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7. You have indicated in the table on page 288 of your submission that there may be cases in which the product was not evaluated for infectious substances or contains infectious substances based on reactive test results. However, the final product label you provided does not contain the required text relevant to these situations. Specifically, the following text should be provided on the final product label, when appropriate:
- a. "Not evaluated for infectious substances" in the case donor screening and testing are not completed.
 - b. "WARNING: Reactive test results for (name of disease agent or disease)" in the case of abnormal results of donor screening.

Please submit final product labels demonstrating that the labels will contain this text in the required situations:

8. You have stated that the Wharton's Jelly is either applied to the defect with sterile forceps or loaded in a capped syringe for injection into the defect. Thus, we recommend that you evaluate the feasibility of both application methods based on the handling characteristics and mechanical properties of the Wharton's Jelly. We also recommend that you assess if the resulting characteristics of the Wharton's Jelly, and specifically characteristics relevant to any therapeutic effects, vary depending on the application method.

Your responses to any non-hold issues should be addressed in a separate amendment to the IND.

If you have any questions, please contact the Regulatory Project Manager, Nevitt Morris, at (240) 402-8269.

Sincerely yours,

Wilson W. Bryan, M.D.

Wilson W. Bryan, M.D.

Director

Office of Tissues and Advanced Therapies

Center for Biologics Evaluation and Research

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product, including but not limited to evaluating the cellular component (e.g., cell viability, cell phenotype, and cell number) and other matrix components (e.g., hyaluronic acid, collagen, or factors contained within the matrix). We also recommend that you incorporate these evaluations as part of release testing on every lot of your final product. You may consider collecting information on these parameters during your Phase 1 trial in order to establish and refine acceptance specifications for later phase studies.

4. You have proposed to assess the potency of your final product by evaluating the osteogenic differentiation potential. In order to refine your approach to measuring potency, as well as to inform if additional testing should be incorporated into your potency assay, we recommend that you continue to collect product characterization data throughout your Phase 1 clinical trial. Additional characterization data may inform decisions on specifications used to ensure product and process consistency. We recommend that you develop potency assays based on specific attributes of the proposed product, including functional aspects of the product. Please note that a potency assay will be required before initiating your Phase 3 trial.

For guidance, please refer to Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM243392.pdf>.

5. We recommend that you perform in-process testing, with established acceptance criteria, on the incoming umbilical cord material and Wharton's Jelly prior to freezing. This testing may include, but is not limited to, an evaluation of umbilical cord dimensions and sterility and of Wharton's Jelly volume and sterility.
6. We note that you evaluated the stability of the in-process materials (i.e., umbilical cord) out to 24 hours and the final product out to 3 months following storage at appropriate temperatures by determining the viability of the cells within the Wharton's Jelly. However, you have stated that the final autologous product will not be administered to the patient until 12-18 months of age. Thus, in order to ensure the final product is stable throughout the duration of the clinical trial, we recommend that you continue to evaluate the stability of the frozen final product out to at least 18 months or until administration of the product, whichever is longer. In addition, we recommend that your stability studies include an evaluation of product sterility, identity, purity, quality, and potency. We also recommend that in addition to evaluating cell viability, your stability studies incorporate methods to evaluate cell function and vitality following storage at appropriate temperatures and holding times.

For more information on evaluating product stability, please refer to the Guideline for Industry: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (1996) (ICHQ5C) found at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073466.pdf> for advice on the development of stability protocols.

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- a. This study should include an assessment of the quality and durability (e.g., μ CT, histomorphometric, and biomechanical analyses) of the newly formed bone in the implant site over time.
 - b. We recommend that your animal study include a minimum of three evaluation time points to enable: 1) early assessment of product resorption, new bone formation, and inflammatory reaction; 2) establishment of interim product behavior and a documented reduction in inflammatory response; and 3) demonstration of bone healing and the effects of any residual product material.
2. Section 3 of the IND, 'Investigators Brochure', contains a brochure prepared by the American Association of Blood Banks on information for the use of cellular therapy products. This information does not constitute an Investigator Brochure (IB) per 21 CFR 312.23(a)(5). We also note that since this is a single-site, sponsor-investigator IND, per 21 CFR 312.55(a) you are not required to submit an IB. Therefore, please either withdraw the IB, or submit a new IB that meets the requirements of the regulation. For additional recommendations on the preparation and content of your IB, please refer to the guidance document titled, *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* (April 1996, available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073122.pdf>).

You must not conduct studies in humans under this IND until we have received and reviewed your response to the above deficiency(ies), and notified you that you may proceed with the investigation.

When you respond to all issues identified above, please identify your response as a "CLINICAL HOLD COMPLETE RESPONSE" and submit this information to the IND. We recommend that you restate each item and follow it with your explanation or clarification. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference. Following receipt of your complete response, we will notify you of our decision within 30 days. An incomplete response will not start the review clock. For additional information, please refer to the FDA Guidance: *Submitting and Reviewing Complete Responses to Clinical Holds – October 2000* (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127538.pdf>).

In addition, we have the following comments and requests for additional information that are not clinical hold issues.

PRODUCT INFORMATION

3. We note that you have not included identity testing, as defined in 21 CFR 610.14, as part of the release testing of your final product. Please note that identity testing is recommended by Phase 2 and required prior to initiation of a Phase 3 clinical trial. Thus, we recommend that you continue to characterize your final



FDA U.S. FOOD & DRUG
ADMINISTRATION

Our Reference: IND 17215

January 11, 2017
CLINICAL HOLD

Charles S. Cox, Jr., M.D.
Professor, Department of Pediatric Surgery
University of Texas at Houston Medical School
6431 Fannin Street, Suite 5.236
Houston, TX 77030

Dear Dr. Cox:

We have reviewed the October 28, 2016, submission to your Investigational New Drug Application (IND) for "Autologous Human Wharton's Jelly."

As discussed during the December 14, 2016, telephone conversation between you and Nevitt Morris of this Office, your study under this IND has been placed on clinical hold and subjects may not be given the investigational drug.

We are placing your IND on clinical hold because human subjects are or would be exposed to an unreasonable and significant risk of illness or injury (21 CFR 312.42(b)(1)(i)).

The following are the specific deficiencies and the information needed to resolve them.

PHARMACOLOGY/TOXICOLOGY INFORMATION

1. To support the initiation of your proposed clinical trial in pediatric subjects you provided data from a 24-week study in a rat alveolar defect model. According to 21 CFR 50.52, Subpart D, administration of investigational products in pediatric patients should not involve greater than minimal risk, or may involve greater than minimal risk if there is a prospect of direct benefit to the individual subjects. While the submitted rat study provides initial proof-of-concept data to support the formation of new bone following administration of human Wharton's Jelly (WJ), it does not provide sufficient information to assess the safety of administration of WJ in pediatric subjects to repair alveolar cleft palate. Furthermore, we note that this study did not assess the durability of the newly formed bone (i.e., quality of the bone and its ability to bear weight over time), which contributes to the overall safety of the product. Therefore, the rat study is not only insufficient to address safety, but also does not support the prospect of direct benefit of implanting WJ for repair of alveolar cleft palate in a pediatric population. Please conduct a study in a relevant large animal model to evaluate the safety and activity of WJ for alveolar cleft palate. We have the following general comments regarding this study.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
 FOOD AND DRUG ADMINISTRATION
 OFFICE OF ISSUES AND ADVANCED THERAPIES
 10903 NEW HAMPSHIRE AVENUE
 SILVER SPRING, MD 20993-0002

Telephone: (240) 402-8277

Fax: (301) 595-1303

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Fax To: Dr. Charles S. Cox

Facsimile: (713) 500-0714

From: Nevitt Morris, Regulatory Project Manager

Email: Nevitt.Morris@fda.hhs.gov

MESSAGE: IND 17215

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