Amniotic Therapies LLC. 8/17/16

Department of Health and Human Services

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

WARNING LETTER
AUG 17, 2016

CBER-16-03

UPS EXPRESS MAIL & ELECTRONIC MAIL

Mr. Bryant Gaines
Chief Executive Officer
Amniotic Therapies, LLC
11496 Luna Road
Suite 800
Farmers Branch, TX 75234-9417

Dear Mr. Gaines:

During an inspection of your firm, Amniotic Therapies, LLC (Amniotic Therapies), located at 11496 Luna Road, Suite 800, Farmers Branch, TX 75234, conducted between March 23 and May 4, 2016, the United States Food and Drug Administration (FDA) found that your firm receives amniotic tissue that has been recovered from cesarean section births and processes the amnion, a structural tissue, from donors for allogeneic use. During the inspection, FDA further noted that your firm **(b)(4)** amniotic tissue to manufacture AlphaGEMS Micro and AlphaGEMS Nano products. In addition, FDA noted that your firm manufactures AlphaGEMS product by **(b)(4)** the amniotic tissue to produce **(b)(4)**.

Based on the labeling, advertising, or other indications of your objective intent available, for example, on your firm's website, AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano are intended for use, among other things, to enhance tissue healing and repair as, for example, adhesion barriers around nerve repairs and for chronic tendinosis, chronic tendinitis, intra-articular injection for chronic inflammatory disease, and intra-articular injection for degenerative joint disease. Accordingly, these products are drugs as defined under section 201(g) of the Federal Food, Drug,

and Cosmetic Act (the FD&C Act) [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the Public Health Service Act (PHS Act) [42 U.S.C. 262(i)].

These amniotic-based products (which your firm describes as morselized, **(b)(4)** are also human cells, tissues, or cellular or tissue-based products (HCT/Ps) as defined in 21 CFR 1271.3(d). However, the products are HCT/Ps that do not meet all of the criteria in 21 CFR 1271.10(a) and therefore do not qualify for regulation solely under section 361 of the PHS Act [42 U.S.C. 264] and the regulations in 21 CFR Part 1271. Specifically, the products do not meet the minimal manipulation criterion set forth in section 1271.10(a)(1) and defined for structural tissue in section 1271.3(f)(1), because the **(b)(4)** processes alter the original relevant characteristics of the structural tissue relating to the tissue's utility for reconstruction, repair, or replacement. In addition, these amniotic-based products do not meet the homologous use criterion set forth in 21 CFR 1271.10(a)(2) and defined in section 1271.3(c), because the labeling, advertising, or other indications of your objective intent available, for example, on your firm's website, indicate that these products are intended for use as an adhesion barrier and have numerous common applications related to "healing" and "repair," such as those noted above, which are not homologous uses of amniotic membrane. Homologous uses of amniotic membrane include covering, protecting, serving as a selective barrier for the movement of nutrients between the external and in utero environment, and retaining fluid in utero.

Please be advised that in order to lawfully market a drug that is also a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after a showing of safety and efficacy for the product's intended use. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an investigational new drug (IND) application in effect as specified by FDA regulations [21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312]. The AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano products are not the subject of an approved biologics license application (BLA), nor are there INDs in effect for any of these products.

Additionally, during the inspection, FDA investigators documented evidence of significant deviations from current good manufacturing practice (CGMP) in the manufacture of AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano products. These deviations from CGMP include deviations from the applicable requirements of Section 501(a)(2)(B) of the FD&C Act, Sections 351(a) of the PHS Act, and 21 CFR Parts 210 and 211.

At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, which FDA subsequently revised and issued to you in amended form on May 24, 2016. The inspection revealed a number of significant objectionable conditions relating to your firm's compliance with CGMP. These include, but are not limited to, the following:

1. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)]. For example:

a. Approximately 25 of **(b)(4)** vials of AlphaGEMS manufactured from amnion recovered from a single donor (lot# **(b)(4)**) on **(b)(6)**, were distributed and linked to four adverse events, including two infections from *Mycoplasma hominis.* Two unopened vials from the same lot were tested by an outside laboratory and confirmed positive for *M. hominis.* Even if AlphaGEMS is no longer labeled as sterile, the product purports to be sterile and is expected to be sterile by the nature of its intended use and method of administration. For example, your firm's website states that the product is "easy to inject" and "may be applied directly to interior or exterior wounds" or "damaged tissue." Furthermore, your firm's website states that AlphaGEMS undergoes sterility testing.

b. Environmental monitoring for the presence of microorganisms is not conducted during the manufacture of AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano. As with AlphaGEMS, AlphaGEMS Micro and AlphaGEMS Nano purport to be sterile by the nature of their intended uses and method of administration. Furthermore, the Amniotic Therapies website states that these products undergo sterility testing.

2. Failure to establish and follow 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) and (b)]. For example:

a. The manufacturing process has not been adequately validated for AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano.

b. Changes to the production processes for AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano have not been validated. Specifically, **(b)(4)** testing was conducted on **(b)(4)** lots of AlphaGEMS and **(b)(4)** lot of AlphaGEMS Nano which remained in inventory in response to reports of four adverse events for AlphaGEMS product. The additional testing was a change to the established production process and was not validated. Approximately **(b)(4)** vials from **(b)(4)** of the AlphaGEMS lots were subsequently distributed.

3. Failure to establish and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures [21 CFR 211.80(a)]. Specifically, there are no written procedures describing in sufficient detail the criteria for approval or rejection of amnion, based on the results of pre-processing cultures and supported by validation of the manufacturing process.

4. Failure to maintain laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include a determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products [21 CFR 211.160(b)].

5. Failure to test the AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano products, non-penicillin drug products, for the presence of penicillin although a reasonable possibility exists that the non-penicillin drug products have been exposed to cross contamination with penicillin [21 CFR 211.176]. Specifically, **(b)(4)** of approximately **(b)(4)** vials of AlphaGEMS Micro and approximately **(b)(4)** vials of AlphaGEMS from November 2015 to February 2016 and there is no documentation that testing for penicillin has been performed.

Additionally, FDA observed significant deviations in the manufacture of your amnion intermediates during the inspection. Specific areas of concern include, but are not limited to:

PRODUCTION AND PROCESS CONTROLS

6. Your firm has not adequately validated the manufacturing process for your amnion intermediates for AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano.

7. An **(b)(4)** was added to the production procedure for the manufacturing of your amnion intermediates for AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano in November 2015, in response to the reports of adverse reactions in September 2015. This process change was not validated.

8. Environmental monitoring for the presence of microorganisms is not conducted during the manufacture of the amnion intermediates for AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano.

9. There are not adequate written procedures that describe the in-process controls, and tests, or examinations to be conducted on the amnion intermediates for AlphaGEMS, AlphaGEMS Micro, and AlphaGEMS Nano, to assure batch uniformity and integrity.

CONTROL OF COMPONENTS

10. There are not adequate procedures for receipt, identification, storage, handling, sampling, testing, and approval or rejection of the following supplies and components used to **(b)(4)** the amnion intermediates.

a. **(b)(4)**
b. **(b)(4)**
c. **(b)(4)**

REVIEW OF YOUR INSPECTIONAL RESPONSES

We acknowledge receipt of your written response dated June 7, 2016, which responds to the inspectional observations on the Form FDA 483, and we have reviewed its contents. We have concluded that the response does not provide sufficient detail to fully assess the adequacy of your corrective actions. In addition, we have the following specific comments.

Form FDA 483 Observation 2

Your firm's process validation does not include an evaluation of incoming bioburden in order to set adequate acceptance criteria based on the capacity of your process. In addition, we note that a **(b)(4)** does not provide much assurance from the

introduction, transmission or spread of communicable disease, unless the incoming amnion has extremely low bioburden.

Form FDA 483 Observation 3
Your response noted that each lot of incoming amnion is tested for microorganisms, **(b)(4)**, and that the results are evaluated prior to distribution. However, the response does not specify rejection criteria for high bioburden and/or objectionable microorganism(s). Nor does your response describe Amniotic Therapies' plan to mitigate the potential for cross contamination when amnion with high bioburden and/or objectionable microorganisms is processed in the same facility with the same equipment.

Neither this letter, nor the observations listed on the Form FDA 483, is intended to be an all-inclusive list of your firm's deviations from applicable laws and regulations. It is your responsibility to ensure that your firm is in compliance with the provisions of the FD&C Act, PHS Act, and all applicable Federal laws and regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions may include seizure and/or injunction.

For further information about IND requirements, contact Dr. Patrick Riggins, Director of Regulatory Management Staff, Office of Cellular, Tissue, and Gene Therapies, at (240) 402-8346. Please include a copy of this letter with your initial submission to CBER.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted deviations and to prevent their recurrence. Include any documentation necessary to show that corrective action has been achieved. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., WO71 - G112, Silver Spring, MD 20993-0002. If you have any questions regarding this letter, please contact the Division of Case Management, CBER at 240-402-9155.

Sincerely,
/S/
Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research