senior Director BSH Quality, dated October 15, 2024, concerning our investigator's observations noted on the Form FDA 483 (FDA 483), List of Inspectional Observations, that was issued to your firm. We are aware that Hologic has made the decision to discontinue the manufacture of the BioZorb product line. We address your response below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. Failure to establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met, as required by 21 CFR 820.30(a). You did not implement your Design Control Procedures, including Design Control SOP0018 dated 01/31/2017, Product Development Procedure ENG0100 dated 03/19/2024 and User Needs and Intended Use Statement Procedure ENG-0100-02 dated 04/21/2022. Specifically:

a. You failed to establish design inputs to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient, as required by 21 CFR 820.30(c). The design history file for the BioZorb medical device product family:
• Did not identify the intended patient population, nor did it address intended anatomy types, nor the surgical requirements such as the appropriate placement and fixation of the device, nor the appropriate depth of the implant into the soft tissue.
• Did not include a requirement related to how in-vivo radiation treatments can impact the performance of the device and the ability of the device to resorb into the patient's body.
• Did not define the length of time for when the spacer material would be completely resorbed.

b. You failed to verify your device design to confirm that the design output meets the design input requirements, as required by 21CFR 820.30(f).
• Your firm does not have any verification testing to demonstrate that the bioabsorbable spacer material (poly lactic acid) is absorbed by the body. Your Design Description Document DDD-0001 dated August 22, 2017, includes a user requirement that the BioZorb medical device spacer material is resorbable into soft body tissue. Your verification testing report, VER-10394 dated June 27, 2022, only documents the inherent viscosity profile of the spacer during in-vitro degradation and does not provide sufficient data to support the claim that that spacer material is absorbed by the body. Your firm received complaints and filed Medical Device Reports regarding devices requiring explant and a lack of resorption, including Hologic Complaint Report CPT-01345922 which stated that the device failed to dissolve for almost five (5) years.

c. You failed to validate your device design to ensure that devices conform to defined user/patient needs and intended uses, as required by 21 CFR 820.30(g).
• Your Design Validation studies performed under Marker Simulated Use Test Report TR-004 Rev P dated 08/17-20/2018 and Marker Simulated Use Test Report TR-004 Rev L dated 02/09/2016 did not take the following critical user needs into account: variation in soft tissue types, anatomies of the patient population, the appropriate placement and fixation of the device into the patient, nor the appropriate depth of the implant into the soft tissue.

d. You failed to ensure that the device design is correctly translated into production specifications, as required by 21 CFR 820.30(h).
• The production of the devices was transferred to Costa Rica in November of 2022 after the quality system was updated to include BioZorb medical devices. Your Design History File does not include documentation that the device design was appropriately translated into production specifications and does not include identification of the product undergoing transfer and design review as required by Design Control SOP0018 dated 03/01/2011 and current Product Development Procedure ENG0100 dated 03/19/2024.

We reviewed your firm's response and concluded that it is not adequate. We are aware that The BioZorb Product Line was put on Stop Ship Notice on September 29, 2024, and Hologic will not continue to manufacture the BioZorb product. We also understand that you will not be performing any specific design studies to address the above deficiencies. FDA continues to have safety concerns for patients in whom this device has been implanted. You have not appropriately evaluated your device design to ensure the following risks are mitigated for patients that already have the Biozorb device implanted, such as and not limited to: the potential of device interference with detection of cancer recurrence or new cancers; whether in-vivo radiation treatments can impact the performance of the device; and the ability of the device to resorb into the patient's body. Your firm should address the contribution of the device design to adverse events and identify those patients who may be at risk for adverse events and therefore potentially benefit from intervention by device explantation.

Additionally, you will be reviewing and revising design control procedures that focus on your remaining BSH products. However, your response does not yet include the documentation that includes your retrospective review of your BSH products and any remediation efforts that may be warranted after this review is completed.

2. Failure to establish and maintain procedures for implementing corrective and preventive actions, including requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems

using appropriate statistical methodology, as required by 21 CFR 820.100(a)(1). Specifically, your Corporate Corrective Action Preventive Action (CAPA) Procedure CORP-00007, Rev. 007 is not adequate. For example:

• Your review of quality data was not sufficient to detect recurring problems. For example, in September of 2023, your firm received a spike of adverse event complaints regarding breast discomfort/pain, erythema, itching sensation, burning sensation, infection, scar tissue, sleep dysfunction, seroma, necrosis, additional surgery/device explantation, medication/scanning required, deformity/ disfigurement, migration, device palpability, and tissue damage/skin erosion. Your CAPA procedure only defines opening a CAPA if the severity of risk is considered high which the procedure defines as a severity level of 4 (critical) or 5 (catastrophic). Your firm's management stated there is no justification for this rationale and a CAPA was not opened until May of 2024, to investigate the root cause of the adverse events that may not have risen to a severity level of 4 or 5.

• You did not calculate the occurrence rate accurately when evaluating a spike of BioZorb medical device complaints and Medical Device Reports. Your Health Risk Assessment RSK-04622, dated March 8, 2024, does not take the patient population into account as required by Health Risk Assessment (HRA) procedure QUA-2364, dated August 14, 2020. This Assessment utilized units sold from 2016 to 2024 whereas the complaint data utilized in this review was from 2021 to 2024. Your procedure, QUA-3106, Investigation of Post Market Surveillance Spikes and Adverse Trends, step 7.2.3. discusses occurrence estimation and includes, "**(b)(4)**." Neither the above referenced procedures, or your CAPA procedure, provide sufficient instructions for calculating an accurate occurrence rate when complaint spikes and adverse trends are identified, nor do they clearly define when a CAPA should be opened.

We reviewed your firm's response and concluded that it is not adequate. We understand that you will be reviewing and revising your CAPA procedures moving forward. However, you have not described how you will be able to prevent this lack of oversight of your implementation of CAPA procedures in the future.

Our inspection also revealed that your firm's BioZorb Marker is 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 violations include, but are not limited to, the following:

Failure to submit a report to FDA no later than 30 calendar days after the day that the firm received or otherwise became aware of information, from any source, that reasonably suggests that a device that the firm markets may have caused or contributed to a death or serious injury, as required by 21 CFR 803.50(a)(1).

The information provided in the Complaint Reports CPT-00635201, CPT-00661454, CPT-00624611, CPT-00732163, and CPT-00775690 reasonably suggests that patients developed infections following the implantation of your firm's BioZorb Marker, needing antibiotic treatment and in some cases, surgical device explantation. We believe these medical or surgical interventions were needed to preclude permanent impairment of a body function or permanent damage to a body structure. Furthermore, there is no information in your firm's complaint records that definitively rules out that the device may have been a factor in these serious injuries. As such, each of the referenced adverse events represents an MDR reportable serious injury event, as defined in 21 CFR 803.3. Your firm became aware of the events associated with CPT-00635201 on February 4, 2020, CPT-00661454 on April 14, 2020, CPT-00624611 on January 17, 2020, CPT-00732163 on September 16, 2020, and CPT-00775690 on December 7, 2020.

However, your firm failed to submit an MDR for each referenced adverse event within the required 30-calendar-day timeframe.

The adequacy of your firm's response dated October 15, 2024, cannot be determined at this time.

In the response, your firm states that it has initiated corrective actions to address the underlying root causes and plans to conduct a retrospective review of all BioZorb complaints for reportability. The response also noted your firm **(b)(4)**. However, your firm did not provide documentation or evidence of implementation of its systemic corrective actions as the planned corrective actions are still ongoing.

Our inspection also revealed that your firm's BioZorb Sizer Set accessory devices 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:

Failure to submit any report required within 10 working days of initiating a correction or removal, as required by 21 CFR 806.10. For example: your firm conducted a correction of your BioZorb Sizer Set accessory device which can lead to probability of a serious adverse health consequence or death occurring as a result of using the device(s) under review is “reasonable”. You sent a customer notification letter to your customers instructing them to 1) immediately steam autoclave F0101 in accordance with the revised IFU sterilization parameters, and 2) when sterilizing the F0101, do not use the 2 layers or one layer of 2-ply wrap to provide a sterile barrier for each sterilization tray. The IFU supplied for these instructions for the sizers within F0101 has not yet been updated to reflect this change. This action meets the definition of a medical device correction or removal initiated to remedy a violation which may present a risk to health, for which you are required to submit a Report of Correction or Removal to FDA. As of 11/26/2024, your firm submitted a Medical Device Report of Correction or Removal to FDA for this action.

Your firm’s response(s) to the FDA-483, dated 10/15/2024, is adequate. You submitted a Report of Correction or Removal to FDA as of 11/26/2024. However, your response does not contain evidence of completion of the updated procedures and documents. We recommend updating your procedures to follow the requirements under 21 CFR Part 806 Medical Devices; Reports of Corrections and Removals to ensure compliance; and recommend using the guidance provided by the 21 CFR Part 7 Recall Policy to ensure that all required information is provided or documented. In addition, we further recommend that you conduct health risk assessments following the definition of risk to health in 21 CFR 806.2(j), to support the reporting decisions for future medical device corrections or removals.

Your firm should take prompt action to address any violations identified in this letter. Failure to adequately address this matter 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.

Other federal agencies may take your compliance with the FD&C Act and its implementing regulations into account when considering the award of federal contracts. Additionally, should FDA determine that you have Quality System regulation violations that are reasonably related to premarket approval applications for Class III devices, such devices will not be approved until the violations have been addressed. Should FDA determine that your devices or facilities do not meet the requirements of the Act, requests for Certificates to Foreign Governments (CFG) may not be granted.

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 address 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 (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. Your firm’s response should be comprehensive and address any violations included in this Warning Letter. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration as part of your response.

Your firm’s response should be sent by email to CDRHWarningLetterResponses@fda.hhs.gov to the attention of Gina Brackett, Assistant Director, Establishment Assessment Team 1. Refer to CMS case #698214 when replying. If you have any questions about the contents of this letter, please contact: Karen Archdeacon, Compliance Officer, at (781-587-7491) or karen.archdeacon@fda.hhs.gov.

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 any violations and take prompt actions to address any violations and bring the products into compliance.

Sincerely yours,
/S/

RDML Sean M. Boyd, MPH, USPHS
Director
Office of Regulatory Programs

Office of Product Evaluation and Quality
Center for Devices and Radiological Health

CC: Adam Gorzeman, Senior Director BSH Quality, **(b)(4)**

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