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WARNING LETTER

Cord for Life, Inc.

MARCS-CMS 572770 — 29/03/2019

Product: Biologics

Recipient:

Syed M. Raheel

President and Owner

Cord for Life, Inc.

270 Northlake Blvd., Suite 1012
Altamonte Springs, FL 32701
United States

Issuing Office:

Division of Biological Products Operations I

555 Winderley Place, Suite 200
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United States

WARNING LETTER

VIA UNITED PARCEL SERVICE

SIGNATURE REQUIRED

March 29, 2019

Warning Letter #OBPO 19-05

Syed M. Raheel, President and Owner

Cord for Life, Inc.

270 Northlake Blvd., Suite 1012

Altamonte Springs, FL 32701

Dear Mr. Raheel,

During an inspection of your firm, Cord for Life, Inc., located at 270 Northlake Blvd., Suite 1012, Altamonte Springs, FL 32701, conducted from November 26 to November 30, 2018, the Food and Drug Administration (FDA) documented that your firm processes human umbilical cord blood derived cellular products PremierMaxCB Platinum, PremierMaxCB Gold, and PremierMaxCB Silver for allogeneic use (referred to as "umbilical cord blood products" or "products"). Among other customers, you distribute your products to **(b)(4)**, located in **(b)(4)**, and **(b)(4)**, located in **(b)(4)**. You also contract with **(b)(4)**, located in **(b)(4)** and **(b)(4)**, to market and sell your products. The instructions for use for your products state that each product is administered by "applying/injecting it on/in the patient."

Information and records gathered during and following the inspection, reflect that your products, which your firm refers to as "regenerative products" or "regenerative medicine" products, are intended for "therapeutic uses" to treat, for example, orthopedic conditions. Therefore, your products are drugs as defined in 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)]. They are also human cells, tissues, or cellular or tissue-based products (HCT/Ps) as defined in 21 CFR 1271.3(d)[1] (http://wcms.fda.gov/ucm/resources/wcm/sitestudio/elements/fckwysiwyg.htm#_ftn1) and are subject to regulation under 21 CFR Part 1271, issued under authority of section 361 of the PHS Act [42 U.S.C. 264]. However, Cord for Life does not qualify for any exception in 21 CFR 1271.15, and the products fail to meet all the criteria in 21 CFR 1271.10(a). Therefore, your products are not regulated solely under section 361 of the PHS Act [42 U.S.C. 264] and the regulations in 21 CFR Part 1271.

Specifically, the umbilical cord blood products fail to meet 21 CFR 1271.10(a)(2)'s criterion that the HCT/P be "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent."[2] (http://wcms.fda.gov/ucm/resources/wcm/sitestudio/elements/fckwysiwyg.htm#_ftn2) As noted above, the umbilical cord products are intended for "therapeutic use" to treat, for example, orthopedic conditions. Because the umbilical cord blood products are not intended to perform the same basic function or functions of umbilical cord blood in the recipient as in the donor, such as forming and replenishing the lymphohematopoietic system, using the umbilical cord blood products to treat orthopedic conditions is not homologous use as defined in 21 CFR 1271.3(c).

In addition, the umbilical cord blood products fail to meet the criterion set forth in 21 CFR 1271.10(a)(4). Specifically, the products, manufactured from donated umbilical cord blood, are dependent on the metabolic activity of living cells for their primary function and are not for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use.

As stated above, because your products do not meet all the criteria in 21 CFR 1271.10(a), and Cord for Life does not qualify for any exception in 21 CFR 1271.15, the products are regulated as drugs as defined in section 201(g) of the FD&C Act [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)]. Please be advised that to lawfully market a drug that is a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after showing that the product is safe, pure, and potent. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an investigational new drug application (IND) 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 umbilical cord blood products are not the subject of an approved biologics license application (BLA) nor is there an IND in effect. Based on this information, we have determined that your actions have violated the FD&C Act and the PHS Act.

Additionally, during the inspection, FDA investigators documented evidence of significant deviations from current good manufacturing practice (CGMP), including deviations from section 501(a)(2)(B) of the FD&C Act and 21 CFR Parts 210 and 211. The deviations in manufacturing processes observed as well as those noted in documents collected during the inspection indicate that the use of your products raises potential significant

safety concerns. For example, Cord for Life's unvalidated manufacturing processes, uncontrolled environment, and inadequate personnel aseptic practices, as described below, pose a significant risk that your products may be contaminated with microorganisms or have other serious product quality defects.

At the close of the inspection, FDA investigators issued a Form FDA 483 to you listing inspectional observations, which described a number of significant deviations from CGMP. FDA has found additional significant deviations upon further review of the information collected during the November 2018 inspection, as discussed below. The deficiencies 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. Your firm failed to validate the aseptic process used to manufacture PremierMaxCB® since manufacturing operations began in March 2018. By the nature of their routes of administration, your products purport to be sterile and are expected to be sterile.

b. During the inspection, the investigators observed personnel practices that do not adequately protect against microbiological contamination of your products, including:

i. Operators were observed leaving and returning to aseptic operations in Biological Safety Cabinets (BSCs) without changing or disinfecting gloves. This practice of re-entering BSCs after touching papers, equipment, and/or utensils creates the potential for bringing contaminants into the BSCs.

ii. Operators re-using non-sterile smocks for up to 2 weeks.

iii. Operators failed to use hair coverings, face masks, and goggles, and were observed with exposed skin and watches during processing operations in BSCs.

iv. Gloves worn in the ISO 5 BSCs are non-sterile.

c. Final drug product was observed in an open tray immediately adjacent to the exterior edge of the BSC.

d. Between July and October 2018, 23 out of **(b)(4)** personnel fingertip monitoring samples were positive for microbial contamination with no investigation conducted or corrective action taken. During that same time, **(b)(4)** per **(b)(4)** test in BSCs **(b)(4)** and **(b)(4)** revealed gram positive rods, gram positive cocci, coagulase negative staphylococcus, micrococcus, and mold. 20 results were marked as passing; however, your firm failed to conduct an investigation, including further identification of the microorganisms, or document any corrective action.

2. Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c)(10)(iv)]. For example:

a. Viable air, surface and personnel monitoring in the BSC is not conducted for each fill. Such monitoring is only conducted **(b)(4)**.

b. The BSCs are cleaned prior to collection of the **(b)(4)** post-processing and fingertip samples. Therefore, the Environmental Monitoring (EM) samples are not representative of conditions existing during aseptic processing.

c. There are no alert and action limits for EM in the ISO 5 BSCs. Any result less than **(b)(4)** Colony Forming Units (CFUs) is considered passing. However, the current industry standard is <1 CFU/m^3 for active air sampling and <1 CFU/4 hours for settling plate action levels. This allowance for such high numbers of microorganisms could contribute to product contamination and pose a potential significant safety concern. For additional information, we recommend that you review FDA Guidance for Industry, Sterile Drug Products

Produced by Aseptic Processing – Current Good Manufacturing Practice, available at https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf (https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf).

3. Failure to establish and follow written procedures for cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)]. For example:

a. Your firm failed to validate the cleaning process for your BSCs.

b. Your Standard Operating Procedure (SOP) H.13 entitled "Operation and Maintenance of the Laminar Flow Biological Safety Cabinet" lacks adequate cleaning procedures for your BSCs **(b)(4)**, including but not limited to, use of a sporicidal agent, frequency of reagents used, and contact times. Additionally, this SOP does not address cleaning between batches.

4. Failure to establish 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)]. Specifically, the manufacturing process has not been validated for your products.

5. Failure to establish laboratory controls that include 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 [21 CFR 211.160(b)].

a. You have not established specifications, standards, sampling plans and test procedures for testing your products for identity, strength, quality, and purity.

b. Sterility testing conducted with your **(b)(4)** system may not detect product contamination, creating a potential significant safety concern. For example:

i. Sampling for release testing is not conducted on final product. After sampling, the product **(b)(4)**.

ii. The sterility test method was validated using a **(b)(4)**, however, your **(b)(4)** system only **(b)(4)**.

iii. **(b)(4)** bottles with a sample size of **(b)(4)** are used for aerobic testing. This lower sample volume size could result in lower recovery/sensitivity.

6. Failure to establish and follow a written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates [21 CFR 211.166(a)]. Specifically, you assign a three-year expiration date without supporting data.

We received your firm's written response, dated December 19, 2018, regarding the inspectional observations on the Form FDA 483, and we have reviewed its contents. In your response, you explained that your firm will be taking steps to address the observations. The response references corrected documents, equipment changes, studies to be performed and revision of SOPs. In addition, your response details the plans for renovating your ISO 7 clean room. However, to date your firm has not submitted any substantive evidence that any of the proposed corrective actions were implemented. In addition, as noted above, in order to lawfully market a drug that is a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after showing that the product is safe, pure, and potent. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an IND 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 umbilical cord blood products are not the subject of an approved BLA nor is there an IND in effect for your products.

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 at your facility. It is your responsibility to ensure full compliance with the FD&C Act, PHS Act, and all applicable regulations.

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

For further information about IND requirements for biological products, contact the Center for Biologics Evaluation and Research (CBER), Division of Regulatory Project Management, Office of Tissues and Advanced Therapies, at (240) 402-8190, or OTATRPMS@fda.hhs.gov (mailto:OTATRPMS@fda.hhs.gov). Please include a copy of this letter with your initial submission to CBER.

We request that you respond 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 correct the noted violations and prevent their recurrence. Include any documentation necessary to show that correction has been achieved. 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. If you cannot complete all corrections within fifteen (15) working days, please explain the reason for your delay and the time frame within which the remaining corrections will be completed.

Your response should be sent to the following address: Daniel W. Cline, Compliance Officer, U.S. Food and Drug Administration, 19701 Fairchild, Irvine, CA 92612 or emailed to Daniel.Cline@fda.hhs.gov (mailto:Daniel.Cline@fda.hhs.gov). If you should have any questions, please contact Daniel Cline, Compliance Officer at 949-608-4433 or via e-mail.

Sincerely,

/S/

Elizabeth A. Waltrip

Program Division Director

Office of Biological Products Operations - Division I

cc:

(b)(4)

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[1] (http://wcms.fda.gov/ucm/resources/wcm/sitestudio/elements/fckwysiwyg.htm#_ftnref1) HCT/Ps are defined as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.” 21 CFR 1271.3(d).

[2] (http://wcms.fda.gov/ucm/resources/wcm/sitestudio/elements/fckwysiwyg.htm#_ftnref2) 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. FDA considers the objective intent of all firms involved in the manufacture, within the meaning of 21 CFR 1271.3(e), of an HCT/P in evaluating whether the product is "intended for homologous use only" under 21 CFR 1271.10(a)(2).

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