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U.S. Manufacturing Waiver Request Form

Submitted to:
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Invention Report Number: 1524003-01-0013

Grantee/Contractor Org: 1524003 University of Oklahoma Health Sciences Center

Grant/Contract Number: GM035978

Invention Title: Streptococcus Equisimilis Hyaluronan Synthase Gene and Expression Thereof in Bacillus Subtilis

Invention Docket Number: 98HSC027-1

Patent Docket Number: 35541.048

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RE: U.S. Manufacturing Waiver Request for Invention Report Number: 1524003-01-0013

I. Introduction

The University of Oklahoma, with funding from the NIH, developed technology for the recombinant production of hyaluronic acid ("rHA"), and subsequently licensed the technology to Hyalose, LLC, a company based in Texas, in 2000. In June 2001, Hyalose, LLC entered into an exclusive option and license agreement with Novozymes A/S ("Novozymes") for the rHA technology.

Novozymes, Hyalose, LLC, and The University of Oklahoma subsequently conducted a joint research project, with funding from Novozymes, aimed at demonstrating the potential for commercial production using the technology. Due in part to the success in meeting early project milestones, Novozymes exercised its option for an exclusive license to the rHA technology in May 2002.

Subsequent feasibility analyses to assess commercialization options for rHA, however, have revealed and led to the conclusion that it is not financially feasible to manufacture rHA in the United States ("U.S.") due to prohibitive costs and lack of consistent production capacity resulting from inadequate equipment. For the reasons provided in this letter, the University of Oklahoma submits, and jointly with Novozymes and Hyalose hereby requests a waiver of the substantially manufactured clause.

II. Significance of rHA

HA is a key ingredient in a large number of medical and cosmetic applications and products. Technical cosmetic applications include high-end care topical moisturizers, high-end suntan lotions, an ingredient in nutraceuticals, and an injectable wrinkle remover and lip augmenter. Some key medical applications of HA include intra-articular injections for osteoarthritis, prevention of post-operative adhesions, intra-ocular surgeries and dermal fillers for cosmetic surgery and urinary incontinence. U.S. companies hold a market leading position in these market segments based on their innovative HA-based products. Examples are listed below:

US-based Companies	Application	Leading Brand
Genzyme	Intra-articular injections for treatment of osteoarthritis	Synvisc
Genzyme	Prevention of post-operative adhesions	Sepra
Alcon / Abbott	Intra-ocular surgeries	Viscoat / Healon
Allergan	Dermal fillers for cosmetic surgery	Juvederm / Hylaform / Captique

Because of its multiple and frequently used applications, HA is one of the most used biomaterials for medical devices in the U.S., and as depicted in the table below, these procedures touch millions of U.S. patients each year, and generate significant income for U.S. based companies:

Indication area	U.S. procedures 2008	U.S. sales 2008 (in millions)
Intra-articular injections for osteoarthritis	3,960,000	535
Prevention of post-operative adhesions	990,000	154
Intra-ocular surgeries	4,370,000	218
Dermal fillers for cosmetic surgery	1,924,000	399
Total	11,244,000	1,306

Source: Market research reports[i].

Benefits of recombinant HA technology

The rHA technology has the potential to deliver a number of important benefits to U.S. patients using HA-based products, as well as U.S. companies sourcing HA for medical applications. Indeed, the technology recently received the golden innovation award during the 2008 Congress on Pharmaceutical Ingredients and Intermediates (CPHI) in recognition of its potential to improve HA sourcing, and also has been referenced in several journals as an important milestone in the development of a high quality HA production system for medical applications.[ii]

Prior to the discovery of the rHA manufacturing technology, there were only two production methods for HA, both of which come with inherent problems that can potentially result in significant quality and safety related issues for patients using HA products, and for companies sourcing HA. This recombinant production technology for HA addresses many of the problems inherent in existing production methods and sets a new benchmark for the manufacture of an important medical ingredient that has been used in the U.S. medical industry for several decades.

The first generation of HA production technology, which is slowly being phased out, is based on extraction of HA from the combs of specially bred roosters. The rooster combs have a high concentration of HA, which has traditionally been extracted in a process involving use of chloroform and multiple organic solvents.

The resulting material has been very expensive to manufacture and given the animal-derived source, there is a potential risk for viral contamination and the presence of avian contaminants that may elicit an immunogenic response[iii]. Several of the marketed products based on avian sourcing thus carry a warning label regarding avian allergies. Examples of major products still using avian sourced material in the U.S. are listed below:

U.S.-based Companies	Indication area	Leading Brand
Genzyme	Intra-articular injections for treatment of osteoarthritis	Synvisc
Alcon / Abbott	Intra-ocular surgeries	Viscoat / Healon
Allergan	Dermal fillers for cosmetic surgery	Hylaform

A second generation technology for HA production was developed to deal with the issue of avian based production. This technology used the pathogenic bacteria *Streptococcus equisimilis* and *zooepidermicus*. Both of these bacteria have a capsule of HA surrounding them, which they use to evade the immune system of both humans and animals during infection[iv].

The use of *Streptococcus* has largely removed the concern regarding an animal extracted source, but has left other issues of concern. In particular, the pathogenic nature of these organisms presents a risk in terms of the potential presence of hemolytic toxins and antigenic proteins. However, manufacture of HA with these strains often requires the use of complex media that contain animal derived components, and close control of the molecular weight of the produced HA polymer is not easily achieved.[v]

The rHA technology is a new source for HA production designed to address the needs for increased purity of HA, as well as an interest in tighter process control that can yield more defined HA polymers in terms of molecular weight[vi]. In particular, a recombinant HA process results in:

- ***Higher purity HA***. The recombinant process is documented to be completely non-animal and thus free of any concerns associated with viral contaminants from animal sourcing. The strain (*Bacillus subtilis*) is non-pathogenic and does not produce any endotoxins or exotoxins, and is used for production of several GRAS (Generally Regarded As Safe) products already approved by the FDA. Furthermore, the purification process employed does not use any organic solvents and is capable of delivering a significantly purer HA product when compared to competing sources of HA. This should translate into purer HA products that will result in fewer potential adverse events for patients, and a greater confidence by U.S. companies in applying HA for applications that require a high degree of control with respect to product purity. Today, there is a strong focus among U.S. companies and the FDA on the presence of endotoxins and antigenic proteins present in some HA sources. In fact, some biomedical companies are pushing, along with the FDA, for tighter controls on these contaminants, which Novozymes believes will be substantially accomplished with the new rHA technology.[vii] The rHA technology makes higher purity HA.

- ***Increased consistency***. Another major issue is that the first and second generation production systems for HA do not yield a reproducible product in terms of the molecular weight of the polymer. This has significant implications for companies working with HA, particularly with large volumes of HA, as it makes it exceedingly difficult to control both the functionality of the final product that is related to the molecular properties and the processing of HA into its final form for medical applications. Many of the U.S. companies Novozymes has spoken with have expressed a very strong need for improved consistency in current sourcing and believe the technology for rHA production can deliver this. Several customers have in fact already signed either letters of intent or supply agreements for the purchase of rHA. The rHA technology makes a better product.

- ***Ability to target molecular weight***. A final consideration is the ability for recombinant technology to deliver a more targeted and defined molecular weight for applications where HA plays a biological role in pharmaceutical applications. By using a well controlled production system, Novozymes has demonstrated the ability to target a specific molecular weight within a very narrow band. Until now this was not possible with the first and second generation production technologies at a large scale. Several companies have expressed a strong interest in this capability. Among the most exciting opportunities are applications for HA within the oncology field, where several studies have shown that very specific molecular weights of HA may have the potential to significantly increase the effect of oncology products and reduce the off-target effects through active targeting of tumor sites. It is believed this occurs in part through the binding of HA to the receptor CD44, thereby resulting in improved therapy options for cancer patients at a much reduced cost versus current targeted biologic therapeutics. The rHA technology makes better medicines.

Beyond the significant technological and health benefits to the U.S. from an improved source for HA, there are several other benefits that can be expected to directly result from a larger scale commercialization of this technology for cosmetic and medical applications:

- ***License fees***. The University of Oklahoma and Hyalose will both receive license income resulting from the sale of rHA products on a global basis. However, sales of HA in the U.S. market is the key driver for value in this case, and without sales in the U.S. market there would be no rationale for commercializing rHA in any other markets. Thus, the current focus is developing a commercial platform for production that can address the needs of the U.S. market.

- ***Increased availability and distribution of the technology***. A waiver will allow full-scale commercial production and increase the availability and distribution of the technology in cosmetic and health products to a greater population through major U.S. companies. Novozymes currently has a significant customer base willing and able to purchase and incorporate technical grade rHA for

cosmetic applications available to U.S. citizens including, [redacted] (b)(4) Further, a waiver will allow for increased availability of higher quality HA for medical applications for the general public, including: visco-elastic devices for joint treatment, dermal fillers, adhesion prevention, ocular visco-elastic devices, dermatology, topical eye care, injectable drug delivery, cell therapy, cystitis, and haemostasis.

- ***Tax revenue***. The commercialization of the rHA and sales in the U.S. will result in tax revenues for the Government.

- ***Job creation***. The commercialization of rHA has the potential to create new jobs in the U.S. to facilitate the sale and distribution of the new product. For example, Novozymes alone has established a US commercial organization based in Boston (Novozymes Biopharma US), which currently has [redacted] (b)(4) sales and sales support staff employed who are involved in the sale of rHA. As the business for HA expands, this group is expected to be further expanded to handle sales and sales support for rHA, resulting in further job creation opportunities over the next 5-10 years.

III. Possible U.S. Manufacturing Facilities Currently Do Not Exist

Unfortunately, as explained below, the benefits of the rHA technology will not be realized if the rHA is required to be manufactured in the U.S. Current HA manufacturing facilities are not set up for rHA production and do not have the necessary capacity and equipment.

A. Manufacturing Requirements

The manufacturing process for recombinant *Bacillus*-derived HA differs significantly from HA produced from the first and second generation processes where the recovery/purification processes are based on precipitation in organic solvents (*e.g.*, ethanol). The manufacturing process for recombinant *Bacillus*-derived HA draws on a mix of processes for biological pharmaceutical ingredients (API's), such as proteins and peptides, and biological polymers. Recombinant *Bacillus* HA manufacturing is based on standard fermentation conditions, which can be controlled in standard fermentation equipment for biological API's (proteins/peptides). Recovery/purification, however, is different from most biological API's. Although the equipment used is not uncommon, the recovery/purification process consumes a disproportionately large amount of filtration capacity and water compared to current biological API processes. The requirements for the bulk product formulation are also extraordinary compared to other biological API's as the *Bacillus* process involves spray drying, a process not commonly used for biological pharmaceutical ingredients. Moreover, the overall process (fermentation → recovery/purification → spray drying) has to be done as one continuous process because the liquid concentrate is not microbially stable during longer storage time. This means that all steps have to take place within the same plant. Finally, because of the medical applications for HA, it is necessary to manufacture HA in a facility with pharmaceutical quality controls (Q7 cGMP), which makes it very difficult to retrofit any non-pharmaceutical facility that would otherwise have been useful.

B. Lack of Capacity at Existing U.S. Facilities

Given the special needs for manufacturing of recombinant *Bacillus*-based HA, especially regarding spray drying, it has not been possible to identify existing production capabilities or capacity in the U.S.

After licensing the rHA technology from the University of Oklahoma, Hyalose LLC hired a consultant to perform market research to identify potential sublicensees for the technology. Hyalose LLC was able to identify eleven companies, many of which were foreign companies, with potential manufacturing capabilities. Hyalose LLC reached out to these companies, but was unable to identify any that had, or were willing to develop, full-scale production capabilities for the new technology. Further, existing U.S. facilities that were screened lacked the right equipment, setup and quality controls, and would thus require substantial retrofitting in order to be useful for rHA production. Indeed, there are no commercially relevant production facilities for cosmetic grade HA producers in the U.S. today.

IV. Assessment of Potential U.S. Manufacturing Options Reveals Domestic Manufacture of HA is not Commercially Feasible

Novozymes, which was not of the eleven companies originally identified by Hyalose LLC (likely due to the fact that Novozymes was not in the HA production business at the time), reached out to Hyalose LLC regarding a potential sublicense for the rHA. Some time thereafter, Hyalose LLC and Novozymes entered into a sublicense for the rHA technology and Novozymes initiated a major strategic review of manufacturing options for long term production of rHA. As set forth in greater detail below, in order to be able to deliver rHA to the U.S. and other markets, production of rHA will have to be placed outside of the U.S. in a lower cost region that allows for lower capital expenditure and lower running capital cost.

Because current U.S. facilities lack the capacity for rHA manufacturing, domestic manufacturing would require either (1) significant redesign and retrofitting of existing facilities at substantial cost, or (2) construction of an entirely new production facility dedicated for this product. Moreover, the operation costs alone of a U.S. facility, whether it be in a retrofitted or new facility, are commercially prohibitive and would ultimately increase the cost of rHA – potentially a very important medical ingredient.

A. Current Facilities Lack Ability to Manufacture rHA

Novozymes began producing rHA for technical applications at its enzyme production facilities in Denmark. Novozymes chose its Denmark facilities for production because they replicated the current production systems available in the U.S., and had food grade GMP equipment that could be adapted reasonably for large scale testing of the new HA production system. Novozymes' U.S. facility also was considered as a possible location for production, and while this facility has some of the equipment needed, it is designed only for production of technical enzyme products within feed, food and technical applications and cannot meet the general equipment and quality requirements for production of rHA.

In addition, Novozymes began testing for different HA applications, including cosmetics and eye care. The testing revealed that full scale production of rHA using the existing equipment at the current U.S. facilities (including Novozymes' Franklinton, North Carolina facility) would not be commercially feasible due to prohibitive costs and lack of suitable production capacity resulting from improper and inadequate equipment. Indeed, to date, production testing for HA at Novozymes' Danish facilities has shown a (b)(4) (b)(4). The conclusions of Novozymes' production testing are supported by the fact that there are no commercially relevant production facilities for cosmetic grade HA within the U.S.

B. Construction of New U.S. Manufacturing Facility Not Feasible

Building and operating a new U.S. facility is not commercially feasible based on cost estimates for U.S. pharmaceutical cGMP facilities and the costs associated with U.S. manufacturing operations when compared against the projected average sales price for HA. The cost of a new facility, even if at Novozymes' current site, where infrastructure, waste water treatment and basic utilities are in place, is estimated to be at least (b)(4) The high investment cost, especially impacts return on investment in the first 3-4 years after launch, where volumes are low and the cost of goods sold ("COGS") exceed the average sales prices substantially. Although average sales price is predicted to climb above COGS long term, this return comes too late to cover the cost of the facility and furthermore is associated with a significant downside risk if average prices in the market drop further (a likely scenario as the patents covering rHA technology begin to run out in 2014 and forward). Regardless, even without the costs associated with construction of a new facility in the U.S., the operation costs alone make domestic manufacture of HA not commercially feasible.

Costs associated with production in U.S.

The total cost associated with production of HA can be divided into variable costs (*e.g.*, raw materials and utilities like electricity and steam consumption), fixed costs (*e.g.*, labor), depreciation of investments and other costs including sales, marketing and R&D support.

Variable costs

The raw material costs are assumed to be the same no matter where in the world the production is planned. This is because of the need for high quality/compendial grade raw materials. The variable costs are estimated on average to be approximately (b)(4) kg HA.

Fixed costs

A major part of the fixed costs are labor costs. An organization and labor analysis was done for operations at a new facility on an existing site (area services such as security and area maintenance not included). The conclusion of the analysis indicates an organizational requirement of (b)(4) full time employees in different positions to run a new HA facility with the requirements for quality, capacity and processes (see Table 1 below). Based on the average employee cost at Novozymes biotech enzyme production plant in Franklinton, North Carolina (see Table 2), labor costs alone for a domestic facility are estimated to be (b)(4)

Table 1: Labor for new HA facility.

(b)(4)

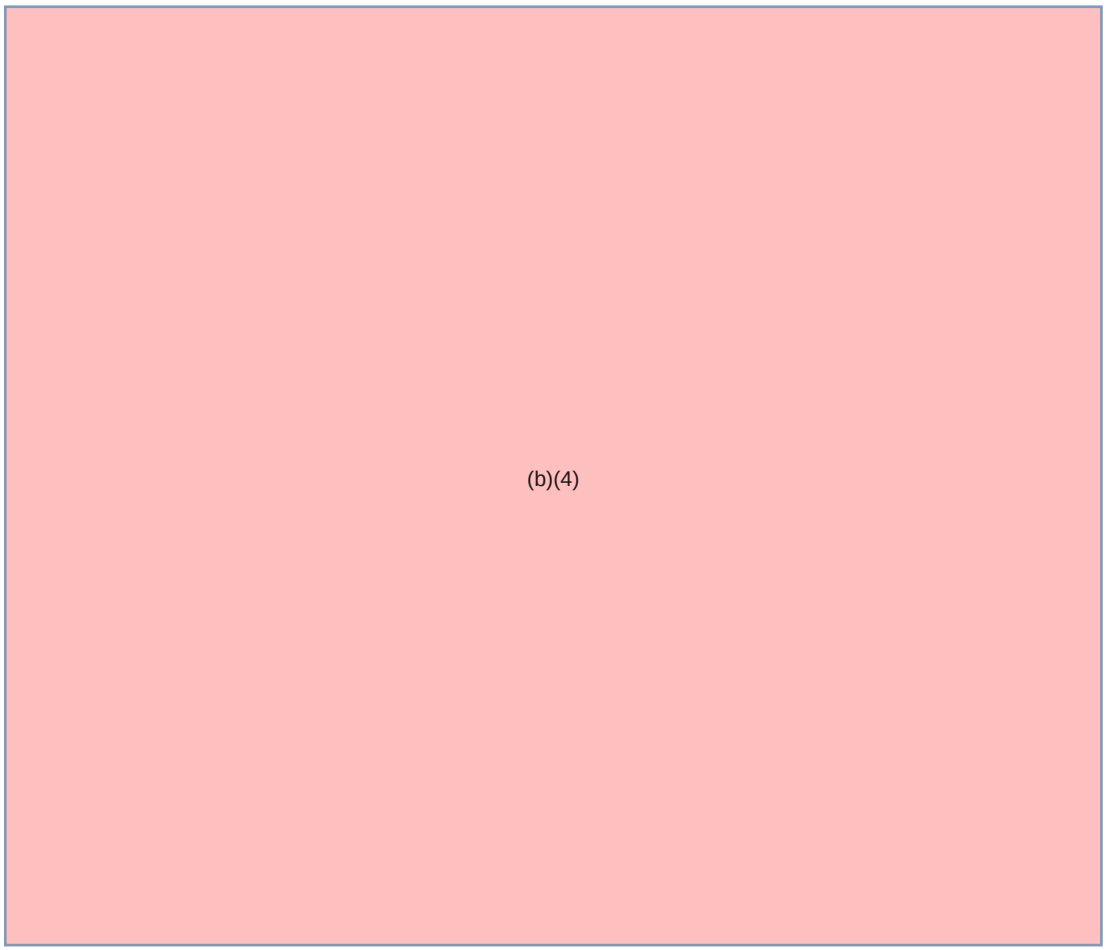
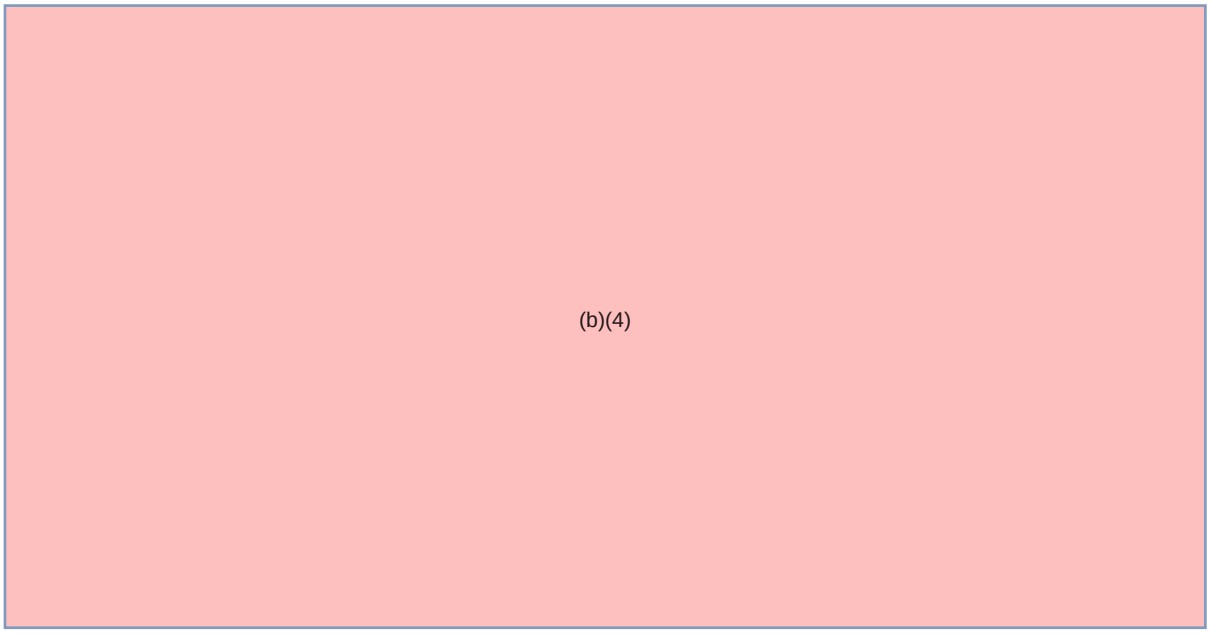


Table 2 Total average employer costs, Novozymes site in Franklinton, NC, 2009.
The average costs include salary/wages, Social Security, Medicare, Unemployment, Occupational Injury, Pension, Medical, Life & Accident Insurance and bonus.
Source: P&O, Novozymes, Franklinton, NC.



Cost of Goods sold (COGS) and sales prices

The resulting total costs of goods sold, including variable and fixed production costs, depreciation and other costs such as sales, marketing and R&D are in the range of (b)(4) kg HA, depending on volume (see figure 1 below).

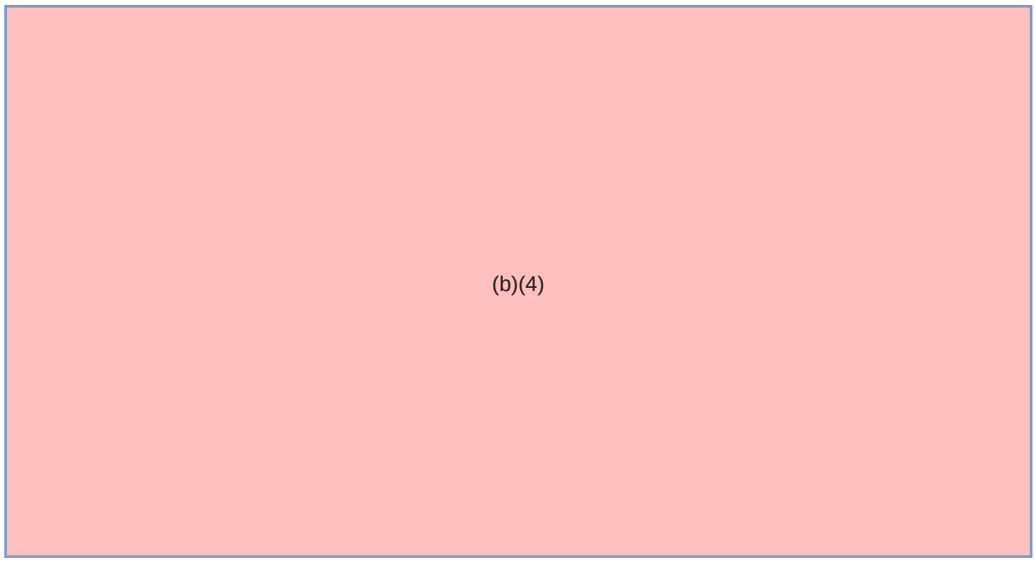


Figure 1. HA sales prices and costs of goods sold per kg assuming production in a new facility in U.S. on an existing site.

Given that average sales prices are expected to be in the range (b)(4) per kg HA (see figure 1 below) it has not been possible to develop a viable business case for establishing U.S.-based manufacturing. This conclusion also is reflected in the discounted cash flow models that Novozymes has used as a basis for a decision on manufacturing options. In this case, Novozymes' model yields a substantial negative return on investment and would lead Novozymes to stop all efforts in commercialization of the rHA technology.

The key issue here is the high investment cost, which especially impacts return on investment (b)(4) While the average sales price is predicted to climb above COGS long term, this return comes too late to cover the cost of the facility and is furthermore associated with a significant downside risk if average prices in the market drop further (a likely potential scenario as the patents covering rHA technology begin to run out in 2014 and forward).

V. Non-Domestic Manufacturing Would Allow Commercialization

In contrast, Novozymes has determined that manufacturing HA in a foreign location, such as China, would allow for financially viable commercial production due to lower capital and labor costs. For example, Novozymes has run a similar cost analysis exercise on facility construction in China, using the same raw material costs and the same expenditure for sales, marketing, R&D. The same requirements regarding quality, capacity, process and equipment were applied in the hypothetical, thus allowing a direct comparison between domestic and foreign facility investment costs and labor costs. As set forth below, non-domestic manufacturing makes commercial production possible.

Manufacturing in a new China facility on Novozymes' existing site

As with the cost estimates for domestic manufacturing, the foreign manufacturing cost estimates assume construction of a new facility at an existing Novozymes' site. Novozymes has non-occupied land in Tianjin, China with existing infrastructure, waste water treatment and basic utilities in place. Investment in a new facility on the existing site in Tianjin is estimated to be approximately (b)(4) the cost for a U.S. facility. Reference: NNE-Pharmaplan basic design cost estimates for China HA pharmaceutical cGMP facility.

Fixed costs

The organization set-up and labor numbers in China are assumed to be the same as in US estimate, however, there is a significant difference in average labor costs. Based on the average salaries for Novozymes' Tianjin site (see Table 3 below), the total labor costs for China have been calculated to (b)(4)

(b)(4)

Table 3: Total average employer costs, Novozymes site in TEDA, Tianjin, China 2008.
The average costs include salary/wages, government mandatory benefits (pension, medical insurance, unemployment insurance, occupational injury insurance, maternity leave and housing), bonus and Novozymes supplementary benefits.
Source: P&O, Novozymes, Tianjin, China.

Cost of Goods sold (COGS) and sales prices

The resulting total costs of goods sold, including variable and fixed production costs, depreciation and other costs including sales, marketing and R&D are in the range (b)(4) /kg HA depending on volume (see figure 2). Based on expected sales prices, the overall business case for China is positive and with a reasonable margin for downside risks such as delays and price erosion. Moreover, obtaining reduced production costs will prevent significant product price increases for the consumer.

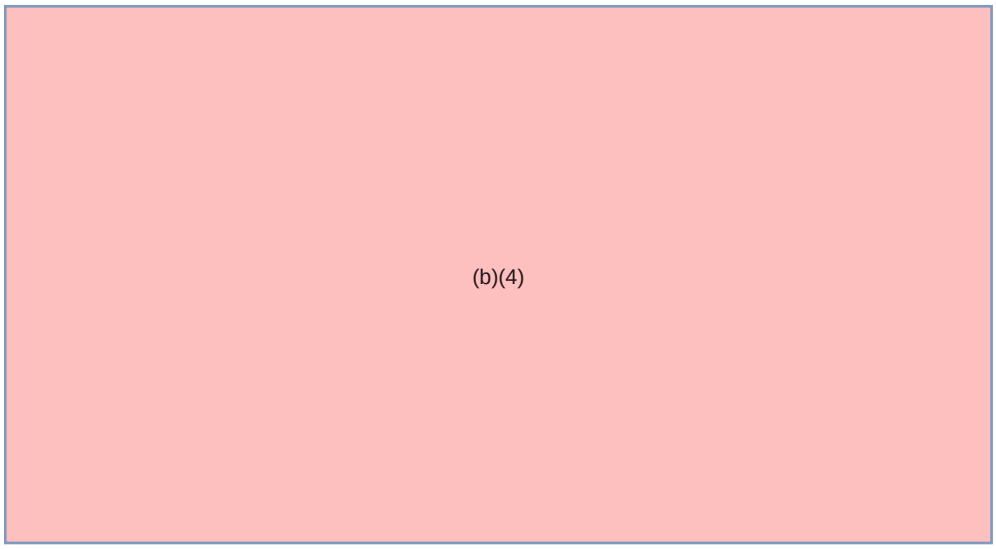


Figure 2. HA sales prices and costs of goods sold (COGS) per kg assuming production in a new facility in China on an existing Novozymes site.

VI. Summary

Substantially manufacturing rHA in the U.S. is not commercially feasible based on economics and logistics. The cost and economic analyses indicate that domestic rHA production cannot be profitable at the present time. Further, no existing U.S. facility currently is capable of manufacturing rHA. However, a domestic manufacturing waiver would allow Novozymes to proceed with full-scale production of rHA and bring an exciting and valuable product to U.S. consumers, including patients, at a lower cost. More importantly, the technology developed by The University of Oklahoma, in cooperation with Novozymes and Hyalose, has the potential to deliver a number of important benefits to both U.S. patients using HA-based products, as well as U.S. companies sourcing HA for medical and technical applications.

Therefore, the University of Oklahoma submits, and jointly with Novozymes and Hyalose hereby requests a waiver of the substantially manufactured clause.

Thank you for your attention to this matter. We look forward to hearing from you.

Colin M. FitzSimons
Associate Vice President for Technology Development
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[i] Frost & Sullivan, U.S. and Western European Adhesion Prevention Products Market, April 2009. Millennium Research Group, Global markets for hyaluronic acid in aesthetic, orthopedic, ophthalmic, and emerging applications, 2008.
[ii] Kogan et al., Biotechnology Letters 2007, 29: 17-25
[iii] Nakano T, Sim JS, Poult Sci. 1994 Feb;73(2):302-7, Rooster comb and wattle tissues contain an anti-keratan sulfate monoclonal antibody epitope.
[iv] J Rheumatol., Sep 1990, 17(9):1230-6, Septic arthritis due to group C streptococcus: report and review of the literature.
[v] Chong BF, Blank LM, Mclaughlin R, Nielsen LK. Appl Microbiol Biotechnol. 2005 Jan; 66(4):341-51, Nov 13, 2004, Microbial hyaluronic acid production.
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[vii] ISTA Pharmaceuticals, Petition for Reconsideration Docket No. FDA-2008-P-0625, June 30, 2009.

Pages 13 through 357 redacted for the following reasons:

Removed by agreement