WARNING LETTER

EUCYT Laboratories LLC

MARCS-CMS 607182 — JUNE 04, 2020

Delivery Method:

VIA UNITED PARCEL SERVICE

Product:

Biologics

Recipient:

Travis H. Bird

Chief Executive Officer

EUCYT Laboratories LLC

5670 Wynn Road, Suite D
Las Vegas, NV 89118
United States

Issuing Office:

Office of Biological Products Operations - Division II

United States

WARNING LETTER

Warning Letter #OBPO 20-603498

June 04, 2020

Dear Mr. Bird:

During an inspection of your firm, EUCYT Laboratories, LLC (EUCYT), located at 5670 Wynn Road, Suite D, Las Vegas, NV 89118, conducted between November 12, 2019, and November 21, 2019, the United States Food and Drug Administration (FDA) documented EUCYT's manufacture of products derived from human umbilical cord blood and umbilical cord, VidaCord™, VidaGel™ and VidaStem™; an exosome product, XOsomes™; and an amniotic fluid derived product, VidaFlo™, all for allogeneic use. You distribute your products to multiple health care providers and facilities throughout the United States.

Information and records gathered prior to, at the time of, and following the inspection, including product labeling and information on the EUCYT website, https://eucyt.com, reflect that the above-referenced products are intended for clinical use in humans to treat a variety of diseases or conditions. Therefore, these products are drugs as defined in section 201(g) of the Federal Food, Drug, and Cosmetic Act (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)].

Some of the products are also human cells, tissues, or cellular or tissue-based products (HCT/Ps) as defined in 21 CFR 1271.3(d)[1] 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), and when no exception in 21 CFR 1271.15 applies, are not regulated solely under section 361 of the PHS Act [42 U.S.C. 264] and the regulations in 21 CFR Part 1271. 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 appropriate premarket review.

EUCYT does not qualify for any exception in 21 CFR 1271.15, and your HCT/Ps derived from umbilical cord blood or umbilical cord fail to meet all the criteria in 21 CFR 1271.10(a). 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.

Specifically, your HCT/Ps derived from umbilical cord blood or umbilical cord fail to meet the criterion in 21 CFR 1271.10(a)(2) that the HCT/Ps be "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent."[2] Because these products are not intended to perform the same basic function or functions of umbilical cord blood or umbilical cord in the recipient as in the donor, such as forming and replenishing the lymphohematopoietic system (for cord blood) and serving as a conduit (for umbilical cord), using the products to treat arthritis or for cushioning joints, for example, is not homologous use as defined in 21 CFR 1271.3(c).

In addition, your HCT/Ps derived from umbilical cord blood or umbilical cord fail to meet other criteria set forth in 21 CFR 1271.10(a). For example, your umbilical cord blood product, VidaStem™, fails to meet 21 CFR 1271.10(a)(4). This product, manufactured from donated umbilical cord blood, is dependent on the metabolic activity of living cells for its primary function and is not for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use. Additionally, the umbilical cord derived products, VidaGel™ and VidaCord™, 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). These products do not meet this criterion because your processing alters the original relevant characteristics of the umbilical cord related to its utility for reconstruction, repair, or replacement.

With regard to your unapproved exosome product XOsomes™, we direct your attention to FDA's Public Safety Notification on Exosome Products, available at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products). FDA issued that public safety notification following multiple reports of serious adverse events experienced by patients who were treated with XOsomes™.

Most recently, you began marketing an exosome product, COVIXO, for the treatment or prevention of patients' Coronavirus Disease 2019 (COVID-19).[3] Your https://eucyt.com/products/covixo/ website states "COVIXO drives cellular functionality including augmenting the type 1 interferon pathway . . . that is important for anti-SARS-CoV-2 activity" and "[t]he unique mechanism of action for COVIXO enables each patient to generate their own adaptive immune response against SARS-CoV-2, including memory T cells and antibodies, which will further protect each patient from subsequent exposures and infections."

These exosome products, XOsomes™ and COVIXO (formerly known as XOCYT™) are regulated as drugs and biological products under section 351 of the PHS Act and the FD&C Act and are subject to premarket review and approval requirements.

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]. None of your products are the subject of an approved biologics license application (BLA), nor is there an IND in effect for any of them. 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) and current good tissue practice (CGTP),[4] including deviations from section 501(a)(2)(B) of the FD&C Act and 21 CFR Parts 210, 211, and 1271. 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, EUCYT's deficient donor eligibility practices, unvalidated manufacturing processes, deficient environmental monitoring, and inadequate aseptic practices, as described below, pose a significant risk that your products may be contaminated with viruses or microorganisms or have other serious product quality defects. Additionally, there have been reported safety concerns with one of your products.

At the close of the inspection, the FDA investigators issued a Form FDA 483 to you listing inspectional observations, which described a number of significant CGMP deviations applicable to all your products that were the subject of the inspection as well as significant CGTP deviations applicable to your HCT/Ps. FDA has found additional significant deviations upon further review of the information collected during the November 2019 inspection, as discussed below. The deficiencies include, but are not limited to, the following:

1. Failure of a responsible person to determine and document the eligibility of a cell or tissue donor based upon the results of donor screening and donor testing [21 CFR 1271.50(a)]. EUCYT is the establishment responsible for making donor eligibility determinations for donors of umbilical cord blood and/or umbilical cord sourced from your supplier, **(b)(4)**. Although your firm receives relevant medical records, including a donor medical history interview and a physical examination from your supplier, you have not determined donor eligibility for the donors of umbilical cord blood and/or umbilical cord used to manufacture your products. Since operations began in April 2018, your firm has failed to document whether donors of umbilical cord blood and/or umbilical cord sourced from **(b)(4)** are eligible.

2. Failure to screen a donor of human cells or tissue by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases [21 CFR 1271.75(a)]. FDA has identified Zika virus (ZIKV) as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(2); therefore, review of relevant medical records, as defined in 21 CFR 1271.3(s), must indicate that a potential donor is free from risk factors for, or clinical evidence of, ZIKV infection for the purpose of determining donor eligibility. The DT-001 Form 4 "Donor Risk Assessment Interview" your firm receives from its primary cord and cord blood supplier, **(b)(4)**, does not adequately assess a donor's risk for ZIKV. We note that **(b)(4)** is located in **(b)(4)**, which has been identified by the Centers for Disease Control and Prevention as an area with current or past transmission of ZIKV.

3. Failure to establish and maintain procedures for all steps performed in testing, screening, and determining donor eligibility, and complying with all other requirements of Subpart C "Donor Eligibility" in 21 CFR 1271.45-1271.90. "Establish and maintain" means define, document (in writing or electronically), and implement; then follow, review, and as needed, revise on an ongoing basis [21 CFR 1271.47(a)]. Specifically, your firm failed to establish and maintain procedures for determining donor eligibility to adequately and appropriately reduce the risk of transmission of relevant communicable diseases.

4. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including procedures for validation of all aseptic and sterilization processes [21 CFR 211.113(b)]. For example:

A. The aseptic processes used to manufacturer your products, VidaCord™, VidaGel™, VidaStem™, XOsomes™, and VidaFlo™ have not been validated since manufacturing operations began in April 2018. Based on your product labeling, these products purport to be sterile and are expected to be sterile.

B. Written procedures have not been established and followed for gowning.

C. During the inspection, FDA investigators observed personnel practices that do not adequately protect against microbiological contamination of your products, including operators with exposed skin and hair, as well as non-sterile gowns, gloves, bouffant caps and shoe covers.

5. Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c)(10)(iv)]. Specifically, your firm has not established an adequate system for environmental and personnel monitoring in the aseptic processing area where the products are manufactured. Only **(b)(4)** step of processing is monitored **(b)(4)** with settle plates.

6. Failure to establish written procedures for production and process controls 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 processes for your products have not been validated.

7. 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)]. For example, there are no written procedures describing in sufficient detail the criteria for approval or rejection of incoming umbilical cord blood and umbilical cord.

8. 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 has not adequately established and followed written procedures for cleaning and maintenance of the **(b)(4)** Biological Safety Cabinets (BSCs) used to manufacture your products:

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

ii. Cleaning with **(b)(4)** is conducted **(b)(4)** of a BSCs; however, your SOP entitled “Use and Maintenance of **(b)(4)** Biological Safety Cabinet” does not require cleaning in between the manufacture of batches.

iii. Your firm does not maintain cleaning records.

iv. There is no data or rationale for the cleaning agents used or their rotation.

v. Expired **(b)(4)** were observed being used to clean BSC #**(b)(4)** after production of VidaCordTM (Donor ID #**(b)(6)**) on **(b)(4)(b)(6)**.

B. Your firm has not adequately established and followed written procedures for cleaning and maintenance of the cutting boards used in the aseptic processing of umbilical cord. On November 13, 2019, cleaning of a plastic cutting board in the eye wash station was observed.

9. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed. [21 CFR 211.192]. For example, from April 2018 to November 2019, your firm failed to thoroughly investigate 152 sterility failures. The overall failure rate per product ranged from approximately **(b)(4)**%.

i. The contaminating organism(s) were identified, but your firm destroyed these batches without conducting thorough investigations. Organisms included: *Acidovorax temperans, Clostridium perfingens, Enterococcus faecalis, Escherichia coli*, Gram positive cocci, Gram negative rods, *Klebsiella pneumonaie, Kocuria varians*, and *Streptococcus*.

ii. Corrective or preventive actions were not implemented.

iii. In one instance, your firm failed to thoroughly investigate the failure of a lot (Lot # **(b)(4)**, Donor ID #**(b)(6)**) to meet specifications after a sterility failure for *E. coli*. The firm discarded the lot without conducting a thorough investigation that extended to other lots manufactured the same day (**(b)(4)(b)(6)**). Another lot manufactured that day (Lot #**(b)(4)**, Donor ID #**(b)(6)**) was later associated with a report of a patient testing positive for *E. coli*.

10. Failure to establish and follow a written testing program designed to assess the stability characteristics of drug products and to use the results of such stability testing to determine appropriate storage conditions and expiration dates [21 CFR 211.166(a)]. For example, your firm assigns a two-year expiration date without supporting data for your VidaCord™, VidaGel™, VidaStem™ and XOsomes™ products.

11. Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198(a)]. For example, your firm has not established and followed written procedures that describe a process for documenting and investigating complaints.

12. Failure to test your 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]. For example, penicillin was used in an **(b)(4)** during the manufacture of VidaCord™ and XOsomes™, from **(b)(4)** to **(b)(4)** and there is no documentation that testing for penicillin has been performed.

13. Failure to prepare batch production and control records that include documentation of the accomplishment of each significant step in manufacturing, processing, packing, or holding [21 CFR 211.188(b)]. For example, the aseptic processing steps described in your SOP entitled "Processing and Storage of Umbilical Cord Tissue - **(b)(4)**", were not documented to assure that all steps were performed as directed, including the total time of the **(b)(4)**.

We have reviewed your written response, dated December 10, 2019, to the inspectional observations on the Form FDA 483 issued at the conclusion of the inspection. We acknowledge your commitment at that time to quarantine all products processed from HCT/Ps recovered in Zika risk areas, and to accept only HCT/Ps recovered within the continental United States. We also acknowledge your commitment to implement corrective actions for the CGMP and CGTP deficiencies documented on the FDA 483; however, the adequacy of all corrective actions will need to be verified during reinspection of your firm.

During a subsequent FDA investigation at your firm, conducted from February 19 through February 20, 2020, our investigator confirmed that your finished product inventory was under quarantine and remained the same as the finished product inventory documented at the conclusion of the November 12 through November 21, 2019, FDA inspection of your firm. At the time of the February 2020 investigation, you stated that you had not shipped or destroyed any finished product since the conclusion of the November 2019 inspection. Further, you represented to FDA that, as of February 20, 2020, no product had been distributed from EUCYT since November 21, 2019.

During the February 2020 investigation, you also stated that in January 2020, you had processed umbilical cord into both Wharton's jelly and exosome products that had resulted in **(b)(4)** vials of XOsomes™ and VidaGel™; you further stated that these finished products were in quarantine. As of February 4, 2020, you represented to FDA that your firm is not conducting any manufacturing operations including processing, labeling, storing or shipping.

We note that FDA has also observed other products marketed on EUCYT's website that were not the focus of the agency's inspection or investigation. These products, which appear to be HCT/Ps, include EUFILL™, an allogeneic product derived from donated birth tissue, and OsteoFlow™ and OsteoGel™, products consisting of, in part, cortical and cancellous and demineralized cortical allograft bone **(b)(4)**, respectively. Based on our review, it appears that EUCYT does not qualify for any exception in 21 CFR Part 1271.15 and that these

products fail to meet all the criteria in 21 CFR 1271.10(a) for regulation solely under section 361 of the PHS Act and regulations in 21 CFR Part 1271. As such, it appears that these products would be regulated as drugs, devices, and/or biological products under the FD&C Act and/or section 351 of the PHS Act and subject to additional regulation, including appropriate premarket review

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 violations. Failure to promptly do so may result in regulatory action without further notice. Such actions include seizure and/or injunction.

For further information about IND requirements, please 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. 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. If you have any questions, please contact Mr. Cline at (949) 608-4433 or via e-mail.

Sincerely,
/S/

Karlton T. Watson
Program Division Director
Office of Biological Products Operations – Division II

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1 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). The definition of HCT/P excludes secreted or extracted human products; accordingly, secreted body fluids, such as amniotic fluid, are generally not considered HCT/Ps subject to regulation under 21 CFR Part 1271. Although not an HCT/P, your product derived from amniotic fluid, VidaFlo™, is also regulated as a drug and biological product under section 351 of the PHS Act and the FD&C Act.

2 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.”

3 There is currently a global outbreak of respiratory disease caused by a novel coronavirus that has been named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). The disease caused by the virus has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Secretary of Health and Human Services Alex M Azar, Determination that a Public Health Emergency Exists. Jan. 31, 2020. (Accessible at: https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx (https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx)). The declaration was renewed for another 90 days on April 21, 2020. Secretary of Health and Human Services Alex M. Azar II, Renewal of Determination that a Public Health Emergency Exists. April 21, 2020. (Accessible at: https://www.phe.gov/emergency/news/healthactions/phe/Pages/covid19-21apr2020.aspx (https://www.phe.gov/emergency/news/healthactions/phe/Pages/covid19-21apr2020.aspx)). In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19. President Donald J. Trump, Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19). Mar. 13, 2020. (Accessible at: https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/ (https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/)).

4 During the November 2019 inspection, FDA investigators also gathered evidence of your manufacture of another HCT/P, EuFixx™, an amniotic membrane patch product for allogeneic use. Although EuFixx™ is not the focus of this letter, we note that certain of your CGTP deviations described below also pertain to your manufacture of EuFixx™.

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