



## DEPARTMENT OF HEALTH & HUMAN SERVICES

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

### ORDER TO CEASE MANUFACTURING, RECALL, AND DESTROY HCT/Ps

August 16, 2016

#### **HAND DELIVERED**

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

Dear Mr. Gaines:

Your establishment, Amniotic Therapies, LLC (Amniotic Therapies or establishment), located at 11496 Luna Road, Suite 800, Farmers Branch, TX, manufactures human cells, tissues, or cellular or tissue-based products (HCT/Ps).<sup>1</sup> The Food and Drug Administration (FDA or Agency) conducted an inspection of your establishment between March 23 and May 4, 2016, and at the conclusion of the inspection, the FDA investigator issued you<sup>2</sup> a Form FDA-483, List of Inspectional Observations.<sup>3</sup> Based on a review of these inspectional findings and other available information, FDA has found that there are reasonable grounds to believe that the HCT/Ps manufactured by Amniotic Therapies are violative HCT/Ps because they were manufactured in violation of Title 21, Code of Federal Regulations, Part 1271 (21 CFR 1271), issued under the authority of Section 361 of the Public Health Service Act (PHS Act) [42 United States Code (USC) 264] and, therefore, the conditions of manufacture of your HCT/Ps do not provide adequate protections against the risks of communicable disease transmission. Furthermore, FDA has determined that Amniotic Therapies is in violation of the regulations at 21 CFR 1271 and, therefore, does not provide adequate protections against the risks of communicable disease transmission. The Agency further concludes that there are reasonable grounds to believe the HCT/Ps manufactured by your establishment pose a danger to health. Accordingly, FDA issues this order to cease manufacturing, effective immediately, and

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<sup>1</sup> This order does not apply to the following products that are manufactured by Amniotic Therapies: AlphaGEMS, AlphaGEMS Nano, and AlphaGEMS Micro. Accordingly, references in this order to HCT/Ps do not include such products. FDA intends to communicate with Amniotic Therapies separately regarding these products.

<sup>2</sup> Throughout this order, “you” refers both to the establishment, and/or you personally, as well as in your capacity as Chief Executive Officer of the establishment, as appropriate.

<sup>3</sup> FDA issued the original Form FDA-483 on May 4, 2016, subsequently revised it, and issued an amended Form FDA-483 to you on May 24, 2016.

further orders the recall and destruction of HCT/Ps within five (5) working days from the date of receipt of this order, as set forth below.

Pursuant to 21 CFR 1271.440(a)(1) and (3), FDA hereby orders you to:<sup>4</sup>

1. Immediately cease all manufacturing of HCT/Ps until compliance with the regulations in 21 CFR 1271 has been achieved and you have been provided written authorization from FDA to resume operations. Under 21 CFR 1271.3(e), manufacture means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor;
2. Destroy all HCT/Ps that are in your possession; and
3. Within five (5) working days from the date of receipt of this order, recall, and destroy all HCT/Ps distributed since September 11, 2014, the date you began manufacturing HCT/Ps.

Please forward your consignee/customer notification letter to FDA (contact provided below) for review and approval prior to sending to your consignees/customers.

FDA's inspection and record review revealed significant noncompliance with the relevant federal regulations, including, but not limited to, the following violations,<sup>5</sup> some of which are recurring:<sup>6</sup>

## **CURRENT GOOD TISSUE PRACTICE VIOLATIONS**

### Process Validation

Failure to validate and approve a process according to established procedures where the results of processing cannot be fully verified by subsequent inspection and tests. The validation activities and results must be documented, including the date and signature of the individual(s) approving the validation. [21 CFR 1271.230(a)].

For example, you have failed to document adequate validation of the manufacturing processes that you perform on your HCT/Ps to ensure that contamination or cross-contamination does not occur during processing, and to ensure that processing prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

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<sup>4</sup> Neither this order, nor the observations listed on the Form FDA-483, are intended to be an all-inclusive list of your violations. FDA reserves the right to seek any and all other actions and remedies relating to the violations described in this order or any other violations.

<sup>5</sup> The following discussion of violations does not include FDA's evaluation of Amniotic Therapies' response to the Form FDA-483, which is discussed in a separate section of this order.

<sup>6</sup> FDA previously inspected Amniotic Therapies in March and April 2015, and documented some of the same violations cited in this order.

### Receipt

1. Failure to evaluate each incoming HCT/P for the presence and significance of microorganisms, and inspect for damage and contamination. Under the applicable regulations, you must determine whether to accept, reject, or place in quarantine each incoming HCT/P, based upon pre-established criteria designed to prevent communicable disease transmission [21 CFR 1271.265(a)].

For example, you do not perform pre-processing cultures on incoming HCT/Ps, specifically, amnion recovered from cesarean section births, to determine the presence and significance of microorganisms prior to processing HCT/Ps.

2. Failure to establish and maintain procedures, including release criteria, for activities relating to the receipt of HCT/Ps [21 CFR 1271.265(e)].

For example, you have not established and maintained procedures for evaluating incoming HCT/Ps (amnion) for the presence and significance of microorganisms and for determining whether to accept, reject, or place in quarantine incoming HCT/Ps, based upon pre-established criteria designed to prevent communicable disease transmission.

### Processing and Process Controls

Failure to process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P. You must ensure that specified requirements for in-process controls are met, and that each in-process HCT/P is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received and documented. [21 CFR 1271.220(a) and (c)].

For example, your manufacturing processes do not include in-process controls, such as pre-processing and post-processing/pre-irradiation cultures, to prevent contamination or cross-contamination during processing and to prevent the introduction, transmission, or spread of communicable disease through the use of the HCT/Ps.

### Environmental Monitoring

Failure to monitor environmental conditions where they could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents [21 CFR 1271.195(c)].

For example, you do not perform environmental monitoring for the presence of microorganisms in the room where HCT/Ps are processed.

## Records

Failure to include in the summary of records a statement that the communicable disease testing was performed by a laboratory that is certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR Part 493 or that has met equivalent requirements determined by the Centers for Medicare and Medicaid Services. The summary of records also failed to contain the name and address of the establishment that made the donor-eligibility determination [21 CFR 1271.55(b)(1) and (3)].

For example, the summary of records that accompanies your HCT/Ps does not contain a statement that the communicable disease testing was performed by a laboratory certified to perform such testing on human specimens under the Clinical Laboratory Act of 1988 or that has met equivalent requirements determined by the Centers for Medicare and Medicaid Services. The summary of records also does not contain the name and address of the establishment that made the donor-eligibility determination.

## **RESPONSE TO FORM FDA-483**

We acknowledge receipt of your written submission dated June 7, 2016, which responds to the inspectional observations on the Form FDA 483 issued at the close of the inspection, and we have reviewed its contents. Your responses fail to demonstrate that you have implemented adequate corrective actions. For example:

1. Process validation. In response to observation 2, you state, among other things, that you have partnered with a third-party facility to design and execute validation protocols of your processing steps. You also mention that AlphaPATCH and AlphaVISION HCT/Ps are (b) (4) [REDACTED], which validated the (b) (4) [REDACTED] process using the (b) (4) [REDACTED]. However, we cannot evaluate your response because you have provided no documentation to support that you have validated all of the processing steps that you perform on your HCT/Ps.

Although this order does not apply to AlphaGEMS, we also note that a validation study you provided regarding the (b) (4) [REDACTED] step that occurs as part of the processing of AlphaGEMS does not sufficiently demonstrate the adequacy of the corrective actions you are taking regarding process validation. For example, the validation study does not include an evaluation of incoming bioburden in order to set adequate acceptance criteria based on the capacity of your process.

We also note that your response states that you will “not be manufacturing amnion product for distribution” while making certain updates to your processing validation. Although we agree in part with this decision, we note that the definition of manufacture in 21 CFR 1271.3(e) includes, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor. It is not clear from your statement that you have ceased all of these steps in the manufacturing process. Moreover, your statement suggests that you would resume “manufacturing . . . for distribution” when

your processing validation updates are complete. However, you have not provided sufficient supporting documentation to allow us to evaluate the adequacy of these updates or your other corrective actions.

2. Receipt. In response to observation 3, you state, among other things, that you are now testing each lot of incoming amnion for the presence of microorganisms, (b) (4), and that all testing results will be evaluated before release for distribution. However, we cannot evaluate your response because of a lack of supporting documentation. While your response references a Standard Operating Procedure for the production of AlphaGEMS, you have not provided documentation regarding your other products.

In addition, your response does not discuss the implementation of specific criteria for accepting, rejecting, or placing in quarantine each incoming HCT/P based on an evaluation of the HCT/P for the presence and significance of microorganisms and an inspection of the HCT/P for damage and contamination.

3. Processing and process controls. Your response to observation 4 states, in part, that you have established microbiological testing for incoming amnion, implemented additional in-process controls and testing of final products, and are currently implementing process validation studies. However, due to insufficient supporting documentation, we are unable to evaluate your response.

Under 21 CFR 1271.220(a), you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P. This requirement is met, in part, through in-process control and testing under 21 CFR 1271.220(c).

Pre-processing cultures are an important in-process control, as discussed in FDA's Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells Tissues and Cellular and Tissue-Based Products (HCT/Ps). If HCT/Ps are processed with a bioburden in excess of the level that a sterilization process has been validated to reduce or eliminate, there is no assurance that processing will reduce or remove bioburden to acceptable limits or reduce the risk of transmission of communicable disease risk. Pre-processing cultures play a critical role in monitoring the process input to ensure that the process capability will not be affected. Thus, (b) (4) should not be used as an alternative to performing pre-processing cultures. In addition, if you do not perform post-processing/pre-irradiation cultures, or incoming bioburden studies, the type or number of microorganisms on your products is unknown. Therefore, we cannot evaluate to what degree your (b) (4) process minimizes the risk of communicable disease transmission.

4. Environmental monitoring. In response to observation 6, you state in part that you are working with a third party to develop and implement an environmental monitoring

program. However, your response cannot be evaluated due to a lack of supporting documentation. Specifically, you have not provided details regarding what is included in your environmental monitoring program.

5. Records. Your response to observations 7 and 8 includes, among other things, a statement that you have revised your product inserts to include the required information. However, we cannot evaluate your response because you have not provided supporting documentation.

This letter also confirms the telephone conversation on August 16, 2016, between you and FDA representatives during which FDA notified you that, pursuant to 21 CFR 1271.440(a)(1) and (3), upon receipt of this order, you must cease manufacturing, recall, and destroy HCT/Ps, as set forth above. Please be reminded, as explained during that conversation, that you must not resume operations without prior written authorization from FDA. Before FDA will issue such authorization, you must demonstrate compliance with FDA's regulations in 21 CFR 1271 – including, but not limited to, the Donor Eligibility and current Good Tissue Practice requirements in 21 CFR 1271, Subpart C and Subpart D. Any shipment of HCT/Ps in violation of this order constitutes a violation of Section 368 of the PHS Act [42 USC 271], for which criminal penalties may be imposed.

Within five (5) working days from the receipt of this Order to Cease Manufacturing, Recall, and Destroy, you may request a hearing on the matter in accordance with 21 CFR Part 16 (copy attached), to Mary A. Malarkey, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., WO71-G112, Silver Spring, MD 20993-0002 (telephone: 240-402-9153).

Failure to request a hearing within the specified time period constitutes a waiver of the right to a hearing. The Agency's guidelines regarding electronic media coverage of its administrative proceedings can be found at 21 CFR 10, Subpart C.

Sincerely,

Peter Marks, M.D., Ph.D  
Director  
Center for Biologics Evaluation and Research

Effective Date: \_\_\_\_\_ Time: \_\_\_\_\_

Attachments (2)  
21 CFR Part 1271  
21 CFR Part 16