DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

January 12, 2012

Mr. James H. Bratton, Executive Director,
University of Oklahoma Office of Technology Development
Three Partners Place, Suite 120
201 David L. Boren Boulevard
Norman, OK 73019

Re: Response to Request for Clarification of Waiver of Preference for United States Industry
EIR Titles:
(1) Novel Kinetic Properties of Hyaluronic Synthases (1524003-01-0014)
(2) Group C Hyaluronan Synthase Gene and Uses Thereof (1524003-01-0018)
(3) Streptococcus Equisimilis Hyaluronan Synthase Gene and Expression Thereof in Bacillus Subtilis (1524003-01-0013)

Inventors' Names: Kshama Kumari, Paul Weigel, et al.

Dear Mr. Bratton:

This letter is in response to the University of Oklahoma ("Grantee") e-mail request of May 10, 2011 requesting a clarification of the conditions attached to the Grant of a Waiver of the Preference for United States Industry letter that this office sent on November 19, 2010. While granting the waiver, that letter attached certain conditions that the Grantee wished NIH to clarify regarding the manufacture of the Subject Inventions.

The previous manufacturing waiver approval contained a limitation to the use of a *single* new facility in *either* Bulgaria *or* China which could be used to manufacture recombinant Hyaluronic Acid (rHA). This letter clarifies and amends that decision letter.

Grantee has confirmed that its exclusive licensee has developed two separate products based on the Subject Inventions. These two separate products require that two separate manufacturing sites are necessary due to the two different products being sufficiently unique and not having economies of scale resulting from combining their production into a single facility. In addition, the regulatory reporting requirements are different and the technical demands for purity require different equipment, processes, and techniques. As the Grantee has demonstrated in its request that requiring U.S. manufacture is not commercially feasible at this time, the manufacturing waiver request is approved to take place in two different manufacturing plants, as follows:

i. At a single, existing facility in Bulgaria to be used for the production of cosmetic-grade recombinant hyaluronic acid (rHA); and

ii. At a single facility in China for the production of pharmaceutical-grade rHA.

Grantee should be reminded that the approval of this manufacturing waiver request is for these specific circumstances and does not change any of Grantee's other obligations under the terms and conditions of the funding awards under which the Subject Inventions were made. Grantee's continuing obligations would include, for example:

(1) Grantee is required to request a new U.S. Manufacturing waiver from the NIH that shows it has had unsuccessful efforts to grant licenses on similar terms to potential licensees that would likely manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible at such time as:

   a. Another manufacturing facility is needed because the current facilities in either Bulgaria and/or China become inadequate or insufficient, or for any other reason another manufacturing facility is needed outside the United States; or

   b. Additional products that embody the Subject Inventions are made.

(2) Grantee understands and agrees that the use, license, or transfer of the Subject Inventions will continue to be in compliance with the terms and conditions of the NIH Grants Policy Statement, including both NIH's "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Grants and Contracts" 64 Fed. Reg. Page 72090 (Dec. 23, 1999) (the "NIH Research Tools Policy") and NIH's "Best Practices for the Licensing of Genomic Inventions: Final Notice" 70 Fed. Reg. Page 18413 (Apr. 11, 2005);

(3) Grantee understands and agrees that Grantee and the Subject Inventions will continue to remain subject to 35 U.S.C. §§ 202-212 and 37 C.F. R. Part 401;

(4) Grantee will provide annual reports to NIH regarding how Grantee (and its exclusive licensee) is complying with the terms and conditions of this waiver approval; and

(5) Grantee will provide additional reports/information as requested by NIH, consistent with applicable NIH grants policies, laws, and regulations.

In addition to any other remedy afforded to the U.S. Government for any material breach by Grantee or Grantee's Exclusive Licensee of the conditions of this manufacturing waiver approval (as determined by NIH at its sole discretion), Grantee shall be responsible for the material breach being cured within thirty (30) days after notice by NIH, or any other timeframe determined solely by NIH ("the Cure Period"). If after the Cure Period the material breach has not been cured, NIH may take appropriate action to remedy the material breach, up to and including, but not limited to, revoking all or part of NIH's grant of this waiver approval.

Based on the information the Grantee has provided about the current circumstances for this technology, the NIH approves Grantee's request for a Manufacturing Waiver for two separate locations as described above. Grantee is responsible for ensuring that both the Grantee and its exclusive licensee abide by the terms and conditions of this waiver approval.

This letter supplements earlier correspondence to provide additional clarification as requested. Please refer to the other correspondence for background, history, rationales, other information, etc.

Please feel free to contact us should you have any additional questions regarding this matter.

Sincerely,

John Salzman

Assistant Extramural Inventions Policy Officer
Division of Extramural Inventions and Technology Resources
Office of Policy For Extramural Research Administration, OER, OD

Please direct all correspondence regarding this letter to:
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Pages 4 through 40 redacted for the following reasons:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

November 24, 2010

Mr. Colin M. FitzSimons
Associate Vice President for Technology Development
Executive Director, Intellectual Property Management Office
University of Oklahoma
Three Partners Place, Suite 120
201 David L. Boren Boulevard
Norman, OK 73019-5710

Re: Amendment and partial reconsideration of a Waiver of Preference for United States Industry
EIR Titles: Novel Kinetic Properties of Hyaluronic Synthases (1524003-01-0014)
Group C Hyaluronan Synthase Gene and Uses Thereof (1524003-01-0018)
Streptococcus Equisimilis Hyaluronan Synthase Gene and Expression Thereof in Bacillus Subtilis (1524003-01-0013) **

Inventors' Names: Kshama Kumari and Paul Weigel

Dear Mr. FitzSimons:

This letter is in response to a request by the University of Oklahoma ("Grantee") of July 27, 2010, requesting a reconsideration of conditions attached to a Grant of a Waiver of the Preference for United States Industry as outlined in a letter from this office dated April 22, 2010. That letter, while granting the waiver; attached conditions that the Grantee wishes NIH to reconsider and amend. In addition, the Grantee's request for reconsideration expanded the scope of the Intellectual Property to be covered by the waiver by incorporating additional Subject Inventions as listed above and related Patents. We understand that these were inadvertently omitted from the previous request.

Below is a summary of the commercialization review of the Subject Inventions that are the subject of this Waiver reconsideration. This Office concurs with the review and also agrees that it is in accord with the terms and conditions of the funding agreements under which it was made.

Commercialization Analysis

This case involves a request to manufacture hyaluronic acid (HA) products in a new manufacturing facility to be constructed outside of the United States. The inventors have discovered a means of expressing this protein using a harmless bacterium, *Bacillus subtilis*. The FDA has designated the use of recombinant *B. subtilis* for large-scale bioreactor fermentations as "Generally Recognized as Safe."

The previous manufacturing waiver approval contained an incorrect limitation to the use of an existing facility in Denmark which could be adapted to the manufacture of recombinant HA (rHA).

The principal justification for the current expanded waiver request is that the differential in the labor cost between the U.S. and Bulgaria and/or China is sufficient to make the investment in building a new facility in those locations cost-effective, whereas retrofitting or constructing a facility in the United States or Denmark would not be.

The University of Oklahoma also indicated that its licensee, Hyalose, attempted and failed to license the technology within the United States, hiring a contractor to search for all companies with the capacity to manufacture rHA. They detected eleven such companies (most were foreign); the University of Oklahoma reached out to them to offer licenses, and none expressed an interest in the technology.

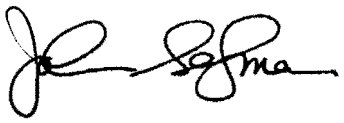
It is apparent that requiring either the construction of the new facility or the retrofit of an existing facility in the United States will unnecessarily delay the introduction of rHA made using the patented technology until after the patents expire. While granting this waiver of the Preference for United States Industry (35 USC 204 and 37 CFR 401.14(i)) will not directly benefit the economy of the United States, this outcome will be outweighed by the public health benefit through the rapid introduction of new, better products, and more vibrant competition for existing products.

As the University of Oklahoma has demonstrated in its request both that requiring U.S. manufacture is not commercially feasible and that the University of Oklahoma has made reasonable but unsuccessful efforts to license within the United States, the waiver is approved for a single new facility in either Bulgaria or China.

Based on the information you have provided about the current circumstances for this technology, your request for a manufacturing waiver has been approved. By each 3rd year anniversary of the date of this letter, you will need to keep our office apprised of what good faith efforts were continuing to be made to consider substantially manufacturing in the US for this technology during each applicable 3 year period. If we do not timely receive this information for each period, then this approval may need to be revisited.

Please feel free to contact us should you have any additional questions regarding this issue.

Sincerely,



John Salzman
Assistant Extramural Inventions Policy Officer
Division of Extramural Inventions and Technology Resources
Office of Policy For Extramural Research Administration, OER, OD

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** (EIR 1524003-01-0013 was the subject of a previous U.S. Manufacturing Waiver and is partially amended and superseded by this approval)

Pages 43 through 46 redacted for the following reasons:

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