# Genetech Inc 11/29/18

**WARNING LETTER**

**VIA UNITED PARCEL SERVICE**
**SIGNATURE REQUIRED**

November 29, 2018

Warning Letter #OBPO 19-03

Edwin N. Pinos, President
Genetech, Inc.
3030 Bunker Hill Street, Suite 308
San Diego, CA 92109-5757

Dear Mr. Pinos,

During an inspection of your firm, Genetech, Inc., located at 3030 Bunker Hill Street, Suite 308, San Diego, CA 92109, conducted between June 18 and June 22, 2018, the Food and Drug Administration (FDA) documented that your firm processes human umbilical cord blood derived cellular products ReGen®5, ReGen®10, and ReGen®30 for allogeneic use (hereinafter, "umbilical cord blood products" or "products") that you distribute to Liveyon LLC (Liveyon), located in Yorba Linda, CA. The umbilical cord blood products are administered via intra-articular injection and in some cases intravenously or "applied directly to the affected soft tissue."

Information and records gathered during the inspection and information available on the Liveyon website, www.liveyon.com, reflect that your products are intended to treat a variety of 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 cell, tissue, or cellular or tissue based products (HCT/P) as defined in 21 CFR 1271.3(d)**1** 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, Genetech 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 the criterion established by 21 CFR 1271.10(a)(2), that "The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent."***2*** As noted above, the umbilical cord blood products are intended to treat a variety of 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-decree blood relative, or reproductive use.

As stated above, because your products do not meet all the criteria in 21 CFR 1271.10(a), and Genetech does not qualify for any exception in 21 CFR 1271.15, the products are regulated as drugs under 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 ifthe 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) and current good tissue practice (CGTP), 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, Genetech's deficient donor eligibility practices, unvalidated manufacturing processes, uncontrolled environment, lack of control of components used in production, such as the addition of **(b)(4)**, and lack of defined areas or a control system to prevent contamination and mix-ups, as described below, pose a significant risk that your products may be contaminated with microorganisms or have other serious product quality defects. Furthermore, FDA has received numerous reported safety concerns involving your products.

At the close of the inspection, an FDA investigator issued a Form FDA 483 to you listing inspectional observations, which described a number of significant deviations from CGMP and CGTP. FDA has found additional significant deviations upon further review of the information collected during the June 2018 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)].** For example:

a. Genetech is the establishment responsible for making the donor eligibility determination, but since operations began in mid-2017, Genetech has failed to document whether donors of umbilical cord blood are eligible. Neither you, Liveyon, nor your suppliers have determined donor eligibility for the umbilical cord blood used to manufacture your products.

b. When Genetech receives relevant medical records, including the medical/social history interview and physical exams from its supplier, those records are not reviewed to determine donor eligibility.

**2. Failure to screen a donor of cells or tissues by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases [21 CFR1271.75(a)].** For example, 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 **(b)(4)** Recovery Site Assessment" you receive from your primary cord blood supplier, **(b)(4)** located in **(b)(4)**, does not adequately assess a donor's residence in, or travel to, areas identified by the Centers for Disease Control and Prevention with active ZIKV transmission. We recommend that you review FDA Guidance for Industry, Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products (updated May 2018), available at **https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm488582.pdf (https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm488582.pdf)**.

**3. Failure to test donor specimens using appropriate FDA-licensed, approved or cleared donor screening tests, in accordance with the manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases [21 CFR 1271.80(c)].** Specifically, umbilical cord blood donor **(b)(6)** was tested for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus-1 (HIV-I) nucleic acids with tests that were not FDA-licensed, approved, or cleared for donor screening. The test results for the HBV, HCV, and HIV-1 NAT or polymerase chain reaction (PCR) assay state: "This assay should not be used for blood donor screening, associated re-entry protocols, or for screening Human Cell, Tissues and Cellular Tissue-Based Products (HCT/P)." In addition, the cord blood donor's specimen was not tested for total cytomegalovirus (CMV), human T-lymphotropic virus I/II (HTL V I/II), or West Nile virus (WNV).

**4. 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, you failed to establish and maintain procedures for determining donor eligibility to adequately and appropriately reduce the risk of transmission of relevant communicable diseases.

**5. Failure to retain the accompanying records with the HCT/Ps at all times following a donor eligibility determination including a statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible; and a summary of records used to make the donor-eligibility determination [21 CFR 1271.55(a)].** Specifically, all products distributed since your firm's manufacturing operation began in mid-2017, were distributed without a statement of donor eligibility and without a summary of records used to make a donor eligibility determination.

**6. Failure to retain documentation of the results and interpretation of all donor screening for communicable diseases in compliance with 21 CFR 1271.75 [21 CFR 1271.55(d)(ii)].** Specifically, you do not consistently receive relevant medical records, including the medical/social history interview and physical exams, from your umbilical cord blood suppliers in order to retain such records.

**7. 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 perform media fill simulations to evaluate the state of control of the aseptic process used to manufacture approximately **(b)(4)** batches of your products since manufacturing operations began in mid-2017. By the nature of their routes of administration, your products purport to be sterile and are expected to be sterile.

b. The manufacturing facility and gowning rooms are not classified with respect to air quality, so they are not controlled and maintained to ensure aseptic conditions.

c. There is no written procedure for gowning. Appropriate gowning reduces the potential for the manufacturing personnel to inadvertently contaminate the product during the aseptic manufacturing process.

d. Your firm utilized a**(b)(4)** and the associated **(b)(4)**) and columns to manufacture approximately **(b)(4)** batches of your products between mid-2017 and June 2018. This **(b)(4)** and associated reagents are labeled "For research use only."

e. Your firm added non-sterile **(b)(4)** to approximately **(b)(4)** batches of your products between mid-2017 and June 2018. These **(b)(4)** are labeled "For research use only."

**8. Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c)(10)(iv)].** For example, your firm has not established an adequate system for environmental and personnel monitoring in the aseptic processing area where the products are manufactured.

**9. Failure to have an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions [21 CFR 211.42(c)(10)(v)].** For example:

a. Your firm failed to validate your cleaning process.

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

c. The cleaning records do not include dilutions or contact times.

d. Cleaning is only performed **(b)(4)** and not in between the manufacture of batches.

**10. 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]).** For example:

a. The manufacturing process has not been validated for your products.

b. Changes to the production process for your products have not been validated. Specifically, the cryopreserving agent was changed from **(b)(4)** Cryopreservation Medium to **(b)(4)**Cryopreservation Medium without validation.

**11. Failure to have separate or defined areas or such other control systems for operations as are necessary to prevent contamination or mix-ups during the course of manufacturing and processing operations [21 CFR 211.42(c)(5)].** During the inspection, FDA investigators observed unlabeled final product vials in the **(b)(4)**Freezer awaiting sterility results. Products manufactured from different donors are separated only by **(b)(4)**

**12. Failure to fully investigate any unexplained discrepancy, or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192].** Specifically, umbilical cord blood stem cell lot number **(b)(4)** failed sterility testing and was discarded without further investigation and identification of the contaminating microorganism.

**13. 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 incoming umbilical cord blood.

**14. 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)].** For example, you have not established specification, standards, sampling plans and test procedures for testing your products for identity, strength, quality, and purity.

**15. Failure to prepare batch production and control records that document each significant step in the manufacture, processing, packing, or holding of your umbilical cord blood products [21 CFR 211.188(b)].** For example, the aseptic processing steps described in GEN-SOP-004 entitled "Purification of **(b)(4)** from Human Umbilical Cord Blood" were not documented to assure that all steps were performed as directed, including the amount of HESpan® added to the cord blood, centrifuge parameters used, amount of **(b)(4)**.

**16. Failure to establish and follow a written testing program designed to assess the stability characteristics of your manufactured umbilical cord· blood products and to use results of the stability testing to determine the appropriate storage conditions and expiration dates [21 CFR 211.166(a)].** Specifically, you assign a one-year expiration date without supporting data.

Furthermore, the potency or cell concentration (total nucleated cells) stated on the label is determined by **(b)(4)**.

**17. Failure to ensure that each lot of components, drug product containers, and closures are withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit [21 CFR 211.84(a)].** For example, the following components and containers are not tested or examined before release:

a. **(b)(4)** of the umbilical cord blood;

b. **(b)(4)** used in association with the **(b)(4)** from the umbilical cord blood;

c. **(b)(4)** used in the manufacture of your products;

d. **(b)(4)** Cryopreservation Medium used in the final formulation of your products.

**18. Failure to generate and maintain distribution records that contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product [21 CFR 211.196].** Specifically, your firm does not maintain distribution records.

**19. Failure to establish a quality control unit that has the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated [21 CFR 211.22(a)].** Specifically, you had no quality control unit from the time manufacturing operations began in mid-2017 through the time of the inspection.

We received your written responses, dated August 7, 2018, and August 10, 2018, to the inspectional observations on the Form FDA 483, and we have reviewed their contents. In both responses, you acknowledge your violations and represent that your firm will be working diligently to correct them. You provided several attachments with your responses, including blank donor history forms, an environmental monitoring service agreement, blank shipment forms, and an umbilical cord blood sedimentation with processing checklist, and you inquire whether these documents demonstrate that you have fulfilled donor eligibility, environmental monitoring, product release, and processing requirements. The documents submitted do not demonstrate that you have corrected the deficiencies noted in the inspectional observations nor do they address your failure to have an IND in effect in order to study your products or your lack of an approved BLA in order to lawfully market your products. We recommend that you review the deviations listed above, consider the potential serious risks to patients your manufacturing violations present, and consult with third-party experts to implement comprehensive corrective action.

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 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:OTA-TRPMS@fda.hhs.gov)**. 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 steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that correction has been achieved. If you do not believe your product is in violation of the FD&C Act, PHS Act, or applicable regulations, include your reasoning and any supporting information for our consideration. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which all 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 have any questions, please contact Mr. Cline at (949) 608-4433 or via e-mail.

Sincerely,
/S/
Karlton Watson
Program Division Director
Office of Biological Products Operations

cc:

John Kosolcharoen, Owner and Chief Executive Officer
Liveyon LLC
22667 Old Canal Road
Yorba Linda, CA 92887-4601

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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).*

***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. Because both Genetech and Liveyon manufacture the umbilical cord blood products, within the meaning of 21 CFR 1271.3(e), FDA considered both firms' objective intent in evaluating whether the products are "intended for homologous use only" under 21 CFR 1271.10(a)(2). At the time of the inspection, Genetech had appointed Live yon as its exclusive distributor of certain biological products, including umbilical cord blood products.*

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