WARNING LETTER

BioStem Life Sciences

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Reference #:

CBER 25-673788

Product:

Biologics

Recipient:

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Issuing Office:

Center for Biologics Evaluation and Research (CBER)

United States

WARNING LETTER

January 17, 2025

CBER 25-673788

Dear Mr. Matuszewski:

The United States Food and Drug Administration (FDA) inspected your facility, located at the above address, between September 11, 2023, and September 15, 2023. During the inspection, FDA documented that your company manufactures cellular products derived from human umbilical cord, including those labeled as Product 401 (OROPRO®), Product 403 (PROVISCUS®), and Product 404 (NEOFYL®) as well as an amniotic membrane combined with amniotic fluid product labeled as RHEO® (collectively, “your products”).

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) requirements, including violations of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 351(a)(2)(B), and 21 CFR parts 210 and 211. Because your methods, facilities, or controls for manufacturing, processing, packing, or holding drugs do not conform to CGMP, your products are adulterated within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. § 351(a)(2)(B). Your adulteration of your products while held for sale after shipment in interstate commerce, or the causing thereof, is a prohibited act under section 301(k) of the FD&C Act, 21 U.S.C. § 331(k).

Based on information and records reviewed by FDA, your products are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or conditions in humans and/or are intended to affect the structure or function of the body. For example,

- NEOFYL®
  - o "Instead of treating pain and injury with surgery and drugs, regenerative medicine supplements your body's own healing system with natural growth factors, cytokines, collagens, and other proteins. This array of components helps cushion and support damaged tissue and joints while providing structure and ideal microenvironment conditions for rebuilding."
  - o "The umbilical cord contains a collagenous matrix that is rich in hyaluronic acid, growth factors, and other cytokines. These elements are reported to have anti-inflammatory, anti-bacterial, and anti-scarring properties, making umbilical cord tissue an attractive biomaterial for use in an outpatient clinic or surgical procedures."
- OROPRO®
  - o "Regenerative medicine harnesses your body's own ability to heal and boosts it in a very powerful and effective way."
  - o "Umbilical cord and Wharton's jelly allografts demonstrate anti-inflammatory, anti-bacterial and anti-fibrotic properties that support repair of damaged tissue."
- PROVISCUS®
  - o "Instead of treating pain and injury with surgery and drugs, regenerative medicine supplements your body's own healing system with natural growth factors, cytokines, collagens, and other proteins."
- RHEO®
  - o "RHEO® is a human perinatal tissue allograft derived from the extracellular matrix of the amniotic membrane. It is aseptically processed to preserve the endogenous cytokines, growth factors and scaffolding proteins present within the amniotic tissue matrix… By supplementing damaged tissue with these factors, you can stimulate the same scaffold creation naturally found in the body and allow the tissue to 'self-heal'."

Therefore, your products are drugs as defined in section 201(g)(1) of the FD&C Act, 21 U.S.C. § 321(g)(1), and biological products as defined in section 351(i) of the Public Health Service Act (PHS Act), 42 U.S.C. § 262(i).

Your cellular products derived from human umbilical cord labeled as Product 401 (OROPRO®), Product 403 (PROVISCUS®), and Product 404 (NEOFYL®) as well as an amniotic membrane combined with amniotic fluid product labeled as RHEO® are also human cells, tissues, or cellular or tissue-based products (HCT/Ps) as defined in 21 CFR 1271.3(d) and are subject to regulation under 21 CFR part 1271, issued under the authority of section 361 of the PHS Act, 42 U.S.C. § 264. HCT/Ps that do not meet all the criteria in 21 CFR 1271.10(a) are not regulated solely under section 361 of the PHS Act and the regulations in 21 CFR part 1271. Unless an exception in 21 CFR 1271.15 applies, such products are regulated as drugs, devices, and/or biological products under the FD&C Act and/or the PHS Act and are subject to additional regulation, including applicable premarket review. Based on a review of relevant materials, Biostem Life Sciences does not qualify for any exception in 21 CFR 1271.15, and your products fail to meet all criteria in 21 CFR 1271.10(a).

For example, your cellular products derived from human umbilical cord labeled as Product 401 (OROPRO®), Product 403 (PROVISCUS®), and Product 404 (NEOFYL®) as well as an amniotic membrane combined with amniotic fluid product labeled as RHEO® fail to meet the minimal manipulation criterion set forth in 21 CFR 1271.10(a)(1) and defined for structural tissue in 21 CFR 1271.3(f)(1), because your processing alters the original relevant characteristics of the umbilical cord (of products OROPRO®, PROVISCUS® and NEOFYL®) and amniotic membrane (of RHEO®) related to their utility for reconstruction, repair, or replacement. The processing of the umbilical cord from the form of a conduit into an injectable form drastically alters the physical state of the HCT/P. The umbilical cord is more than minimally manipulated because such processing alters the original relevant characteristics of the HCT/P relating to its utility to serve as a conduit by effectively altering or eliminating its physical integrity and tubular form. The processing of the amniotic membrane from the form of a sheet into an injectable form drastically alters the physical state of the HCT/P. The amniotic membrane is

more than minimally manipulated because such processing alters the original relevant characteristics of the HCT/P relating to its utility to serve as a barrier by effectively altering or eliminating its physical integrity, tensile strength, and elasticity.

In addition, your products fail to meet the criterion that the HCT/Ps be "intended for homologous use only," which means that the "labeling, advertising, or other indications of the manufacturer's objective intent" demonstrate that the HCT/P is intended to perform "the same basic function or functions in the recipient as in the donor." 21 CFR 1271.3(c) and 1271.10(a)(2). Your products are not intended solely to perform the same basic function or functions of the HCT/P in the recipient as in the donor (e.g., serving as a conduit for umbilical cord or serving as a barrier for amniotic membrane). Rather, your products are intended for use in treating damaged tissues and joints, which are not basic functions of the umbilical cord and amniotic membrane in the donor.

Therefore, these HCT/Ps are not regulated solely under section 361 of the PHS Act, 42 U.S.C. § 264, and the regulations in 21 CFR part 1271.[1] See 21 CFR 1271.20. In addition to being regulated under section 361 of the PHS Act and 21 CFR part 1271, your products are regulated as drugs as defined in section 201(g)(1) of the FD&C Act, 21 U.S.C. § 321(g)(1), and biological products as defined in section 351(i) of the PHS Act, 42 U.S.C. § 262(i), as stated above.

Subject to certain exceptions not applicable here, to lawfully introduce or deliver for introduction into interstate commerce a drug that is a biological product, a valid biologics license application (BLA) must be in effect under section 351(a)(1) of the PHS Act, 42 U.S.C. § 262(a)(1). Such licenses are issued only after showing that the product is safe, pure, and potent. Your products are not the subject of an approved BLA.

CGMP Violations

FDA's inspection of your facility documented evidence of significant CGMP violations. At the conclusion of the inspection, FDA investigators issued a Form FDA-483, List of Inspectional Observations (Form FDA-483). FDA identified additional significant violations upon further review of the evidence collected during the inspection, as set forth below.

The CGMP violations applicable to your products include, but are not limited to, the following:

1. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas to prevent contamination [21 CFR 211.42(c)(10)(iv)]. For example,

a. Your firm has not performed routine (i.e., during every production batch) non-viable particulate monitoring and surface sampling of the critical area (i.e., **(b)(4)** where your products are exposed to the environment). The environmental monitoring frequencies described in SOP QCD-034 titled, "Environmental Controls and Monitoring Procedure" (Effective date: December 12, 2022) are not sufficient to detect potential environmental contamination risks and demonstrate control inside the critical manufacturing area during manufacturing.

b. Your firm does not require microbiological monitoring of operators' arm coverings used in the critical aseptic processing area for manually processing your products.

2. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions [21 CFR 211.42(c)(10)(v)]. For example, your firm has failed to validate your procedure for cleaning and disinfecting the ISO 5 **(b)(4)** and supporting ISO 7 cleanroom where your products are manufactured. Validation of a cleaning process is needed to verify suitable cleaning and disinfecting agents are used to remove potential microbial contaminants from the critical manufacturing areas where your products are exposed during manufacturing.

3. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)]. For example, your firm has not adequately validated your manufacturing processes for your products with respect to identity, strength, quality, and purity. Your testing is limited to **(b)(4)**. These are not sufficient measures of identity, strength, quality, and purity.

Process validation studies determine whether an initial state of control has been established while routine monitoring of process performance and product attributes determines whether control is maintained. Establishment of appropriate attributes relating to identity, strength, quality, and purity of drug products is essential for assuring product quality over the product lifecycle.

4. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)]. The review of batch records and procedure QAD-040 titled "Product Release" (Effective date: September 5, 2023) indicate final product testing is limited to sterility testing and endotoxin testing as measurements of product attributes and such testing does not demonstrate, for example, the identity and/or strength of your products.

5. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates [21 CFR 211.166(a)]. For example, your firm assigned expiration dates between **(b)(4)** months to your products without adequate supporting data that conform to appropriate standards of identity, strength, quality, and purity. For example, your expiration summary reports for RHEO® is limited to **(b)(4)** sterility testing only while Product 401 (OROPRO®) is limited to **(b)(4)** sterility and endotoxin testing. Product 403 (PROVISCUS®) and Product 404 (NEOFYL®) are limited to Hyaluronic Acid concentration only. Appropriate standards of identity, strength, quality, and purity during intervals through the expiry period are needed to ensure product attributes remain for the shelf life of the product.

Responses to the Form FDA-483

We acknowledge receipt of your correspondences dated September 29, 2023; October 13, 2023; October 27, 2023; November 10, 2023; November 28, 2023; December 8; 2023; December 22, 2023; January 5, 2024; January 9, 2024; February 29, 2024 and September 3, 2024 that provide a response to FDA's inspectional observations and describe certain corrective actions. We have reviewed your responses and represented corrective actions and have found that they are inadequate. While you assert that your products were manufactured under section 361 of the PHS Act (and thus are not subject to cGMP regulations), the available evidence shows that your products do not meet the relevant criteria to be regulated solely under section 361 of the PHS Act. We acknowledge your commitment to submit a Pre-Request for Designation to FDA by February 29, 2024; however, this process remains incomplete, for you have not responded to the agency's request for additional information. According to your correspondence, RHEO®, OROPRO®, and 403/404 products have been removed from the market and shall no longer be manufactured by your firm. Your responses do not describe actions you have taken or plan to take to address the impact of the above-described CGMP deficiencies on your distributed products that carry a **(b)(4)**-month shelf life and remain within expiry.

Additional Concern

In addition to the violations described above, we offer the following comment:

- We note that the Instructions for Use for each of your products state, "This allograft is processed aseptically, but is not sterile." If your products are not sterile, FDA has serious safety concerns regarding their use on patients via injection.[2] FDA expects injectable products to be sterile, consistent with basic quality standards and to ensure patient safety.[3] Be advised that, under 21 CFR 211.113(b), appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed, including validation of aseptic and sterilization processes. Please address this issue in your response.

Conclusion

Neither this letter nor the observations noted on the Form FDA-483, which were discussed with you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies that may exist in connection with your products. You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure full compliance with all applicable requirements in the FD&C Act, PHS Act, and all applicable regulations.

This letter notifies you of our concerns and provides you an opportunity to address them. Failure to adequately address these matters may result in action without further notice including, without limitation, seizure and/or injunction.

Please submit your response in writing within fifteen (15) working days from your receipt of this letter, outlining the specific steps you have taken or plan to take to address any violations and prevent their recurrence. Include any documentation necessary to show that the matters have been addressed. If you cannot address these matters within fifteen (15) working days, please explain the reason for your delay and the timeframe for completion. If you do not believe your products are in violation of the FD&C Act, PHS Act, or applicable regulations, include your reasoning and any supporting information for our consideration.

Send your electronic response to CBERDCMRecommendations@fda.hhs.gov. If you have questions regarding this letter, contact the Division of Case Management, CBER at (240) 402-9156.

Sincerely,
/S/

Melissa J. Mendoza
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

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1 Because your products fail to meet at least one criterion in 21 CFR 1271.10(a), this letter does not address whether this product meets other criteria in 21 CFR 1271.10(a).

2 The preparation instructions in the IFUs for your products state, “Apply the allograft using an 18g or larger needle. If applied topically, utilize aseptic technique and caution.” While intravenous or intrathecal application are contraindicated, injection is not contraindicated.

3 See, e.g., USP<1> (“Parenteral articles are prepared scrupulously by methods designed to ensure that they meet Pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of the growth of microorganisms.”).

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