REGENICIN, INC.

FORM 8-K/A

(Amended Current report filing)

Filed 04/27/11 for the Period Ending 08/13/10

Address	10 HIGH COURT LITTLE FALLS, NJ 07424
Telephone	646-403-3581
CIK	0001412659
Symbol	RGIN
SIC Code	3564 - Industrial and Commercial Fans and Blowers and Air Purification Equipment
Industry	Biotechnology & Drugs
Sector	Healthcare
Fiscal Year	09/30

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K/A
Amendment #3

CURRENT REPORT

PURSUANT TO SECTION 13 OR 15(d) OF
THE SECURITIES EXCHANGE ACT OF 1934

Date of Report (Date of earliest event reported): August 13, 2010

REGENICIN, INC.
(Exact name of registrant as specified in its charter)

Nevada	333-146834	27-3083341
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

10 High Court, Little Falls, NJ 07424
Address of principal executive offices

Registrant's telephone number, including area code: (973) 557-8914

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

[ ] Written communications pursuant to Rule 425 under the Securities Act (17CFR 230.425)
[ ] Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
[ ] Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
[ ] Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Explanatory Note

The registrant files this Amendment No. 3 to the Form 8-K filed on October 12, 2010 to include Exhibit 10.4 in its entirety.

SECTION 1 – Registrant's Business and Operations

Item 1.01 Entry into a Material Definitive Agreement

Securities Purchase Agreement

On August 16, 2010, we sold 4,035,524 shares of our common stock as part of a Securities Purchase Agreement with certain accredited investors (the "Purchasers") pursuant to the closing of our Private Placement Offering (the "Offering"). We received aggregate gross proceeds from the Purchasers of $2,502,025 from the sale of the common stock.

The Purchasers are entitled to certain contractual benefits under the Securities Purchase Agreement, which are summarized as follows:

- For as long as any Purchaser holds our securities, the right to participate in any subsequent financing of our company;
- For as long as any Purchaser holds our securities, restrictions on our ability to issue securities that are convertible into common stock at some future or variable price; and
- For twelve months, restrictions on our ability to undertake a reverse or forward stock split of our common stock.

Further under the Securities Purchase Agreement, we are permitted to issue common shares that are exempt from the above restrictions in certain instances, including limited issuances to employees, officers or directors of the Company pursuant to any stock or option plan.

Pursuant to a Registration Rights Agreement that accompanies the Securities Purchase Agreement, we agreed to file an initial registration statement covering the resale of the common stock no later than 45 days from the closing of the Offering and to have such registration statement declared effective no later than 180 days from filing of the registration statement. The Offering has closed. If we do not timely file the registration statement, cause it to be declared effective by the required date, or maintain the filing, then each Purchaser in the offering will be entitled to liquidated damages equal to 1% of the aggregate purchase price paid by such Purchaser for the securities, and an additional 1% for each month that we do not file the registration statement, cause it to be declared effective, of fail to maintain the filing.

The foregoing is not a complete summary of the terms of the offering described in this Item 1.01, and reference is made to the complete text of the Securities Purchase Agreement and the Registration Rights Agreement attached hereto as Exhibits 10.1 and 10.2.

Lonza Agreement

Under the Know How License and Stock Purchase Agreement (the "Lonza Agreement") that we signed with Lonza Walkersville, Inc. ("Lonza"), upon the payment of $3 million to Lonza we will receive an exclusive license to use certain proprietary know-how and information necessary to develop and seek approval by the U.S. Food and Drug Administration ("FDA") for the commercial sale of PermaDerm™, and Lonza will provide us with certain related assistance and support. We have previously paid Lonza a total of $700,000 toward this Agreement. Following the Initial Closing of the above stock sale, we directed our escrow agent to disperse the remaining $2,300,000 to Lonza to fulfill our obligations under the Lonza Agreement.

PermaDerm™ is the only tissue-engineered skin prepared from autologous (patient's own) skin cells. It is a combination of cultured epithelium with a collagen-fibroblast implant that produces a skin substitute that contains both epidermal and dermal components. This model has been shown in preclinical studies to generate a functional skin barrier, and in clinical studies to promote closure and healing of burns. Critically, self-to-self skin grafts for permanent skin tissue is not rejected by the immune system of the patient, unlike with porcine or cadaver grafts in which rejection is an important possibility.

We believe we can create and implement a successful strategy to conduct additional human clinical trials and to assemble and present other relevant information and data in order to obtain the necessary approvals for PermaDerm™ and possible related products.

Lock-up Agreements and Reserve for Equity Incentive Plan

At the close of the Offering, all officers, directors and key employees of our company, as well as any 5% holders of our securities, entered into lock-up agreements with us for a term of 12 months whereby they agreed to certain restrictions on the sale or disposition of all the common shares held by them.

Our CEO, Randall McCoy further agreed to restrict the sale of 11,288,850 shares of his common stock representing 20% of the number of shares of common stock beneficially owned by him, until such time as we receive approval from the FDA for the commercial sale of PermaDerm™.

Mr. McCoy also agreed to cancel and return to our treasury 4,428,360 shares of his common stock to off-set the potential dilution caused by an equity incentive plan for directors involving the same number of shares that we intend to adopt in the near future.

SECTION 3 – Securities and Trading Markets

Item 3.02 Unregistered Sales of Equity Securities

The information set forth in Item 1.01 of this Current Report on Form 8-K that relates to the unregistered sales of equity securities is incorporated by reference into this Item 3.02.

Aside from the $2,502,025 that was raised in the Offering described in Item 1.01, we converted our senior secured convertible promissory notes (the "Bridge Notes") in the aggregate principal amount of $750,000 that were previously issued to ten accredited investors into common stock. The Bridge Notes provided for a conversion rate of one share per $0.465 of principal and interest. These conversion terms effectively represent a 25% discount to the purchase price per share in the Offering. As such, we issued 1,612,903 shares of our common stock to the note holders.

We previously announced that the placement agents in the Offering agreed to exchange their Offering fee of 7% of the aggregate amount raised into an Offering Subscription at the price per share equal to the other Purchasers in the Offering. Instead, however, the placement agents are now to receive their Offering fee in the amount of 7% the aggregate amount raised in the Offering out of the proceeds.

The common stock was offered solely to "accredited investors" in reliance on the exemption from registration afforded by Section 4(2) of the Securities Act of 1933, as amended, and/or Rule 506 of Regulation D promulgated thereunder.

Section 9 – Financial Statements and Exhibits

Item 9.01 Financial Statements and Exhibits

Exhibit No.	**Description**
10.1	Form of Securities Purchase Agreement*
10.2	Form of Registration Rights Agreement*
10.3	Form of Lock-Up Agreement*
10.4	Know-How and Stock Purchase Agreement
10.5	Agreement*

*previously filed

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

REGENICIN, INC.

/s/ Randall McCoy
Randall McCoy
CEO and Director
Date: April 27, 2011

KNOW-HOW LICENSE AND STOCK PURCHASE AGREEMENT

THIS AGREEMENT is made and entered into as of the day it has been signed by both parties below

by and between :

Regenicin, Inc. , having a principal address at 10 High Court, Little Falls, NJ 07424 (hereafter Regenicin); and **Lonza Walkersville, Inc.** , having a principal address at 8830 Biggs Ford Road, Walkersville, MD 21793 (hereafter LWI or Lonza);

INDEX OF ARTICLES

INDEX OF EXHIBITS

Exhibit A - List of Patent Rights

Exhibit B - Hourly rate for calculation of cost of Future Know-How

Exhibit C – AFIRM Grant Application

Exhibit D - The Amended and Restated Exclusive License Agreement between The Regents of the University of California and Cutanogen Corporation.

Exhibit E – The First Amendment to the Amended and Restated Exclusive License Agreement between The Regents of the University of California and Cutanogen Corporation.

Exhibit F - The License Agreement between Cutanogen Corporation on the one hand and the University of Cincinnati and Shriners Hospitals for Children on the other hand.

Exhibit G – Amendment to the License Agreement between Cutanogen Corporation on the one hand and the University of Cincinnati and Shriners Hospitals for Children on the other hand..

Exhibit H - Settlement Agreement and Release dated February 2, 2006 between the Shriners Hospital for Children, Cutanogen Corporation, the Shareholders of Cutanogen Corporation, and Cambrex Bio Science Walkersville, Inc.

Exhibit I - Manufacturing Agreement.

Exhibit J - Stock Purchase Agreement.

WHEREAS , LWI owns all of the issued and outstanding capital stock of Cutanogen Corporation;

WHEREAS , LWI is engaged in the research and development of products used in the life sciences industry, including engineered skin substitute called PermaDerm™;

WHEREAS , Regenicin wishes to assume responsibility for developing PermaDerm™, and to purchase the outstanding capital stock of Cutanogen Corporation;

NOW, THEREFORE , in consideration of the promises and of the mutual covenants and agreements herein set forth, the parties hereto agree as follows:

Article 1. Definitions

1.1 "Affiliate" means any corporation, company or other entity which directly or indirectly controls, is controlled by, or is under common control with, LWI or Regenicin. For the purpose of this definition, the word "control" shall mean the direct or indirect ownership of more than fifty percent (50%) of the outstanding voting stock of the corporation, company, or other entity.

1.2 "Contract Product" means the autologous engineered skin supplement known as PermaDerm™.

1.3 “Current Know-How” means Know-How that is in the possession of LWI, and that exists on the effective date of this Agreement.

1.4 “Future Know-How” means Know-How that is developed after the effective date of this Agreement by LWI at the reasonable request of Regenicin.

1.5 “Know-How” means information in support of a clinical trial for the Contract Product, including, without limitation, information relating to product specifications, manufacturing, testing, facilities, etc. Know-How includes, but is not limited to, Master Batch Records and SOP’s.

1.6 “Patent Rights" shall mean all patents and patent applications in any country or region of the world that cover Contract Product, and that are owned by or are licensed to, LWI including, without limitation, the patents and patent applications that were licensed by LWI from the University of California, and from the University of Cincinnati and the Shriners Hospital for Children. A partial list of Patent Rights is set forth in Exhibit A.

Article 2. Obligations of the Parties

2.1 This Agreement shall only become effective upon Lonza’s receipt of payment in full to be made by Regenicin of the amount due under paragraph 6.1 below (the “Effective Date”).

2.2 During the term of this Agreement, the obligations of LWI shall include, without limitation:

a. produce and transfer Future Know-How to Regenicin in accordance with paragraph 3.2 below;

b. monitor prosecution and maintenance of Patent Rights in accordance with paragraph 5.2 below;

c. maintain the Licenses, as defined below; and

d. execute the Stock Purchase Agreement in accordance with Article 9.1 below.

2.3 During the term of this Agreement, the obligations of Regenicin shall include, without limitation:

a. reimburse LWI for transferring Current Know-How in accordance with paragraph 6.1 below

b. conduct pre-clinical and clinical trials in accordance with paragraph 8.1 below;

c. apply for and obtain approval from the FDA for commercial sales of Licensed Product in accordance with paragraph 8.1 below;

d. reimburse LWI for providing Future Know-How in accordance with paragraph 3.3 below;

e. reimburse LWI for monitoring prosecution of Patent Rights in accordance with paragraph 5.6 below;

f. reimburse LWI for maintaining the Licenses in according with paragraph 5.7 below; and

g. execute the Stock Purchase Agreement in accordance with Article 9.1 below.

h. Pay the purchase price for the outstanding capital stock of Cutanogen Corporation in according with paragraph 6.2 below.

Article 3. Know-How

3.1 Regenicin acknowledges LWI has transferred the Current Know-How.

3.2 Upon the reasonable request of Regenicin, LWI shall produce and transfer to Regenicin Future Know-How.

3.3 LWI shall send invoices to Regenicin for expenses related to the production and transfer to Regenicin of Future Know-How at a rate based on the number of hours spent by employees of LWI in accordance with the rate provided in Exhibit B, which may be updated from time to time by Lonza.

Article 4. Grant

4.1 LWI grants to Regenicin, and Regenicin accepts, an exclusive license to use Know-How for the sole purposes of seeking FDA approval and, upon such approval, to use, market, offer for sale, sell and otherwise dispose of the Contract Product on a worldwide basis, subject to the terms of this Agreement. Notwithstanding the foregoing, to the extent that any grant of rights to Regenicin hereunder would constitute a transfer, assignment or sublicense of Lonza's or Cutanogen Corporation's right, interest or title in intellectual property that would trigger any milestone payments under the Stock Purchase Agreement, dated December 2005, by and among Lonza, Cutanogen Corporation and the shareholders of Cutanogen Corporation, then such portion of such grant shall be of no force and effect.

4.2 No licenses or rights, including, without limitation, sublicenses under the Licenses, other than those explicitly granted hereunder are, or shall be deemed to have been, granted under this agreement.

4.3 LWI applied for a grant from the Armed Forces Institute of Regenerative Medicine relating to the Contract Product on March 3, 2009 (hereafter AFIRM Grant Application, attached hereto as Exhibit C). Any money received by Lonza during the term of this agreement as a result of the AFIRM Grant Application shall be applied by LWI to development of the Contract Product in compliance with the conditions of the grant, and the results thereof transferred to Regenicin to the extent permitted under the grant.

4.4 LWI applied for a grant from the Department of Defense relating to the Contract Product (hereafter DoD Grant Application). Any money received by Lonza during the term of this agreement as a result of the DoD Grant Application or any other grant relating to the Contract Product shall be applied by LWI to development of the Contract Product in compliance with the conditions of such grant, and the results thereof transferred to Regenicin to the extent permitted under such grant.

4.5 With respect to the AFIRM grant and any other grant that Lonza or its affiliates receives relating to the Contract Product, including, but not limited to, any grant from the Department of Defense, Lonza or its affiliate(s), as the case may be, shall control all such grants and shall be the only point of contact or interface with the grantor. Regenicin shall not be permitted to communicate, directly or indirectly, with the grantor without the express written permission of Lonza.

Article 5. Patent Rights

5.1 The parties acknowledge that certain Patent Rights relating to the Contract Product were licensed to LWI in the following agreements (hereafter, collectively, the Licenses):

Amended and Restated Exclusive License Agreement between The Regents of the University of California and Cutanogen Corporation for "Living Human Skin Replacements and Cultured Skin Substitutes" effective March 3, 2001 (hereafter California Agreement, attached hereto as Exhibit D;

First Amendment to the Amended and Restated Exclusive License Agreement between The Regents of the University of California and Cutanogen Corporation effective November 23, 2005 (hereafter California Amendment, attached hereto as Exhibit E;

License Agreement between Cutanogen Corporation on the one hand and the University of Cincinnati and Shriners Hospitals for Children on the other hand, effective as of August 24, 1998 (hereafter Cincinnati/SHC agreement), attached hereto as Exhibit F; and

Amendment to License Agreement between Cutanogen Corporation on the one hand and the University of Cincinnati and Shriners Hospitals for Children on the other hand, effective as of December 29, 2005 (hereafter Cincinnati/SHC amendment), attached hereto as Exhibit G.

5.2 LWI shall continue to monitor the prosecution and maintenance of Patent Rights that were licensed to LWI under the Licenses, and shall use its reasonable best efforts to obtain effective patent protection for the Contract Product under Patent Rights licensed thereunder.

5.3 Upon execution of the Stock Purchase Agreement in accordance with paragraph 9.1 below, the California Agreement and the California Amendment will be assigned to Regenicin, subject to the written consent of the University of California in accordance with paragraph 22 of the California Agreement.

5.4 Upon execution of the Stock Purchase Agreement in accordance with paragraph 9.1 below, the Cincinnati/SHC Agreement and the Cincinnati/SHC Amendment will be assigned to Regenicin, subject to the prior consent of the University of Cincinnati and Shriners Hospitals for Children in accordance with paragraph 14.4 of the Cincinnati/SHC Agreement.

5.5 Following the execution of the Stock Purchase Agreement in accordance with paragraph 9.1 below, LWI will use reasonable efforts to obtain, at Regenicin's sole expense, any consent required as a condition to the assignment of the California Agreement, the California Amendment, the Cincinnati/SHC Agreement and the Cincinnati/SHC Amendment.

5.6 LWI shall send invoices to Regenicin for all expenses related to the prosecution and maintenance of Patent Rights.

5.7 LWI shall send invoices to Regenicin for all expenses related to the maintenance of the Licenses, including, without limitation, the license maintenance fee of Article 6 of the California Agreement.

Article 6. Payments

6.1 Regenicin shall pay to LWI $3,000,000 (three million dollars) as consideration for Current Know-How and other value transferred or to be transferred by Lonza to Regenicin.

6.2 Regenicin shall pay to LWI $2,000,000 (two million dollars) upon approval by the United States Food and Drug Administration of the commercial sale of the Contract Product as the purchase price of the outstanding capital stock of Cutanogen Corporation transferred to Regenicin under the Stock Purchase Agreement in accordance with paragraph 9.1 below.

6.3 Regenicin shall pay to LWI 33% (thirty three percent) of any money received by Lonza or its affiliates during the term of this Agreement as a result of the AFIRM grant application in consideration for the development of the Contract Product conducted by LWI, and the transfer of the results thereof to Regenicin in accordance with paragraph 4.3 above.

6.4 Regenicin shall pay to LWI 33% (thirty three percent) of any money received by Lonza or its affiliates during the term of this Agreement as a result of any other grant application(s), including, but not limited to, as a result of any Department of Defense grant application, in consideration for the development of the Contract Product to be conducted by LWI, and the results thereof to be transferred to Regenicin in accordance with paragraph 4.4 above, with such payment to be made upon receipt of such grant.

6.5 Regenicin shall be responsible for any milestone payments that are owed, whether upon execution of the Stock Purchase Agreement in accordance with paragraph 9.1 below or otherwise, as well as any milestone payments that, but for this Agreement, would not have been owed by LWI to one or more, including all, former owners of Cutanagen Corporation, including, without limitation, Stephen Boyce, the University of Cincinnati and the Shriners Hospital for Children. Milestone payments covered under this paragraph 6.5 include, without limitation, any milestone payments would have been owed under the Settlement Agreement and Release dated February 2, 2006 between the Shriners Hospital for Children, Cutanogen Corporation, the Shareholders of Cutanogen Corporation, and Cambrex Bio Science Walkersville, Inc. (Exhibit H).

Article 7. MANUFACTURING

7.1 During the term of this Agreement and following execution of the Stock Purchase Agreement in accordance with paragraph 9.1 below, LWI will retain the exclusive right to manufacture Contract Product at a customary margin level as more definitively set forth in the Manufacturing Agreement attached hereto as Exhibit I. Regenicin shall order amounts of Contract Product from LWI for clinical trial, and LWI shall manufacture Contract Product in accordance with the Manufacturing Agreement.

7.2 Regenicin shall pick up the Contract Product manufactured by LWI in accordance with Paragraph 7.1 above, and shall arrange for transportation from a facility designated by LWI to a facility designated by Regenicin for each delivery of Contract Product. All costs, taxes and other expenses relating to such delivery and transport, including, without limitation, insurance premiums, shall be at Regenicin's expense.

7.3 Title, and risk of loss or damage, to any shipment of Contract Product shall belong to Regenicin upon pick up of Contract Product by Regenicin in accordance with Paragraph 7.2 above.

7.4 If, at any time following execution of the Stock Purchase Agreement in accordance with paragraph 9.1 below, LWI is, for any reason, unable or unwilling to supply Regenicin’s reasonable requirements for commercial supply of Contract Product and notifies Regenicin to that effect, LWI agrees that Regenicin may then have the Contract Product manufactured by one or more third parties to the extent necessary in order to permit Regenicin to obtain supply of its requirements of Contract Product (and the license grant set forth in paragraph 4.1 above shall be deemed to be modified to the extent necessary for such purpose).

Article 8. Clinical Trials

8.1. During the term of this Agreement, Regenicin shall prepare for and conduct pre-clinical and clinical trials. Regenicin shall use its best efforts during such trials to obtain approval from the FDA for the commercial sale of Contract Product.

8.2 LWI will support the pre-clinical and clinical trials conducted by Regenicin in accordance with paragraph 8.1 above by providing Current Know-How and Future Know-How in accordance with Article 3 above.

Article 9. Stock Purchase Agreement

9.1 Upon payment by Regenicin to LWI of the milestone payments provided for in paragraphs 6.2 and 6.5 above, Regenicin and LWI shall execute the Stock Purchase Agreement attached hereto as Exhibit J. For the sake of clarity, the Stock Purchase Agreement shall not be effective until all of the milestones due under paragraphs 6.2 and 6.5 above are paid in full.

Article 10. Distribution

10.1 After execution of the Stock Purchase Agreement, LWI will retain exclusive distribution rights for the sale of the collagen sponge of the Contract Product to a third party in accordance with a Distribution Agreement to be negotiated by the parties in good faith. Under the Distribution Agreement, LWI will keep 15% of the sale price as a logistics/distribution fee. Any remaining profit from the sale of the collagen sponge will be split equally between the parties.

10.2 The Distribution Agreement will contain a grant by Regenicin to LWI of a worldwide, transferable, non-revocable license under intellectual property owned by or licensed to Regenicin enabling LWI to satisfy its obligations to manufacture Contract Product under paragraph 7.1 above and to distribute Contract Product under paragraph 10.1 above.

Article 11. Payments

11.1 Except for payment under paragraph 6.1, which is due concurrently with the execution hereof, all payments due in accordance with this agreement shall be made in United States dollars within thirty (30) days of the due date or, as the case may be, of the invoice date. Invoices shall be sent to Regenicin and payments shall be made to LWI at the addresses provided in paragraph 15.5 below.

Article 12. Confidentiality

12.1 Each party acknowledges and agrees that the other party (hereinafter the "Donor Party") owns certain confidential information regarding the Contract Product.

12.2 Confidential Information shall mean all information regarding the Contract Product that is hereafter received by a party to this Agreement (hereinafter the "Receiving Party") from the Donor Party, except that which:

(a) was in the public domain prior to the receipt under this Agreement, or thereafter becomes part of the public domain through no fault of the Receiving Party; or

(b) the Receiving Party can show, by credible written records, was in its possession at the time of receipt under this Agreement; or

(c) is received by the Receiving Party from a third party that is not under an obligation to the Donor Party to maintain the information in confidence.

12.3 All Confidential Information received under this Agreement shall be maintained by the Receiving Party in confidence and shall not be disclosed to any other person or entity without prior written approval of the Donor Party, except as is necessary for the Receiving Party to carry out its obligations under this Agreement.

12.4 All physical material containing Confidential Information shall be returned to the Donor Party prior to or immediately upon any termination of this Agreement, provided however, that the Receiving Party may retain one copy of written materials containing Confidential Information strictly for use as a record of information disclosed by the Donor Party, and to be used for no other purpose without the Donor Party's express written consent.

12.5 The Receiving Party hereby indemnifies and holds harmless the Donor Party against any loss resulting from unauthorized disclosure or use of the Confidential Information by the Receiving Party, its agents, or others to whom the Confidential Information has been disclosed by the Receiving Party pursuant to this Agreement.

Article 13. Term And Termination

13.1 Unless otherwise terminated as provided hereunder, this Agreement shall become effective in accordance with paragraph 2.1 and remain in force from its Effective Date until execution of the Stock Purchase Agreement in accordance with Article 9.1 above.

13.2 In the event either party fails or refuses to perform any of its obligations hereunder (hereafter the Defaulting Party), the other party (hereafter the Terminating Party) may, without waiving any other rights, terminate this agreement.

13.3 If the Terminating Party wishes to terminate this agreement in accordance with paragraph 13.2 above, the Terminating Party shall first provide the Defaulting Party with written notice specifying the particulars of such failure or refusal. This Agreement shall terminate thirty (30) days after receipt of such notice by the Defaulting Party unless, within such thirty (30) day period, the default is fully remedied. Notwithstanding the foregoing, this Agreement may be terminated immediately (i) by the non-Defaulting Party in the event the Defaulting Party breaches paragraph 12 above or (ii) by Lonza in the event Regenicin breaches paragraph 11.1.

13.4 Termination of this Agreement shall not relieve either party to this Agreement of its obligations to make any payment that accrue hereunder prior to such termination, or of its obligations of confidentiality in accordance with Article 12 above.

13.5 In the event this Agreement is terminated earlier than provided for in paragraph 13.1 above by either party for any reason, any money transferred to LWI by Regenicin in accordance with Article 6 above shall be non-refundable.

13.6 In the event this Agreement is terminated earlier than provided for in paragraph 13.1 above by either party for any reason, Regenicin shall return all Current Know-How and Future Know-How to LWI, and will not use Current Know-How or Future Know-How for any purpose.

Article 14. Infringement and Indemnity

14.1 LWI represents to Regenicin that, at the time this Agreement is entered into, LWI has no knowledge of any proprietary right that is owned by a third party that would be infringed by Regenicin's sale or use of Contract Product pursuant to this Agreement. However, LWI does not represent or warrant that Regenicin will not be subject to claims by a third party for infringement of a third party's proprietary rights of which LWI is unaware at the time this Agreement.

14.2 Regenicin agrees to hold harmless, defend and indemnify LWI against all damage, claim, expense and liability, including attorney fees, arising in any way from (i) the offering to sell, sale, or use of Contract Product by Regenicin or its agents or (ii) any actions whatsoever taken by Regenicin, its affiliates, or any of its or its affiliates' respective officers, directors, employees, agents, consultants, independent contractors or representatives in connection with this Agreement, the Contract Product, or Lonza's (or its affiliates') relationship with Regenicin.

Article 15. Miscellaneous

15.1 This Agreement shall be governed by and construed in accordance with the laws of The State of New York, without regard to its conflicts of laws rules.

15.2 This Agreement may only be amended in writing signed by both parties. There are no other understandings, agreements or representations, express or implied, not specified herein. If any provision of this Agreement is held to be unenforceable, such provision shall not render this Agreement or any other provision thereof unenforceable. In the event a provision of this Agreement is held to be unenforceable, the parties shall negotiate in good faith so that such unenforceable provision may be replaced by another provision of similar, but enforceable, effect. If such a replacement is not possible or cannot be agreed upon, the parties will negotiate in good faith so that the value of this Agreement to both parties remains the same despite the loss of the provision held to be unenforceable.

15.3 Regenicin shall not use the name Lonza or LWI or the trade name of a Lonza or LWI product without the express written consent of LWI.

15.4 This Agreement shall not be assigned by either party to this Agreement to a third party without the written consent of the other party to this Agreement, such consent not to be unreasonably withheld.

15.5 Any notice required to be given under this Agreement shall be in writing, and shall be deemed to have been received on the day the notice has been transmitted by facsimile to the correct facsimile number, or three days after deposit in the mail, postage prepaid for first class mail, whichever occurs first. All mail shall be addressed as follows:

If to Regenicin:
Regenicin, Inc.
10 High Court
Little Falls, NJ 07424
Attn: Randal McCoy
With a copy to:
Stevens & Lee
100 Lenox Drive, Suite 200
Lawrenceville, NJ 08648
Attn: Richard J. Pinto, Esq.

If to LWI:
Lonza Walkersville, Inc.
8830 Biggs Ford Road
Walkersville, MD 21793
Attn: David Smith
With a copy to:
Lonza America, Inc.
25 Commerce Drive
Allendale, NJ 07401
Attn: General Counsel

or to such other address as may be specified from time to time in a written notice.

[remainder of page intentionally left blank]

Regenicin, Inc.	Lonza Walkersville, Inc.
By:	By:
Name: Randall McCoy	Name:
Title: Chief Executive Officer	Title:
Date:	Date:

Exhibit A – List of Patent Rights

SURGICAL DEVICE FOR SKIN THERAPY OR TESTING

Country	Filing Date	Serial No.	Issued	Patent No.	Status
United States	6-Mar-02	10/092,237			Published
Canada	3-Mar-03	2478107			Pending
Japan	3-Mar-03	2003-5474811			Published
Europe	3-Mar-03	3713880.7	13-May-09	1483373	Issued
Europe	3-Mar-03	N/A			Pendind
Japan	9-Apr-08	2008-101712			Published

APPARATUS FOR PREPARING A BIOCOMPATIBLE MATRIX

Country	Filing Date	Serial No.	Issued	Patent No.	Status
United States	6-Mar-02	10/091,849	14-Jun-05	6,905,105	Issued
Europe	3-Mar-03	3711377.6			Pending
Canada	3-Mar-03	2478100			Pending
Japan	3-Mar-03	2003-574769			Published
United States	2-Jun-05	11/142,950	18-Nov-08	7,452,720	Issued
United States	23-Oc:-08	12/257,056			Published

Exhibit B – Hourly Rate for calculation of cost of Future Know-How

Lonza Cell Therapy – 2009 Fee Schedules

Labor

Description	Rate
Copying or scanning of records or printed materials at the request of the Client	$85 per hour
Project Management and Technical Documentation This labor rate is for document preparation, technical writing, batch record review, product release, quality reporting, project management, and other technical non-laboratory project related activities as specified by the client	$150 per hour
Tech Transfer Labor This labor rate includes production for tech transfer activities and training runs in a training laboratory	$250 per hour (suite fees do not apply to unclassified labor)
Clinical Production Labor Production of engineering and clinical materials in a cGMP clinical, commercial, or EU suite	$190 per hour + applicable suite fees
Specialist Labor Validation, Regulatory, and/or Tissues Acquisition consulting activities	$300 per hour
Process Development and Bioservices Labor Development activities such as process scale up, assay development, media optimization, performance of bioassays and stability studies	$325 per hour
On-Call Services Surcharge Services requested by the client specifically related to production during off-business hours. Applies to all manufacturing services after 11p.m. and before 6 a.m. as well as for QA/QC services after 6p.m. and before 8a.m	$500 per day per person (in addition to above labor rate)

Other Fees

Description	Fees
Security Deposit Required before Technology Transfer to assure scheduled production and laboratory time	20% of project cost, or $100,000, whichever is less
Standard Regulatory Prices CMC Section, preparation of new DMF – template document describing the LWI manufacturing facility, support of Biologic License Application (BLA) filing	$17,500 for IND $50,000 for BLA
Consumables / Materials (non-GMP) Standard consumable fee capturing all handling and entrance costs for process and assay development	Cost + 15 %
Consumables / Materials (cGMP) Standard consumable fee capturing all handling and entrance costs for cGMP production or testing	Cost + 20 %

Facilities

Description		Shared		Dedicated	
		Weekly	Monthly	Weekly	Monthly
Production Suite	Small Clinical	$24,000	$80,000	$38,000	$140,000
	Large Clinical	$26,000	$100,000	$48,000	$175,000
	Commercial & EU	$35,000	$125,000	$62,000	$225,000

*There is a minimum booking requirement of 1 week in order to transition projects in and out of production suites.

Storage Rates

Post Production Storage of Product: LWI will store in-process, quarantine, and released product for the client in a validated, monitored, controlled Refrigerator, Freezer (<-20 °C), Ultra Low Freezer (<-70 °C) or LN2 freezer at the cost outlined below:

Sample Storage Fee (based on total number of samples stored)

Number of Samples	Price
< 500 samples	$200.00 / month
501 – 1,000 samples	$300.00 / month
1,001 – 2,000 samples	$400.00 / month
2,001 – 5,000 samples	$500.00 / month
5,001 – 10,000 samples	$650.00 / month

LN2 Storage: LWI imposes an additional recurring monthly fee for LN2 freezer unit maintenance and storage of samples. These fees are dependent upon the ownership of the LN2 freezer unit:

LWI-owned unit	$800.00 / month
Client-owned unit	$400.00 / month

Storage rates take effect at the beginning of the month following completion of production. Rates are then prorated upon removal of product from storage.

Shipping Rates

Post Production Shipment of Product: LWI will ship in-process, quarantine, or released product for a shipping fee plus freight. Client may designate carrier and may use their account number for direct billing of freight charges. LWI shipping fees are outlined below:

Shipping Condition	Price
Ambient	$100.00 / shipment
Refrigerated (2-8 ° C)	$100.00 / shipment
Frozen (<-10 °C)	$125.00 / shipment
Dry Ice (<-70 °C) *	$150.00 / shipment
LN2 Shipper (<-140 °C)*	$250.00 / shipment

*Freight is charged for both outbound and return shipments if the container is reusable.

Testing Rates

Testing	Test Code	List Price
Sterility - USP/EP Final Product Testing, Direct Method	6595	$608.00
Sterility - USP/EP Qualification Test, Direct Method (Bacteriostasis & Fungistasis)	6719	$1,750.00
Sterility - Final Container Testing, Membrane Filtration	1226	$608.00
Sterility - Qualification Test, Membrane Filtration (Bacteriostasis & Fungistasis)	6718	$1,750.00
Mycoplasma- Detection Assay, FDA PTC	6606	$1,300.00
Mycoplasma - Qualification of the Test Article for Detection Assay, FDA PTC	7612	$4,620.00
Endotoxin - FDA end product release	6422	$285.00
Endotoxin - Qualification of the Test Article, FDA PTC	80-501	$630.00
Flow Cytometry Test (up to 4 markers)	7621	$1,800.00
Flow Cytometry Test (each additional marker)	7622	$450.00
Sample Handling- Submission of Sample Back to Client	7623	$110.00
Cell Bank Amp - Cell Count (Hemacytometer)	6347	$400.00
Contract Lab Sample Processing	6348	$140.00
Guava Cell & Viability Count	6445	$288.00
Bioburden- General	6428	$795.00

Note: Other test development and testing is available. Please inquire regarding current rates.

Exhibit C – AFIRM Grant Application

02 March 2009

Prof. David Devore
Chief Operating Officer
CeMAR and RCC Consortium of AFIRM
NJ Center for Biomaterials
145 Bevier Road
Piscaraway, NJ 08854

Dear Professor Devore:

On behalf of Lonza Walkersville Inc. (LWI) we submit our grant proposal titled “Expedited availability of autologous engineered human skin for treatment of burned soldiers” to the Rutgers – Cleveland Clinic Consortium of the Armed Forces Institute of Regenerative medicine for your consideration.

Please note that the information from LWI contained in this proposal is confidential in nature and describes proprietary facilities, processes and testing. Please treat our confidential information appropriate.

LWI appreciates the opportunity Dr. Kohn provided to us by allowing us to participate in this proposal. We have greatly appreciated the support and guidance provided by the RCCC-AFIRM team durning development of this proposeal. Should the proposeal receive funding, LWI looks forward to working with RCCC-AFIRM to carry out the clinical trial of LWI’s Engineering Skin Substitute in the near future.

Please do not hesitate to contact LWI should you have any questions about our proposal of need additional information.

Sincerely,

/s/ Shawn Cavanagh	/s/ Kim Warren
Shawn Cavanagh	Kim Warren
President and Head,	Lonza Co-Prinicpal Investigator
Lonza Bio Science	Head of Cell Therapy
	Development
	Lonza Walkersville, Inc.

Proposal
Clinical Trial Supplemental Funding
Due: March 3, 2009

Project: Expedited availability of autologous engineered human skin for treatment of burned soldiers

Period:	1 July 2009 – 30 Jun 2011	
Funds requested:	$1,500,000	
Institution:	Lonza Walkersville, Inc. (LWI)	
Co-PIs:	For LWI as study sponsor:	Kim Warren, PhD
	For AFIRM as compliance officer:	Stanton Gerson, MD
	For the clinical performance sites:	Steven Wolf, MD
Academic partners:	For technical consultation:	Steven Boyce, PhD
Industry partners:	Lonza Walkersville, Inc. (LWI)	
	For regulatory consultation	Howard Schrayer

Project Title:

Expedited Availability of Autologous Engineered Skin Substitutes for Treatment of Burned Soldiers

1.1 Overview

This proposed study involves the production of a novel and superior engineered skin substitute for the treatment of patients suffering from extensive, deep burns. The autologous engineered skin offers reductions in morbidity and mortality after life-threatening burns by decreasing dramatically the need for skin grafts to complete wound closure. Secondary benefits of the engineered skin may include, but not be limited to: fewer surgical procedures for skin grafting, improved cosmetic outcomes, and shorter hospital length of stay. To date, these projected advantages have been demonstrated in a clinical trial involving over 50 pediatric patients
1-3. Specifically, the funding being requested for this phase of the program will support the following deliverables:

- Implementation of cGMP manufacturing for the Engineered Skin Substitute "ESS" (trade name, PermaDerm) by Lonza Walkersville, Inc. (LWI) which holds licenses to patents for the platform technologies. LWI has proven capabilities for manufacture and delivery of cell therapies with operational systems for full validation of product purity and safety. (See section 4.3)

- Preparation and submission of an Investigational Device Exemption (IDE) application to the US Food and Drug Administration (FDA) to perform a limited study with ESS in patients with full-thickness burns involving greater that 50% of the Total Body Surface Area (TBSA). (See section 5)

- Performance of an initial clinical trial in 8-10 subjects to demonstrate safety and to prove the principle for reduced morbidity with ESS in comparison to meshed, split-thickness skin grafts. Successful completion of this study is expected to enable performance of a pivotal trial and lead to FDA approval of this advanced therapy. (See section 6)

1.2 Clinical Setting and Unmet Needs . Medical needs . Mortality and morbidity from burns, trauma, and other skin loss injuries remain significant medical and socio-economic problems estimated to cost more than $1 billion annually in treatment costs and lost productivity 4,5. Burns in the civilian population cause more than 900,000 hospital days in the US annually 6,7, and full-thickness burns require treatment by excisional debridement and split-thickness skin grafting. From 2003-2007, the burn unit at Fort Sam Houston (USAISR) had 1497 hospitalizations, including 656 military, of which 540 were related to the conflict in Iraq 8. However, victims of large burns do not have sufficient donor skin to complete grafting without multiple reharvestings of donor sites at 7-10 day intervals. With each harvest, healing time increases as epithelial sources (glands, follicles) are removed, leaving wounds and donor sites susceptible to microbial contamination. Sepsis, which develops in part from microbial contamination and invasion in wounds, accounts for 75% of deaths from burn injuries9, and is often associated with multiple organ failure10. Other major aspects of recovery from burns, including immune function, positive nitrogen balance 11,12 and physical therapy, all depend on completion of wound closure. A significant source of long-term morbidity is development of scar at both the donor sites of skin grafts, and in wounds grafted with meshed and widely-expanded skin grafts. Conversely, it is well-known that grafting of wounds with sheet grafts suppresses scar formation.

1.3 Technology Overview . Autologous Engineered Skin Substitutes (ESS) . Over more than 20 years, preclinical and clinical studies have resulted in development of autologous ESS. Classified as a medical devices, ESS currently consists of a lyophilized sponge of collagen and chondroitin-sulfate, populated with cultured dermal fibroblasts and epidermal keratinocytes which organize into an analog of skin tissue (Figure 1). The device develops epidermal barrier and basement membrane 13, and releases high levels of angiogenic growth factors, including but not limited to, Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF), and Transforming Growth Factor-beta 1 (TGF-β1) 14-16. In addition, both eratinocytes and fibroblasts in culture are known to release inflammatory mediators which promote transient development of fibro-vascular tissue 17.

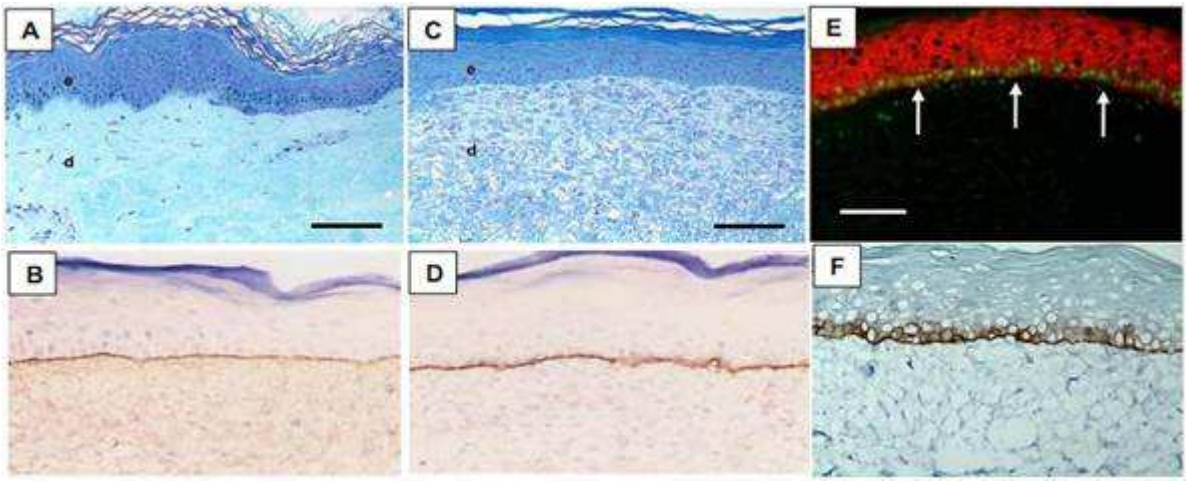


Figure 1. Histology of **A)** native human skin (NHS), and **C)** engineered skin substitute (ESS). The epidermal anatomy of ESS resembles closely that of NHS with proliferating keratinocytes of the epidermal component (e) attached to the dermal component (d), nucleated suprabasal cells analogous to the spinous layer in NHS, and a keratinized surface layer that resembles the protective stratum corneum. Adhesion of the epidermis results from development of basement membrane proteins, **B)** collagen IV and **D)** laminin 5; **E)** BrdU-positive nuclei; **F)** Integrin β4. Scale bar = 0.1 mm.

1.4 Technology transfer and commercial development of ESS . Platform technologies for ESS were originated by Steven Boyce, PhD, at the University of Cincinnati and the Shriners Hospitals for Children between 1989-2009, and at the University of California San Diego between 1985-1988. These technologies are covered by five US patents 18-22, and two European patents 23,24 (see section 11). Based on clinical successes with these technologies, they were licensed to Cutanogen Corporation which was founded by Dr. Boyce. A business plan was developed which included alternative pathways to product manufacturing and marketing through the Investigational Device Exemption (IDE)/Pre-Market Approval (PMA), and/or Humanitarian Device Exemption (HDE) mechanisms of regulatory clearance by FDA. In 2006, Cutanogen Corporation was acquired by Cambrex BioScience Walkersville, Inc (CBSW). In 2007, CBSW and Cutanogen were acquired by Lonza Corporation which is a global biopharma company based in Basel, Switzerland, and which reported 2008 revenues of CHF 2.94 billion 25. Subsequently, CBSW changed its name to Lonza Walkersville, Inc. (LWI), but continued operations from its facilities in Walkersville, Maryland. LWI has made a corporate commitment to the field of cell therapy, and has comprehensive facilities for manufacture of cellular therapeutics in full compliance with regulatory standards for current Good Manufacturing Practices (cGMP; see details in section 4.3). LWI has proceeded with technology transfer for ESS, and has completed multiple engineering runs to manufacture PermaDerm branded ESS. With capabilities in formulation of pharmaceutical-grade nutrient media, tissue acquisition, cell and tissue culture, and cell banking, LWI has an established record as a leader in development and delivery of tissue engineered medical products for regenerative medicine.

In this context, ESS remain the most advanced autologous skin grafts that have been tested in extensive clinical trials. As described above, the dermal component promotes development of epidermal barrier, basement membrane, and release of angiogenic factors to stimulate rapid vascularization. ESS can be handled easily, and forms functional skin tissue within two weeks after transplantation allowing early rehabilitation. By four weeks after grafting, pressure garments can be worn without mechanical loss of healed skin. The primary benefits which have been demonstrated in burns involving greater than 50% of the total body surface area (TBSA) are: a) reduction of requirements for harvesting of donor skin to complete closure 1,26; and, b) lower mortality27. Secondary benefits may include fewer surgical procedures for grafting, earlier wound closure, shorter length of hospitalization, and reduced morbidity from scar. A more complete summary of clinical results is shown below in Preliminary Data.

2. Benefits to the patient:

Clinical Need : Prompt and effective wound closure remains a rate-limiting factor in recovery from extensive, deep burn injuries. To address this limitation, autologous engineered skin substitutes (ESS) have been developed and clinically tested as an adjunctive treatment to conventional skin grafting. Completed clinical studies show a reduction in the requirement for harvesting donor skin to complete wound closure. Technology for ESS has been licensed to Lonza Walkersville, Inc. which has completed technology transfer and product development. ESS may allow reductions in morbidity and mortality for soldiers who are casualties of combat-related burn injuries. Stated simply, autologous ESS offer a life-saving alternative therapy to patients with catastrophic burn injuries.

This proposal complements the funded AFIRM project for ESS by expediting the path to clinical treatment of wounded soldiers. This supplement provides precisely the resources needed to facilitate and expedite the availability of ESS for clinical study and treatment of extensive burns in military populations. The requested funding will also serve to establish a platform of clinical studies at the USAISR or other clinical centers to which advanced models of ESS with pigment or vascular networks may proceed more rapidly. Performance of the clinical studies will be sponsored by the Lonza Walkersville, Inc., with full regulatory support from the Clinical Trials Core facility of the RCCC-AFIRM directed by Stanton Gerson, MD, at the Case Western Reserve University.

3. Impacts:

Availability of autologous ESS will reduce morbidity from harvesting of donor skin autografts, and reduce mortality as previously demonstrated in pediatric populations with burns of greater than 50% TBSA 1,26,27. The enrollment criterion of 50% TBSA burns relates to the amount of available donor skin, and 4-week time period required to fabricate the study device. Patients with burns smaller than 50% TBSA can be treated by conventional grafting in about 4 weeks. For massive burns (>50% TBSA), increased availability of engineered skin is also expected to reduce total numbers of surgical procedures for skin grafting, total length of hospital stay intensive care days, total blood loss and requirements for transfusion, and to improve functional outcome and quality of life after discharge from the hospital. However, the full impact of this therapy has been reduced by the limited quantity of devices which can be generated in Dr. Boyce's research laboratory (i.e., ~900 cm2 or ~1 ft2 each week). Based on an approximate TBSA of an adult male of 2.0 m2, and a demonstrated ability to expand donor skin by 100 times its original area, about 0.02 m2 (200 cm2), or 1% TBSA of uninjured skin is needed to resurface the entire body. This principle for conservation of donor skin will be proven in the proposed study, but on a reduced scale to meet the requirements of statistical power analysis (see section 6.5) and the available budget. An average dosage of study devices will be 0.4m2 (4,000 cm2) generated from a skin biopsy of 40 cm2. This dosage in an adult male represents ~20% of the TBSA. Table 1 shows an example for an adult with a full-thickness burn of 80% TBSA. This example assumes expansion of AG by 1:4, and ESS by 1:100.

Table 1. Theoretical (white middle row) and proposed (shaded bottom row) impacts (shaded columns) of ESS compared to split-thickness skin autograft (AG) for a full-thickness burn of 80% TBSA

A	B	A*B	C	A*C	A*C*0.25	D	A*D	A*D0.01
TSBA (cm2)	Burn % TSBA	Burn (cm2)	AG TSBA	AG (cm2)	AG Donor Area (cm2)	ESS TSBA	ESS (cm2)	ESS Donor Area (cm2)
20,000	80%	16,000	20%	4,000	1,000	60%	12,000	120
20,000	80%	16,000	60%	12,000	3,000	20%	4,000	40

The budget of this proposal will provide 40,000 cm2 of ESS for a clinical trial in 8-10 subjects. Therefore, the dose of ESS for each subject will average 4,000 cm2 (4.4 ft2) and be generated from a skin biopsy of an average area of 40 cm2 (0.044 ft2). This design will prove the principle of the primary end point which is reduction of donor skin harvested for wound closure. The full clinical impacts of the ESS technology will require larger doses of ESS per patient which will require commercial scale-up after successful completion of this study. After scale-up, 1 m2 of ESS could be delivered in 4-6 weeks.

4. Preliminary Data:

4.1 Preclinical studies . Characterizations of ESS in vitro have included anatomic and physiologic comparisons with natural human skin, incorporation of melanocytes to generate pigmentation (Figure 2), addition of microvascular endothelial cells to promote organization of a vascular plexus 28, and grafting to athymic mice to assess changes in these properties, and stability of healed skin over extended periods of time 13,29. Genetically-modified ESS have also been reported by Dorothy Supp, Ph.D., for expression of PDGF, VEGF, beta-defensins, both in vitro and in after grafting to athymic mice 30,31. This model has also been used to study electro-spun biopolymer scaffolds and stem cell populations. The model is also readily adaptable for studies of regeneration of nerve and epidermal adnexi (glands and hair).

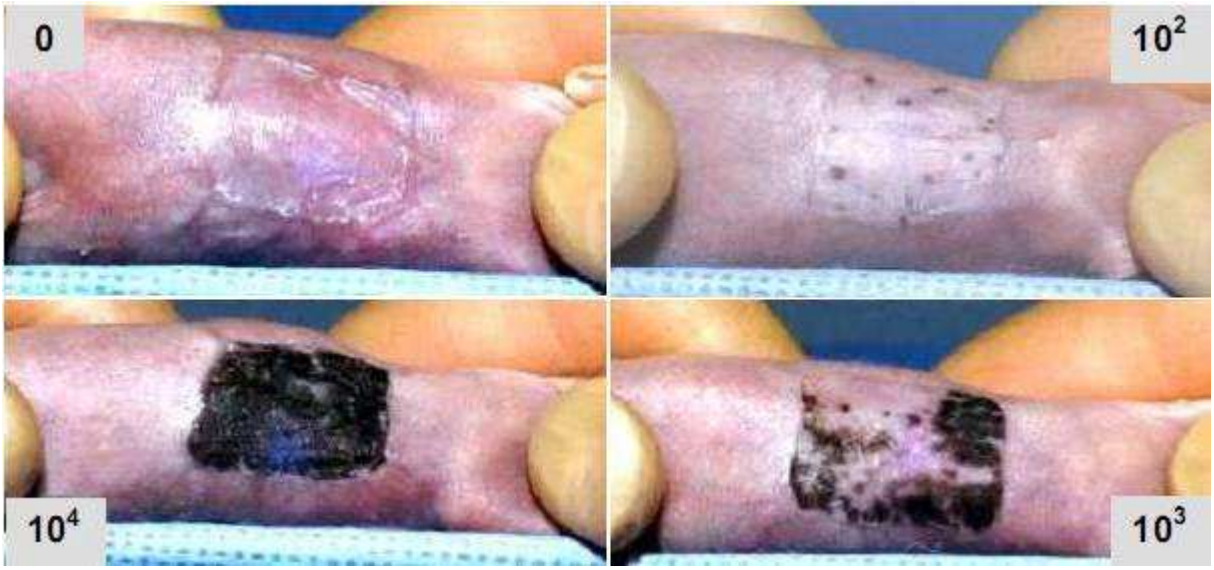


Figure 2 . Density-dependent pigmentation of ESS at 5 weeks after grafting to athymic mice. **Upper left**) 0 HM added, and no pigment develops. **Upper right**) 400 HM added to a 4 cm2 ESS graft (1X102 HM/cm2) develop infrequent (<40) foci of pigment. **Lower right**) HM added at 1X103 HM/cm2 develop partial (~50% area) pigmentation. **Lower left**) Addition of 1X104 HM/cm2 generates complete pigmentation in 5 weeks.

4.2 Clinical studies of ESS in burns . *Boyce et al. 2006. J Trauma Crit Care 60(4):821-829* . Engineered skin substitutes (ESS) were evaluated in 40 patients under IDE G980023 between 1998 and 2003. From 2003-2005, an additional 14 patients were evaluated for a total of 54.2 Although ESS remain investigational, they have become part of the local treatment protocol for patients suffering from burns of greater than 50% of the total body surface area ("TBSA"; Fig 3). Data on the following pages describe the impacts of ESS on quantitative coverage of burns, and on qualitative assessment of scar. ESS protocols now conform to clinical schedules for grafting in a two-stage procedure, irrigation with antimicrobials for 5 days, and initiation of rehabilitation at 7-10 days after grafting. The primary benefits to patient recovery are reduction of requirements for donor skin harvesting, and reduction in the mesh ratio for split-thickness skin grafts. These benefits result in fewer donor sites, less pain and reduced scar at both the harvest site and the graft site.
Patients and their families affirm these benefits. Percentages of treated areas closed at post-operative day POD 14, and the ratio of closed to donor areas at POD 28 (54 patients) are shown in Figure 4. Engraftment at POD 14 was 79.5 ± 2.1% for ESS and 95.7 ± 2.0% for skin autograft AG, (Fig 4A). Wounds closed with ESS covered 61.5 ± 8.4 times the area of the donor biopsy (Fig 4B) compared to 4:1 expansion of meshed autograft. These values were different statistically ($p=0.006$) by one-sample t-test, and demonstrate the reduction of donor skin harvesting by grafting of ESS in place of AG. This result defines a new medical benefit to burn patients by autologous ESS. These data demonstrate that comparable rates of engraftment for ESS and AG, and that 1% TBSA of donor skin can close ~60% TBSA of excised burn. Vancouver scores for ESS were statistically lower ($p<0.05$) than AG during the first six months after grafting, and not different at six months or after (Fig 4C).

Figure 3. Clinical photos after grafting of engineered skin substitutes (ESS) and meshed, split-thickness skin autograft (AG) to the torso of a patient with 77% TBSA burns. **A,B)** ESS applied in the operating room; **C)** Post-operative day (POD) 14, wounds closed & rehab begins; **D)** POD 69, stable wound closure, no blisters, no regrafting, **E)** POD 479, pliable, hypopigmented skin. Scales in centimeters.

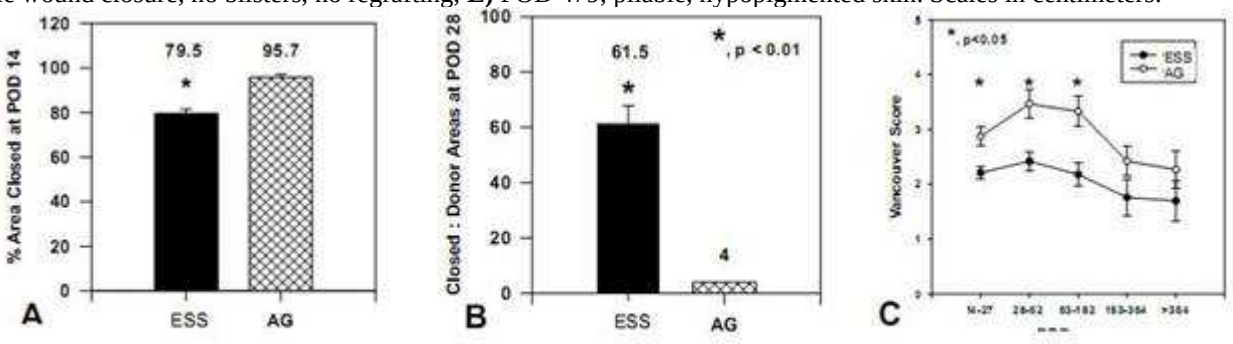


Figure 4. Quantitative outcomes of ESS and AG in treatment of pediatric burns (n = 54). A) % of treated area closed shows ~80% engraftment of ESS; B) Closed: donor ratio; C) Vancouver scores for ESS were as good or better than AG during the first year after grafting. (*, $p<0.05$) Importantly, the closed: donor ratio of ~60 (B) demonstrates a significant reduction in donor skin harvesting for patients treated with ESS, and defines a new medical benefit for these patients.

Two recent cases of pediatric burns of greater than 90% TBSA were treated successfully with auto-ESS. ESS were prepared from split-thickness skin biopsies collected after enrollment of the burn patients by Informed Consent into a study protocol approved by the local Institutional Review Board. Subject #130 was a 10 year-old male who sustained 94% TBSA burns, and Subject #131 was a 2 year-old female who sustained 90% TBSA burns. The injuries were all full-thickness, and occurred in separate building fires in 2007. ESS were prepared from autologous keratinocytes and fibroblasts which were isolated from split-thickness skin, cultured, and cryopreserved for later use. Cells were combined with collagen-based sponges, and incubated at the air-liquid interface to promote formation of epidermal barrier. ESS and split-thickness skin autograft (AG) were applied in a matched-pair design with each patient serving as their own control. The first application of ESS was compared to AG for all end points, and subsequent applications of ESS were added to the first and quantify device efficacy. Data collection consisted of photographs, area measurements of donor skin and healed wounds at post operative days (POD) 14 and 28 after grafting, and healed tissue biopsies as available. Data are expressed below as mean values for these two subjects for: A) % area closed at post-operative day (POD) 14, B) %TBSA closed at POD 28, and C) ratio of closed to donor areas at POD 28. Due to the small sample size, mean values were calculated, but no statistical analyses were performed.

Figure 5. Comparative grafting of engineered skin substitutes (ESS) and meshed, split-thickness skin autograft (AG). **Left)** ESS is applied readily with forceps and adheres rapidly to wounds. **Right panel)** Comparative grafting of ESS and AG on the anterior torso of subject #130. Scale in centimeters.

Prior to treatment with ESS, wounds were excised, and grafted with either meshed, allograft skin or Integra Dermal Regeneration Template. Two-stage grafting was performed in which the allograft or silicone layer of Integra was removed, and wounds were treated overnight at two-hour intervals with alternating irrigations of 5% Sulfamylon solution and double antibiotic solution (200 U/mL polymyxin B and 40 μg/mL neomycin) 32. The following morning, the dressings were removed in the operating room, hemostasis was obtained with electrocautery and compression. Autograft skin was harvested at a thickness of 0.010-0.012 inches thickness, and meshed and expanded 1:2. ESS were applied with a dressing of N-Terface, and AG was applied directly to the prepared wounds. Grafts were stapled to the wounds, dressed with fine-meshed gauze and bulky gauze with perforated red rubber catheters and secured either with a Spandex stent or with elastic wrap bandages. Sites were irrigated for five days with a formulation of non-cytotoxic antimicrobial agents 1 at a dosage of 1mL/cm2 three times per day. Dressings were changed on POD 2. On POD 5, wet dressings were discontinued, and all dressings and staples were removed. Open areas of ESS were dressed with a topical ointment consisting of equal parts Neosporin, Bactroban and Nystatin on Adaptic. Open areas of AG were dressed with a topical cream consisting of equal parts Silver sulfadiazine, Bacitracin and Nystatin on Adaptic. Keratinized areas of ESS were treated with moisturizing lotion (i.e., Curel) beginning at POD 11, and moisturizing cream (i.e., Eucerin) was applied to AG beginning at POD 7. Both graft types were treated according to the AG protocol beginning at POD 15. Results: Subject #130 received 12 applications of ESS over 4 months, and Subject #131 received 7 applications of ESS over 3 months. Average % engraftment (dry epithelium) at POD 14 was 72.4% for ESS and 96.9% for AG. Partial regrafting was performed in 8 of 12 ESS sites (66%) for Subject #130, and 4 of 7 ESS sites (57%) for Subject #131. The average ratio of closed wound area to donor skin area at POD 28 was 125.5 for ESS, compared to 4.0 for AG. Average %TBSA closed at POD 28 was 51.4% for ESS, and 40.6% for AG. Physical therapy was resumed beginning at POD 7, and ESS which was healed at POD 28 did not blister or ulcerate subsequently. Patients wore pressure garments over all treated areas. Pigmentation of areas treated with ESS was deficient, but pliability of healed skin was acceptable. Figure 6 shows images of Patient A at the time of hospital discharge, 187 days after the first treatment with autologous engineered skin.

Conclusions: These results illustrate that ESS offers the potential to reduce requirements for donor skin harvesting for grafting of excised, full-thickness burns involving most of the TBSA. Survival of these two patients after treatment with ESS is consistent with previous findings that autologous engineered skin is associated with reduced harvesting of donor skin autograft 1, and decreased mortality in matched patient populations 27. Availability of ESS for treatment of extensive, deep burns may reduce time to wound closure, morbidity and mortality in this pediatric patient population.

Figure 6. Subject #130, a 94% TBSA burn with healed ESS and AG at POD 187. Top panels) Torso and arms. Bottom panels) Legs. Wounds close rapidly because of epidermal keratinization in vitro, and do not blister because of basement membrane formation. igmentation of most areas treated with ESS was deficient, but pliability of healed skin was acceptable. The patient wore pressure garments over all treated areas. Application as non-expanded sheets reduces granulation and scar to generate a relatively smooth surface. Scale in cm.

Figure 7. Photos of subject #131 at post-burn day 370 after grafting of engineered skin substitutes (ESS) and meshed, split-thickness skin autograft (AG) for treatment of 90% TBSA burns. Left panels, anterior) ESS provides stable wound closure and generates skin which is smooth, soft and strong. Right panels, posterior) Pliability of healed skin allows free ambulation. Scales in centimeters.

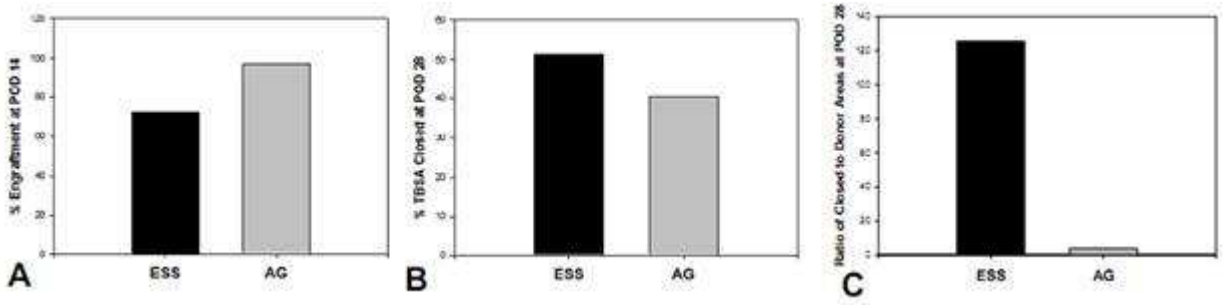


Figure 8. Quantitative outcomes of ESS and AG in treatment of two pediatric patients with ≥90% TBSA burns. **A)** % of treated area closed at POD 14 was 72.4% for ESS and 96.7% for AG **; B)** % TBSA closed at POD 28 was 51.4% for ESS and 40.6% for AG; and, **C)** Closed:donor ratio at POD 28 was 125.5 for ESS compared to 4 for AG. Importantly, the closed:donor ratio of ~125 (C) demonstrates a significant reduction in donor skin harvesting for patients treated with ESS, and defines a new medical benefit for these patients.

Taken together these studies provide a solid foundation for prospective studies with ESS in adults, and for increased availability through fabrication by a commercial manufacturer. The requested funding is anticipated to expedite the availability of ESS to wounded soldiers, to reduce their suffering during hospitalization, decrease morbidity and to improve their long-term quality of life.

4.3 ESS process

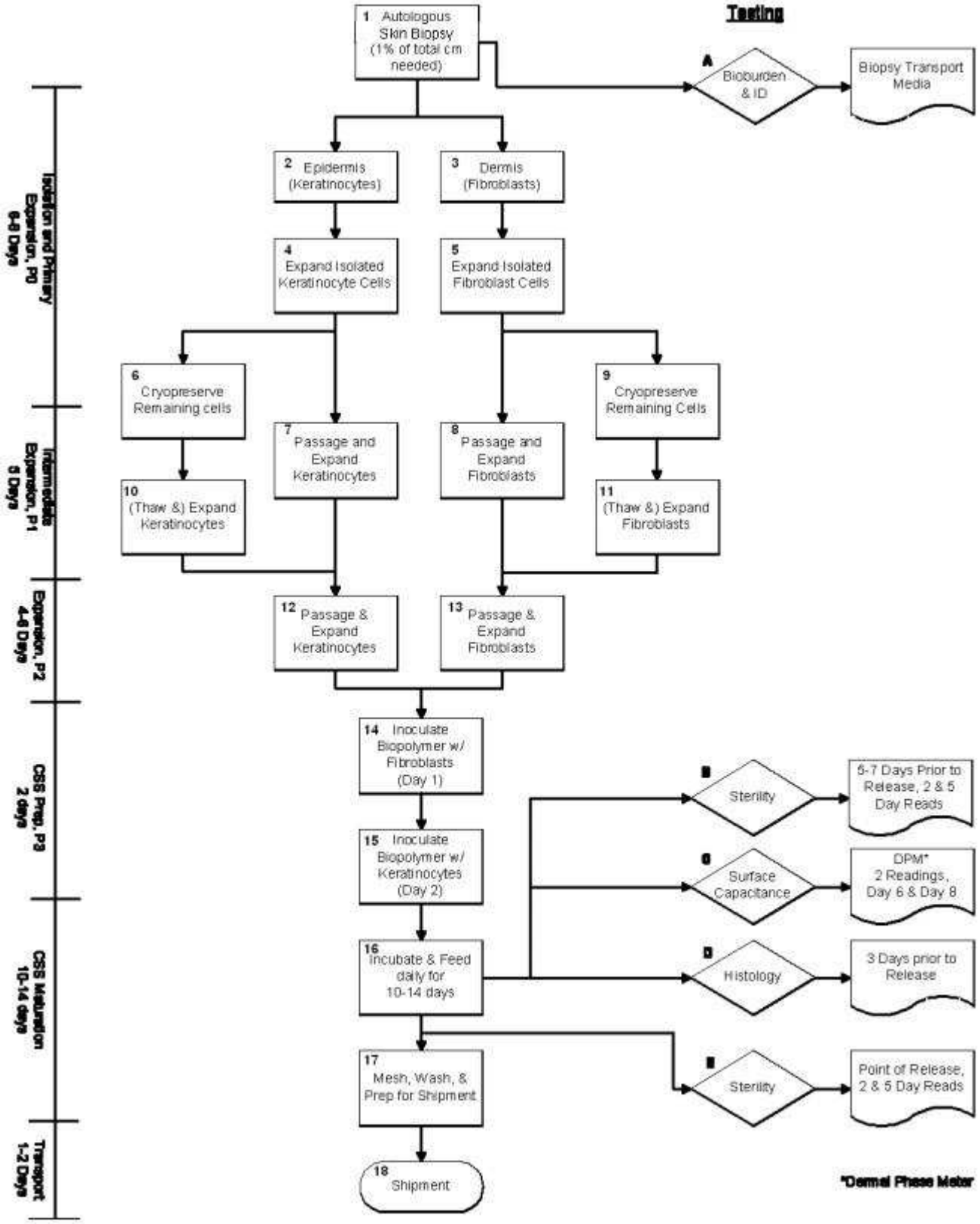
The technology transfer of the ESS manufacturing process took place in 2006 and included activities such as set-up of all project-specific parts, technician training on cell isolation, cell expansion and inoculation, lab set-up, and acquisition of all necessary equipment. Technical transfer and training also included release assays and in process testing procedures, including histology and surface hydration testing.

4.3.1 Current manufacturing process

Lonza's Cell Therapy Process Development staff has made significant improvements to the process since its acquisition. Lonza has qualified new raw material suppliers and improved formulations, including changes to the media, antibiotics, and a decrease in growth factors used in the process. Lonza also made changes to cell culture vessels and purchased a custom-made material for ESS lifting. The current process begins with an isolation of keratinocytes and fibroblasts from a donor biopsy. Each cell type is expanded separately until 75-95% confluent (6 to 8 days). This stage of culture is referred to as Passage 1 (P1). At this point, a portion of the cells are expanded through P2 and P3, with a passage occurring every 6 to 8 days. The remaining portion of the cells is cryopreserved for a second round of expansion and ESS production. Each patient receives two ESS grafts approximately two weeks apart. When the expanded cells reach confluence in the P3 stage, they are harvested and inoculated onto pre-hydrated collagen biopolymers. On the first day of inoculation, fibroblasts are harvested, concentrated, and seeded onto biopolymers in a dropwise fashion at a specified concentration. The fibroblasts absorb onto and migrate through to the lower surface of the biopolymer over the next 24 hours. The next day, keratinocytes are harvested, concentrated, and put onto the same biopolymers in a dropwise fashion. The keratinocytes continue to grow on the upper surface of the ESS. Inoculated grafts sit on sterile lifting frames so that they receive the correct amount of moisture on the lower surface (fibroblast surface) and little to no moisture on the upper surface (keratinocyte inoculated surface). The biopolymer is a collagen-glycosaminoglycan (CAG) substrate produced by lyophilization of the collagen-GAG slurry, followed by dehydrothermal treatment and terminal sterilization by gamma irradiation. It has been and will continue to be produced by Lyophilization Services of New England (a FDA registered cGMP manufacturer with expertise in collagen substrate production), or a comparable supplier. An outline of the process is in Figure 9.

Figure 9.

Process Flow



4.3.2 Development of Manufacturing Batch Records (MBR) for cGMP manufacture .

Beginning in 2006, Lonza developed a comprehensive set of standard operating procedures for manufacturing for ESS. These procedures are referred to as Manufacturing Batch Records on which each procedural step is specified and verified for each manufacturing run. Examples of MBRs include, but are not limited to:

4.3.2.1 Skin biopsy collection and shipping
4.3.2.2 Cell isolation and primary culture of fibroblasts and keratinocytes
4.3.2.3 Harvesting of cultured cells for:
Serial passage
Cryopreservation in liquid nitrogen
4.3.2.4 Recovery from cryopreservation and subculture
4.3.2.5 Expansion of cell populations
4.3.2.6 Inoculation of cells onto biopolymer sponges
4.3.2.7 Incubation at the air-medium interface
4.3.2.8 Quality Assurance testing by histology and epidermal surface hydration
4.3.2.9 Sterility testing for product release

These MBR procedures have been organized into a process flow diagram which is shown on the following page (Figure 9). This process has been used repeatedly in development and engineering runs at Lonza to reproduce the ESS technology, and to upgrade the procedures and reagents used previously to meet standards for current Good Manufacturing Practices. This process and these procedures will be combined with documentation for facilities validation and reagent certifications to submit to FDA for clearance to manufacture ESS for the proposed clinical trial.

4.3.3 Development Runs at Lonza

The ESS project at Lonza has included research and development for process improvements. Currently Lonza has performed 6 development experiments, 9 full engineering runs, and 22 partial engineering runs. Developmental research at Lonza has been focused on the reduction of animal origin materials, media optimization, improved cell yield from isolation, reduction of growth factors, and comparable or improved growth of keratinocytes and fibroblasts before and after inoculation of ESS. Engineering runs and experiments varied in size and remained small for training purposes. Expected yields can be based on the following results:

Development Run Example A
Biopsy size= 30 cm2
Number of days in culture: P1= 6 P2= 5 P3= 5 on ESS= 13
Total Number of days before release= 30
Total ESS made from 2E6 fibroblasts and 4E6 keratinocytes= 8
Potential total amount of ESS produced per lot= 2385 cm2
Total skin expansion = ESS area / biopsy area = 2385 / 30 = 80 fold

Development Run Example B
Biopsy size= 42 cm2
Number of days in culture: P1= 7 P2= 6 P3= 6 on ESS= 14
Total Number of days before release= 33
Total ESS made from 2E6 fibroblasts and 4E6 keratinocytes= 4
Potential total amount of ESS produced per lot= 4706 cm2
Total skin expansion = ESS area / biopsy area = 4706 / 30 = 157 fold

Estimated Model for Clinical production lots
Biopsy size= 30 cm2
Number of days in culture: P1= 6 P2= 6 P3= 6 on ESS= 13
Total Number of days before release= 31
Total ESS made from 2E6 fibroblasts and 4E6 keratinocytes= 20
Potential total amount of ESS produced per lot= 3600 cm2
Total skin expansion = ESS area / biopsy area = 3600 / 30 = 120 fold

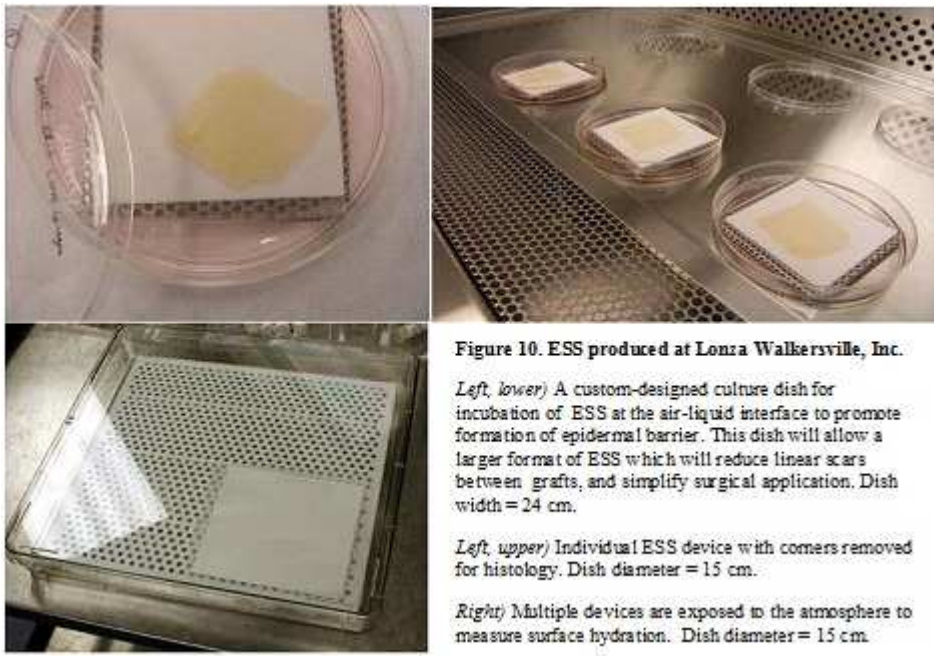


Figure 10. ESS produced at Lonza Walkersville, Inc.

Left, lower) A custom-designed culture dish for incubation of ESS at the air-liquid interface to promote formation of epidermal barrier. This dish will allow a larger format of ESS which will reduce linear scars between grafts, and simplify surgical application. Dish width = 24 cm.

Left, upper) Individual ESS device with corners removed for histology. Dish diameter = 15 cm.

Right) Multiple devices are exposed to the atmosphere to measure surface hydration. Dish diameter = 15 cm.

4.3.4 Production Plan

Lonza plans to carry out additional development runs including final engineering runs. Lonza will then be prepared for the isolation and expansion of a 30-40 cm2 biopsy per patient over a 4-6 week time period into multiple ESS grafts. Two production runs of ESS grafts will result in a final total area of 3,600 to 4,200 cm2 for each patient. The ESS grafts will be applied in two separate procedures approximately two weeks apart. The second cell expansion will be performed using the cryopreserved P1 cells (as referenced in section 4.3.1).

4.3.5 Status of GMP process and compliance

Lonza has developed this product and manufactured ESS grafts that are acceptable according to histology testing, surface hydration testing, visual inspection and safety testing procedures. Product made at LWI has not yet been used in a clinical trial or transplanted to patients. All MBRs exist in draft form and will be finalized and entered into Lonza's document control system before being used in clinical production. Other key steps to compliance and certification of the product will include in-house tech transfer of the remaining release tests to the Cell Therapy QC group. Once documentation and training are complete, Lonza production staff will perform 2-3 Engineering Runs. The entire process to initiation of GMP manufacturing will take about 12-16 weeks.

4.3.6 Quality

The LWI Quality Department is composed of Quality Assurance, Regulatory Affairs, Document Control, Label Control, Inspection, Validation, and Quality Control. This department operates independently from management and production. Responsibilities include in-process monitoring and the establishment of standards for personnel, facilities, procedures, equipment, testing, and record keeping. Lonza Walkersville Inc. maintains dedicated Quality Assurance and Quality Control staff to monitor all processes.

The Quality Assurance group supports the manufacture and release of product from Cell Therapy. The Quality Control laboratories are divided into Cell Biology, Microbiology and Molecular Biology and staffed by a group of over 65 individuals. All activities are coordinated by a centralized receiving and logging process to assure cGMP compliance. An additional testing lab is available within the designated manufacturing area to provide additional in-process support.

4.4 ESS product testing rationale and product tests . The in-process and final release testing for ESS is described below

4.4.1 Bioburden

Bioburben testing is performed on the biopsy transport medium using a protocol in accordance with USP<61> Microbial Test Limits. Identification of microbial agents detected will be reported as “For Information Only” (FIO).

4.4.2 Sterility

Grafts are tested for sterility during maturation (6-7 days prior to product release) and at final release. Samples are generated by pooling of 1 ml spent medium from 100% of the grafts followed by testing in accordance with USP<71> Sterility using the membrane filtration method. An additional 1 ml sample is retained for retesting if necessary.

4.4.3 Surface Electrical Capacitance (SEC)

SEC is measured with a Nova Dermal Phase Meter (DPM 9003) as a quantitative surrogate index of epidermal barrier formation in the ESS. Four locations are tested on every graft on days 6 or 7 and a second test on days 8 or 9 of incubation. The data are averaged and demonstration of a time-dependent SEC decrease yields a passing graft.

4.4.4 Histology

Evidence of a stratified epidermal substitute attached to a dermal substitute populated with fibroblasts indicates ESS acceptable for grafting. To minimize graft handling, 10% of grafts will be tested in a non-destructive manner (as can be seen in Figure 10).

4.5 ESS Summary

The product is an engineered skin substitute (ESS) consisting of autologous skin cells within a degradable biopolymer substrate. Isolated epidermal keratinocytes and dermal fibroblasts are cultured in nutrient media to promote population expansion. The cells are separately seeded onto a biopolymer substrate fabricated from collagen and carbohydrate polymers (glycosaminoglycan). The ESS device has been shown in preclinical studies to generate a functional skin barrier and in clinical studies to promote closure and healing of burns. This is the only medical device known at present for the treatment of full-thickness burns with autologous cells combined with a polymeric substrate.

With extensive cell therapy expertise and manufacturing capabilities, Lonza is well positioned to produce ESS at the Walkersville, MD facility. Based on yields generated during engineering runs and development runs, it is projected that cells isolated from a 30-40 cm2 biopsy, would generate an approximate yield of 3600 cm2 per lot of ESS material. Production of ESS would be staggered using two lots to produce enough product per patient in 6-8 weeks.

5. Proposed Research and Methods:

5.1 Specific Aims. The main objective of the work that will be supported by this supplemental funding is to expedite availability of ESS by performance of a limited study (8-10 subjects) under an Investigational Device Exemption (IDE) protocol, with ESS generated by the commercial manufacturer, Lonza Walkersville, Inc (LWI). ESS remains an investigative device which has been studied previously as described above. Toward these objectives, two specific aims are proposed:

5.1.1 Planning for delivery of ESS (trade named, PermaDerm) to a qualified burn center from Lonza Walkersville, Inc. for application to burn patients under an IDE protocol. Availability requires: a) verification of device manufacture under standards for current Good Manufacturing Practices (cGMP); b) demonstration of quality assurance criteria for product release; c) development of packaging materials and shipping protocols; d) development, validation and FDA acceptance of a clinical trial protocol; e) compliance systems through the AFIRM Clinical Trials Office at Case Western Reserve University; and, f) permission from FDA to proceed with the clinical study.

5.1.2 Comparison of ESS and meshed, split-thickness autograft in a controlled, prospective study . The proposed study will follow an open-label, randomized, matched-pair, internally-controlled design similar to previous studies, but in adult burn patients. The hypothesis of the study is that ESS provides a quantitative reduction in donor skin required to complete wound closure, and scar which is not statistically different from, or better than meshed and expanded split-thickness skin autograft. End points for the study are described below in section 6.

5.2 Research Plan.

5.2.1 Diagram of the research plan .

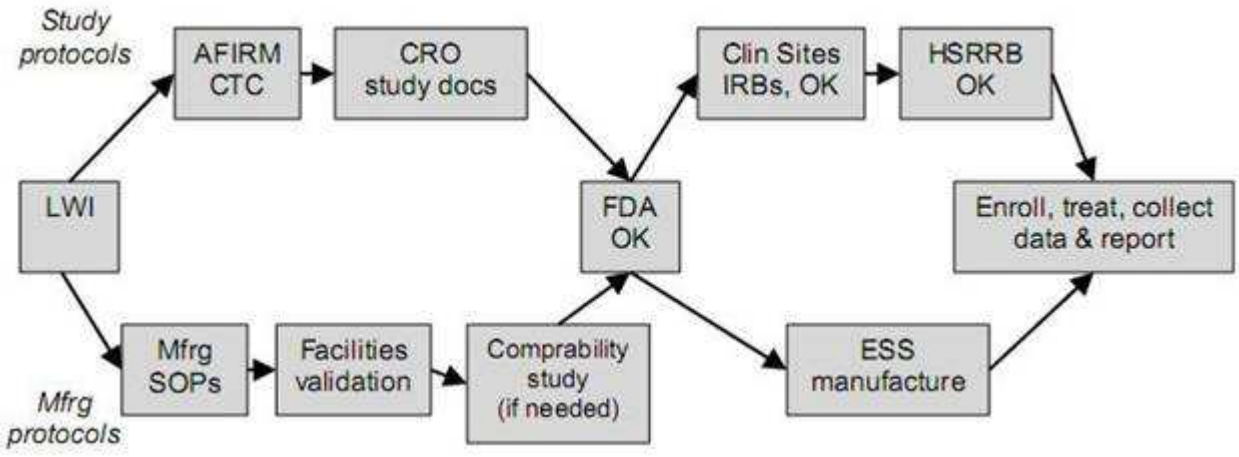


Figure 11. Diagram of the research plan . Lonza Walkersville, Inc. (LWI) is the applicant and study sponsor. The study design (top) will be submitted to the AFIRM Clinical Trials Core ("CTC"; Dr. Gerson) for review, and addition of compliance procedures (e.g., DSMP, DSMB). The AFIRM-CTC will advise a clinical research organization (CRO) which will assemble the Sponsor's and Investigator's Brochures, Case Report Forms, and the study notebook for each subject. LWI will submit the IDE protocol to FDA. After FDA acceptance, the CRO will work directly with the clinical performance sites to submit protocols to the local Institutional Review Boards, and then to the Human Subjects Research Review Board (HSRRB) at USAMRMC at Ft. Detrick. After all permissions are obtained, the CRO will serve as the sponsor's agent to monitor enrollment and treatment of subjects, data safety and study reporting. Manufacturing protocols (bottom) will follow established procedures at Lonza for regulatory acceptance.

5.2.2 Device manufacture under cGMP processes . LWI will confirm completion of Standard Operating Procedures (SOPs) for manufacture of ESS under conditions which comply with standards for current Good Manufacturing Practices (cGMP). The batch size (e.g., 2,000 cm2) will determine the specific cGMP suite which LWI will assign for this project. After assignment, the suite will be equipped, staffed, and validated for manufacturing. This step in the project is expected to require about 3 months.

5.2.3 Validation of quality assurance (QA) criteria for product release . Quality assurance criteria for product release will include both general safety criteria for medical devices (sterility, mycoplasma, endotoxin), and specific criteria for product potency (epidermal barrier, cellular organization, device thickness) which constitute criteria for product release. The general criteria are routine practices at LWI, and will be included in the facility activation. The specific criteria have been included in engineering runs at LWI, and SOPs for those assessments have been developed.

5.2.4 Validation of clinical study design through the RCCC-AFIRM Clinical Trials Office . The study design will be adapted from previous studies with engineered skin substitutes (see section 6). That design will be submitted for review to the RCCC-AFIRM Clinical Trials Core under the direction of Stanton Gerson, MD in the Center for Stem Cell and Regenerative Medicine at the Case Western Reserve University. The AFIRM-CTC will format the documents, review the safety and efficacy end points of the study, and consider any revisions which may be needed to the statistical analyses of the data. The AFIRM-CTC will assure compliance of the study with standards for current Good Clinical Practices (cGCPs).

5.2.5 Engagement of a Clinical Research Organization (CRO) for daily management of the clinical trial . A CRO with experience in medical device evaluation will be selected and retained to serve as the sponsor's agent and manager of the clinical trial. The CRO will have responsibilities to assemble and finalize the study documents, including but not limited to: a) clinical trial protocol; b) the Investigator's Brochure; c) clinical monitoring plan; and, d) approvals from the Institutional Review Boards (IRBs) of performance sites, and the Human Subjects Research Review Board of the DoD.

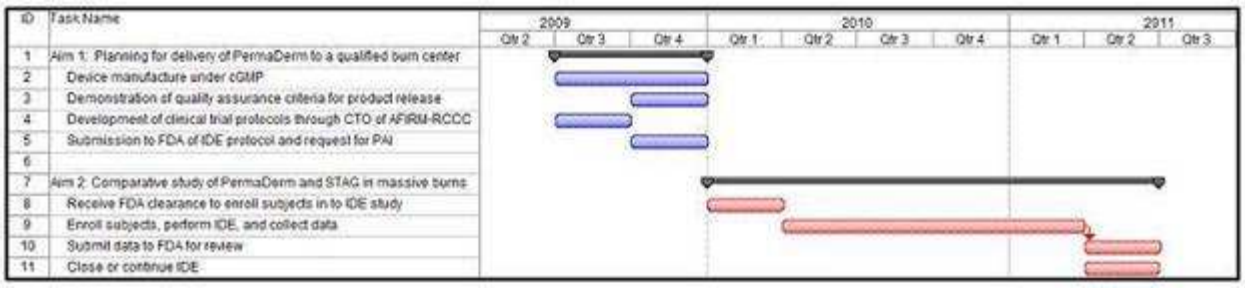
5.2.6 Regulatory protocol development and submission . LWI will be responsible for device manufacturing, process validation, regulatory submissions, and clinical performance at one or more qualified burn center(s). Lonza has initiated technology transfer for manufacture of the ESS device (trade named PermaDerm™) under cGMP (i.e., clean room) conditions. Devices produced by Lonza have not yet been compared directly to devices fabricated in the Dr. Boyce's research laboratories in Cincinnati, OH. Comparability testing will be performed as required by FDA with support from Lonza as a contribution in kind to the project.

5.2.7 Commitment of sites for clinical performance of the study . Because the AFIRM program is directed toward new therapies for wounded warfighter, the first choice for a clinical study site for burn repair is the Burn Unit of the US Army Institute for Surgical Research (ISR) at the Brooke Army Medical Center of Fort Sam Houston in San Antonio, Texas. In conference with Steven Wolf, MD, director of clinical investigations at the ISR, some, but perhaps not all, of 8-10 subjects for this proposed study may be available for accrual within the planned study enrollment period of one year. Drs. Wolf and Blackbourne have committed for the ISR to participate in this study (see appendix). In the event that a sufficient number of subjects is not expected to be available at the Burn Unit of the ISR, one additional site will be recruited for subject enrollment. Several burn centers (Indianapolis, Seattle, Los Angeles, Phoenix, Baltimore, Washington, DC) have sufficient census records to meet the requirements of the study, and will be interviewed as candidates for participation. Dr. Boyce will assist LWI with this recruitment.

5.2.8 Timetable for availability of autologous ESS for massive burns .

As described above, the requested support will be applied to activation of cGMP manufacturing of ESS from Lonza Walkersville, Inc., and to planning for clinical availability to the USAISR, or other qualified burn center. Below is a Gantt chart (Table 2) which summarizes the schedule for completion of regulatory and operational requirements for the project, based on the assumption that all parties make reasonable efforts to complete the project according to this timeline. Assuming start of funding by 1 Jul 2009, and with the collaborative efforts of all parties, the applicants believe this goal can be reached in the second calendar quarter of 2010.

Table 2. Schedule for project performance.



6. Clinical Trial:

Planning of the clinical study trial design will be based on previous studies under IDE G980023, with revisions according to advice of the investigators at the USAISR, the RCCC-AFIRM Clinical Trials Core Facility, and discussions with FDA.

6.1 Experimental design and end points. A matched-pair comparison format will be used to evaluate ESS and conventional split-thickness skin graft for closure of full-thickness, excised burns. This study will be performed in a prospective, randomized fashion with each pair in the same patient on wounds of similar size and depth. For each administration of ESS to a wound site, a comparative site will be treated with meshed split-thickness autograft skin (AG). Application of the specific treatment to site A or B will be randomized prior to initiation of the study. Up to 10 randomized pairs will be generated.

Wound treatment and dressings . Burns will be debrided by excision as early as possible after burn injury and wounds will be covered with fresh or cryopreserved cadaver allograft or Integra Dermal Regeneration Template™ (IDRT). One day prior to surgery, allograft or the silicone cover on IDRT will be removed, the wounds will be irrigated overnight with an appropriate antimicrobial solution (i.e., 5% wt/vol Sulfamylon solution), and the graftswill be applied the following day32Wound preparation for each site will be recorded at the time of surgery. Wound dressings will be administered as described previously26,33,34, using a non-adhesive porous dressing (ie., N-Terface, Winfield Laboratories) in direct contact with the cultured skin covered with fine mesh gauze and bulky dressings. Dressings for skin substitutes will be irrigated32 with nutrients, plus non-cytotoxic antimicrobial drugs (i.e., GU irrigant, polymyxin B, mupirocin, ciprofloxacin, amphotericin B)35 over the N-Terface for 5 days. On POD 5, wet dressings will be discontinued, and changed into an ointment-impregnated synthetic mesh (i.e., Adaptic) until complete wound closure is achieved. For ESS a topical ointment consisting of equal parts Neosporin, Bactroban and Nystatin (NBN) will be used.

6.2 Enrollment criteria.

6.2. 1 Medical indication . Patient has full-thickness burns equal to, or greater than, 50% of the Total Body Surface Area.

6.2.2 Medical conditions . Patient is not septic, and is expected to require ongoing skin grafting for a period longer than 3 weeks after collection of a skin biopsy to generate ESS

6.2.3 Age and gender . Age 18 years or older, either gender.

6.2.4 Social requirements . Patient is not pregnant or lactating, not a prisoner, and not mentally incompetent.

6.2.5 Completion of Informed Consent Form, and Health Insurance Portability and Accountability Act (HIPAA) forms.

6.3 Study end points for safety. Device safety will be assessed in comparison to AG by: a) frequency of regrafting on or before POD 28; b) anticipated and unanticipated adverse device effects; and c) histopathologic interpretation of healed wound biopsies. Late graft stability will be recorded but is not a safety endpoint.

6.3.1 Frequency of regrafting of comparative sites will be recorded at POD 28. Each site will be scored for regrafting as None, Partial, or Total. Comparative sites will be randomized according to a pre-determined schedule prior to the placement of the ESS.

6.3.2 Anticipated and unanticipated adverse device effects will be adapted from a list of approved by FDA from the previous study of the prototype device (see section 6.6). Those events will be incorporated into the Investigators Brochure, and recorded in the Case Report Forms. Serious adverse events will be reported within 72 hrs to the sponsor, local IRB, AFIRM Clinical Trials Unit and FDA IDE office.

6.3.3 Histopathologic interpretation will be made by a dermato-pathologist from histological slides of biopsies (up to 4/pt during first year after grafting) taken from healed wounds. Interpretations of the epidermis, the dermal-epidermal junction, and dermis will be made according to dermato-pathological standards.

6.4 Study end points for efficacy . The primary end point for device efficacy is a statistically significant increase in the donor skin area of the closed wound at post operative day (POD) 28 divided by the area of the donor skin used to close that area (section 6.4.1). Secondary end points for efficacy include: a) Percentage engraftment (i.e., closed wound) at POD 14 (section 6.3.2); b) Percentage TBSA closed at POD 28; and c) scoring of scar qualities of erythema, pigmentation, pliability and scar height by the Vancouver Scar Scale.

6.4.1 Donor skin expansion ratio . This ratio of healed wound area to biopsy skin area allows determination of donor site utilization. For ESS donor skin area will be traced at the time of isolation of cells to initiate device fabrication. For AG, donor skin area will be traced after application to the comparative site, and the mesh ratio (i.e., 1:2; 1:3; 1:4) will be recorded. The areas of the tracings will be determined by computer assisted image analysis. The donor skin expansion ratio will be calculated for each treatment site from at POD 28 as:

Closed wound area / donor skin area = donor skin expansion ratio

The donor skin expansion ratio for ESS, the prototype of ESS has been reported to be more than 10X greater than for AG 27,28. This outcome defines a primary medical benefit of ESS compared to AG in the treatment of extensive, full-thickness burns.

6.4.2 Percentage engraftment is determined by tracings of the grafted sites at POD 14 followed by planimetry. The tracing at POD 14 allows determination of % engraftment as healed area/treated area X 100.

6.4.3 Percentage TBSA closed is determined by dividing the absolute values of all of the areas closed, as measured by tracings and planimetry at POD 28, by the absolute value of the TBSA, and multiplying X 100. The percentage TBSA covered with split-thickness skin autograft is determined by subtracting the absolute value of the area closed with ESS from the absolute value of the area grafted, dividing by the absolute value of the TBSA, and multiplying X 100.

6.4.4 Scar qualities by the Vancouver Scar Scale 36 . Both sites will be scored for erythema, pigmentation, pliability and scar height on semi-quantitative, ordinal scales. Erythema ranges from 0 (normal) to 3 (purple), pigmentation is rated from 0 (hypo) to 3 (hyper), scar height is scored from 0 (flat) to 3 (>5 mm), and pliability from 0 (normal) to 5 (contracture).

6.4.5 Long term efficacy observations . This trial is designed as a short term feasibility study. However, recipients will be monitored at 12 months after application for efficacy parameters including overall medical condition and complications referable to the burn; skin coverage assessed by the Vancouver Scar Scale, frequency of regrafting and evidence of inflammation by histopathology.

6.4.6 Table of safety and efficacy end points for assessment of ESS

Table 3. Data collection schedule for assessment of ESS and AG in burn patients.

Primary Analyses at 4 weeks & 1 year after comparative treatment								
Type	Endpoint	POD	-7	0	7±3	14±3	28±3	365±30
Safety	Microbiology cultures of wound		X	X	X	X		
Efficacy	% Engraftment					X		
Efficacy	Donor skin expansion ratio						X	
Efficacy	% TBSA closed						X	
Efficacy	Vancouver Scar Scale						X	X
Efficacy	Photography			X	X	X	X	X
Safety	Frequency of regrafting						X	
Safety	Histopathology						X	X

6.5 Statistical power analysis.

Based on the data collected for determination of device efficacy as the ratio of closed wound areas to donor skin areas, a statistical power analysis was performed using data from 54 subjects previously reported 2. The mean ratio of the autologous ESS device was 63.9. This value for ESS was compared to a single value of 4.0 which was assigned to split-thickness skin autograft (AG) because the combined areas treated with AG were not measured directly, but were calculated by subtraction of the total area closed with ESS from the total burn area. In practice, the ratio for AG was actually closer to 2.0. Table 3 below shows that for power values of 0.95, 0.90, 0.80, and 0.50, the sample sizes required are 11, 10, 8 and 5 respectively. Therefore, it is expected that efficacy of the ESS device can be demonstrated in less than one year of enrollment of adult subjects at the USAISR, and at another qualified burn center which treats adults.

Table 4. Statistical power analysis for clinical trial of ESS compared to meshed autograft skin based on expansion ratios. This analysis was performed using a 2-sided, one sample paired T-test.

Power analysis for Prospective Trial of *ESS*							
Alpha	Beta	power	ESS mean	AG mean	difference	Std	n
0.05	0.05	0.95	63.93	4.0	59.96	48.8	11
0.05	0.10	0.90	63.93	4.0	59.96	48.8	10
0.05	0.20	0.80	63.93	4.0	59.96	48.8	8
0.05	0.50	0.50	63.93	4.0	59.96	48.8	5

This analysis makes two important assumptions that the ESS device performs comparably:
a) to the ESS device used in previous studies; and, b) in adults as in pediatric subjects.

Based on this analysis and the resources available, this initial trial proposes to treat no less than 8, and no more than 10 subjects as a proof-of-principle (i.e., pre-pivotal) study. Lonza will deliver up to 40,000 cm2 (4.0 m2) of autologous engineered skin for the proposed study.

6.6 Process for review, performance and compliance of FDA-regulated, clinical trials through the AFIRM consortium.

Several considerations for study validity and regulatory compliance are required prior to initiation of clinical trials. This study with engineered skin is one example of a general process for clinical trial and technology transfer. The RCCC-AFIRM consortium has established a Clinical Trials Core located at Case Western Reserve University and the Cleveland Clinic Foundation for data management and regulatory oversight of studies it supports.

6.6.1 Data Safety Monitoring

Each clinical trial site will have its own management plans for data safety monitoring. A CRO will provide external oversight of data collection and audit compliance with all aspects of the study. If two sites are used for the clinical trial, an independent Data Safety Monitoring Board will be established to review adverse event (AE) reporting during the conduct of the trial. This independent body will report information to the PI, the AFIRM Clinical Trials Core, and will advise on reporting to the institutional IRBs and the FDA.

The AFIRM Clinical Trials Core will coordinate the multi-site clinical data using a web-based CFR Part 11-compliant electronic database for recording and verification of data collection in real time. The Core will monitor IRB and FDA approvals, amendments, and annual reports. Updated consents and clinical protocol will be available for online access. It will maintain records for subject registration, patient demographics, accrual dates, key event dates, including graft placement and timed follow-up assessment results. It will record all clinical data on electronic Case Report Forms (CRFs).

Major outcome and study endpoint parameters will be monitored, including overall medical condition and complications referable to the burn, such as skin coverage assessed by the Vancouver Scar Scale, frequency of re-grafting, and evidence of inflammation by histopathology. Adverse and serious adverse event data collected at the study sites will be maintained and monitored. Serious adverse event definitions will be compliant with national reporting standards and will use conventional definitions for burn patients. All organ assessment and adverse events will be recorded during the 28 d observation period after graft placement.

The Clinical Trials Core database will be available under secure access for audit, and will be reported to the AFIRM executive committee, individual PIs and the device supplier, Lonza Walkersville, Inc.

6.6.2 Data Safety Monitoring Plan

Each institution will utilize its own Data Safety Monitoring Plan. The following list outlines general components that will be included:

- Review by a Data, Safety and Toxicology Committee (DSTC)
- Review of annual and special reports
- Management of Oversight Conflict of Interest
- Plans for Assuring Compliance with the Requirements Regarding Reporting of Adverse Events
- Plans for Assuring Temporary or Permanent Suspension of Clinical Trial Protocols
- Plans for Assuring Data Accuracy and Protocol Compliance
- Compliance Audits
- Quality Assurance (Database Edit Checking, Chart Audits, Protocol Compliance, Registration On-Study, Internal Audit Process)
- Management of Multi-center Trials (Industry and Academic trials)
- Study Coordinator Reviews
- Corrective Actions

6.6.3 Reviews required prior to clinical protocol approval and activation:

• AFIRM scientific review committee.
• USAMRMC clinical trials office at Fort Detrick.
• Review and IRB approval by performance site (ISR and other).
• Review and permission to proceed from FDA.
• The pre-IDE meeting with the FDA will be scheduled within three months of project activation.
Documents submitted will be used to develop specific questions for the pre-IDE meeting. At that point, LWI will submit to FDA the IDE with final protocol, final manufacturing SOPs for the PermaDerm product and monitoring plans for the trial. We expect to have provisional IRB review pending IDE review by the FDA. Once the IDE is allowed, after the 30 day review period, we will seek final site approval of the IRB.
• Data collection, internal review and reporting to FDA. Complete enrollment and file final report.

The application of resources from this supplement is anticipated to expedite the availability of ESS for treatment of bured soldiers in 12-18 months from initiation of funding, rather than 24-36 months if supplemental support is not available. The expedition of delivery of ESS is expected to demonstrate proof-of-principle for life-saving medical benefits and improvements in outcome for military and civilian patients with massive burn injuries.

7. Abbreviations and Acronyms:

AFIRM:	Armed Forces Institutes for Regenerative Medicine
AG:	split-thickness skin AutoGraft
CBSW:	Cambrex BioScience Walkersville, Inc.
cGCP:	current Good Clinical Practices
cGMP:	current Good Manufacturing Practices
CRFs:	Case Report Forms for the study
CTC:	Clinical Trials Core facility of the RCCC-AFIRM at Case Western Reserve University
ESS:	autologous Engineered Skin Substitutes
FDA:	United States Food and Drug Administration
HSRRB:	Human Subjects Research Review Board
HUD:	Humanitarian Use Device
IDE:	Investigative Device Exemption
IDRT:	Integra Dermal Regeneration Template™
IRB:	Institutional Review Board
LWI:	Lonza Walkersville, Inc.
ORCRA:	Office of Research Compliance and Regulatory Affairs
ORP:	Office of Research Protections
PD:	PermaDerm™; trade name for engineered skin substitutes
PMA:	Pre-Market Approval
POD:	Post-operative day
SEM:	Standard error of the mean
TBSA:	Total Body Surface Area
USAISR:	United States Army Institute for Surgical Research
USAMRMC:	United States Army Medical Research and Materiel Command
DMEM:	Dulbecco's Modified Eagle Medium
KGM-CD:	Keratinocyte Growth Medium - Chemically Defined
UCMC:	ESS Keratinocyte Growth and Culture Mediu

8. References

1. Boyce ST, Kagan RJ, Greenhalgh DG et al. Cultured skin substitutes reduce requirements for harvesting of skin autograft for closure of excised, full-thickness burns. J Trauma 2006; 60:821-829.
2. Boyce ST, Greenhalgh DG, Palmieri T et al. Autologous cultured skin substitutes reduce requirement for split-thickness skin autograft in treatment of excised, full-thickness burns. J Burn Care Res 2006;27:S59.
3. Boyce ST, Simpson PS, Kagan RJ. Survival of burns involving 90% of the total body surface area after treatment with autologous engineered skin substitutes. Proc of 2008 Army Science Conference . 2008.
4. Hall JR. The total cost of fire in the United States through 1991. In: Quincy MA ed. National Fire Protection Association. 1993:1-20.
5. Shires GT. Evolution of trauma and trauma research. J Trauma 1990; 30:107s-115s.
6. American Burn Association. National Burn Repository: 2005 Report. 2006. American Burn Association.
7. The Burn Foundation. Burn incidence and treatment in the United States. www.burnfoundation.org. 1999. Philadephia, PA.
8. Renz E, Barnes S. Long-range air transport of combat-related burn casualties. Proc ATACCC . 2007.
9. Hansbrough JF, Dominic W, Gadd M et al. Burns: critical decisions. Prob Crit Care 1987; 1(14):558-610.
10. Burn Registry Committee ABA. Comparison of hospital days, ICU days, and days on ventilator support. National Burn Repository 2002; 2002:7-35.
11. Kagan RJ. Restoring nitrogen balance after burn injury. Compr Ther 1991; 17(3):60-67.
12. Kagan RJ, Warden GD. Management of the burn wound. Clin Dermatol 1994; 12:47-56.
13. Boyce ST, Supp AP, Swope VB et al. Vitamin C regulates keratinocyte viability, epidermal barrier, and basement membrane in vitro, and reduces wound contraction after grafting of cultured skin substitutes. J Invest Dermatol 2002; 118:565-572.
14. Supp DM, Karpinski AC, Boyce ST. Vascular endothelial growth factor overexpression increases vascularization by murine but not human endothelial cells in cultured skin substitutes grafted to athymic mice. J Burn Care Rehabil 2004; 25:337-345.
15. Goretsky MJ, Harriger MD, Supp AP et al. Expression of interleukin 1α, interleukin 6, and basic fibroblast growth factor by cultured skin substitutes before and after grafting to full-thickness wounds in athymic mice. J Trauma 1996; 40:894-900.
16. LePoole IC, Boyce ST. Keratinocytes suppress transforming growth factor beta-1 expression by fibroblasts in cultured skin substitutes. Br J Dermatol 1999; 140:409-416.
17. Boyce ST. Epidermis as a secretory tissue. J Invest Dermatol 1994; (editorial)102:8-10.
18. Boyce ST. Method and apparatus for preparing composite skin replacements. University of California San Diego. [5,273,900]. 1993. United States of America.
19. Boyce ST. Apparatus for preparing composite skin replacements. University of California San Diego. [5,711,172]. 1998. United States of America.
20. Boyce ST. Method and apparatus for preparing composite skin replacements. University of California San Diego. [5,976,878]. 1999. United States of America.
21. Boyce ST. Apparatus for forming a biocompatible matrix. University of Cincinnati and Shriners Hospitals for Children. [6,905,105]. 2005. United States of America.
22. Boyce ST. Apparatus for preparing a biocompatible matrix. University of Cincinnati and Shriners Hospitals for Children. [7,452,720B2]. 2008. United States of America.
23. Boyce ST. Method and apparatus for preparing composite skin replacements. University of California San Diego. [363,400]. 1993. Europe.
24. Boyce ST. A surgical device for replacement of skin. University of Cincinnati and Shriners Hospitals for Children. 47359. 2007. European Union.
25. Lonza Group Ltd. Lonza full-year 2008 results. 2009. Lonza Corporation.
26. Boyce ST, Kagan RJ, Yakuboff KP et al. Cultured skin substitutes reduce donor skin harvesting for closure of excised, full-thickness burns. Ann Surg 2002; 235:269-279.
27. Armour AD, Dorr BA, Kagan RJ, Boyce ST. Mortality of acute burns treated with cultured skin substitutes. J Burn Care Res 28[2], S96. 2007.

28. Supp DM, Wilson-Landy K, Boyce ST. Human dermal microvascular endothelial cells form vascular analogs in cultured skin substitutes after grafting to athymic mice. FASEB J 2002; 16:797-804.
29. Boyce ST, Foreman TJ, English KB et al. Skin wound closure in athymic mice with cultured human cells, biopolymers, and growth factors. Surgery 1991; 110:866-876.
30. Supp DM, Supp AP, Morgan JR et al. Genetic modification of cultured skin substitutes by transduction of human keratinocytes and fibroblasts with Platelet Derived Growth Factor-A. Wound Repair Regen 2000; 8:26-35.
31. Supp DM, Boyce ST. Overexpression of vascular endothelial growth factor accelerates early
vascularization and improves healing of genetically modified cultured skin substitutes. J Burn Care Rehabil 2002; 23:10-20.
32. Warden GD, Saffle JR, Kravitz M. A two-stage technique for excision and grafting of burn wounds. J Trauma 1982; 22:98-103.
33. Boyce ST, Greenhalgh DG, Kagan RJ et al. Skin anatomy and antigen expression after burn wound closure with composite grafts of cultured skin cells and biopolymers. Plast Reconstr Surg 1993; 91:632-641.
34. Boyce ST, Goretsky MJ, Greenhalgh DG et al. Comparative assessment of cultured skin substitutes and native skin autograft for treatment of full-thickness burns. Ann Surg 1995; 222(6):743-752.
35. Boyce ST, Warden GD, Holder IA. Non-cytotoxic combinations of topical antimicrobial agents for use with cultured skin. Antimicrob Agents Chemother 1995; 39(6):1324-1328.
36. Sullivan T, Smith H, Kermode J et al. Rating the burn scar. J Burn Care Rehabil 1990; 11(3):256-260.

10 Facilities and equipment descriptions

10.1 General Description

Manufacturing of ESS will be performed at Lonza's facility in Walkersville, Maryland. Lonza is a leading manufacturer of specialty cellular biotherapeutics. Regulatory licenses include:

Device Registration Number 1114298
Tissue Registration Number 1114298
CBER License Number 1701
SO Certification Number FM67851
Federal ID Number 953917176

Lonza also manufactures endotoxin detection products at the Walkersville facility that are licensed by the FDA. The facility has been regularly inspected in conjunction with licensure of these products. As ESS is not a commercial product, inspection by the FDA has not yet been triggered. are licensed by the FDA. The facility has been regularly inspected in conjunction with licensure of these products. As ESS is not a commercial product, inspection by the FDA has not yet been triggered.

10.2 Facilities at Lonza Walkersville, Inc.

The Walkersville facility currently has eight completed suites, each ranging in size from 340 to over 800 square feet (+/- 5%) of core lab space and full suite areas (including staging areas and gown in/ gown out) ranging from 600 to 1380 (see schematic floor plans). Lonza also has additional commercial-scale suites under construction in Walkersville. There are also four suites dedicated to cell therapy manufacturing at the Verviers, Belgium facility. The Walkersville facility currently has eight completed suites, each ranging in size from 340 to over 800 square feet (+/- 5%) of core lab space and full suite areas (including staging areas and gown in/ gown out) ranging from 600 to 1380 (see schematic floor plans). Lonza also has additional commercial-scale suites under construction in Walkersville. There are also four suites dedicated to cell therapy manufacturing at the Verviers, Belgium facility.

ESS production will likely be performed in Cell Therapy Suite A. Room 2306 is a Class 10,000 (ISO Class 7) production suite. It includes four Class 100 biological safety cabinets, 18 humidified incubators, 1 freezer, and 1 refrigerator. Cell Therapy Suite A consists of 6 rooms. It includes 2 class 100,000 airlocks (Room 2302 and 2304) and class 10,000 ingress/egress areas (Rooms 2305 and 2307), a staging area (Room 2317) and a Cell Culture Production area (Room 2306). A materials pass through is built in the wall separating Rooms 2306 and 2305. The walls are composed of fiberglass (FRP board). The floors are made of a troweled epoxy covering. The class 10,000 area is at a positive differential pressure to the outside. The room also includes HEPA filters on the ceiling and return grates on the wall. The utility systems are independent of clean rooms. ESS production will likely be performed in Cell Therapy Suite A. Room 2306 is a Class 10,000 (ISO Class 7) production suite. It includes four Class 100 biological safety cabinets, 18 humidified incubators, 1 freezer, and 1 refrigerator. Cell Therapy Suite A consists of 6 rooms. It includes 2 class 100,000 airlocks (Room 2302 and 2304) and class 10,000 ingress/egress areas (Rooms 2305 and 2307), a staging area (Room 2317) and a Cell Culture Production area (Room 2306). A materials pass through is built in the wall separating Rooms 2306 and 2305. The walls are composed of fiberglass (FRP board). The floors are made of a troweled epoxy covering. The class 10,000 area is at a positive differential pressure to the outside. The room also includes HEPA filters on the ceiling and return grates on the wall. The utility systems are independent of clean rooms.

Figure 12. Typical cell therapy manufacturing suite at Lonza Walkersville, Inc. LWI has several manufacturing suites for cell therapy

including all support facilities, a proven track record of compliance with cGMP/ISO standards, and highly trained staff with all of the expertise needed for this project.

Figure 13. Cell therapy suites at Lonza Walkersville, Inc. The most recent addition to the Walkersville facility includes these 4 suites including 3 class 10,000 suites and a single class B suite. There is more than 2,800 square feet of classified space in this addition

10.3 Equipment:
Each of the Cell Therapy facilities is equipped with state-of-the-art manufacturing and analysis equipment to meet the needs of our many clients. This equipment includes everything required for cell culture and expansion, process development, quality assurance, labeling, packaging, and storage and shipping. Equipment is maintained in a validated/calibrated state and remotely alarmed providing 24 hour monitoring. Below is a list of equipment that will be used for the performance of this proposal.

Table 5. Manufacturing Equipment:

Item	Manufacturer	Qty	Comments
Biosafety Cabinets	Various	20	Between 1 and 4 BSCs are available within each suite
Incubators	Thermo 3950 Thermo 3110 Sheldon Belco	11 51 2 29	These incubators have various capacities and are organized among the Walkersville suites.
Centrifuges	Sorvall	8	Each suite is equipped with a refrigerated centrifuge
Inverted microscope and camera	Various	Several	Each suite is equipped with an inverted or standard microscope. Cameras can be attached to camera ports for documentation
Refrigerator	Various	Several	Each suite has a minimum of one refrigerator for materials and/or product storage. Refrigerators are alarmed.
Freezer	Various	Several	Each suite has a minimum of one freezer for materials and/or product storage. Freezers are alarmed.
Liquid Nitrogen Dewers	Various	Several	Liquid nitrogen is available as needed and is handled through Dewar containers.
Transport Dewers	Various	Several	Carts, dewars and appropriate transport equipment is available to all suites
Cell counter (nucleated)	Guava PCA	Several	Shared resource and QA lab is equipped with cell counters to support suite activities

Controlled rate freezers	Thermo Cryomed	Several	Most suites are equipped with controlled rate freezers

10.4 Regulatory and Commercialization Plan

Since its inception in January 2002, Lonza's Cell Therapy business unit has developed a global leadership position in cell therapy manufacturing and process development. With the purchase of the ESS device/ESS technology in 2006 and the expansion of manufacturing facilities in Walkersville, Maryland, Lonza is positioned to meet the regulatory and manufacturing requisites for the commercialization of the ESS technology. It is anticipated that the successful completion of the clinical trial design, as described in this proposal, with a limited number of patients, will accelerate commercial launch by providing statistically significant data on the primary efficacy of the ESS technology (i.e., closure rate) in severely burned soldiers within a short timeframe.

With the support of the Rutgers/Cleveland Clinic Consortium of the AFIRM network, Lonza will be positioned to commercialize the ESS technology for critically burned patients, for both soldiers and civilians alike. In conjunction with AFIRM consultants, Lonza anticipates scheduling a pre-IDE meeting with the FDA within three months with the goal of an IDE submission by Q2 2009, and enrolling patients in Q1 2010. Lonza is responsible for the IDE submission, and Lonza will make reasonable efforts to prepare the components necessary for the IDE submission, including but not limited to generation of SOPs, preparation of facilities, regulatory compliance of manufacturing, release and shipping, training, preparation for inspections, and pilot or engineering runs as directed by the FDA. Lonza expects to manage and engage a CRO for assistance in two critical areas:

1) Author full clinical protocol
2) Trial oversight (e.g. – coordination, implementation, investigator notebooks, case report forms, perform monitoring, reporting, data safety monitoring plan)

Additionally, Lonza will continue to work with AFIRM resources to ensure clinical trial compliance. Following the IDE submission and clinical data evaluation, Lonza intends to follow the FDA recommendations on a PMA submission for market approval of the ESS device.

The ESS technology will require a manufacturer with significant experience in tissue engineering and the resources to scale to meet commercial needs. Lonza has the commitment and expertise to support these requirements. Since the catastrophic burn market is relatively small (estimated at 2,000 patients annually in the U.S), patients are treated at a small number of centers in the US, requiring a limited investment in sales and marketing efforts. Lonza has a focused technical staff to successfully complete the coordination and training necessary to meet market requirements.

Depending on clinical trial outcomes, Lonza is prepared to invest as necessary, to support pursuit of ESS development along the commercial pathway. To ensure that the timeline for marketing approval is as expeditious as possible, Lonza may collaborate with a commercial partner who has specific expertise in the wound care market. Lonza is committed to manufacturing of the ESS device to support patients' needs.

11. Patents relevant to autologous engineered skin substitutes.
11.1 **Boyce ST** . 1993. European Patent 363,400, "Method and apparatus for preparing composite skin replacement". Assignee: University of California.
11.2 **Boyce S** T. 1993. US Patent 5,273,900, "Method and apparatus for preparing composite skin replacement." Assignee: University of California.
11.3 **Boyce ST** . 1998. US Patent 5,711,172, “Apparatus for preparing composite skin replacement”. Assignee: University of California.
11.4 **Boyce ST** . 1999. US Patent 5,976,878, “Method and apparatus for preparing composite skin replacement”. Assignee: University of California.
11.5 **Boyce ST** . 2005. US Patent 6,905,105, “Apparatus for fabricating a biocompatible matrix”. Assignees:University of Cincinnati and Shriners Hospitals for Children.
11.6 **Boyce ST** . 2007. European Patent application #47359, "A surgical device for replacement of skin". Assignees: University of Cincinnati and Shriners Hospitals for Children. Claims allowed, 11 Jul 2007.
11.7 **Boyce ST** . 2008. US patent 7,452,720B2, “Apparatus for preparing a biocompatible matrix”. Assignees: University of Cincinnati and Shriners Hospitals for Children. Claims allowed, July 2008.
11.8 **Boyce ST** . 2002. US patent application, publication #US2003/0170892, “A surgical device for replacement of skin”. Assignees: University of Cincinnati and Shriners Hospitals for Children. Pending review.

12. Intellectual and material property plan. (see sections 1.4 and 10)

Budget Justification:

Personnel – Faculty
The management of this project will be a coordinated effort by three Principal Investigators, one each from:
1. Lonza Walkersville, Inc (LWI) for overall project performance, device manufacture and quality assurance, and regulatory management with FDA.
2. The Clinical Trials Office of the AFIRM-RCCC at Case Western Reserve University for trial design, data safety monitoring, and regulatory compliance of the study with standards required by the USAMRMC and AFIRM.
3. The Institute for Surgical Research at the Brooke Army Medical Center at Fort Sam Houston which will be one of two clinical performance sites.

Kim Warren, PhD will serve as principal investigator for the project at LWI. Dr. Warren is the Head of Cell Therapy Development at LWI and guides the Process Development and R&D Departments in the Cell Therapy business unit. Together with the Cell Therapy production and regulatory divisions at LWI, Dr. Warren will coordinate the manufacture of the autologous engineered skin device, ESS, and its delivery to the clinical performance sites. She will also serve as liaison to a Clinical Research Organization (CRO) which will be contracted by LWI to generate documentation needed for the study, and track the activities of the CRO.

Stanton Gerson, MD serves as the Director of the Center for Stem Cell & Regenerative Medicine at Case Western Reserve University. He has extensive experience is performance of clinical trials with cancer treatments, including stem cell therapies. Dr. Gerson will provide assurances of regulatory compliance, data safety monitoring, and assist with review of the study design and statistical analysis of study data. His Center has successfully conducted numerous clinical trials with full regulatory compliance. The Center will work directly with the CRO on contract from Lonza develop the regulatory documents for the study, the investigators brochure and case report forms for data collection. Participation of Dr. Gerson's Center provides great confidence that regulatory compliance of the study will be fully satisfactory to AFIRM and FDA.

Jane Reese serves as Operations Director of the Center for Stem Cell & Regenerative Medicine at Case Western Reserve University and works closely with Dr. Gerson. She will assist with data monitoring and compliance and coordination of the multi-site clinical trial.

Steven Wolf, MD holds positions as Professor of Surgery in the Department of Surgery at the University of Texas Health Sciences Center in San Antonio, and director of clinical research at the USAISR. Dr. Wolf will provide advice on planning of clinical applications of autologous engineered skin substitutes at the burn unit at the USAISR. His experience and guidance will greatly facilitate the prospective availability of the investigative therapy for wounded soldiers.

Howard Schrayer is an independent consultant to the medical device industry, with more than 25 years experience. His consulting activities are focused on formulating regulatory strategies for medical devices. Mr. Schrayer will serve as a regulatory consultant for this project. His approximate 5% effort contribution is funded by RCCC-AFIRM.

Steven Boyce, PhD is the inventor of the ESS technology, and will serve as a technical consultant to the project up to two days per month (10% time). He holds positions as Professor in the Departments of Surgery and Biomedical Engineering at the University of Cincinnati, and directs the Engineered Skin Laboratories at the Cincinnati Shriners Burns Hospital. He will be available to advise on the development of the IDE application, study documents, and will assist with recruitment of a second study site. In addition, Dr. Boyce will continue to provide technical advice for the manufacture of ESS, design of shipping materials and logistics, and training of staff at the study sites.

Personnel – Staff

Three staff positions are requested at 25% FTE.

Production Manager – Mark Tracy: will oversee the production staff and operations for the production of the engineered skin devices for qualification runs and clinical trial. Mark and his staff are responsible for carrying out the production process including isolation, expansion, seeding and harvest. Mark will also oversee completion of MBRs, cGMP documentation, and in-process testing. Mark has 6 years experience in cell therapy production at LWI, including 4 years in a supervisory role.

Quality Control Manager – John Semon: will oversee release testing of the engineered skin devices for qualification runs and clinical trial. John and his staff are responsible for carrying out the bioburden, sterility, surface electrical capacitance and histology tests. John has been a Quality Control Manager for more than 10 years.

Quality Assurance Manager – Vicki Meckley: will oversee quality assurance of production activities, QA audits, controlled documentation and release of engineered skin devices for qualification runs and clinical trial. Vicki has been managed the Quality Assurance team for 4 years and has approximately 10 years experience in the field of biotechnology.

Device Manufacture

The ESS will be relatively expensive to produce for this initial clinical study from LWI. It is planned that the study will require approximately 4m2 (40,000 cm2) with a cost of goods of $27.47/cm2 for an estimated total cost of $1,098,800; $889,552 of which is charged to the grant budget. The remainder of the cost is a Lonza in-kind contribution. This amount of ESS is required to provide between 0.36 and 0.42 m2 (3,600 - 4,200 cm2) for each of the 10 prospective subjects in the study. This amount per study subject is needed to demonstrate the primary medical benefit which is conservation of donor skin. The study design would propose to manufacture the ESS from a biopsy of split-thickness of an approximate area of 30-40 cm2 for an approximate expansion of the biopsy area by 100 fold. This expansion will demonstrate the primary medical benefit of the device which is reduction of skin harvesting to complete wound closure.

Travel

Travel costs are requested for the study sponsor (LWI; $15,000), and the associated participants ($10,000). Sponsor related travel will include pre-study visits to the performance sites, training visits, and study closure visits for two staff members. Travel for associated participants will include two on-site visits with the sponsor by Dr. Gerson, Ms. Reese, and Dr. Boyce.

Subcontracts:

A contract research organization (CRO) will manage the daily operations of the study ($332,000). The CRO partner will be chosen by Lonza. The budget is estimated based on a quote from a representative CRO.

Each clinical site will receive a contract for actual costs to perform the study ($126,724 per site X 2 =$253,448). The budget is based on treating 5 patients per clinical site. Final patient enrollment will depend on patient availability.

Contributions in-kind from Lonza:

1. Preparation of facilities including certification and inspection.
2. Development of packaging and shipping materials.
3. Comparability study (as needed).
4. Project administration.
5. Salaries of key personnel.
6. Majority of production staff payroll expense.
7. Dr. Steven Boyce consultancy.
8. Intellectual Property expenses

9. Process development expenses.
10. Site and manufacturing regulatory compliance.

Appendix List:

1. Letter of collaboration, USAISR
2. Letter of consultation, Steven Boyce, PhD
3. Case Report Forms from previous study
4. Boyce publications
4.1. ASC 2008
4.2. J Trauma 2006

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS:

* Budget Type: ☐ Project ☐ Subaward/Consortium

Enter name of Organization:

* Start Date: 07/01/2008 * End Date: 06/30/2011 Budget Period 1

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Dr.	Mary	Kim	Warren	PhD	PD/PI		3.00			0.00	0.00	0.00
2.	Mr.	Mark		Tracy		Production Manager		3.00			0.00	0.00	0.00
3.	Mr.	John		Semon		QC Manager		3.00			0.00	0.00	0.00
4.	Ms.	Vicki		Meckley		QA Manager		3.00			0.00	0.00	0.00
5.	Ms.	Kelly		Green		Finance		0.50			0.00	0.00	0.00
6.													
7.													
8.													

9. Total Funds requested for all Senior Key Persons in the attached file

Total Senior/Key Person 0.00

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

	* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
		Post Doctoral Associates						
		Graduate Students						
		Undergraduate Students						
		Secretarial/Clerical						
	4	Cell Therapy Production Staff - 4 Techs at $175/hour for 1410 hours				29,721.60	7,430.40	37,152.00
	4	Total Number Other Personnel					Total Other Personnel	37,152.00

Total Salary, Wages and Fringe Benefits (A+B) 37,152.00

OMB Number: 4040-0001
Expiration Date: 04/30/2008

RESEARCH & RELATED Budget (A-B) (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS:

* Budget Type: ☐ Project ☐ Subaward/Consortium

Enter name of Organization:

* Start Date: 07/01/2009 * End Date: 06/30/2011 Budget Period 1

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	Total funds requested for all equipment listed in the attached file	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	15,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	15,000.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	10,000.00
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	Total Participant/Trainee Support Costs 10,000.00

RESEARCH & RELATED Budget (C-E) (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 04/30/2008

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS:

* Budget Type: ☐ Project ☐ Subaward/Consortium

Enter name of Organization:

* Start Date: 07/01/2009 * End Date: 06/30/2011 Budget Period 1

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	332,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	253,448.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Investigational Devices: 40,000 sq cm x $21.31/sq cm	852,400.00
9.	
10.	
Total Other Direct Costs	1,437,848.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	1,500,000.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				
	Total Indirect Costs			

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	1,500,000.00

J. Fee	Funds Requested ($)

K. * Budget Justification [Add Attachment] [Delete Attachment] [View Attachment]

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 04/30/2008

RESEARCH & RELATED Budget (F-K) (Funds Requested)

RESEARCH & RELATED BUDGET - Cumulative Budget

		Totals ($)
Section A, Senior/Key Person		0.00
Section B, Other Personnel		37,152.00
Total Number Other Personnel	4	
Total Salary, Wages and Fringe Benefits (A+B)		37,152.00
Section C, Equipment		
Section D, Travel		15,000.00
1. Domestic	15,000.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		10,000.00
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel	10,000.00	
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		1,437,848.00
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services	332,000.00	
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	253,448.00	
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	852,400.00	
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		1,500,000.00
Section H, Indirect Costs		
Section I, Total Direct and Indirect Costs (G + H)		1,500,000.00
Section J, Fee		

OMB Number: 4040-0001
Expiration Date: 04/30/2008

Steven Boyce, Ph.D.
Professor
Division of Burn Surgery
Department of Surgery
College of Medicine
P.O. Box 670558
Cincinnati OH 45267-0558
Phone: (513) 872-6080
Fax: (513) 872-6107
Email: boycest@uc.edu

23 February 2009

Kim Warren, Ph.D.
Lonza Walkersville, Inc. (Lonza)
8830 Biggs Ford Road
Walkersville, MD 21793

Re: Proposal for clinical trial of PermaDerm for burns

Dear Dr. Warren:

I am pleased to serve as a consultant to Lonza's proposal to perform a clinical trial of PermaDerm, an autologous engineered skin substitute for treatment of life-threatening burns.

As ou know, I have extensive expertise in the development of human cell culture systems, skin biology, wound healing, and biocompatability of implantable materials. My research interests include mechanisms of wound healing with engineered human skin, and biologic fidelity of engineered tissues to natural tissues by regulation of cellular phenotypes. My laboratory has developed engineering systems for skin substitutes that are used to treat burn wounds with significant advantages to traditional split thickness skin grafting procedures. These technologies have been translated to clinical investigations, patented, and licensed to Cutanogen Corporation which is a subsidiary of Lonza. As the founder of Cutanogen Corporation, I have an established working relationship Lonza which will facilitate accomplishment of the proposed clinical trial.

The study which Lonza proposes is relatively simple in design, but will require both technical advice and close tracking of activities to complete successfully. I shall be available to assist with study design, review of manufacturing procedures, and recruitment of clinical study sites as needed. I shall also be available to act as liaison to other work groups within the RCCC-AFIRM consortium to facilitate performance of the project.

There delivery of an autologous engineered skin substitute for catastrophic burn injuries promises to raise the standard of burn care nationwide, and reducing morbidity and mortality in this high-risk population of patients. I look forward to working with Lonza to demonstrate these benefits, and to deliver this important new therapy.

I wish you every success with the proposal.

Sincerely,

/s/ Steven Boyce
Steven Boyce, Ph.D.

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE# G980023

SCHEDULE FOR DATA COLLECTION

DATA COLLECTED	Prestudy	CSS Surgery Day 0	POST-OPERATIVE DAY						
			7	14	28	91	182	365	Later if possible
Informed Consent	X								
Past Medical History	X								
Physical Exam	X	X			X	D/C			
Serum for Antibodies	X				X				
Skin Biopsy for Tracing & Culture	X								
Pretreatment of Sites	X								
Biopsy & Photo of Recipient Sites		X							
Microbial Culture of Recipient Sites	X	X	X	X					
Photography		X	X	X	X	X	X	X	X
CSS Tracing In Vitro		X							
Study Site Tracings				X	X				
% Engraftment				X	X				
Healed Area : Donor Area Ratio					X				
Qualitative Outcome				X	X	X	X	X	X
Healed Wound Biopsy (as possible)			X	X	X	X	X	X	X
Adverse Event Summary				X	X				
Investigator Global Assessment				X	X			X	

*Primary data analysis will be performed on post-operative day 28, and as close as possible to day 365.
Punch biopsies (3mm) will be obtained at scheduled time points, not to exceed a total of 6 samples nor 5% of the healed graft.

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE# G980023

Registration Form

Patient Initials: _____ Study Registration Number: CSS_____
Hospital ID#: _____ Gender: M / F
Birthdate: _____ Age: _____ Race: _____
M / D / Y

Burn Date: _____
Admission Date: _____ M / D / Y
M / D / Y

TSBA (m2, from nomogram): _____ % burned: _____ % 2º: _____ % 3º: _____

Allergies: _____

Inclusion - Must answer "Yes" to the following:

Yes	No	
		Age is birth - 75 years
		TBSA $50% (or $10% full thickness)
		Burn includes full thickness
		Patient is not showing signs of sepsis
		Expected to need grafting after 3 weeks post primary biopsy
		Informed Consent signed

Exclusion - Must answer "No" to the following:

Yes	No	
		Patient is pregnant or lactating
		Patient is a prisoner
		Patient is mentally incompetent

Date enrolled: _____
M / D / Y

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials: _____ Date: _____
Study Registration Number: C S S Study Day: Prestudy

PAST MEDICAL HISTORY

	No	Yes	Comments
HEENT			
Respiratory			
Cardiovascular			
Gastrointestinal			
Genitourinary			
Musculoskeletal			
Neurological			
Endocrine			
Substance Abuse			
Psychological			
Other			

Form CSS 7.3
Revised: October 2003

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials: _____ Date: _____
Study Registration Number: C S S Study Day: _____

PHYSICAL EXAM

_____ Admission
_____ Pre-surgery
_____ POD 28
_____ Discharge

	Normal	Abnormal	Comments
HEENT			
Respiratory			
Cardiac			
Circulation check			
Gastrointestinal			
Genitourinary			
Musculoskeletal			
Neurological			
Endocrine			
Integumentary			

Serum for circulating antibodies obtained:

☐ Prestudy _____
Date

☐ Study Day #28 _____
Date

Form CSS 7.4
Revised: October 2003

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Burn Estimate and Diagram
Age vs. Area

Initial Evaluation

Pt. Initials:

Pt. Reg. No.: _____

Investigator _____

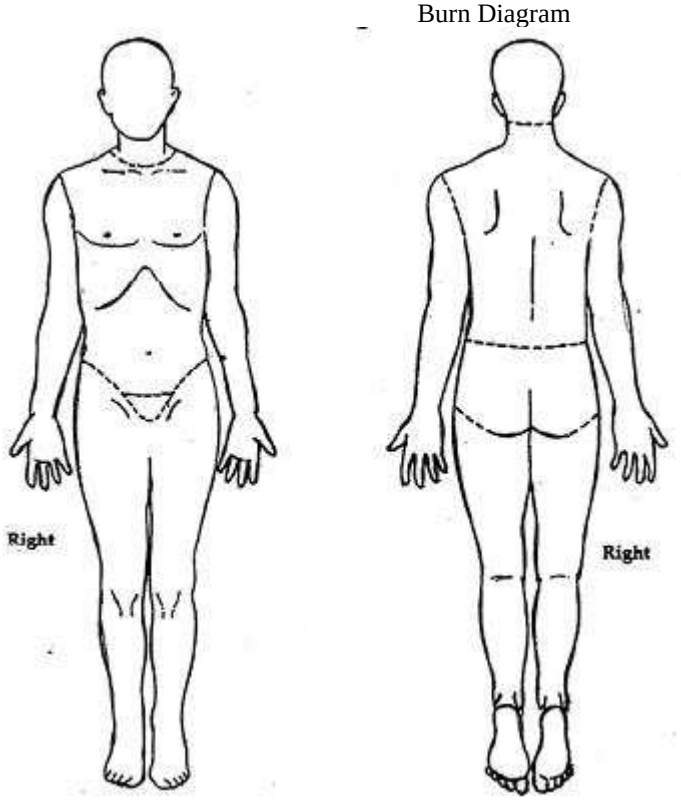
Completing Burn Diagram _____

Color Code

Red - 3º

Blue - 2º

Burn Diagram



Area	Birth 1 yr.	1-4 Yrs.	5-9 Yrs.	10-14 Yrs.	15 Yrs	Adult	2º	3º	Total	Donor Areas
Head	19	17	13	11	9	7				
Neck	2	2	2	2	2	2				
Ant. Trunk	13	13	13	13	13	13				
Post. Truck	13	13	13	13	13	13				
R. Buttock	2 ½	2 ½	2 ½	2 ½	2 ½	2 ½				
L. Buttock	2 ½	2 ½	2 ½	2 ½	2 ½	2 ½				
Genitalia	1	1	1	1	1	1				
R.U. Arm	4	4	4	4	4	4				
L.U. Arm	4	4	4	4	4	4				
R.L. Arm	3	3	3	3	3	3				
L.L. Arm	3	3	3	3	3	3				
R. Hand	2 ½	2 ½	2 ½	2 ½	2 ½	2 ½				
L. Hand	2 ½	2 ½	2 ½	2 ½	2 ½	2 ½				
R. Thigh	5 ½	6 ½	8	8 ½	9	9 ½				
L. Thigh	5 ½	6 ½	8	8 ½	9	9 ½				
R. Leg	5	5	5 ½	6	6 ½	7				
L. Leg	5	5	5 ½	6	6 ½	7				
R. Foot	3 ½	3 ½	3 ½	3 ½	3 ½	3 ½				
L. Foot	3 ½	3 ½	3 ½	3 ½	3 ½	3 ½				
						Total:				

Shriners Hospital for Children
Cincinnati Burns Institute
Burn Diagram

Form CSS 7.5

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials: _____ Date: _____
Study Registration Number: C S S Study Day: Prestudy

PRESTUDY DATA

Primary Biopsy for Skin Cell Cultured obtained _____ Date
_____ PBD
from _____ Donor site

Parameter	Date	Site A AG	Site A CSS	Site B AG	Site B CSS
Excision of Eschar					
Temporary wound coverage achieved with:					
Organisms Isolated (only one pre-application Microbiology culture needed)					
Pretreatment Topicals Used:					

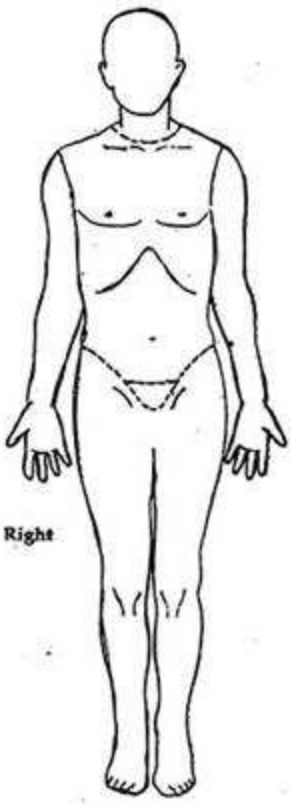
Blood Culture	Organism Isolated	Treatment Meds	Systemic Treatment (dates)

Form CSS 7.6
Revised: October 2003

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials: _____ Date: _____
Study Registration Number: C S S Study Day: #0

Set # _____
CSS SURGERY DIAGRAM

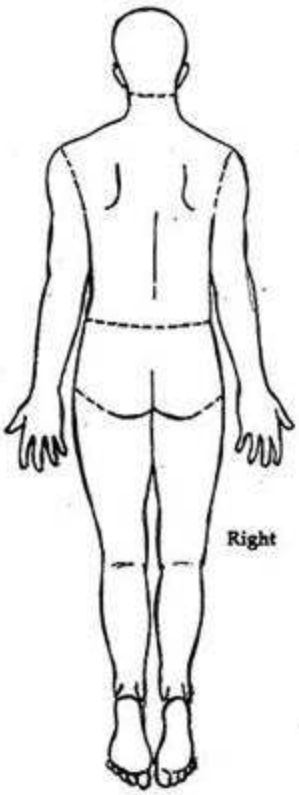


Date _____
PBD _____

Randomization

Site ___ Cultured Skin Substitute (CSS)

Site ___ Autograft (A/G)



Recipient Wound Bed					
	Pre-Application Data				Post-Application Data
Study Site	Temporary Cover Excised	Punch Biopsy Taken	Microbial Culture Taken	Photos Taken	Type & Size of Grafts Applied
A	_/_/_ (Date)	_ Y _ N	_ Y _ N	_ Y _ N	
B	_/_ /_ (Date)	_ Y _ N	_ Y _ N	_ Y _ N	
			Site Identification		
Study Site	Location		Landmarks		
A	_____		From ( ) to the center of Study Site measures ( )		
B	_____		From ( ) to the center of Study Site measures ( )		
			From ( ) to the center of Study Site measures ( )		
			From ( ) to the center of Study Site measures ( )		

CULTURED SKIN SUBSTITUTE
Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient initials: _____
Patient registration number: CSS_____

ADVERSE MEDICAL EVENTS

List below any new event(s) or changes in the status of previously recorded event(s) including cessation of event(s)

Instructions: Frequency: Check if constant or place a number that best describes frequency in the per day column. Duration: If not consistent, indicate the duration per episode. Place a number in box that best describes duration.	Date Started M/D/Y	CONTINUING	Date Stopped M/D/Y	Frequency		Duration			Relationship to Test Materials If unlikely, or not test material related, indicate probable cause	Action(s) Taken (List as many as apply)	OUTCOME
				CONSTANT	Per Day	MINUTES	HOURS	DAY			
EVENTS ☐ **None**											

Keys:

SEVERITY

1. Mild
2. Moderate
3. Severe
4. Life-threatening or intolerable
5. Fatal

Relationship to test material:

1. Not related
2. Unlikely related
3. Possibly related
4. Probably related
5. Definitely related

Action(s) Taken:

1. None
2. Test Material Dosage Reduced
3. Test Material Administration Interrupted, Reinstated at Same Dose
4. Test Material Administration Interrupted, Reinstated at Lower Dose
5. Test Material Discontinued
6. Medication Administered
7. Treatment other than Medication Administered - Specify*
8. Laboratory or other Diagnostic Test(s) Done
9. Randomization code broken. Date __/__/__.

Outcome:

1. Recovered with treatment
2. Recovered without treatment
3. Alive with sequelae
4. Event is continuing and controlled with treatment
5. Event is continuing without treatment
6. Patient died
7. Unknown

— Record in Concomitant Medications section of Case Report form
* Record in Comments below
^ Note - REPORT TO FDA and IRB, IF MEDICAL EVENT IS UNEXPECTED, SEVERE, LIFE THREATENING OR FATAL

Comments: _____ _____ __/__/__
_____ Investigator

Form CSS 7.8
Revised: October 2003

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials		Date:	
Pt. Reg. No.	C S S	Study Day:	

Qualitative Outcome

Site B
____ % healed ____ % healed
____ % open ____ % open

(The following scores will reflect only those areas which are healed.)
*Required Study Day: #14, #28, and subsequent clinic visits.

Parameter	Site A score						Site B score					
Percentage: 1) Erythema	___ 0 normal	___ 1 pink		___ 2 red		___ 3 purple	___ 0 normal	___ 1 pink		___ 2 red		___ 3 purple
Percentage: 2) Pigmentation	___ 0 none	___ 1 hypo		___ 2 normal		___ 3 hyper	___ 0 none	___ 1 hypo		___ 2 normal		___ 3 hyper
Percentage: 3) Skin Pliability	___ 0 Normal	___ 1 Supple	___ 2 Yielding	___ 3 Firm	___ 4 Rope	___ 5 Contract	___ 0 Normal	___ 1 Supple	___ 2 Yielding	___ 3 Firm	___ 4 Rope	___ 5 Contract
Percentage: 4) Scar Height	___ 0 Flat	___ 1 < 2mm		___ 2 > 2mm		___ 3 > 5mm	___ 0 Flat	___ 1 < 2mm		___ 2 > 2mm		___ 3 > 5mm
5) Site regrafting: (If partial or total, see below)	Total	Partial		None			Total	Partial		None		

SITE RECONSTRUCTION

	Site A	Site B
Surgery date Study day # Procedure % CSS remaining Was CSS excised?		

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials _____ Date: _____
Pt. Reg. No. C S S Study Day # _____

Investigator's Global Assessment at POD 14

1) Percentage healed graft (from tracing): Site A: _____ Site B: _____
A) Cause(s) of failure of auto-CSS:

_____
_____

B) Is regrafting needed: Yes □ No □
C) Date that the manufacturer was notified of device failure:
D) Enter the date of the Monday of the week in which regrafting is expected to be performed: _____
E) State the type of graft that is expected to be used: auto-CSS □ skin autograft □
State reason for choice: _____

2) Healed area: donor area ratio for cultured skin substitute?

3) Were there any adverse events during the course of this study?

No ___ Yes ___ (see adverse event record)

4) Status of subject

___ Continues in study
___ Discontinued from study (see number 5)

5) If subject was discontinued from the study, indicate reason:

___ graft failure
___ adverse event
___ subject request
___ protocol violation
___ other, please specify _____

6) Was the subject discharged with cultured skin intact?

Yes ___ No ___ Not yet discharged ___ Discharge date

To Be Completed and Signed by Investigator

_____ Date Signed: _____
Principal Investigator

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials		Date:	
Pt. Reg. No.	C S S	Study Day #	

Investigator's Global Assessment at POD 28

1) Percentage healed graft (from tracing): Site A ___ Site B ___

2) Healed area: donor area ratio for cultured skin substitute?
_____

3) Were there any adverse events during the course of this study?

No ___ Yes ___ (see adverse event record)

4) Status of subject
___ Continues in study
___ Discontinued from study (see number 5)

5) If subject was discontinued from the study, indicate reason:

___ graft failure
___ adverse event
___ subject request
___ protocol violation
___ other, please specify _____

6) Was the subject discharged with cultured skin intact?

Yes ___ No ___ Not yet discharged ___ Discharge date

To Be Completed and Signed by Investigator

_____ Date Signed: _____
Principal Investigator

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials _____ Pt. Reg. No. CSS

Date	Study Day	Site A	Site C
	Day # 0 (wound bed)		
	Day # 7 (healed wound)		
	Day # 10		
	Day # 14		
	Day # 28		
	Day # 91		
	Day # 182		
	Day # 365		
	Post 1 year		

* Punch biopsies will be obtained at scheduled time points, not to exceed a total of 6 healed wound samples nor 5% of the healed graft.

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials ____________________ Pt. Reg. No. CSS ________

Microbiology

	Site A	Site B
Date: ________ Day of Study: ____ (recipient wound bed)	Site: Organism: Site: Organism:	Site: Organism: Site: Organism:
Date: ________ Day of Study: ____	Site: Organism: Site: Organism:	Site: Organism: Site: Organism:
Date: ________ Day of Study: ____	Site: Organism: Site: Organism:	Site: Organism: Site: Organism:
Date: ________ Day of Study: ____	Site: Organism: Site: Organism:	Site: Organism: Site: Organism:
Date: ________ Day of Study: ____	Site: Organism: Site: Organism:	Site: Organism: Site: Organism:
Date: ________ Day of Study: ____	Site: Organism: Site: Organism:	Site: Organism: Site: Organism:
Date: ________ Day of Study: ____	Site: Organism: Site: Organism:	Site: Organism: Site: Organism:
Date: ________ Day of Study: ____	Site: Organism: Site: Organism:	Site: Organism: Site: Organism:

*Note- (S) Swab or (Q) Quantitative
(Required Study Day #0, #7, #14)

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials _____ Pt. Reg. No. CSS

Blood Cultures

	Organisms Isolated
Date:	
Day of Study	Medication Treatment:
	Dates:
Date:	
Day of Study	Medication Treatment:
	Dates:
Date:	
Day of Study	Medication Treatment:
	Dates:
Date:	
Day of Study	Medication Treatment:
	Dates:

Systemic Antibiotic Therapy

Dates	Medication

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials _____ Pt. Reg. No. CSS _____

Photography Log

Date	Study Day	Site A	Site B	Photographers ID
	Day # 0 Wound bed			
	Day # 0 Post graft			
	Day #			
	Day # 5			
	Day # 7			
	Day #			
	Day #			
	Day # 10			
	Day #			
	Day #			
	Day # 14			
	Day #			
	Day #			
	Day # 28			
	Day #			
	Day #			
	Day # 91			
	Day #			
	Day #			
	Day # 182			
	Day #			
	Day #			
	Day # 365			
	Day #			
	Day #			

Form CSS 7.15
Revised: October 2003

CULTURED SKIN SUBSTITUTE
IRB Protocol #95-7-26-1 (autologous CSS)
IDE # G980023

Patient Initials _____ Pt. Reg. No. CSS_____

Site Regrafting Log

Regrafting Date	Site regrafted (CSS or AG)	POD of Site Regrafted	Graft type used for regrafting (CSS or AG)	Wound closure completed by POD 14

POD, post-operative day

Form CSS 7.16
Revised: October 2003

Cultured Skin Substitutes Reduce Requirements for Harvesting of Skin Autograft for Closure of Excised Full-Thickness Burns

Steven T. Boyce, PhD, Richard J. Kagan, MD, David G. Greenhalgh, MD, PetraWarner, MD, Kevin P. Yakuboff, MD, TinaPalmieri, MD, and Glenn D. Warden, MD

Background : Rapid and effective closure of full-thickness burn wounds remains alimiting factor in burns of greater than 50% of the total body surface area (TBSA). Hypothetically, cultured skin substitutes (CSS) consisting of autologous cultured keratinocytes and fibroblasts attached to collagen-based sponges may reduce requirements for donor skin, and morbidity from autograft harvesting and widely-meshed skin grafts.
Methods : To test this hypothesis, CSS were prepared from split-thickness skin biopsies collected after enrollment of 40 burn patients by informed consent into a study protocol approved by the local Institutional Review Boards of three participating hospitals. CSS and split-thickness skin autograft (AG) were applied in a matched-pair design to patients with full-thickness burns involving a mean value of 73.4% of the TBSA. Data collection consisted of photographs, are a measurements of donor skin and healed wounds after grafting, qualitative outcome by the Vancouver. Scale for burn scar, and biopsies of healed skin.
Results : Engraftment at post operative day (POD) 14 was 81.5 2.1% for CSS and 94.7 2.0 for AG.Percentage TBSA closed at POD 28 was 20.5 2.5% for CSS , and 52.1 2.0 for AG. Theratio of closed to donor areas at POD 28 was 66.2 8.4 for CSS, and 4.0 0.0 for each harvest of AG. Each of these values was significantly different between the graft types. Correlation of percent TBSA closed with CSS at POD 28 with percent TBSA. full-thickness burn generated an r2 value of 0.37 ($p < 0.0001$).Vancouver Scale scores at 1 year after were not different for erythema, pliability, or scarheight, but pigmentation remained deficient in CSS.
Conclusions : These results demonstrate that CSS reduce requirements for donor skin harvesting for grafting of excised, full-thickness burns of greater than 50% TBSA with qualitative outcome that is comparable to meshed AG. Availability of CSS for treatment of extensive, deep burns may reduce time to wound closure, morbidity, and mortality in this patient population.
KeyWords : Burns, Wound healing, Cultured skin, Skin grafts.

JTrauma. 2006;60:821–829.

Permanent wound closure remains a limiting factor in recovery from extensive, full-thickness burn injuries. Recovery from massive burns requires complex critical care that includes, but is not limited to: resuscitation from burn shock, stable respiration, nutritional support of metabolic requirements, restoration of immune flll1ction, and management of microbial contamination and infection. However, recovery depends ultimately on closure of the wounds with autologous epidermis and connective tissue to provide stable healing with minimal amounts of scar. 1.2

Submitted for publication March 10. 2005. Accepted for publication September 1,2005.

From the Department of Surgery, University of Cincinnati and the Shriners Burn Hospital, Cincinnati. Ohio (S.T.B., RJ.K., P.W., K P.Y., G.D. W.) and the Shriners Hospitals for Children Northern California, Sacramento. California (0.0.0., T.P.).
Presented at the 2004 meeting of the American Burn Association. March 23-26. 2004, Vancouver, British Columbia, Canada.
This study was supported by grants from the US Food and Drug Administration (FD-R-OOOti72), the National Institutes of Health (GM50509), and the Shriners Hospitals for Children (8670 and 8450).
Address for reprints: Steven T. Boyce, PhD. Department of Surgery, University of Cincinnati. P.O. Box 670558, Cincinnati. OH 45267-0558; email: boyccst@uc.cdu.

Furthermore, although wound closure is a requirement for discharge from the hospital, skin pliability and stability are essential for the recovery of range of motion, 3-5 and contribute importantly to long-term quality of life.
Because closure of excised, full-thickness burns is a definitive requirement for recovery, several alterative have been studied to accomplish more rapid wound closure. Cultured epithelial autografts applied as partially stratified, keratinocyte sheets have been studied extensively, but are reported to blister, ulcerate, and remain mechanically fragile due to poor foundation of basement membrane.6-7 Cultured keratinocytes have also been applied by spraying of cell suspensions over an appropriate wound base, or a de1111al substitute, 8-9 but the time to healing may be lengthy due to the slow organization of the cultured cell suspensions into stratified, keratinized epidermis. Replacement of dermal tissue has also been shown to reduce long-term morbidity from scarring. Dermal analogs from natural or engineered sources 10-15 have been reported to provide connective tissue beneath either skin epidermal autograft, or cultured keratinocytes. However, none of these alternatives compares favorably to unmeshed, split-thickness skin autograft, which has been reported to provide superior results in pediatric burns and grafting to the face or genitalia.15-17

Previous reports from this laboratory have reported the design and testing of cultured skin substitutes (CSS) prepared from epidermal keratinocytes and dermal fibroblasts attached to collagen-glycosaminoglycan substrates.1R•19 The epidermal substitute stratifies and keratinizes in vitro to initiate formation of epidermal barrier.20•21 Proliferating keratinocytes attach directly to dermal fibroblasts on the surface of the biopolymer sponge and initiate development of a basement membrane, which inhibits blistering after healing. Climcal experience \vith this model has shown rapid healing of bums, surgical wounds, or chronic wounds, but pigmentation has been deficient.22-2(i Addition of cultured epidermal melanocytes in preclimcal models has restored skin color, and cultured microvascular endothelial cells have formed vascular analogs after grafting.27,2H The present study is a prepivotal investigation of autologous cultured skin substitutes to evaluate whether or not this device provides new medical benefits for treatment of burns of greater than 50% of the total body surface area (TBSA). In addition, the present study includes treatment of patients at a distant hospital and evaluates whether skin healed with CSS grows proportionally to the growth of pediatric patients.

MATERIALS AND METHODS

This study was performed with permIssIOns from the Institutional Review Boards of thc University of Cincinnati and the Univcrsity of California Davis, and from the US Food and Drug Administration wldcr an Investigational Device Exemption (IDE) protocol. All patients were enrolled into the study by completion of Informed Consent forms.

The study design consisted of a prospective, randomized, open-label, paired-site comparison of grafting of excised, full-thickness burns with CSS, and split-thickness skin autograft (AG). CSS was meshed at a ratio of 1 to 1.5 and not expanded, and AG was meshed and expanded between 1 to 1,5, and 1 to 4. Application sitcs were paired by selecting adjacent, contra-lateral or anterior-posterior areas that required skin grafting. Two sites ("'-150 cm2 each) were randomized as "A" or "B" before the bcginning of the study. Site A was defined as the rightmost. uppermost, or frontmost of the pair, and site B as the leftmost, lowermost, or rearmost. Comparative grafting was performed in one procedure for each patient, If additional applications of CSS were performed, they were evaluated only for quantitative closure of wounds. If additional applications of AG were performed, they were not evaluated,23 The main hypotheses of the study were that CSS close greater areas of wound than AG per unit of skin autograft harvested and that CSS provide qualitative outcome that is not different from AG.

Two data sets were collected to test these hypotheses.

Quantitative measurements consisted of tracings and planimetry of skin biopsies from which CSS were generated and tracings of treated areas Oll postoperative days (POD) 14 and 28. The tracings were measured for total area and wOlmd tracings were segmented into closed or open areas. Areas were expressed in square centimeters (cm1). Eleven tracings were also performed in nine patients at time points between 2 to 7 years after grafting to evaluate if there was any change of CSS area associated with the growth of pediatric patients. Differences in CSS area were compared by student's t test to changes in TBSA to determine whether CSS were growing proportionally to the individual. TBSA was calculated according to Mosteller,29 and percent burn by using the Lund-Browder formula.30 From the area tracings, the following calculations were performed:

(1) Percent area closed at POD 14 and 28 = (closed area/total treated area) X 100

(2) Ratio of closed:donor areas at POD 28 = area closed with CSS/donor area

(3) Percent TBSA closed at POD 28 = (area closed with CSS/TBSA) X 100

Engraftment was defined as the percent of the treated area that was closed at POD 14. For AG, the ratio of c1osedto-donor areas was assigned as the maximum value of 4 per harvest, and the percent TBSA closed was calculated as the percent TBSA full-thickness burn minus the percent TBSA closed with CSS. Multiple harvests of donor sites were considered independent events with each harvest of AG expanded by a factor of not greater than 4.

Qualitative data were collected according to the Vancouver Scale for burn scar assessment31 with a minor modification. The scale for pigmentation in this study was: a = nonc, 1 = hypopigmented, 2 = normal pigmentation, and 3 = hyperpigmented. The individual values for erythema, pigmentation, pliability, and scar height of the Vancouver Scale were added, and expressed as a composite score.

Enrollment criteria included patients with greatcr than 50% TBSA full-thickness cutaneous bw·ns. Between February 1998 and December 2003. 70 patients were enrolled into the IDE protocol, of which 62 were acute burns. Of thosc 62, 49 were treated, of which five expired and four were excluded from evaluation (Table 1). Of the 40 patients evaluated, there were 26 males and 14 females. The age (mean :!:SEM) was 7.5 :!: 0.9 years (range 0.6-17 years), the percent TBSA burns were 75.8 :!: [,7% (rangc 53-95%), and the percent TBSA full-thickness burns of 73.4 ::!: 2.2% (range 34-95%). The percent rBSA treated with CSS per patient of 27,8 :!: 3.1 % (range 5-88%), and the days to initial CSS treatment were 32,8 :!: I.I (range 24-56; Table 2). Tbirtyseven patients were treated at the Shriners Bums Hospital in Cincinnati, OH, and three at the Shriners Hospital for Children in Northem California (Sacramento, CA.

Table 1 Enrollment and Treatment Data

Parameter	Enrolled	Treated
Totals	70	49
Survived	55	44
Expired	15	5

Excluded	9
Evaluated	40

Table 2 Demographic Data of the Patient Population

Parameter	Mean ± SEM	Range
Age (years)	7.5 ±0.9	0.6-17
Male/female	26/14	
TBSA burn (%)	75.8 ± 1.7	53-95
TSBA FT burn (%)	73.4 ± 2.2	34-95
TSBA CSS/patient (%)	27.8 ± 3.1	5-88
Days to first CSS	32.8 ± 1.1	24-56

Biopsy samples of split-thiclmess skin were collected as early as possible after injury, usually during the first week of the hospitalization. The absolute areas (en}) to be treated with CSS, and for CSS biopsy for each patient were estimated with the following formulae [23] : (4Al % TBSA eligible for ess = (% TBSA of full-thickness bumH40% TBSA treated with AG) (4B) Absolute area (cm ^{2}) to be treated with CSS = (% TBSA eligible for eSS) X TBSA (cm ^{2}) (5) Absolule area (em ^{2}) ofeSS biopsy = Absolute area (cm ^{2}) to be treated with ess X 0.01 Formula 4A assumed that about 40% TBSA would be treated with AG during the time of ess preparation. This assumption was based on performance of two skin grafting operations during about 4 weeks covering about 20% TBSA pcr operation. In cases of very extensivc bums (e.g., >80% TBSA), the value of 40% TBSA coverage with AG was revised downward upon the advice of the medical staff, with a consequent increase in biopsy area (Formula 5). Splitthickness skill samples for preparation of ess were collected with a dermatome set at a depth 01'0.010 to 0.012 inches and transferred to the laboratory for cell culture. Keratinocytes were isolated from epidermis; fibroblasts were isolated from dermis of each biopsy and placed into selective cell cultures as described previously"-I,32.33 in 5% eO,/95% air atmosphere with saturated humidity at 37°C. Du~ing primary culture, human keratinoeytes were incubated in coculture with lethally-irradiated murine 3T3 fibroblasts in semm-free medium. At near-confluencc of thc primaty eulturc, or tirst subculture, part of each population was eryopreserved by controlled-rate freezing and part was continued in culture. After sufficient populations of keratinocytes and fibroblasts were available, fibroblasts were harvested and inoculated at an approximate density of 3.75 to 5.0 X 10 ^{5} cells/cm ^{2} onto collagen-glycosaminoglycan substrates [34] and incubated at least 18 hours to allow cell attachment. Next, keratinocytes were harvested and inoculated at an approximate density of 0.75 to 1.0 X 1Q(i cells/cm ^{2} , which was defined as incubation day 0 for CSS. ess were incubated at the air-liquid interface to stimulate keratinization and formation of epidermal barrier. [21] ess were usually scheduled for surgical application on incubation days 10 to 14 ("-28-35 days after biopsy collection), subject to patient condition. In preparation for grafting, ess (approximately 36 cm ^{2} each) were meshed at a ratio of I: 1.5, but not expanded, placed in petri dishes with sufficient medium to avoid desiccation, and transported to the operating roOlll. For patients treated in Sacramento, ess were packaged in sealed jars, imlllobilized with sterile gauze packing that was kept moist with irrigation solution (see below), and sent by express delivery for application in the operating room the following day. After initial training of staff at the distant hospital, CSS were delivered without the attendance of laboratory slaff en route. Typically, 600 to 1200 cm ^{2} of ess were applied weekly at each operative procedure until wound closure was completed. Usually, multiple procedures for grafting of ess were required for each patient.

Quality assurance standards were applied to ess before transfer to the operating room. Two parameters of assessment were evaluated: light microscopy by standard histology and surface hydration of the epithelium by surface electrical conductivity/impedanee. [33] Histologic evaluations consisted of examination of 18 of 32 ess prepared for each surgical procedure. CSS epithelia were scored as excellent (well organized and keratinized epithelium), good (organized and stratified epithelium), fair (multilayered, continuous epithelium), or poor (discontinuous, hcterogcneous epithelium), and scores of excellent, good and fair were considered acceptable for transplantation. Epithelial surface hydration was measured with a Nova 9003 Dermal Phase Meter (DPM; Nova Technology Corporation, Portsmouth, NH), which reports a high value on a wet surface or a 1m:\' value on a dry surface. For clinical use, DPM values for each ess demonstrated a decrease in DPM values on two successive readings of 2 or more clays apart.

Burn eschar was excised as early as possible after completion of resuscitation, and sites planned for treatment with CSS were covered with cadaveric allograft or the dermal replacement, Integra Dermal Regeneration Template (Integra LifeSciences Corp, Plainsboro, NJ).22,35 For excised bums covered with allograft, it was usually excised 1 day before grafting of ess and AG, and irrigated at alternating 2-hour intervals with 5% wt/vol solution of mafenide acetate in water, and a solution of 40 *JLg/mL* neomycin and 700 U/mL polymyxin B in saline, delivered through perforated red rubber catheters into bulky gauze. The following day, dressings were removed, hemostasis was obtained, and prepared wounds were irrigated with a solution of nutrients and antimicrobials. For excised bW'J1s covered with the dermal replacement, Integra Dern1al Regeneration Template, the outer silastie layer ,vas removed to expose the vascularized WOlU1d bed and prepared W01U1ds were irrigated as above. The irrigation solution consisted of a modified formulation of Dulbecco's Modified Eagle's nutrient medium that was supplemented with 5 I-tg/mL htunan recombinant insulin, 0.5 I-tg/mL hydrocortisone, 40 JLg/mL neomycin, 700 U/mL polymyxin B, 20 l-tg/mL mupirocin, 20 JLgil11L ciprolloxacin, and I I-tg/mL amphotericin B. [36] - [38] After irrigation of the prepared wound beds, ess were gralled using a backing of N-terface (Winfield Laboratories,

Richardson, TX) dressing and stapled in place. Split-thickness AG, meshed at ratios between 1 to 1.5 and

I to 4 was expanded and stapled to wounds. CSS and AG were dressed with fine mesh gauze, and covered with bulky gauze containing perforated red rubber catheters that were secured with Spandex (De Royal, Pmvell, TN) that was stretched to apply gentle pressure and to immobilize the grafted sites. If CSS and AG were LUlller the same dressing, the irrigatiun solutiun fur CSS was used.

Postoperatively, CSS were irrigated with the solution of nutrients and antimicrobials described above, at a dosage of 1 mL per c.m ^{2} CSS three times per day for 5 to 7 days. Dressing changes for CSS and AG were routinely performed on postoperative days (POD) 2 and 5, and all staples and N-terface were removed on POD 5. CSS were treated with an ointment (NBN) consisting of equal parts NeoSporin (Pfizer; New York, NY), Bactroban (GlaxoSmithKline; London, UK), and Nystatin (Wyeth Pharmaceuticals; Madison. NJ), and covered with dry bulky gauze. Dry, keratinized areas were treated with Curci (Kao Brands Co .• Cinciru1ati, OH) lotion and wet areas were treated with NBN ointment on Adaptic (Johnson & Johnson; New Bruswick, NJ) until healing was complete. Daily dressing changes were performed from POD 6 to 7, after which dressings were changed t\.vice daily. If healing was not complete by POD 15, routine wound care for AG was performed on CSS sites. AG was usually irrigated for 5 days with alternating solutions of 5% wt/vol mafenide acetate in water and a solution of 40 J.Lg/mL neomycin and 700 U/mL polymyxin B in saline. Dry dressings for AG routinely consisted of Adaptic coated with an ointment consisting of either 3 parts bacitracin and 1 part silver sulfadiazine if no yeast species were cultured from the grafts, or equal parts silver sulfadiazine, bacitracin, and nystatin if yeast were cultured.

Statistical Analvsis

Primary analyses of data were performed on POD 28 for quantitative and qualitative endpoints. and at 1 year ± 1 month for qualitative outcome. Qualitative data sets \vcre analyzcd for ovcrall significance by the Kruskal-Wallis test. If overall significance was found. then differences were subjected to Wilcoxon's rank sum test. Data from positive! negative scoring of site regrafting was subjected to Fischer's exact test. For the endpoint, ratio of closed-to-donor areas, which is defined in the IDE protocol as the primary medical benefit, a statistical power analysis was pertormed based on preliminary data. For an alpha value of 0.05, and beta values ranging from 0.95 to 0.80, tbe estimated size ofthe population to detem1ine a statistical difference between the CSS and AG treatments was 13-21 patients. For that endpoint. a single-value I test was applied to compare CSS to a maximum value of 4 per harvest of AG. Values for expansion of AG were most often less than 3, but were not recorded for all AG applied to all patients in this study. Tllis statistical approach minimizes the benefit of CSS for tllis endpoirit, and therefore was considered the most conservative statistical analysis.

RESULTS

Figure I shows microscopic anatomy of AG (left panel) and CSS (right panel) before grafting. Both have dermal and epidermal components with a total thickness of less than 400 *J.Lm.* The dermal component of CSS consists of reticulations of collagen-glycosaminoglycan (GAG) biopolymer populated with cultured fibroblasts to which the epidermal component is attached biologically. The epidermal component consists of cultured keratinocytes that stratify and differentiate to form an analog of stratum corneum, which is a precursor of functional epidermal barrier. The CSS generally resemble the anatomy of splitthickness skin but lack blood vessels. Therefore, CSS develop vascular perfusion entirely by angiogenesis, rather than by inosculation of blood vessels in the wound to those in the graft as occurs in AG. Most CSS in this study were approximately 6 X 6 cm in area, but a limited number of CSS of larger area (-12 X 12 cm) were also applied.

Surgical application and healing during the first year after surgery are shown in Figure 2. Not sUllJrisingly, it was found that overlapping of the edges of CSS suppressed formation of granulation tissue between grafts and reduced linear scars after healing. In this patient, CSS were applied over excised, full-thickness burns and accomplished more than 90% wound closure at POD 14. At POD 28, the closed wounds are stable and use of pressure garments was begun. The healed CSS was stable, pliable, and hypopigmented at POD 69 and remained pliable and hypopigmented at POD 479. By 1 year after grafting in this patient, the autograft had developed greater areas of hypertrophic scar than the CSS. Epithelial engraftment and wound closure at POD 14 (Fig. *3A)* was 81.5% tor CSS compared with 94.7%, tor AU which was statistically significant *(p < 0.05)*. A need tor regrafting of CSS (13 of 40) was observed, but not for AG (0 of 40). Nonetheless, the magnitude of regrafting was usually small and the quantitative closure of wounds was much greater for CSS than AU (Fig. 38). The ratio of closed wound area to donor skin area tor CSS was 66.2 versus a maximum of 4 per harvest of AG. This difference is highly significant *(p* < 0.0 I), represents a reduction of donor skin harvesting of more than an order of magnitude by use of CSS, and detines the medical benefit or this alternative therapy for burn pa-

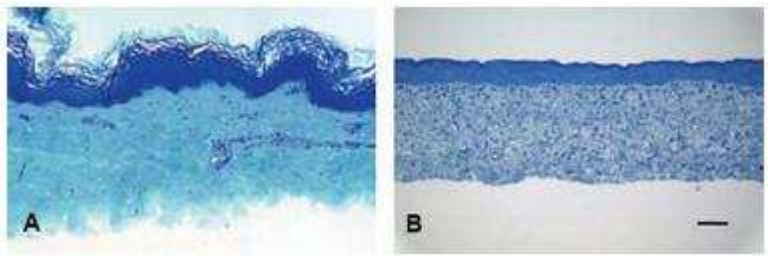


Fig. 1. *Histologic anatomy of split-thickness skin and cultured skin substitutes before Surgery. (A) Split-lhickness skin has a fully keratinized epidermis and vascularized dermis. (B) Cultured skin substitute has partial keratinized epidermis and dermal substitute without a vascular network. Scale bar = 0.1 mm.*

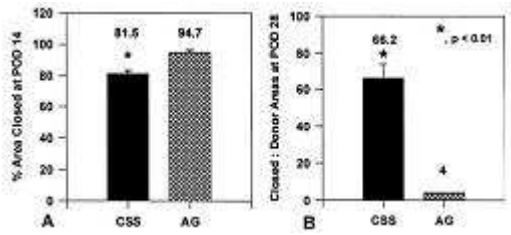


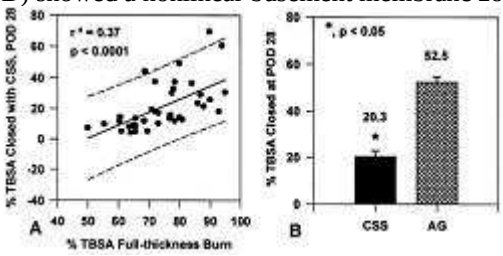
Fig. 3. Engraftment and donor skin reduction. (A) Percentage areas (mean ± SEM) closed at POD 14 were 81.5 ± 2.1 for CSS and 94.7 ± 2.0 for A G. (B) Ratios of closed-to-donor areas at POD 28 were 66.2 ± 7.6 for CSS and 4.0 ± 0.0 for A G.

cases, emphasizing the therapeutic impact of this device in life-threatening burns. On averagc, ess covered 20.3% TBSA, and AG covered 52.5% (Fig. 4B).

No differences in qualitative outcome between CSS and AG were found at I year after grafting (Fig. 5) according to ordinal scoring by the Vancouver Scale for scar assessment. Significant differences were found between ess and AG at time points of 6 months and earlier. Application of ess without the expanded mesh of AG generated a smoother surface and CSS were consistently hypopigmented. Both of these factors contributed to lower scores for ess before 6 months.
Histologic anatomy of ess and AG is shown in figure 6. At 5 months after grafting, the epidermis had matured and remaincd stable and tightly-adhcred to conncetive tisslle. Neither healed AG (Fig. 6A) nor ess (Fig. 6B) developed glands or follicles. Vascularity had decreased and collagen distribution was orthogonal, not linear as in scar. The epidermal surface and dermal-epidermal junction remained relatively linear indicating the absence of rete peg formation. At 15 months after grafting, AG (Fig. 6C) had developed a well interdigitated dermal-epidermal junction, and CSS (Fig. 6D) showed a nonlinear busement membranc zone.

Fig. 2. Clinical observation and healing during the first postoperative year. (A) Surgical application of large (.wlid box) and small (dotted box) formats of cultured skin substitutes (CSS). (B) Postoperative day (POD) 14. (C) POD 28 shml's areas treated with split-thickness autograft or CSS. (D) POD 69. (E) POD 479. Scales in mm.

tients. This is the primary benefit that is reported to the US FDA for measurement of the efficacy of this device.
A positive correlation was found between the percent TBSA of wound closure with ess at POD 28, and the percent TBSA full-thickness burn (Fig. 4A). Importantly, the range of percent TBSA closed extended to 60% or greater in selected



Fin. 4. Correlation of percent total body surface area (TBSA full-thickness burn and percent TBSA closed. (A) Positive correlation (r2 = 0.37. p < 0.0001) was detected between percent TBSA closed with CSS and percent TBSA burned. (B) TBSAs (mean ± SEM) closed at POD 28 were 20.3 ± 2.0 for CSS and 52.5 ±2.0 for AG

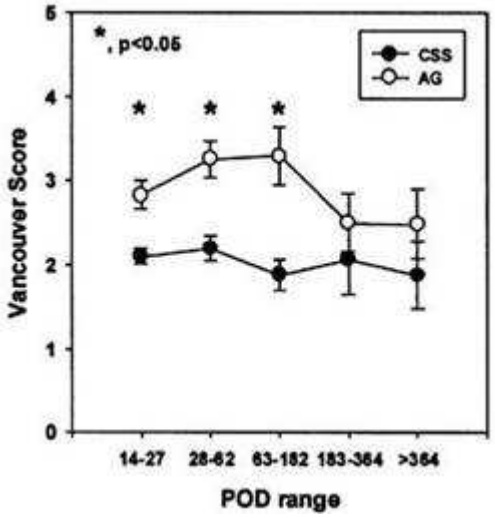


Fig. 5. Modified Vancouver Scale of qualitative outcome. Cultured skin substitllles (CSS) have statistically lower scores than autograft (AG) during the first 6 months after grafting. By 1 year or longer after grafting, no differences are found in the Vancouver Score.

Similar clinical results have been obtained with CSS treatment of patients at the Shriners Hospital for Children in Northern California. Figure 7 shows complete healing at POD 28 of thc anterior torso of paticnt 64 in Sacramento. These results demonstrate that autologous CSS can be prepared and delivered wlattended to hospitals in distant locations.

Because this study was performed in a pediatric population. it was possible to follow the long-term outcome as the patients grew. Figure 8 shows anecdotal data from 11 measurements of ch:.ll1ge of ess area in nine patients, compared with im:reases of TBSA. ess area increased at least as much as TBSA (61. 7%, versus 50.5%) demonstrating that ess grew

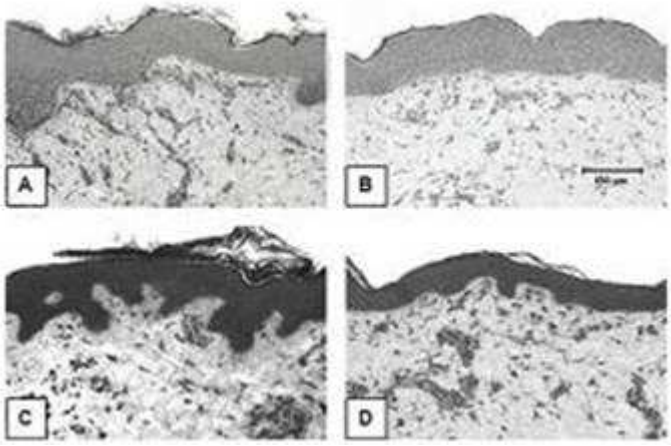


Fig. 6. *Histologic anatomy of closed wounds. Autografi (A) and culturPllskin mh.l·titute (B) shfllvn ,; m(JI1th.~ ajter grafting. Autograft (C) and cultured skin substitute (D) shown* 25 *II/onths alier grqjiing. Both tissue sources have a mature epidermis, a Ivel/-vascularized dermis with orthogonal distributions of col/age/I, and lack epidermal adnexi. Scale har = n.} 11/111.*

Fig. 7. Qualitative outcome in Sacramento, California, with CSS from Cincinnati, Ohio. A skin biopsy was harvested from this patient in Sacramento and sent by express delivery to Cincinnati. where CSS were prepared. They were returned to Sacramento where they were applied to a 4 year-old patiellt with 85% TBSA burns. At POD 99, the healed skin from CSS on the anterior torso is smooth, soft, strong and hypopigmented. These results are directly comparable to treatments with CSS in Cincinnati and demonstrale feasibility for distribution of CSS within the continential United States.

proportionally with these children over 2 to 7 years after treatment.

DISCUSSION

Data from this study support the hypothesis that autologous CSS reduce harvesting of donor skin tor closUJe of burn injuries involving greater than 50(% TBSA. This reduction in donor site harvesting represents a new medical bene tit in the treatment of extensive, full-thickness burn injuries. The reduction in donor skin rcquirements implies reductions ill donor site morbidity, numbers of skin-grafting operations, and intensive care days, but those data were not collected in this smdy. The reduction in dOlior site harvesting is interpreted to result from qualitative and quantitative advantages provided by ess.

Because the epithelium of ess torms partial balTier and basement membrane in vitro,20, 21 epithelial closure occurs rapidly after grafting. Effectively, the keratinized epithelium provides a biological closUJe to the wound at the time of grafting and the basement membrane anchors the epithelium to the connective tissue. Engraftment of ess occurs between connective tissue in the wound and in the graft in analogy to AG. Upon vascularization of the dem1al component of CSS, which occurs by POD 5, the ess begins to stabilize as barrier function and basement membrane are restored. By POD 7, engrafted CSS have closed the wounds with a pennanent.

Fig. 8. ***Increase in area of TBSA and CSS in pediatric patients. Serial examinations were performed over* 2 *to* 7 *years of 11 sites in nine patients. Left and center panels. patient* 3 **at** *age* 3 *and age* 7 *years. Increase of CSS area in these 11 sites averaged* 61.7%. *and increase of TBSA averaged 50.5% demonstrating that CSS grow proportionally with pediatric patients. Scale in cm.***

natural tissue. By POD 14 (Fig. 28), healed ess has sufficient mechanical strength to allow physical therapy to begin. By POD 28, pressure gannellts, which help to control bum scar, can bc worn without loss of ess. Furthermore, application of CSS without expansion of the mesh that was used in AG may suppress the initiation of scar foundation. Unmeshed AG applied as sheet gralls on the hands and face has been reported to reduce scar formation and improve functional and cosmetic outcomes. 15, 39, 40 In tlus paticnt population, engraftment (Fig. 3A *)* was greater than 80% but remained statistically lower than AG. This difference introduced a requirement for nunor regrafting of CSS sites at a higher frequency than AG, despite a reduction in donor site harvesting.

The primary medical benefit of CSS is defined by a ratio of closed areas to donor areas of greater than 65. This value was compared statistically to a maximum expansion of 1:4 for AG. but the actual cxpansion of AG was not measured in this study. In most cases, the usual expansion of AG was 1:2 at the performance site in Cincinnati. Therefore, the conservation of donor skin with CSS compared with AG may actually have been as much as 30-fold. The factor of donor skin expansion of greater than 65-told by CSS suggests hypothetically that less than 2% TBSA of donor skin is sufficient to resurface the body completely with CSS. This benefit has been realized in selected cases of greater than 90% TBSA full-thickness burns, in which excised bums of greater than 50% TBSA were closed with CSS from a biopsy of less than 1% TBSA. In addition to reduction of donor skin harvesting, this conservation of donor skin offers a definitive benefit for closure of lite-threatening burns. Based on these selected cases, it may be possible that broad use of CSS could increase the LD_{50} for burns, which is estimated to be 70% to 80% TBSA in healthy adults, but is much lower in the elderly and the very young. [36] The positive correlation of percent TBSA closed with CSS to percent TBSA full-fuickness bum demonstrates fuat ess remain effective even as the magnitude and complexity of the burn injury are at their greatest. This was shown not to be true for cultured epithelial auto grafts, in which effectiveness correlated inversely with burn magtutude. [41]

Despite conservation of donor skin, less average area (20.3% TBSA) was covered with CSS than AG (52.5% TBSA). This apparent anomaly was attributed to greater frequencies of burns between 50% and 80% TBSA in which lower percent TBSA is treated with CSS, and limited capacity to generate the cultured grafts. Due to limited laboratory facilities, about 1000 cm2 of CSS was applied each week, which decreased the rate at which wounds were treated with CSS and allowed more grafting with AG. Nonetheless, the range of areas closed with CSS extended to about 70% TBSA. It was also observed that because of the sparing of donor skin by CSS, the mesh ratio tor AG for most cases could be reduced to 1:2 or less, compared with as much as 1 :4. This reduction of mesh ratio resulted in faster healing and less scarring of wounds closed with AG. This indirect benefit is also believed to contribute to improved functional outcome and long-term recovery.

Qualitative outcome by a modified Vancouver Scale was not difterent between treatments at I year aner grafting. However, subjective differences between ess and AG can be accounted for by lower pigmentation and less raised scar in CSS. Reduced pigmentation is understood to result trom dilution of epidermal melanocytes during selective culture of keratinocytes, and poor survival during clyopreservation. 42 As discussed above, reduction in raised scar may result from application of CSS without expanded mesh and AG with expanded mesh. Histologic anatomy of healed CSS is consistent with the general process of scar maturation observed in AG. These results suggest that skin tissue generated from CSS is regulated by the same physiologic mechanisms of healing as AG. However, CSS respond somewhat differently than AG because of anatomic ditIerences such as fewer melanocytes and absence of a vascular plexus or immune cells at the time of grafting. Data for growth of CSS was collected anecdotally from a subset of paticnts after clinical examinations over several years. Proportional increases of areas of CSS and body surface area suggests normalization of tissue anatomy and physiology and limited scar formation in sites treated with CSS. Considerable effort was made during

the development of surgical and nursing protocols to manage CSS as similarly as possible to AG. Therefore, training of the staff at the Sacramento Shriners Hospital consisted of one inservice before the initial application of ess and provision of detailed written protocols for postoperative care. Successful use of CSS with this limited training proviJes feasibility for performance of a multicenter study of this medical device which is required before premarket approval can be received.

Remaining anatomic limitations of ess compared with AG include (but are not linlited to) hypopigmentation and absence of blood vessels, glands, or follicles. Operational limitations includc the timc to first application, compromise of tissue biopsies or CSS grafts during transport, microbial contamination in skin samples that may be carried into the cell cultures, or variability in materials used in CSS fabrication. Among these limitations, the time to first application may be reduced somewhat by more efficient culture processes. However, the delivery of a cultured graft with a keratinized epidermis, basement membrane, and dermal substitute requires time for these biological structures to form. The formation of these epidermal structures is required ultimately for stable wound closure and this model controls the formation of these struchlres in the laboratory rather than on the wound. Therefore, medical efficacy must consider not only time of preparation and delivery of a cultured cell graft to the patient, but also thc total timc to complete healing and the long-term outcome. Together, these operational limitations are expected to be reduced greatly as tlus technology moves from the research laboratory to a process of current good manufacturing practices for medical devices. If sufficient facilities were available and greater amounts of ess were generated, this therapeutic approach would allow coverage of wounds of virtually any magnitude in approximately 6 weeks after initiation of the process for CSS preparation. Hypopigmentation and lack of a vascular plexus have been addressed in preclinical studies from tlus laboratory.27, 28 Pigmentation has been regulatcd by the addition of epidermal melanocytes to ess and the addition of dermal microvascular cndothclial cclls has resulted in formation of vascular analogs that form tubular structures after grafting. Hypothetically, hair follicles and sweat and sebaceous glands may be regenerated in vitro, but accomplishment ofthese goals will require regulation of developmental signals in vitro, which is beyond the scope of the present studies. However, it is important to recognize that split-thickness skin AG also docs not regenerate glands or follicles. Therefore, regeneration of hair and/or glands in ess would offer anatomic stmetures found only in fullthickness skin.

CSS has also been used successfully in treatment of congenital giant hairy nevus and postbum scar reconstmction. For these elective applications, the time of preparation docs not limit the time of recovery because there is not an emergent need for treatment. Also, if patients for bum scar reconstmction had been treated with CSS during their acute care hospitalization, then cryopreserved cells may be used to prepare CSS and eliminate the need for donor site harvesting for these procedmes. Together, these advantages offer new alternatives for reduced harvesting of donor skin to patients with needs for closure of extensive full-thickness burns or with lin1ited donor site availability for skin grafting. These therapeutic advantages may be realized for faster recovery with improved outcome for patient populations with burns, bum scars, chronic wounds, and congenital skin diseases.

ACKNOWLEDGMENTS

The authors grateflilly acknowledge the expert technical assistance of Todd Schuermann, Jodi !Vliller, Christopher Lloyd, lvlelissa Reed, Mary Rieman, Johanna Sanders, and Marybeth Lawless for assistance in performance of this study.

REFERENCES

1. Herndon DN. *Total Burn Care* . Philadelphia: WB Saunders: 1996.
2. Canougher GJ. *Burn care and therapy* . St. Louis: Mosby: 1998.
3. Schwanholt CA, Ridgway CL, Greenhalgh DG, et a1. A prospective study of burn scar maturation in pediatrics: does age matter? *J Burn Care Rehabil* . 1994;15:416-420.
4. Covey MH, Dutcher K, Marvin JA, Heimbach DM. Efficacy of continuous passive motion (CPM) devices with hand burns. *J Burn Care Rehabil* . 1988;9:397-400.
5. Lawrence JW, Fauerbach JA, Heinberg L, Doctor M. Visible vs hidden scars and their relation to body esteem. *J Burn Care Rehabil* . 2004;25:25-32.
6. Desai MH, Mlakar JM, MeCauley RL, et al. Lack of long term durability of cultured keratinocyte burn wound coverage: a case report. . *J Burn Care Rehabil* . 1991 ;12:540-545.
7. Woodley DT, Peterson HD, Herzog SR, ct aI. Burn wounds resurfaced by cultured epidermal autografts show abnormal reconstitution of anchoring fibrils. *JAMA* . 1988;259:2566-267 I.
8. Currie LJ, Martin R, Sharpc JR, Jamcs SE. A comparison of keratinocyte cell sprays with and without fibrin glue. *Burns* . 2003; 29:677-685.
9. Navarro FA, Stoner ML, Lee HB, Park es, Wood FM, Orgill DP. Melanocyte repopulation in full-thickness wounds using a cell spray apparatus . . *J Burn Care Rehabil* . 200 I :22:41-46.
10. Sheridan RL, Morgan JR, Cusick JL, Petras LM, Lydon MM, Tompkins RO. Tnitial experience with a composite autologous skin substitute. *Burns* . 2001;27:421-424.
11. Kopp.l, Jeschke MG, Bach AD, Kneser lJ, Horch RE. Applied tissue engineering in the closure of severe burns and chronic wounds using cultured human autologous keratinocytes in a natural fibrin matrix. *Cell tissue Bank* . 2004;5:89-96.
12. Mis B, Rolland E, Ronfard V. Combined use of a collagen-based delmal substitute and a .fibrin-based cultured epithelium: a step toward a total skin replacement for acute wounds. *Burns* . 2004; 30:713-7 I 9.
13. Rehder J, Souto LR, Bernardino CM,lssa M, Puzzi MH. Model of human epidermis rcconstructed in vitro with keratinoc.ytes and melanocytes on dead de-epidermized human dermis. *Sao Paulo Med J.* 2004; 122:22-25.
14. Chester DL, Balderson DS, Papini RP. A review of keratinocyte delivery to the wound bed. *J Burn Care Rehabil* . 2004;25:266-275.
15. Housinger TA. Hills J, Warden GD. l\·1anagcment of pediatric facial burns *J Burn Care Rehabil* . 1994; 15:408-411.
16. Archer SB, Henke A, Greenhalgh DG, Wardell GO. The use of sheet auto grafts to cover extensive burns in patients. *J Burn Care*

Rehabil . 1998: 19:33-38.
17. Housinger TA, Keller B, Warden GD. Management of burns of the penis. *J Burn Care Rehabil* . 1993: 14:525-527.

18. Supp DM, Karpinski AC, Boyce ST. Expression of human beta-defensins HBD-1, HBD-2, and HBD-3 in cultured keratinocytes and skin substitutes. *Burns* . 2004;30:643-648.
19. Boyce ST, Warden OD. Principles and practices for treatment of cutaneous wounds with cultured skin substitutes. *Am J Surg* . 2002; 183:445-456.
20. Boyce ST, Supp AP, Harriger MD, Pickens WL, Wickett RR, Hoath SB. Surface electrical capacitance as a noninvasive index of epidermal barrier in cultured skin substitutes in athymic mice. *J Invest Dermatol* . 1996;107:82-87.
21. Boyce ST, Supp A P, Swope VB, Warden GD. Vitamin C regulates kcratinoeyte viability. epidermal barrier. and basement membrane lormation in vitro, and reduces wound contraction after grafting of cultured skin substitutes. *J Invest Dermatol* . 2002; 118:565-572.
22. Boyce ST, Kagan RJ, Meyer NA, Yakuboff KP. Warden GO. Cultured skin substitutes combined with Integra to replace native skin autograft: and allograli for c1osure of full-thickness burns. *J Burn Care Rehabil* . 1999;20:453-461.
23. Boyce ST, Kagan RJ, Yakuboff KP, et al. Cultured skin substitutes reduce donor skin harvesting for closure of excised, full-thickness burns. *Ann Surg* . 2002;235:269-279.
24. Hansbrough JF, Boyce ST, Cooper ML, Foreman n. Burn wound closure with cultured autologous keratinocytcs and fibroblasts attached to a collagen-glycosaminoglycan substrate *JAMA* . 1989; 262:2125-2130.
25. Passaretti 0, Billmire 0, Kagan R. Corcoran .1, Boyce S. Autologous cullurcd skin substitutes conserve donor autograft in e1ective treatment of congenital giant melanocytic nevus. *Plast Reconstr Surg* . 2004: 114: 1523-1528.
26. Boyce ST. Glatter R, Kitzmiller W J. Trcatment of chronic wounds with cultured cells and biopolymers: a pilot study. *Wounds* . 1995; 7:24-29.
27. Swope VB, Supp AI', Boyce ST. Regulation of cutaneous pigmentation by titration of human melanocytcs in cultured skin substitutes grafted to athymic mice. *Wound Rep Reg* . 2002;10:378-386.
28. Supp Dlvl. Wilson-Landy K, Boyce ST. Human dermal microvascular endothclial cells form vascular analogs in cultured skin substitutes aller gral1ing to athymic mice. *FASEB J* . 2002; 16:797-804.
29. Mosteller RD. Simplified calculation of body-surface area. *N Engl .J Med* . 1987;317: 1098.
30. Lund CC, Browder NC. The estimate of areas of burn. *Surg Gynecol Obstet* . 1944;79:352-:158.
31. Sullivan T, Smith 11, Kermode J. Mciver E, Courtemanche DJ. Rating the burn scar. *J Invest Dermatol* . 1990;] 1 :256-260.
32. Boyce ST, Ham RG. Cultivation, frozen storagc, and clonal growth of normal human epidermal keratinocytes in serum-free media. *J Tiss Cult Meth* . 1985:9:83-93.
33. Boyce ST. Fabrication, quality assurance, and assessment of cultured skin substitutes for treatmcnt of skin wounds. *Biomed Eng J* . 2004; 20:107-112.
34. Boycc ST, Christianson DJ, Hansbrough .IF. Structure of a collagen-GAG dermal skin substitute optimized for cultured uuman epidermal keratinocytes. *J Biomed Mater Res.* 1988;22:939-957.
35. Heimbach D, Luterman A, Burkc JF, et al. Artificial dermis tor major bums; a mulli-center randomized clinical trial. *Ann Surg* . 1988;208:313-:120.
36. American Born Association. National Burn Repository: 2002 Report. Chicago: American Burn Association; 2002.
37. Boyce ST, Wardcn GO, Holder IA. Non-cytotoxic combinations of topical antimicrobial agents for use with culturcd skin. *Antimicrob Agents Chemother* . 1995;39: 1324-1328.
38. Boyce ST, Supp AP, Harriger MD, Greenhalgh DG, Warden GD. Topical nutrients prnmote engraftment and inhihit wound contraction of cultured skin substitutes in alhymic mice. *J Burn Care Rehabil* . 1995; 1 04:345-349.
39. Warden GD, Same JR., Kravitz M. A two-stage technique for excision and grafting of burn wounds . *J Trauma* . 1982:22:98-103.
40. Carsin H, Ainaud P, Le Bcvcr H, cl aJ. Cultured epithelial autografts in extcnsive burn coverage of severely traumatized patients: a live year single-center experience with 30 patients. *Burns* . 2000;26:379-387.
41. Williamson J, Snelling C, Clugston P, MacDonald T, Germann E. Cultured epithelial autograft: Five years of clinical cxpcrience with twenty-eight paticnts *J Trauma* . 1995;39:309-319.
42. Compton CC, Warland G, Kratz G. Mclanocytes in culrured epithelial autografts are depicted with serial subcultivatioo and cryoprescrvalion: implications for clinical outcomc. *J Burn Care Rehabil* . 1998: 19:330-336.

SURVIVAL OF BURNS INVOLVING 90% OF THE TOTAL BODY SURF ACE AREA AFTER TREATMENT WITH AUTOLOGOUS ENGINEERED SKIN SUBSTITUTES

Steven Boyce, PhD* 1,2; Peggy Simpson, RN"; and Richard Kagan, MD1,2

Department of Surgery, University of Cincinnati 1, P.O. Box 670558, Cincinnati, OH 45267-0558, Shriners Hospitals for Children - Cincinnati Burns Hospital"; 3229 Burnet Avenue, Cincimmti, Ohio 45229 USA

ABSTRACT

Rapid and effective closure of full-thickness bum wounds remains a limiting factor for survival after bums involving most of the total body surface area (TBSA). Hypothetically, engineered skin substitutes (ESS) consisting of autologous cultured keratinocytes and fibroblasts attached to collagen-based sponges may reduce requirements for donor skin, numbers of grafting procedures, and time of intensive care during hospitalization. To demonstrate feasibility for this approach, ESS were prepared from split-thickness skin biopsies collected after enrollment of 2 burn patients by InfOlmed Consent into a study protocol approved by the local Institutional Review Board. Patient A was a 10 yearold male who sustained 94% TBSA burns, and patient B was a 2 year-old female who sustained 90% TBSA burns. The injuries were all full-thickness, and occurred in separate building fires in 2007. ESS and split-thickness skin autograft (AG) were applied in a matched-pair design with each patient serving as their own control. Data collection consisted of photographs, area measurements of donor skin and healed wounds after grafting. Data are expressed below as: A) % area closed at post-operative day (POD) 14, B) %TBSA closed at POD 28, and C) ratio of closed to donor areas at POD 28. Patient A received 12 applications of ESS over 4 months, and patient B received 6 applications of ESS over 3 months. Average % area closed (dry epithelium) at POD 14 was 72.4% for ESS and 96.9% for AG. Frequency of patiial regrafting was higher for ESS than for AG. Average %TBSA closed at POD 28 was 51.4% for ESS, and 40.6% for AG. The average ratio of closed wound area to donor skin area at POD 28 was 125.5 for ESS, compared to 4.0 for AG. ESS which was healed at POD 28 did not blister or ulcerate subsequently. Patients wore pressure garments over all treated areas. Pigmentation of areas treated with ESS was deficient, but pliability of healed skin was acceptable. These results demonstrate that ESS reduce requirements for donor skin harvesting for grafting of excised, full-thickness burns involving most of the TBSA. Availability of ESS for treatment of extensive, deep bums may reduce time to wound closure, morbidity and mortality in this patient population.

1. INTRODUCTION

Rapid and effective closure of full-thickness burn wowlds remains a limiting factor for survival after burns involving most of the total body surface area (TBSA). Hypothetically, engineered skin substitutes (ESS) consisting of autologous cultured keratinocytes and fibroblasts attached to collagen-based sponges may reduce requirements for donor skin, numbers of grafting procedures, and time of intensive care during hospitalization. Preclinical studies have shown that ESS (previously referred to as cultured skin substitutes, CSS) fonn partial epidermal bamer and basement membrane in vitro (Boyce et al. 2002b), and express angiogenic factors, including but not limited to Vascular Endothelial Growth Factor, basic Fibroblast Growth Factor and Transforming Growth Factor P-l (Supp et al. 2000;LePoole and Boyce 1999). After grafting to full-thickness wounds in athymic mice, ESS containing epidermal melanocytes restore skin pigmentation (Swope et al. 2006), or containing microvascular endothelial cells torm hwnan vascular analogs (Supp et al. 2002). Previous clinical studies with ESS have demonstrated a reduction in requirements tor halvesting of donor skin autograft in bums greater than 50% TBSA (Boyce et al. 2002a;Boyce et al. 2006), grafting of excised giant congenital melanocytic nevus (Passaretti et al. 2004), atld chronic wounds (Boyce et al. 1995a). Although several alternatives for treatment of extensive, deep burns have been reported (MacNeil 2007;Supp and Boyce 2005), closure of very large TBSA burns remains challenging during acute hospitalization, and can result in long-term morbidity from scars. In this sUldy, autologous ESS were compared with split-thickness, meshed skin autograft treatment of two pediatric patients with burns of 90% TBSA or greater, and evaluated qualitatively for formation of scar, and quantitatively for engraftment at post-operative day (POD) 14, for ratio of closed wound to donor skin areas at POD 28, and for % TBSA closed with ESS or AG.

2. METHODS

To demonstrate feasibility for this approach, ESS were prepared from split-thickness skin biopsies collected after enrollment of 2 burn patients by Informed Consent into a study protocol approved by the local Institutional Review Board. Patient A was a 10 year-old male who sustained 94% TBSA burns, and patient B was a 2 year-old female who sustained 90% TBSA burns. The injuries were all full-thickness, and occurred in separate building fires in 2007. ESS were prepared from autologous keratinocytes and fibroblasts which were isolated from split-thickness skin, culhlred, and cryopreserved for later use (Figure 1). Cells were combined with collagen-based sponges, and incubated at the air-liquid interface to promote formation of epidermal barrier (Figurc 2). ESS and split-thickness skin autograft (AG) were applied in a matched-pair design with each patient serving as their own control (Figure 3). The first application of ESS was compared to AG for all end points, and subsequent applications of ESS were added to the first and quantify device efficacy. Data collection consisted of photographs, area measurements of donor skin and healed wounds at post operative days (POD) 14 and 28 after grafting, and healed tissue biopsies as available. Data are expressed below as mean values for these two subjects for: A) % area closed at post-operative day (POD) 14, B) % TBSA closed at POD 28, and C) ratio of closed to donor areas at POD 28. Due to the small sample size, no statistical analyses were perfornled.

Prior to treatment with ESS, wounds were excised, and grafted with either meshed, allograft skin or Integra Dermal Regeneration Template. Two-stage grafting was performed in which the allograft or silicone layer of Integra was removed, and wounds were treated overnight at twohour intervals with alternating irrigations of 5% Sulfamylon solution and double antibiotic solution (200 U/mL polymyxin Band 40 jlg/mL neomycin) (Warden et al. 1982). The following morning, the dressings were removed in the operating room, hemostasis was obtained with electrocautery and compression. Autograft skin was harvested at a thickness of 0.010-0.012 inches thickness, and meshed and expanded 1:2. ESS were applied with a dressing of N- Terface, and AG was applied directly to the prepared wounds. Grafts were stapled to the wounds, dressed with fine-meshed gauze and bulky gauze with perforated red rubber catheters and secured either with a Spandex stent or with elastic wrap bandages. Sites were irrigated for five days with a formulation of non-cytotoxic antimicrobial agents (Boyce et al. 2006) at a dosage of ImL/cm2 three times per day. Dressings were changed on POD 2. On POD 5, wet dressings were discontinued, and all dressings and staples were removed. Open areas of ESS were dressed with a topical ointment consisting of equal parts Neospori..tl, Bactroban and Nystatin on Adaptic. Open areas of AG were dressed with a topical cream consisting of equal parts Silver sulfadiazine, Bacitracin and Nystatin on Adaptic. Keratinized areas of ESS were treated with moisturizing lotion (i.e., Curel) beginning at POD 11, and moisturizing cream (i.e., Eucerin) was applied to AG beginning at POD 7. 80th graft types were treated according to the AG protocol beginning at POD 15.

3. RESULTS

Patient A received 12 applications of ESS over 4 months, and patient B received 7 applications of ESS over 3 months. Average % engraftment (dry epithelium) at POD 14 was 72.4% for ESS and 96.9% for AG (Figure 4A). Partial regrafting was performed in 8 of 12 ESS sites (66%) for Patient A, and 4 of 7 ESS siles (57%) for Patient B. The average ratio of closed wound area to donor skin area at POD 28 was 125.5 for ESS, compared to 4.0 for AG (Figure 4B). Average %T8SA closed at POD 28 was 51.4% for ESS, and 40.6% for AG (Figure 4C). Physical therapy was resumed beginning at POD 7, and ESS which was healed at POD 28 did not blister or ulcerate subsequently. Patients wore pressure gannents over all treated areas. Pigmentation of areas treated with ESS was deficient, but pliability of healed skin was acceptable. Figure 5 shows images of Patient A at the time of hospital discharge, 187 days after tlte first treatment with autologous engineered skin.

CONCLUSIONS

These results demonstrate that ESS reduce requirements for donor skin harvesting for grafting of excised, fullthickness bums involving 1110St of the TBSA. Survival of these two patients after treatment with ESS is consistent with previous fmdings that autologous engineered skin is associated with reduced harvesting of donor skin autograft (Boyce et al. 2006), and decreased mortality in matched patient populations (Armour et al. 2007). Availability of ESS for treatment of extensive, deep burns may reduce time to wound closure, morbidity and mortality in this patient population.

ACKNOWLEDGEMENTS

This study was supported by Shriners Hospitals for Children. The authors acknowledge the teclmical skills and expertise of Christopher Lloyd, Elizabeth Maier, Rachel Zimmemlan, Jill Pruszka, John Besse, and Deanna Leslie for delivery of this investigative device to assist the bum care team with the recovery of these patients.

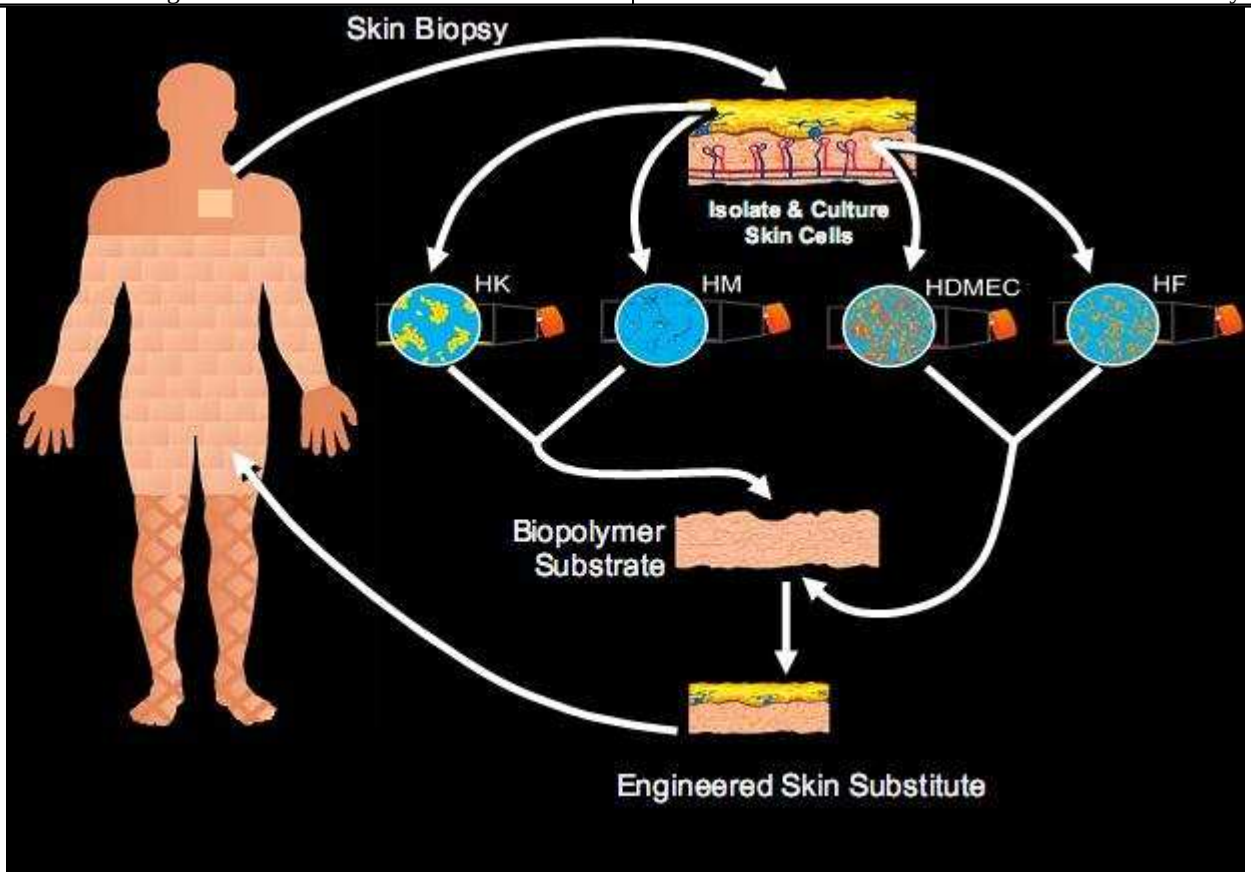


Figure 1. Diagram of the process for fabrication of engineered skin substitutes. A biopsy of split-thickness skin is harvested from an uninjured site, epidermal keratinocytes and dem1al fibroblasts are isolated, the cells are cultured to very large populations, harvested as cell suspensions, inoculated onto collagen-based sponges, incubated in contact with air to stimulated epidermal keratinization, and grafted to excised, full-thickness wounds. The entire process requires approximately 4 weeks.

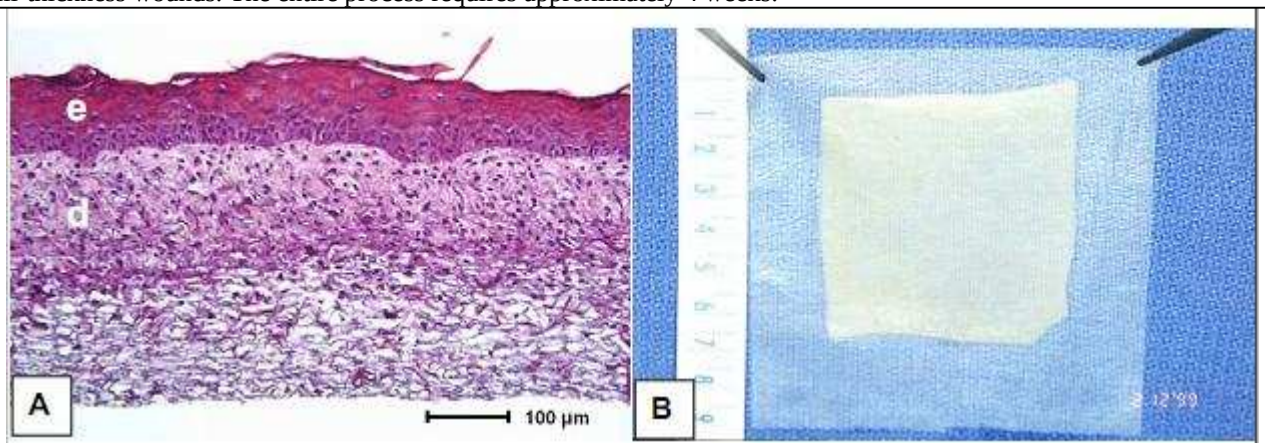
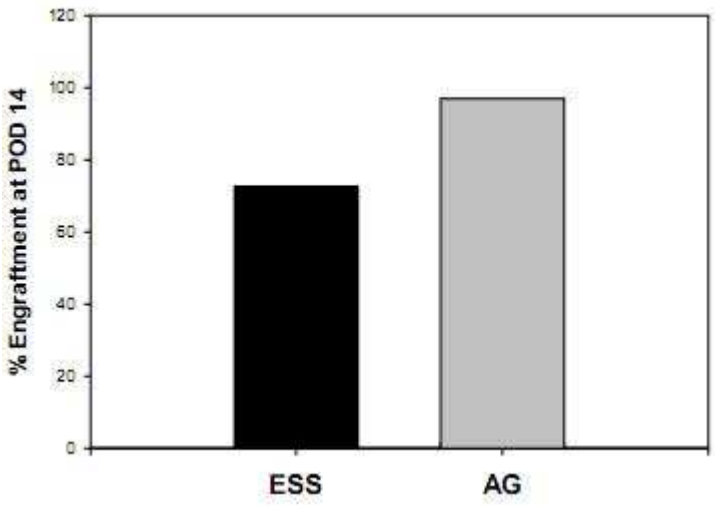


Figure 2. Microscopic and macroscopic anatomies of engineered skin substitutes (ESS). A) Populations of dermal fibroblasts cover the surface of the biopolymer, and are also distributed into its interior to fom1 the dermal substitute (d). Epidermal keratinocytes *(e)* attach to the fibroblasts, form partial basement membrane, stratify, and form partial epidermal barrier before grafting. The engineered skin is avascular and has a total thickness of approximately 0.3 m111. Scale bar = 0.1 mm. B) Macroscopic anatomy of ESS shows a uniform construct approximately 30cm ^{2} which can be handled readily by a surgeon. Scale in cm.

Figure 3. Surgical application of engineered skin substitutes (ESS). Left panel) ESS were applied as meshed, non-expanded sheets, stapled to wounds and irrigated for 5 days with non-cytotoxic antimicrobial agents (Boyce et al. 1995b). Right panel) Grafting of the anterior torso of Patient A with ESS, and split-thickness skin autograft (AG). Integra Dermal Regeneration Template (Integra) was grafted previously. Scale in cm.



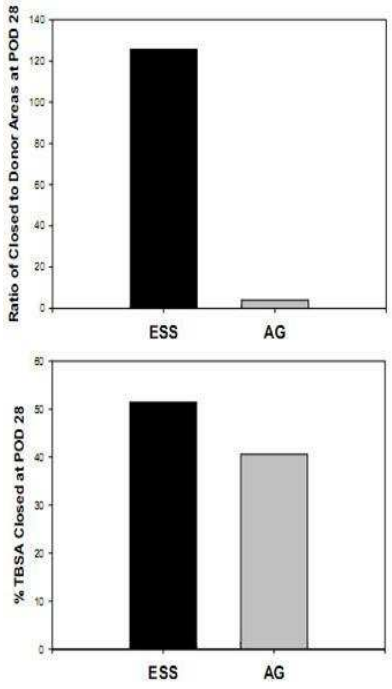


Figure 4. Quantitative comparisons of engineered skin substitutes (ESS) and split-thickness skin autograft (AG). A) Engraftment at post-operative day (POD14) 14 was 72.4% for ESS , and 96.9% for AG. B)The ratios of closed wounds to biopsy area were 125.5 for ESS and 4.0 for AG. This value represents a reduction of donor skin requirements by treatment with ESS. C) Mean total body surface area (TBSA) closed with ESS was 51.4%, and with AG was 40.6%.

Figure 5. Patient A, healed ESS and AG at POD 187. Top panels) Torso and arms. Bottom panels) Legs. Wounds close rapidly because of epidermal keratinization ill vitro, and do not blister because of basement membrane formation. Pigmentation of most areas treated with ESS was deficient, but pliability of healed skin was acceptable. The patient wore pressure garments over all treated areas. Application as non-expanded sheets reduces granulation tissue and scar to generate a relatively smooth surface. Scale in em.

REFERENCES

Armour, A. D., B. A. DOff, R. 1. Kagan, and S. T. Boyce. Mortality of acute burns treated with cultured skin substitutes. J Blml Care Res 28[2J, S96. 2007.

Boyce, S. T., R. Glatter, and W. 1. Kitzmiller. 1995a. "Treatment of chronic wounds with cultured cells and biopolymers: a pilot study." Wounds 7(1)24-9.

Boyce, S. T., R . .T. Kagan, D. G. Greenhalgh, P. Warner, K. P. Yakuboff, T. Palmieri, and G. D. Warden. 2006. "Cultured skin substitutes reduce requirements for harvesting of skin autograft for closure of excised, full-thickness bums." Journal of Trauma 60821-9.

Boyce, S. T., R. 1. Kagan, K. P. Yakuboff, N. A. Meyer, M. T. Rieman, D. G. Greenhalgh, and G. D. Warden. 2002a. "Cultured skin· substitutes reduce donor skin harvesting for closure of excised, fullthickness bums." Ann.Surg 235269-79.

Boyce, S. T., A. P. Supp, V. B. Swope, and G. D. Warden. 2002b. "Vitamin C regulates keratinocyte viability, epidermal barrier, and basement membrane in vitro, and reduces wound contraction after grafting of cultured skin substitutes." Journal of Investigative Dermatology 118565-72.

Boyce, S. T., G. D. Warden, and I. A. Holder. 1995b.
"Non-cytotoxic combinations of topical antinlicrobial agents for use with cultured skin." Antimicrobial Agents and Chemotherapy 39(6) 1324-8.

LePoole, I. C. and S. T. Boyce. 1999. "Keratinocytes suppress transforming growth factor beta-I expression by fibroblasts in cultured skin substitutes." British Journal of Dermatology 140409-16.

MacNeil, S. 2007. "Progress and opportunities for tissueengineered skin." Nature 445874-80.

Passaretti, D., D. Billmire, R. Kagan, J. Corcoran, and S.

Boyce. 2004. "Autologous cultured skin substitutes conserve donor autograft in elective treatment of congenital giant melanocytic nevus." Plastic alld Reconstructive Surgely 1141523-8.

Supp, D. M. and S. T. Boyce. 2005. "Engineered skin substitutes: practices and potentials. Clin.Dermata/23403-12.

Supp, D. M., A. P. Supp, S. M. Bell, and S. T. Boyce. 2000. "Enhanced vascularization of cultured skin substitutes genetically modified to overexpress Vascular Endothelial Growth Factor." Journal of Investigative Dermatology 1145-13.

Supp, D. M., K. Wilson-Landy, and S. T. Boyce. 2002. "Human dermal microvascular endothelial cells form vascular analogs in cultured skin substinltes after grafting to athyrnic mice." F ASEE Journal 16797-804.

Swope, V. 8., A. P. Supp, S. Schwemberger, G. F.
Babcock, and S. T. Boyce. 2006. "Increased expression of integrins and decreased apoptosis cOITelate with increased melanocyte retention in cultured skin substitutes." Pigment Cell Research 19424-33.

Warden, G. D., 1. R. Saffle, and M. Kravitz. 1982. "A two-stage technique for excision and grafting of burn substitutes: practices and potentials."
Clin.Dermata/23403-12.

Exhibit D – The Amended and Restated Exclusive License Agreement between The Regents of the University of California and Cutanogen Corporation.

AMENDED AND RESTATED EXCLUSIVE LICENSE AGREEMENT

Between

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

And

CUT ANOGEN CORPORATION

For

LIVING HUMAN SKIN REPLACEMENTS AND CULTURED SKIN SUBSTITUTES

UC Case No. 86-323

TABLE OF CONTENT

DC Case No(s). 86-323

AMENDED AND RESTATED EXCLUSIVE LICENSE AGREEMENT

For

LIVING HUMAN SKIN REPLACEMENTS AND
CULTURED SKIN SUBSTITUTES

This amended and restated exclusive license agreement (the "Agreement") is made effective this 3 day of March , 2001 (the "Effective Date"), between THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, a California corporation, having its statewide administrative offices at 1111 Franklin Street, 12th Floor, Oakland, California 94607-5200 (“The Regents”), and CUTANOGEN CORPORATION, an Ohio corporation, having a principal place of business at 3130 Highland Avenue, Suite 3420, Cincinnati, Ohio 45219-2374 (the “Licensee”).

BACKGROUND

A. Certain inventions, generally characterized as Living Human Skin Replacements and Cultured Skin Substitutes (collectively the "Invention"), were made in the course of research at the University of California, San Diego by Dr. Steven Boyce and are covered by Regents' Patent Rights as defined below.

B. The development of the Invention was sponsored by the Department of Health and Human Services and, as a consequence, this license is subject to overriding obligations to the United States ("U.S.") Federal Government under 35 U.S.C. §§200-212 and applicable regulations including a non-exclusive, non-transferable, irrevocable, paid up license to practice
or have practiced the Invention for or on behalf of the United States Government throughout the world.

C. Licensee and The Regents executed an exclusive license agreement dated January 12, 1999 with DC. Control No. 99-04-0309 (the "First Agreement"), a First Amendment (D.C. Control No. 99-04-0309A) dated August 26, 1999, and a Second Amendment (U.C. Control No. 99-04-0309B) dated November 10, 1999. The parties now desire to amend and restate such First Agreement as set forth below.

D. Licensee has evaluated the Invention under a Secrecy Agreement with The Regents (V.C. Control No. 97-20-0439) dated March 7, 1997. In addition, Licensee and The Regents executed a Letter of Intent (V.C. Control No. 98-30-0494) dated March 30, 1998, and an Option Agreement (D.C. Control No. 98-30-0494A) dated June 29, 1998. The Secrecy Agreement, Letter of Intent and Option Agreement were terminated in the First Agreement.

E. Licensee wishes to obtain rights from The Regents for the exclusive commercial development, use and sale of products from the Invention, and The Regents is willing to grant those rights so that the Invention may be developed to its fullest and the benefits enjoyed by the general public.

F. Licensee is a "small business firm" as defined in 15 D.S.C. §632.

G. Both parties recognize and agree that royalties due under this Agreement on products and methods will be paid by Licensee on both pending patent applications and issued patents.

-00000-

In view of the foregoing, the parties agree:

1. DEFINITIONS

1.1 "Affiliate" means any corporation or other business entity in which Licensee owns or controls, directly or indirectly, at least fifty percent (50%) of the outstanding stock or other voting rights entitled to elect directors or in which Licensee is owned or controlled directly or indirectly by at least fifty percent (SO%) of the outstanding stock or other voting rights entitled to

elect directors; but in any country where the local law does not permit foreign equity participation of at least fifty percent (50%), then an "Affiliate" includes any company in which Licensee owns or controls, or is owned or controlled by, directly or indirectly, the maximum percentage of outstanding stock or voting rights permitted by local law.

1.2 "Field of Use" means use in connection with growth and maintenance of human skin cells and cell-biopolymer skin substitutes for the treatment of bums, chronic or acute wounds, toxicology testing, skin research or pharmacokinetic research.

1.3 "Licensed Method" means any method that is covered by Regents' Patent Rights, or the use of which would constitute, but for the license granted to Licensee under this Agreement, an infringement of any pending or issued claim within Regents' Patent Rights.

1.4 "Licensed Product" means any material that is either covered by Regents' Patent Rights, that is produced by the Licensed Method or that the use of which would constitute, but for the license granted to Licensee under this Agreement, an infringement of any pending or issued claim within Regents' Patent Rights.

1.5 "Net Sales" means the total of the gross revenue received from Final Sale of Licensed Product to an independent, unaffiliated third party or Licensed Method performed by Licensee, an Affiliate or a sublicensee, less the sum of the following actual and customary deductions where applicable: cash, trade or quantity discounts; sales, use, tariff, import/export duties or other excise taxes imposed on particular sales (excepting value added taxes or income taxes); transportation charges, including insurance; and allowances or credits to customers because of rejections or returns. Final Sale means the sale which is the last act of infringement of Regents' Patent Rights within the control of Licensee, an Affiliate or sublicensee, regardless of whether Licensee, an Affiliate or sublicensee had control over prior infringing acts. For purposes of calculating Net Sales, any distribution or transfer among Licensee, an Affiliate or sublicensee for end use by Licensee, an Affiliate or sublicensee (which event is the last act of infringement of Regents' Patent Rights) will be considered a Final Sale at the price normally charged to independent, unaffiliated third parties.

1.6 "Regents' Patent Rights" means The Regents' interest in the following subject matter:

DC Case Number	U.S. Application Number or U.S. Patent Number	Filing or Issue Date
86-323-1	Application No. 07/043,321, now abandoned	
86-323-2	Application No. 07/186,603, now abandoned	
86-323-3	Application No. 07/398,297, now abandoned	
86-323-4	Application No. 07/437,883, now abandoned	
86-323-5	Patent No. 5,273,900	12-28-93
86-323-6	Application No. 07/759,637, now abandoned	
86-323-7	Application No. 08/052,167, now abandoned	
86-323-8	Patent No. 5,976,878	11-2-99
86-323-9	Patent No. 5,711,172	1-27-98

and continuing applications thereof including divisions and substitutions but excluding continuation-in-part applications (to the extent that claims are not supported in the parent); any patents on said applications including reissues, reexaminations and extensions; and any corresponding foreign applications or patents.

2. LIFE OF PATENT EXCLUSIVE GRANT

2.1 Subject to the limitations set forth in this Agreement, The Regents grants to Licensee a world-wide license under Regents' Patent Rights to make, have made, use, sell, offer to sell and import Licensed Product and to practice Licensed Method to the extent permitted by law.

2.2 Except as otherwise provided in this Agreement, the license granted in Paragraph 2.1 is exclusive for the life of the Agreement.

2.3 The license granted in Paragraphs 2.1 and 2.2 is subject to all the applicable provisions of any license to the U.S. Government executed by The Regents and is subject to the overriding obligations to the U.S. Government under 35 V.S.C. §§200-212 and applicable governmental implementing regulations.

2.4 The license granted in Paragraphs 2.1 and 2.2 is limited to methods and products that are within the Field or Use. For other methods and products, Licensee has no license under this Agreement.

2.5 The Regents reserves the right to use the Invention and associated technology for educational and research purposes including publication of research results and sharing such research results, the Invention and associated technology with other educational and non-profit institutions for their use of similar scope.

3. SUBLICENSES

3.1 The Regents also grants to Licensee the right to issue sublicenses to third parties to make, have made, use, sell, offer to sell and import Licensed Product and to practice Licensed Method in the Field of Use, as long as Licensee has current exclusive rights thereto under this Agreement. To the extent applicable, sublicenses must include all of the rights of and obligations due to The Regents (and, if applicable. the U.S. Government) contained in this Agreement.

3.2 Licensee shall promptly provide The Regents with a copy of each sublicense issued, collect and guarantee payment of all payments due The Regents from sublicensees and summarize and deliver all reports due The Regents from sublicensees.

3.3 Upon termination of this Agreement for any reason, The Regents, at its sole discretion, shall determine whether Licensee shall cancel or assign to The Regents any and all sublicenses.

4. PAYMENT TERMS

4.1 Paragraphs 1.3, 1.4 and 1.6 define Licensed Method, Licensed Product and Regents' Patent Rights, so that royalties are payable on products and methods covered by both pending patent applications and issued patents. Royalties will be based on Net Sales and will accrue in each country for the duration of Regents' Patent Rights in that country and are payable when revenue is received from third party.

4.2 Licensee shall pay to The Regents earned royalties quarterly on or before February 28, May 31, August 31 and November 30 of each calendar year. Each payment will be for earned royalties accrued within Licensee's most recently completed calendar quarter.

4.3 All monies due The Regents are payable in U.S. dollars. Licensee is responsible for all bank transfer charges. When Licensed Product is sold for monies other than U.S. dollars, Licensee shall first determine the earned royalty in the currency of the country in which Licensed Product was sold and then convert the amount into equivalent U.S. funds, using the exchange rate quoted in The Wall Street Journal on the last business day of the reporting period.

4.4 Royalties earned on sales occurring in any country outside the U.S. may not be reduced by any taxes, fees or other charges imposed by the government of such country on the payment of royalty income. Notwithstanding the foregoing, all payments made by Licensee in fulfillment of The Regents' tax liability in any particular county will be credited against earned royalties or fees due The Regents for that country.

4.5 If, at any time, legal restrictions prevent the prompt remittance of royalties by Licensee from any country where a Licensed Product is sold, then Licensee shall convert the amount owed to The Regents into U.S. funds and shall pay The Regents directly from its U.S. source of funds for as long as the legal restrictions apply.

4.6 If any patent or patent claim within Regents' Patent Rights is held invalid in a final decision by a court of competent jurisdiction and last resort and from which no appeal has or can be taken, then all obligation to pay royalties based on that patent or claim or any claim patentable indistinct therefrom will cease as of the date of final decision. Licensee will not, however, be relieved from paying any royalties that accrued before the final decision or that are based on another patent or claim not involved in the final decision or that are based on The Regents' property rights.

4.7 No royalties may be collected or paid on Licensed Product sold to the account of the U.S. Government, or any agency thereof, as provided for in the license to the Government. 4.8 In the event payments, rebillings or fees are not received by The Regents when due, Licensee shall pay to The Regents interest charges at a rate of ten percent (10%) per annum. Interest is calculated from the date payment was due until actually received by The Regents.

5. LICENSE-ISSUE FEE
Licensee shall pay to The Regents a license-issue fee of five thousand dollars ($ 5,000) within seven (7) days after the Effective Date. This fee is non-refundable, non-cancelable and is not an advance against royalties.

6. LICENSE MAINTENANCE FEE
Licensee shall also pay to The Regents a royalty in the form of a license maintenance fee of five thousand dollars ($5,000) beginning on the one-year anniversary of the Effective Date and continuing annually on each anniversary of the Effective Date until and including the fourth anniversary of the Effective Date. Beginning on the fifth anniversary of the Effective Date and continuing annually on each anniversary of the Effective Date Licensee shall pay to The Regents a license maintenance fee of twenty thousand dollars ($20,000). The license maintenance fee is not due on any anniversary of the Effective Date if on that date, Licensee is commercially selling Licensed Product and paying an earned royalty or minimum annual royalty to The Regents on the sales of Licensed Product. License maintenance fees are non-refundable and not an advance against earned royalties.

7. ROYALTIES, MINIMUM ANNUAL ROYALTIES and MILESTONE PAYMENTS

7.1 Licensee shall also pay. to The Regents an earned royalty of five percent (5%) of the Net Sales of Licensed Product or Licensed Method. In the event that Licensee is required to pay royalties to any third party in order to commercialize Licensed Product, the royalty paid by Licensee to The Regents may be decreased by an amount equal to one-half the royalties paid by Licensee to such third party. However, in no event shall the earned royalty payable to The Regents by Licensee be less than three percent (3%) of Net Sales of Licensed Product or Licensed Method.

7.2 Licensee shall pay to The Regents a minimum annual royalty of twenty thousand dollars ($20,000) for the life of Regents' Patent Rights, beginning with the year of the first commercial sale of Licensed Product. Licensee's obligation to pay the minimum annual royalty will be pro-rated for the number of months remaining in that calendar year when commercial sales commence and will be due the following February 28, to allow for crediting of the pro-rated year's earned royalties. For subsequent years, the minimum annual royalty will be paid to The Regents by February 28 of each year and will be credited against the earned royalty due for the calendar year in which the minimum payment was made.

7.3 Licensee shall also pay to The Regents the following milestone payments on each Licensed Product within thirty (30) days of the achievement of each milestone event by Licensee: 7.3.1 Fifty thousand dollars (S50,000) upon applying for marketing approval from the United States Food and Drug Administration; and

7.3.2 One hundred thousand dollars ($100,000) upon receiving marketing approval from the United States Food and Drug Administration.

8. DUE DILIGENCE

8.1 Licensee, upon execution of this Agreement, shall diligently proceed with the development, manufacture and sale of Licensed Product and shall earnestly and diligently endeavor to market the same within a reasonable time after execution of this Agreement and in quantities sufficient to meet market demands.

8.2 Licensee shall endeavor to obtain all necessary governmental approvals for the manufacture, use and sale of Licensed Product.

8.3 Licensee shall:

8.3.1 Complete a first round of equity financing of at least three hundred thousand dollars ($300,000) within four years of the Effective Date;

8.3.2 submit a pre-marketing approval or other marketing approval application covering Licensed Product (the "Primary Application") to the U.S. Food and Drug Administration within four (4) years from the Effective Date;

8.3.3 market Licensed Product in the U.S. within six (6) months of receiving approval of the Primary Application from the U.S. Food and Drug Administration. lfthe Primary Application is rejected (the "Rejection") or no approval is obtained within eighteen (18) months of submission of the Primary

Application then another application (the "Secondary Application") shall be submitted to the U.S. Food and Drug Administration within six months of the Rejection or the end of the eighteen (18) month period, whichever is first; and

8.3.4 market Licensed Product in the U.S. within six months of receiving approval of the Secondary Application from the U.S. Food and Drug Administration if it is necessary to submit a Secondary Application; and

8.3.5 receive approval from the U.S. Food and Drug Administration for either the Primary Application or the Secondary Application within five years from the date of submitting the Primary Application; and

8.3.6 reasonably fill the market demand for Licensed Product following commencement of marketing at any time during the exclusive period of this Agreement.

8.4 If Licensee is unable to perform any of the above provisions, then The Regents has the right and option to either terminate this Agreement or reduce Licensee's exclusive license to a nonexclusive license. This right, if exercised by The Regents, supersedes the rights granted in Article 2 (Life of Patent Exclusive Grant).

9. PROGRESS AND ROYALTY REPORTS

9.1 Beginning March 31, 2001 and semi-annually thereafter, Licensee shall submit to The Regents a written progress report covering Licensee's (and any Affiliate's or sublicensee's) activities related to the development and testing of all Licensed Product and the obtaining of the governmental approvals necessary for marketing. Progress reports are required for each Licensed Product until the first commercial sale of that Licensed Product occurs in the U.S. and shall be again required if commercial sales of such Licensed Product are suspended or discontinued. The Regents shall safeguard progress reports with the same degree of care as it exercises with its own data of a similar nature.

9.2 Progress reports submitted under Paragraph 9.1 shall include, but are not limited to, the following topics:
- summary of work completed;
- summary of work in progress;
- current schedule of anticipated events or milestones;
- market plans for introduction of Licensed Product; and
- a summary of resources (dollar value) spent in the reporting period.

9.3 Licensee has a continuing responsibility to keep The Regents informed of the large or small business entity status (as defined by the U.S. Patent and Trademark Office) of itself and its sublicensees and Affiliates.

9.4 Licensee shall report to The Regents in its immediately subsequent progress and royalty report the date of first commercial sale of a Licensed Product in each country.

9.5 After the first commercial sale of a Licensed Product anywhere in the world, Licensee shall make quarterly royalty reports to The Regents on or before each February 28 (for the quarter ending December 31), May 31 (for the quarter ending March 31), August 31 (for the quarter ending June 30 and November 30 (for the quarter ending September 30) of each year. Each royalty report will cover Licensee's most recently completed calendar quarter and will show (a) the gross sales and Net Sales of Licensed Product sold during the most recently completed calendar quarter; (b) the number of each type of Licensed Product sold; (c) the royalties, in U.S. dollars, payable with respect to sales of Licensed Product; (d) the method used to calculate the royalty; and (e) the exchange rates used.

9.6 If no sales of Licensed Product have been made during any reporting period, then a statement to this effect is required.

10. BOOKS AND RECORDS

10.1 Licensee shall keep accurate books and records showing all Licensed Product manufactured, used and/or sold under the terms of this Agreement. Books and records must be preserved for at least five (5) years from the date of the royalty payment to which they pertain.

10.2 Books and records must be open to inspection by representatives or agents of The Regents at reasonable times. The Regents shall bear the fees and expenses of examination but if an error in royalties of more than five percent (5%) of the total royalties due for any year is discovered in any examination, then Licensee shall bear the fees and expenses of that examination.

11. LIFE OF THE AGREEMENT

11.1 Unless otherwise terminated by operation of law or by acts of the parties in accordance with the terms of this Agreement, this Agreement will be in force from the Effective Date until the date of expiration of the last-to-expire patent licensed under this Agreement; or until the last patent application licensed under this Agreement is abandoned and no patent in Regents' Patent Rights ever issues.

11.2 Any termination of this Agreement will not affect the rights and obligations set forth in the following Articles:

Article 10- Books and Records
Article 14- Disposition of Licensed Product on Hand Upon Termination
Article 15- Use of Names and Trademarks
Article 20- Indemnification
Article 24- Failure to Perform
Article 29- Secrecy

12. TERMINATION BY THE REGENTS

If Licensee fails to perform or violates any term of this Agreement, then The Regents may give written notice of default ("Notice of Default") to Licensee. If Licensee fails to repair the default within sixty (60) days of the effective date of Notice of Default, then The Regents may terminate this Agreement and its licenses by a second written notice ("Notice of Termination"). If a Notice of Termination is sent to Licensee, then this Agreement will automatically terminate on the effective date of that notice. Such termination will not relieve Licensee of its obligation to pay any fees owing at the time of termination and will not impair any accrued right of The Regents. These notices are subject to Article 21 (Notices).

13. TERMINATION BY LICENSEE

13.1 Licensee has the right at any time to terminate this Agreement in whole or as to any portion of Regents' Patent Rights by giving notice in writing to The Regents. Such notice of termination will be subject to Article 21 (Notices) and termination of this Agreement will be effective sixty (60) days from the effective date of such notice.

13.2 Any termination under the above Paragraph 13.1 does not relieve Licensee of any obligation or liability accrued under this Agreement prior to termination or rescind any payment made to The Regents or anything done by Licensee prior to the time termination becomes effective. Termination does not affect in any manner any rights of The Regents arising under this Agreement prior to termination.

14. DISPOSITION OF LICENSED PRODUCT ON HAND UPON TERMINATION

Upon termination of this Agreement, Licensee is entitled to dispose of all previously made or partially made Licensed Product, but no more, within a period of one (1) year provided that the sale of Licensed Product is subject to the terms of this Agreement, including, but not limited to, the rendering of reports and payment of royalties required under this Agreement.

15. USE OF NAMES AND TRADEMARKS

15.1 Nothing contained in this Agreement confers any right to use in advertising, publicity or other promotional activities any name, trade name, trademark or other designation of either party hereto (including contraction, abbreviation or simulation of any of the foregoing). Unless required by law, the use by Licensee of the name "The Regents of the University of California or the name of any campus of the University of California is prohibited.

15.2 The Regents is free to release to the inventors and senior administrators employed by The Regents the terms and conditions of this Agreement. If such release is made, then The Regents shall give notice of the confidential nature and shall request that the recipient does not disclose such terms and conditions to others. If a third party inquires whether a license to Regents' Patent Rights is available, then The Regents may disclose the existence of this Agreement and the extent of the grant in Article 2 (Life of Patent Exclusive Grant) to such third party, but will not disclose the name of Licensee or any other terms or conditions of this

Agreement, except where The Regents is required to release information under either the California Public Records Act, a governmental audit requirement, or other applicable law.

LIMITED WARRANTY

16.1 The Regents warrants to Licensee that it has the lawful right to grant this license.

16.2 This license and the associated Invention are provided WITHOUT WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED. THE REGENTS MAKES NO REPRESENTATION OR WARRANTY THAT LICENSED PRODUCT OR LICENSED METHOD WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT.

16.3 IN NO EVENT MAY THE REGENTS BE LIABLE FOR ANY INCIDENTAL, SPECIAL OR CONSEQUENTIAL DAMAGES RESULTING FROM EXERCISE OF THIS LICENSE OR THE USE OF THE INVENTION OR LICENSED PRODUCT.

16.4 This Agreement does not:

16.4.1 express or imply a warranty or representation as to the validity or scope of any of Regents' Patent Rights;

16.4.2 express or imply a warranty or representation that anything made, used, sold, offered for sale or imported or otherwise disposed of under any license granted in this Agreement is or will be free from infringement of patents of third parties;

16.4.3 obligate The Regents to bring or prosecute actions or suits against third parties for patent infringement except as provided in Article 19 (patent Infringement);

16.4.4 confer by implication, estoppel or otherwise any license or rights under any patents of The Regents other than Regents' Patent Rights as defined in this Agreement, regardless of whether those patents are dominant or subordinate to Regents' Patent Rights; or

16.4.5 obligate The Regents to furnish any know-how not provided in Regents' Patent Rights.

PATENT PROSECUTION AND MAINTENANCE

17.1 As long as Licensee has paid patent costs as provided for in this Article 17 (Patent Prosecution and Maintenance), The Regents shall diligently endeavor to prosecute and maintain the U.S. and foreign patents comprising Regents' Patent Rights using counsel of its choice, and The Regents shall provide Licensee with copies of all relevant documentation so that Licensee may be informed of the continuing prosecution, and Licensee agrees to keep this documentation confidential. The Regents' counsel will take instructions only from The Regents, and all patents and patent applications under this Agreement will be assigned solely to The Regents.

17.2 The Regents shall use reasonable efforts to amend any patent application to include claims reasonably requested by Licensee to protect the products contemplated to be sold under this Agreement.

17.3 Licensee shall apply for an extension of the term of any patent included within Regents' Patent Rights if appropriate under the Drug Price Competition and Patent Term Restoration Act of 1984 andlor European, Japanese and other foreign counterparts of this Law. Licensee shall prepare all documents and The Regents agrees to execute the documents and to take additional action as Licensee reasonably requests in connection therewith.

17.4 If either party (in the case of The Regents, the Licensing Officer responsible for administration of this Agreement) receives notice pertaining to infringement or potential infringement of any issued patent included within Regents' Patent Rights under the Drug Price Competition and Patent Term Restoration Act of 1984 (andlor foreign counterparts of this Law), then that party shall notify the other party within ten (10) days after receipt of notice of infringement.

17.5 Licensee shall bear the costs of preparing, filing, prosecuting and maintaining all U.S. and foreign patent applications contemplated by this Agreement. Costs billed by The Regents' counsel will be rebilled to Licensee and are due within thirty (30) days of rebilling by The Regents. These costs include patent prosecution costs for the Invention incurred by The Regents prior to the execution of this Agreement and any patent prosecution costs that maybe incurred
for patentability opinions, re-examination, re-issue, interferences or inventorship determinations. Costs incurred by The Regents prior to the Effective Date of this Agreement are estimated to be approximately $161,152.90 (actual costs of approximately $204,994.38 less third party reimbursements of approximately $43,841.48) and will be reimbursed by Licensee in three equal annual installments beginning on the fourth anniversary of the effective date of this Agreement and continuing annually for the next two successive anniversaries of the effective date.

17.6 Licensee may request The Regents to obtain patent protection on the Invention in foreign countries if available and if Licensee so desires. Licensee shall notify The Regents of its decision to obtain or maintain foreign patents not less than sixty (60) days prior to the deadline for any payment, filing or action to be taken in connection therewith. This notice concerning foreign filing must be in writing, must identify the countries desired and must reaffirm Licensee's obligation to underwrite the costs thereof. The absence of such a notice from Licensee to The Regents will be considered an election not to obtain or maintain foreign rights.

17.7 Licensee's obligation to underwrite and to pay patent prosecution costs will continue for so long as this Agreement remains in effect, but Licensee may terminate its obligations with respect to any given patent application or patent upon three (3) months' written notice to The Regents. The Regents will use its best efforts to curtail patent costs when a notice of termination is received from Licensee. The Regents may prosecute and maintain such application(s) or patent(s) at its sole discretion and expense, but Licensee will have no further right or licenses thereunder. Non-payment of patent costs maybe deemed by The Regents as an election by Licensee not to maintain application(s) or patent(s).

17.8 The Regents may file, prosecute or maintain patent applications at its own expense in any country in which Licensee has not elected to file, prosecute or maintain patent applications in accordance with this Article 17 (patent Prosecution and Maintenance) and those applications and resultant patents will not be subject to this Agreement.

18. PATENT MARKING

Licensee shall mark all Licensed Product made, used or sold under the terms of this Agreement, or their containers, in accordance with the applicable patent marking laws.

PATENT INFRINGEMENT

19.1 If Licensee learns of the substantial infringement of any patent licensed under this Agreement, then Licensee shall call The Regents' attention thereto in writing and provide The Regents with reasonable evidence of infringement. Neither party will notify a third party of the infringement of any of Regents' Patent Rights without first obtaining consent of the other party, which consent will not be unreasonably denied. Both parties shall use their best efforts in cooperation with each other to terminate infringement without litigation.

19.2 Licensee may request that The Regents take legal action against the infringement of Regents' Patent Rights. Such request must be in writing and must include reasonable evidence of infringement and damages to Licensee. If the infringing activity has not abated within ninety (90) days following the effective date of request, then The Regents has the right to:

19.2.1 commence suit on its own account; or 19.2.2 refuse to participate in the suit, and
The Regents shall give notice of its election in writing to Licensee by the end of the one-hundredth (100th) day after receiving notice of written request from Licensee. Licensee may thereafter bring suit for patent infringement, at its own expense, if and only if The Regents elects not to commence suit and if the infringement occurred during the period and in a jurisdiction where Licensee had exclusive rights under this Agreement. If, however, Licensee elects to bring suit in accordance with this Paragraph 19.2, then The Regents may thereafter join that suit at its own expense. Licensee agrees not to bring suit for patent infringement without following the procedures of this Paragraph, and both parties agree to be bound by an order of a court for patent infringement issues and patent infringement defenses raised through the pendency of such a suit under this Paragraph 19.2.

19.3 Legal action, as is decided on, will be at the expense of the party bringing suit and all damages recovered thereby will belong to the party bringing suit, but legal action brought jointly by The Regents and Licensee and fully participated in by both will be at the joint expense of the

parties and all recoveries will be shared jointly by them in proportion to the share of expense paid by each party.

19.4 Each party shall cooperate with the other in litigation proceedings instituted hereunder but at the expense of the party bringing suit. Litigation will be controlled by the party bringing the suit, except that The Regents may be represented by counsel of its choice in any suit brought by Licensee.

20. INDEMNIFICATION

20.1 Licensee shall indemnify, hold harmless and defend The Regents, its officers, employees and agents, the sponsors of the research that led to the Invention and the inventors of the patents and patent applications in Regents' Patent Rights and their employers against any and all claims, suits, losses, liabilities, damages, costs, fees and expenses resulting from or arising out of exercise of this license or any sublicense. This indemnification includes, but is not limited to, any product liability.

20.2 Licensee, at its sole cost and expense, shall insure its activities in connection with the work under this Agreement and obtain, keep in force and maintain insurance as follows or an equivalent program of self-insurance (including all Affiliates and sublicensees, if any):

20.3 The Licensee shall obtain Comprehensive or commercial form general liability insurance (contractual liability included) with limits as follows:
- Each Occurrence $5,000,000
-Products/Completed Operations Aggregate $5,000,000
-Personal and Advertising Injury $1,000,000
-General Aggregate (commercial form only) $5,000,000

The coverage and limits referred to under the above do not in any way limit the liability of Licensee. Licensee shall furnish The Regents with certificates of insurance showing compliance with all requirements. Certificates must:

-Provide for thirty (30) days' advance written notice to The Regents of any modification;
-Indicate that The Regents has been endorsed as an additional Insured under the coverage referred to under the above;

Include a provision that the coverage will be primary and will not participate with nor will be excess over any valid and collectable insurance or program of self-insurance carried or maintained by The Regents.

20.4 If Licensee is not exercising its right to make, have made, use, sell, offer to sell and import Licensed Product or practicing Licensed Method then Licensee may obtain and carry insurance with a lower coverage level for individual event and aggregate coverage. Licensee must notify The Regents before proceeding to obtain the lower coverage level. Such notification will be given to The Regents 30 days before such action is taken. Licensee shall obtain and carry coverage at the higher level as provided for in Paragraph 20.3 sixty (60) days before exercising its right to make, have made, use, sell, offer to sell and import Licensed Product or practicing Licensed Method, and shall provide The Regents with a notice of intent to obtain coverage at the higher level sixty days before coverage begins. The lower level of insurance will afford no less than the following coverage:

Each Occurrence $1,000,000
Products/Completed Operations Aggregate $5,000,000 Personal and Advertising Injury $1,000,000
General Aggregate (commercial form only) $1,000,000

20.5 The Regents shall notify Licensee in writing of any claim or suit brought against The Regents in respect of which The Regents intends to invoke the provisions of this Article 20 (Indemnification). Licensee shall keep The Regents informed on a current basis of its defense of any claims under this Article 20 (Indemnification).

NOTICES

21.1 Any notice or payment required to be given to either party shall be deemed to have been properly given and to be effective as of the date specified below if delivered to the respective address given below or to another address as designated by written notice given to the other party:

21.1.1 on the date of delivery if delivered in person;

21.1.2 on the date of mailing if mailed by first-class certified mail, postage paid; or

21. 1.3 on the date of mailing if mailed by any global express carrier service that requires recipient to sign the documents demonstrating the delivery of such notice or payment.

In the case of Licensee:	CUT ANOGEN CORPORATION 3130 Highland Ave., Suite 3420 Cincinnati, Ohio 45219-2374 Attention: Steven T. Boyce President
In the case of The Regents:	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA Office of Technology Transfer 1111 Franklin Street, 51b Floor Oakland, CA 94607-5200 Attention: Executive Director Research Administration and Technology Transfer RE: UC Case No. 86-323-2,5,6,8,9

22. ASSIGNABILITY
This Agreement may be assigned by The Regents, but is personal to Licensee and assignable by Licensee only with the written consent of The Regents, which consent will not be unreasonably withheld.

23. NO WAIVER
No waiver by either party of any default of this Agreement may be deemed a waiver of any subsequent or similar default. A suspension of duty under this Agreement due to force majeure shall not be for a period longer than one (1) year.

24. FAILURE TO PERFORM
If either party finds it necessary to undertake legal action against the other on account of
failure of performance due under this Agreement, then the prevailing party is entitled to reasonable attorney's fees in addition to costs and necessary disbursements.

25. GOVERNING LAWS

THIS AGREEMENT WILL BE INTERPRETED AND CONSTRUED IN ACCORDANCE WITH THE LAWS OF THE STATE OF CALIFORNIA WITHOUT REGARD TO CONFLICT OF LAWS OR TO WHICH PARTY DRAFTED PARTICULAR PROVISIONS OF THIS AGREEMENT, but the scope and validity of any patent or patent application will be governed by the applicable laws of the country of the patent or patent application. Disputes between the parties regarding this Agreement will utilize only trial courts within California for disputes that go to court.

26. PREFERENCE FOR U.S. INDUSTRY

Because this Agreement grants the exclusive right to use or sell the Invention in the U.S., Licensee agrees that any products sold in the U.S. embodying this Invention or produced through the use thereof will be manufactured substantially in the U.S.

27. GOVERNMENT APPROVAL OR REGISTRATION

Licensee shall notify The Regents if it becomes aware that this Agreement is subject to any U.S. or foreign government reporting or approval requirement. Licensee shall make all necessary filings and pay all costs including fees, penalties and all other out-or-pocket costs associated with such reporting or approval process.

28. EXPORT CONTROL LAWS

Licensee shall observe all applicable U.S. and foreign laws with respect to the transfer of Licensed Product and related technical data to foreign countries, including, without limitation, the International Traffic in Arms Regulations (IT AR) and the Export Administration Regulations.

29. SECRECY

29.1 With regard to confidential information ("Data"), which can be oral or written or both, received from The Regents regarding this Invention, Licensee agrees:

29.1.1 not to use the Data except for the sole purpose of performing under the terms of this Agreement;

29.1.2 to safeguard Data against disclosure to others with the same degree of care as it exercises with its own data of a similar nature;

29.1.3 not to disclose Data to others (except to its employees, agents or consultants who are bound to Licensee by a like obligation of confidentiality) without the express written permission of The Regents, except that Licensee is not prevented from using or disclosing any of the Data that:

29.1.3.1 Licensee can demonstrate by written records was previously known to it;

29.1.3.2 is now or becomes in the future, public knowledge other than through acts or omissions of Licensee; or

29.1.3.3 is lawfully obtained by Licensee from sources independent of The Regents;

29.1.3.4 is required to be disclosed to a governmental entity or agency in connection with seeking any governmental or regulatory approval, or pursuant to the lawful requirement or request of a governmental entity or agency; and

29.1.4 that the secrecy obligations of Licensee with respect to Data will continue for a period ending five (5) years from the termination date of this Agreement.

29.2 Upon the termination of this Agreement, Licensee must destroy or return to The Regents any Data in its possession within thirty (30) days following the effective date of termination. However, Licensee may retain one copy of Data solely for archival purposes, provided that such Data is subject to the confidentiality provisions set forth in this Article 29 (Secrecy). Within sixty (60) days following termination, Licensee must provide The Regents with a written notice that Data has been returned or destroyed.

29.3 With regard to biological material received by Licensee from The Regents, if any, including any cell lines, vectors, genetic material, derivatives, products progeny or material derived therefrom ("Biological Material"), Licensee agrees:

29.3.1 not to use Biological Material except for the sole purpose of performing under the terms of this Agreement;

29.3.2 not to transfer Biological Material to others (except to its employees, agents or consultants who are bound to Licensee by like obligations conditioning and restricting access, use and continued use of Biological Material) without the express written permission of The Regents, except that Licensee is not prevented from transferring Biological Material that:

29.3.2.1 becomes publicly available other than through acts or omissions of Licensee; or

29.3.2.2 is lawfully obtained by Licensee from sources independent of The Regents;

29.3.3 to safeguard Biological Material against disclosure and transmission to others with the same degree of care as it exercises with its own biological materials of a similar nature;

29.3.4 to destroy all copies of Biological Material at the termination of this Agreement.

30. HUMANITARIAN DEVICE EXEMPTION

The parties agree that certain Licensed Products may qualify as a Humanitarian Use Device ("RUD") pursuant to the Safe Medical Devices Act of 1990 and it may be appropriate to apply for a Humanitarian Device Exemption ("HOE") pursuant to that act. If Licensee decides to seek a HUD designation or apply for an HOE, The Regents agrees to cooperate with the Licensee, to the extent permissible by law and the policy of The Regents, in connection with the HUD and HOE, with any incremental costs at the Licensee's expense.

31. MISCELLANEOUS

31.1 The headings of the several sections are inserted for convenience of reference only and are not intended to be a part of or to affect the meaning or interpretation of this Agreement.

31.2 This Agreement is not binding on the parties until it has been signed below on behalf of each party. It is then effective as of the Effective Date.

31.3 No amendment or modification of this Agreement is valid or binding on the parties unless made in writing and signed on behalf of each party.

31.4 This Agreement embodies the entire understanding of the parties and supersedes all previous communications, representations or understandings, either oral or written, between the parties relating to the subject matter hereof. This Agreement supersedes and replaces the First Agreement, First Amendment and Second Amendment and the First Agreement, First Amendment and Second Amendment shall be of no further force or effect.

31.5 In case any of the provisions contained in this Agreement is held to be invalid, illegal or unenforceable in any respect, that invalidity, illegality or unenforceability will not affect any other provisions of this Agreement and this Agreement will be construed as if the invalid, illegal or unenforceable provisions had never been contained in it.

31.6 None of the provisions of this Agreement is intended to create any form of joint venture between the parties, rights in third parties or rights that are enforceable by any third party.

IN WITNESS WHEREOF, both The Regents and Licensee have executed this Agreement, in duplicate originals, by their respective and duly authorized officers on the day and year written.

CUTANOGEN CORPORATION	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
By: /s/ Steven T. Boyce	By: /s/ Alan B. Bennett
(Signature)	(Signature)
Name: Steven T. Boyce	Name: Alan B. Bennett
Title: President	Title: Executive Director, Research Administration and Technology Transfer
Date: 3/5/01	Date: 03/12/01

Exhibit E – The First Amendment to the Amended and Restated Exclusive License Agreement between The Regents of the University of California and Cutanogen Corporation.

FIRST AMENDMENT TO THE AMENDED AND RESTATED EXCLUSIVE LICENSE AGREEMENT

This amendment ("Amendment") is effective this 23 rd day of November 2005, between The Regents of the University of California ("The Regents), a California corporation, having its statewide administrative offices at 1111 Franklin Street. 12th Floor, Oakland, California 94607-5200 and Cutanogen Corporation ("Cutanogen"), an Ohio corporation, having a principal place of business at 3130 Highland Avenue, Suite 3420, Cincinnati, Ohio 45219.

BACKGROUND

A. The Regents and Cutanogen entered into a license agreement effective March 12, 2001 (UC Control No. 2001-04-0465). entitled AMENDED AND RESTATED EXCLUSIVE LICENSE AGREEMENT for LIVING HUMAN SKIN REPLACEMENTS AND CULTURED SKIN SUBSTITUTES ("License Agreement"). wherein Cutanogen was granted certain rights.

B. Cutanogen desires that the License Agreement be amended to extend a diligence term. and The Regents is agreeable to such substitution.

The parties agree as follows:

1 The Regents and Cutanogen agree to delete paragraph 8.3.2 of the License Agreement and replace it with the following:

"8.3.2 submit a pre-marketing approval or other marketing approval application covering Licensed Product (the "Primary Application") to the U.S. Food and Drug Administration by December 31, 2006".

2 The Regents hereby release Cutanogen, its successors and assigns from all liability and obligations. of any kind whatsoever, which The Regents have ever had. now have or may have under said License Agreement arising before or as of the effective date of this Amendment solely limited to the requirement set forth in paragraph 8.3.2 of the License Agreement deleted by this Amendment, which had required Cutanogen to submit a pre-marketing approval or other marketing approval application covering Licensed Product (as that term is defined in said License Agreement) to the U.S. Food and Drug Administration by July 31.2005.

3 Said License Agreement shall remain unchanged in all other respects and shall remain in full force and effect.

The parties have executed this Amendment in duplicate originals by their respective authorized officers on the following day and year.

CUTANOGEN CORPORATION	THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
By: /s/Steven T Bryc e	By: /s/Neil Kilcoin
Name: Steven T.Bryce	Name: Neil Kilcoin
Title: President	Title: Bus. Development and IP Manager Office of Technology Transfer
Date: 11/16/05	Date: 11/23/05

Exhibit F – The License Agreement between Cutanogen Corporation on the one hand and the University of Cincinnati and Shriners Hospitals for Children on the other hand.

LICENSE AGREEMENT

THIS AGREEMENT is made and effective as of the date of last signing (herein the "Effective Date”) by and among Cutanogen Corporation, a corporation of Ohio having a principal place of business at 3130 Highland Avenue, Suite 3420, Cincinnati, Ohio 45219-2374 (herein referred to as "Cutanogen"); the University of Cincinnati, having a place of business at Room G-7 Wherry Hall, Box 670829, Cincinnati. Ohio 45221-0829 (herein referred to as "UC"); and Shriners Hospitals for Children, having a place of business at PO Box 31356, Tampa, Florida 33631-3356 (herein referred to as "SHC").

INTRODUCTION

1 WHEREAS, UC and SHC (herein known collectively as the "Licensors") have developed and are continuing research in the area of the Technology, as defined in Article 1.1 of this Agreement; and

2 WHEREAS, Cutanogen wishes to acquire license rights to and develop the Technology; and

3 WHEREAS, Cutanogen and the Licensors mutually desire to formalize an agreement which delineates their respective rights and obligations with respect to the Technology;

4 WHEREAS, the Licensors are the lawful joint owners of the Technology and have the right to grant the license as provided herein; and

5 WHEREAS, in order to market products based on the Technology. Cutanogen will have to acquire rights under certain Background Patents, as defined in Article 1.23.

NOW THEREFORE, in consideration of the mutual covenants and promises contained in this Agreement and other good and valuable consideration, the Licensors and Cutanogen agree as follows.

ARTICLE 1 - DEFINITIONS

In the terms defined and used herein, the singular shall include the plural and vice versa. Terms in this Agreement (other than names of Parties and Article Headings) which are set forth in uppercase letters have the meanings established for such terms in the succeeding paragraphs of this Article I.

1.1 "Technology" shall mean the technology described in the Patents and all Improvements thereto.

1.2 "Patents" shall mean all U.S. and foreign patent applications and patents arising from the following UC invention disclosures and SHC Records of Medical Invention and from any Improvements thereto:

UC 90-022	Casting Device for Implantable Biopolymer Substrates
UC 91-017	Lipid...enriched Skin Substitute
UC 94-038	Topical Antimicrobial Mixtures for Wound Care
SHC	Topical Nutrient Formulations for Wound Treatment, signed October 27.1993; submitted to SHC, Tampa., November 8, 1993.
SHC	Cultured Skin Substitutes for Wound Treattnent: Concept, Composition and Uses; signed January 14, 1997; submitted to SHC, Tampa., January 14, 1997.

1.3 "Valid Claim" shall mean any claim in an unexpired patent or pending in a patent application included within the Patents which has not been held unenforceable, unpatentable, or invalid by a decision of a court or other governmental agency of competent jurisdiction. unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable through reissue or disclaimer. For any country in which there should be two or more such decisions conflicting with respect to the validity of the same claim, the decision of the higher or highest tribunal shall thereafter control; however, should the tribunals be of equal rank, then the decision or decisions upholding the claim shall prevail when the conflicting decisions are equal in number, and the majority of decisions shall prevail when the conflicting decisions are unequal in number.

1.4 "Sublicensee" shall mean any person or entity, other than an Affiliate, sublicensed by Cutanogen to practice Patent(s).

1.5 "Product" shall mean any product made, used or sold by Cutanogen and/or a Sublicensee under one or more Valid Claims of Patents.

1.6 "Process" shall mean any and all processes practiced by Cutanogen and/or a Sublicensee under one or more Valid Claims of Patents.

1.7 "Net Sales" shall mean the aggregate gross revenues derived by Cutanogen from Cutanogen' s sale of Produets to or Cutanogen's practice of Processes for an unaffiliated third party in an arms length transaction., less credits granted on account of price adjustments, normal and customary trade discounts, recalls, rejection or return of items previously sold. and excises, sales taxes, duties or other taxes imposed upon and paid with respect to such sales. In the event that Cutanogen is not permitted under an :HDE or other government regulation anywhere in the world to pass on the cost of royalties to its customers, such sales shall be excluded from Net Sales.

1.8 "Calendar Quarter" shall mean the three (3) months ending on the last day of March, June, September and December of each year.

1.9 "Parties" in singular or plural as required by the context shall mean Cutanogen, UC and/or SHC as each of those parties is defined herein.

1.10 "FDA" shall mean the United States Food and Drug Administration, or any comparable government agency of any other country.

1.11 "IDE" shall mean an Investigational Device Exemption filing v.ith the FDA, or a comparable regulatory filing in any other country.

1.12 “HUD" shall mean a Humanitarian Use Device as designated by the FDA pursuant to the Safe Medical Devices Act of 1990 and the FDA regulations at 21 CFR Part 814. or a comparable regulatory designation in any other country.

1.13 "HDE"' shall mean a Humanitarian Device Exemption pursuant to the Safe Medical Devices Act of 1990 and the FDA regulations at 21 CFR Part 814, Subpart H. or a comparable regulatory designation in any other country.

1.14 "Cutanogen" shall mean Cutanogen Corporation and its Affiliates.

1.15 “Affiliate" shall mean any company in which Cutanogen owns or controls at least 50% of the voting stock or which owns or controls at least 50% of the voting stock of Cutanogen, or which, together with Cutanogen, is controlled by a third party which owns or controls at least 50% of the voting stock of each.

1.16 “Term” shall mean the period beginning on the Effective Date and extending to the expiration of the last to expire Patent.

1.17 "lmprovement” shall mean any modification of a Product or Process. or both, or other new invention within the field of skin substitutes made during the Term in whole or in part by a UC Inventor or SHC Inventor using Cutanogen funds or facilities, or working in a contractual consulting or advisory capacity to Cutanogen or any other joint invention of a UC or SHC Inventor and an Cutanogen Inventor within said field, to the extent that UC and SHC have the right to grant a license thereto.

1.18 "UC Inventor" shall mean an inventor either employed by UC or working full-time or part-time in a UC facility.

1.19 "SHC Inventor" shall mean an inventor either employed by SHC or working full-time or part-time in an SHC facility.

1.20 "Cutanogen Inventor" shall mean an inventor employed by Cutanogen who is neither a UC Inventor nor an SHC Inventor.

1.21 "Party" shall mean Cutanogen, UC and/or SHC.

1.22 "Background Patents" shall mean any or all of the following patents, including pending patent applications and foreign patents derived from the same applications, invented in whole or in part by Steven Boyce, which in the absence of a license from the owners would prevent Cutanogen from marketing Products:

Owned by University of California	Owned by University Patents, Inc
US 5,711,172	US 4,940,666
US 5,273,900	US 4,673,649
PCT/UC88/08305	
EP 363,400	
JP 03/502,049	
DE 3,878,909	
US Appl. Ser. No. 08/376,293	
Now: US 5,976,878	

1.23 "Net Sublicensing Fees" shall mean any lump sum fees paid to Cutanogen by a Sublicensee in consideration for sublicense rights to Products or Processes, less any out-of-pocket expenses incurred by Cutanogen that are directly and solely attributable to the negotiation and drafting of the relevant sublicense agreement.

1.24 "First Sale" shall mean Cutanogen's or a Sublicensee's first commercial sale of a Product to, or first commercial practice of a Process for, an unaffiliated third party following regulatory approval Any sale that is made under an HDE or other government regulation anywhere in the world prohibiting the payment of royalties shall not be counted as a First Sale.

ARTICLE 2 – LICENSE

2.1 The Licensors agree to grant and hereby grant to Cutanogen an exclusive, worldwide license, with the right to sublicense, to make, have made, use. market, offer for sale, sell and otherwise dispose of Pro duets and practice Processes under the Patents.

2.2 The exclusive license specified in Paragraph 2.1 is subject to required, limited nonexclusive license rights, if any, of the United States Government: and to a reserved right of the Licensors to utilize the Technology and/or Patents for non-commercial research and educational purposes within facilities owned or operated by either UC or SHC.

2.3 If permissible under FDA regulations, UC agrees to use reasonable efforts to arrange for transfer to Cutanogen of any IDE, HDE or HOD designation that has been granted to UC with respect to Products or Processes.

ARTICLE 3 - R&D PERFORMANCE & MARKETING

3.1 Cutanogen agrees to use efforts consistent with its reasonable, commercial judgment to develop Products and Processes and to otherwise add value to Technology, and will for such purpose make available adequate resources and qualified personnel

3.2 The parties agree that certain Products may serve to treat a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year, and thus that it may be appropriate to seek to have the FDA designate such Product as an HUD and to apply for an HDE for such Product. If Cutanogen decides to seek an HUD designation or to apply for an HDE, UC and SHC agree to cooperate with Cutanogen in connection with the HUD and HDE, with any incremental costs at Cutanogen's expense.

ARTICLE 4 - PATENTS AND PATENT COSTS

4.1 Patents will be owned by UC if invented only by UC Inventors; by SHC if invented only by SHC Inventors; and by Cutanogen if invented only by Cutanogen Inventors. Patents will be jointly owned by UC, SHC and/or Cutanogen if jointly invented by UC. SHC and/or Cutanogen Inventors respectively. Inventors is defined under US patent law.

4.2 Cutanogen shall file in the owners' names, prosecute (including interferences. re-issues, oppositions and appeals), procure and maintain Patents in the United States, and in such foreign countries as Cutanogen may choose. at Cutanogen’s sole expense and in Cutanogen’s sole discretion.

4.3 The Licensors shall cooperate with Cutanogen with respect to patent activities, and Cutanogen agrees to promptly reimburse the Licensors for any out-of-pocket expenses they may incur at Cutanogen's request under this Article 4. Payments not received within thirty (30) days after Cutanogen' s receipt of an invoice from the Licensors shall be subject to an interest charge of one percent (1%) per month.

4.4 Cutanogen and the Licensors shall keep each other informed in timely fashion of all patent actions hereunder. The Licensors shall have the right to approve actions taken on their behalf: but will not unreasonably withhold approval. A patent action shall be deemed approved if no objection is received by Cutanogen within thirty (30) days after notification of both Licensors.

4.5 If Cutanogen elects not to file, prosecute or maintain a patent application or patent included in Patents that is solely or jointly owned by UC and/or SHC, those Parties shall be given the opportunity to do so at their own expense. Said Patent will be free and clear of this Agreement, and in the case of jointly-owned patents, Cutanogen will retain its joint ownership rights and the Parties will have no duty of royalty or accounting to each other with respect to such jointly-owned Patents.

4.6 Within sixty (60) days after any Party receives an invention disclosure on an Improvement, said Party shall send copies of the invention disclosure to the other Parties.

ARTICLE 5 - PUBLICATION RIGHTS

5.1. Work done by employees of or in facilities of UC or SHC in collaboration with Cutanogen must be publishable. The Licensors will require their employees to submit manuscripts describing such work and/or Technology to Cutanogen at least thirty (30) days before presenting same or submitting it for publication or other public disclosure, and at Cutanogen' s request UC or SHC will delete any Cutanogen Confidential Information and will delay presentation or submission for publication or other public disclosure up to an additional 90 days to permit the filing of patent applications.

ARTICLE 6 – PAYMENTS AND ROYALTIES

6.1. In recognition of Cutanogen's anticipated need to obtain rights to the Background Patents from third parties, the Licensors waive any initial licensing fee or milestone payments which might otherwise apply in this situation.

6.2. Cutanogen agrees to pay the Licensors a two percent (2%) running royalty on Cutanogen's Net Sales of Products and Processes.

6.3. a. In the event that Cutanogen sublicenses its rights hereunder independent of the Background Patents, Cutanogen shall pay the Licensors a royalty of fifty percent (50%) of any Net Sublicensing Fees and running royalties received by Cutanogen from Sublicensees.

b. In the event that Cutanogen sublicenses its rights hereunder in combination with the Background Patents, Cutanogen shall pay the Licensors a royalty of one-sixth (1/6) of any Net Sublicensing Fees and running royalties received by Cutanogen from Sublicensees.

6.4. Beginning in the second full calendar year following premarket approval by the FDA or the approval of a product .development protocol by FDA, minimum annual royalties shall be paid to the Licensors as follows in the amount of $25,000 per year. Should the royalties paid to the licensors under Sections 6.2 and 6.3 combined, for moneys received by Cutanogen during each calendar year in question, be less than the minimum royalty allocated for such year, the difference shall be payable by Cutanogen when the royalty payment for the last Calendar Quarter of such year is due in accordance with Section 7.1.

6.5. Cutanogen may reduce royalties otherwise payable under paragraphs 6.2 and 6.3. but not minimum royalties payable under paragraph 6.4, by an amount not to exceed fifty percent (50%) in any calendar quarter, until it has recovered all of its patent and development expenses related to Patents, Products and Processes. Patent expenses under this paragraph shall include the costs of patent prosecution, maintenance and defense, as well as any legal fees, lump sum payments and running royalties paid to a third party, other than the owner(s) of the Background Patents, to settle allegations of infringement of said third party's patents. Development expenses under this paragraph shall include all costs of product development prior to First Sale, as well as all expenses attributable directly to the first three (3) years of post market surveillance of each Product or Process if required by regulatory agencies such as the FDA.

6.6. Payments not received "'within thirty (30) days after the due date shall be subject to an interest charge of one percent (1%) per month.

ARTICLE 7-REPORTS AND CURRENCY CONVERSIONS

7.1. Prior to premarket approval by FDA of, or FDA approval of a product development protocol for, the first Product or Process. Cutanogen shall deliver to Licensors within thirty (30) days after the end of each calendar year a written report showing the progress of its development program, along with any royalties or other payments due under this Agreement for such calendar year and at the same time make said payment. Following premarket approval by FDA of, or FDA approval of a product development protocol for, the first Product or Process, Cutanogen, within thirty (30) days after the close of each Calendar Quarter during the term of this Agreement (including the close of any Calendar Quarter following any termination of this Agreement), shall also report to Licensors all royalties or other payments accruing to Licensors under sections 6.2 and 6.3 during such Calendar Quarter and shall include its sales of Products and its computation of royalties or other payments to Licensors due under this Agreement for such Calendar Quarter. All Net Sales shall be segmented in each such report according to sales on a country-by-country basis including the rates of exchange used for conversion to US dollars from the currency in which such sales were made. Any tax (excluding any penalties or interest) that Cutanogen is required to pay or withhold for the Licensors' accounts will be deducted from the amount of royalties otherwise due.

a) In cases of sales outside the USA royalty payments shall be made in U.S.dollars. The amounts shall be calculated using currency exchange rates as set forth in The Wall Street Journal on the last day of the Calendar Quarter.

b) With respect to Net Sales, except as otherwise allowed in Section 1.7 entitled "Net Sales," all payments due shall be made without deduction for taxes, assessments, or other charges of any kind which may be imposed on Cutanogen by the government of the country where the transactions occur or any political subdivision thereof with respect to any amounts payable pursuant to this Agreement, and such taxes, assessments, or other charges shall be assumed by Cutanogen.

7.2. Cutanogen shall keep for a period of three (3) years following the year to which such records relate, full, true and accurate books of accounts and other records containing all information and data which may be necessary to ascertain and verify the remuneration payable hereunder. During the term of this Agreement and for a period of three (3) years following its termination, Cutanogen's records and books of account shall be open for one inspection annually upon reasonable notice and at reasonable intervals during business hours by an independent certified accountant selected by the Licensors, for the purpose of verifying the amount of payments due and payable. In the event that any such inspection shows an underreporting and underpayment in excess of five percent (5%) for any twelve (12) month period, then Cutanogen shall pay the cost of such examination as well as any additional sum that would have been payable to Licensors had Cutanogen reported correctly, plus interest at one percent (1%) per month.

ARTICLE 8 - INFRINGEMENT

8.1. Each Party shall promptly report in writing to the other Parties during the term of this Agreement any infringement or suspected infringement of any Patent, or unauthorized use or misappropriation of Technology or patents by a third party of which it becomes aware, and shall provide the other Party with all available evidence supporting said infringement, suspected infringement or unauthorized use or misappropriation.

8.2. Except as provided in Section 8.3, Cutanogen shall have the right to initiate an infringement suit or other appropriate action against any third party who at any time has infringed or is suspected of infringing any of the Patents or of using without proper authorization all or any portion of Technology. Cutanogen shall give the Licensors sufficient advance written notice of its intent to initiate such action and the reasons therefor, and shall provide the Licensors with an opportunity to make suggestions and comments regarding such action, and if necessary the Licensors agree to be named as a nominal party therein, subject to the approval of the Attorney General of Ohio on behalf of UC and the General Counsel of SHC on behalf of SHC. Cutanogen shall keep the Licensors promptly informed of the status of any such action. Cutanogen shall have the sole and exclusive right to select counsel for and shall pay all expenses of such action, subject to the approval of the Attorney General of Ohio on behalf of UC and the General Counsel of SHC on behalf of SHC. The Licensors shall offer reasonable assistance to Cutanogen in connection therewith at no charge to Cutanogen except for reimbursement of reasonable out-of-pocket expenses. Cutanogen may settle any such action subject to prior approval of the Licensors, which approval shall not be unreasonably withheld. Any damages, profits or awards of whatever nature recovered from such action over and above expenses, including but not limited to amounts paid to attorneys, shall be treated as Net Sales by Cutanogen under this Agreement's Section 6.2 for purposes of royalty calculations and payments.

8.3. In the event that Cutanogen does not within twelve (12) months of a written request for action from the Licensors (a) secure cessation of the infringement, or (b) enter suit against the infringer, or (c) provide the Licensors with evidence of the pendency of a bona fide negotiation for the acceptance by the infringer of a sublicense under Patents, the Licensors shall have the right but not the obligation to take action against the infringer at their own expense. Cutanogen shall offer reasonable assistance in connection with such action at no charge to the Licensors except for the reimbursement of reasonable out-of-pocket expenses. Any damages, profits or awards of whatever nature recovered from such action shall belong solely to the Licensors.

ARTICLE 9 – CONFIDENTIALITY

9.1. In connection with this Agreement, it is acknowledged that each Party may disclose its confidential and proprietary information to the other Party. Any such information. identified at the time of its initial disclosure as confidential or proprietary, and that is first disclosed in writing, or if disclosed orally is later transmitted in written form within thirty (30) days of said oral disclosure, and in any such initial or subsequent written format is labeled as "Confidential" or "'Proprietary" is referred to herein as "Confidential Information."

9.2. Each Party hereto shall maintain the Confidential Information of the other Party in confidence. and shall not disclose or otherwise communicate such Confidential Information to others, or use it for any purpose except pursuant to, and in order to carry out, the terms and objectives of this Agreement, and hereby agrees to exercise every reasonable precaution to prevent and restrain the unauthorized disclosure of such Confidential Information by any of its directors, officers, employees, consultants or agents.

9.3. The provisions of Section 9.2 shall not apply to any Confidential Information which:

a) has been lawfully disclosed to the recipient without obligation of confidentiality by an independent third party rightfully in possession of the Confidential Information: or

b) has been published or is generally known to the public in accordance with Article 5 or otherwise through no fault or omission by any of the Parties; or

c) was independently known to the recipient prior to receipt from the disclosing Party, as demonstrably documented in wrinen records of the recipient; or

d) is required to be disclosed by any of the Parties to comply with applicable laws, to defend or prosecute litigation or to comply with governmental regulations, provided that such Party takes reasonable and lawful actions to avoid andlor minimize the degree of such disclosure.

ARTICLE 10 - WARRANTIES

10.1. The Licensors hereby represent, covenant and warrant that they have full tide to the Patents and Technology and that neither of them bas sold, licensed or otherwise conveyed to a third party any rights to the Patents or Technology that are or could be inconsistent with the license specified in Paragraph 2.1.

10.2. Nothing in this Agreement shall be construed as:

a) A warranty or representation by the Licensors as to the validity or scope of any patent;

b) A warranty or representation that anything made, used, sold or otherwise disposed of under any license granted in this Agreement is or will be free from infringement of patents, copyrights and/or trademarks of third parties;

c) An obligation of the Licensors to bring or prosecute actions or suits against third parties for infringement;

d) Conferring rights to use the advertising, publicity or otherwise any trademark or the name of UC or SHC, or

e) Granting by implication, estoppel or otherwise any licenses under patents of UC or SHC other than Patents, regardless of whether such other patents are dominant over or subordinate to any Patent.

10.3. Except as expressly set forth in this Agreement. UC AND SHC MAKE NO REPRESENTATIONS, EXTEND NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, AND ASS1JME NO RESPONSIBILITIES WHATEVER WITH RESPECT TO THE USE, SALE OR OTHER DISPOSITION BY Cutanogen OR ITS VENDERS, SUBLICENSEES OR OTHER TRANSFEREES OF PRODUCTS OR PROCESSES INCORPORATING OR MADE BY USE OF INVENTIONS LICENSED UNDER THIS AGREEMENT OR INFORMATION, IF ANY, FURNISHED UNDER THIS AGREEMENT. SUCH INVENTIONS AND INFORMATION ARE PROVIDED AS IS, WITHOUT WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED.

ARTICLE II NOTICES

11.1. Any notice, request, report or payment required or permitted to be given or made under this Agreement by any Party shall be given by sending such notice by certified mail, return receipt requested, to the address set forth below or such other address as such Party shall have specified by written notice given in conformity herewith. Any notice not so given shall not be valid and effective unless and until actually received, and any notice given in accordance with the provisions of this Section shall be effective when mailed.

To Cutanogen:	President Cutanogen Corporation 3130 Highland Avenue, Suite 3420 Cincinnati, Ohio 45221 Fax: 513-221-1891
To UC:	Director Office of Intellectual Property G-7 Wherry Hall P.O. Box 670829 University of Cincinnati Cincinnati, Ohio 45267-0829 Fax: 513-558-2296
To SHC:	Director of Research Programs Shriners Hospitals for Children PO Box 31356 Tampa, Florida 33631-3356 Fax: 813-281-8113

11.2. Cutanogen shall send all reports and communications required under this Agreement to UC with a copy to SHC.

11.3. Cutanogen shall submit all payments due under this Agreement by check made payable to "University of Cincinnati," and to UC at the address given above, or by wire transfer to UC's account, with a copy of either to SHC.

11.4. UC is responsible for administering this License Agreement on behalf of itself and SHC, and will share payments with SHC as stipulated under a separate agreement between the Licensors.

ARTICLE 12 – TERMINATION

12.1. Cutanogen may terminate this Agreement at any time by providing three (3) months' written notice to the Licensors.

12.2. In the event that Cutanogen shall be in substantive default of any of its material obligations hereunder, the Licensors may at their sole option: (a) terminate this Agreement, or (b) convert the exclusive license hereunder to a non-exclusive license. Exercise of option (a) or (b) by the licensors shall be by written notice to Cutanogen specifying the nature of the default including the amount of royalties then due, if any, and shall be effective sixty (60) days following the effective date of said notice unless Cutanogen cures said default prior to the expiration of said period of sixty (60) days.

12.3. Termination of this Agreement as provided under Sections 12.1 or 12.2 shall terminate all sublicenses to Patents which have been granted by Cutanagen, provided that any Sublicensee may elect to obtain a license to said Patents by advising the Licensors in writing, within sixty (60) days after the Sublicensee's receipt of written notice of such termination, of its election, and of its agreement to assume with respect to the Licensors all the obligations relating to said Patents (including obligations for payment) contained in its sublicensing agreement with Cutanogen. Any sublicense granted by Cutanogen shall contain a provision corresponding to this Section 12.3.

12.4. Upon termination of this Agreement or conversion to a non-exclusive license as provided under Sections 12.1 or 12.2, no Party shall be relieved of any obligations incurred prior to such termination or conversion, and the obligations of the Parties under any provisions which by their nature are intended to survive any such termination or conversion shall sur.ive and continue to be enforceable.

ARTICLE 13 - CONFLICTS OF INTEREST

13.1. To reduce the prospect of conflicts of interest, it is agreed that any UC or SHC employees who are concurrently employed by Cutanogen will sign Appendix A, agreeing to the terms and conditions of this Agreement and agreeing to forego any compensation under UC's or SHC's intellectual property policies and procedures in favor of receiving their compensation in whatever form from Cutanogen for their efforts on Cutanogen's behalf

13.2. Cutanogen will use its best efforts to ensure that any of its employees who is concurrently employed by UC and/or SHC will comply with all collateral employment policies and procedures of said institution(s), as well as policies and procedures governing the disclosure and management of potential conflicts of interest.

13.3. Cutanogen agrees not to conduct work directed toward the development of commercial Products and Processes within the laboratories or facilities of either UC or SHC.

ARTICLE 14 – MISCELLANEOUS

14.1.

A. Each Licensor shall indemnify and bold harmless Cutanogen, and will defend Cutanogen at Licensor's expense, from and against all losses, costs, liabilities, demands, damages, fees or expenses arising from the willful acts, omissions or negligence of Licensor's own employees and agents in the performance of this Agreement.

B. Cutanogen shall indemnify and bold harmless the Licensors, and will defend the Licensors at Cutanogen's expense, from and against any and all losses, costs, liabilities, demands, damages, fees or expenses, including but not limited to product liability and patent infringement liability, arising out of the use by Cutanogen or a Sublicensee of Technology or Patents, or out of the manufacture, use, commercialization, marketing., sale or other disposition by Cutanogen or any Sublicensee of any Product or Process.

C. The obligations of the Parties under paragraphs 14.1 a and 14.1 b shall survive any termination or conversion of the Agreement and continue to be enforceable.

D. Notwithstanding the foregoing, no Party shall be required to indemnify, defend or hold harmless another Party unless the first Party has received notice of any claim for which indemnity or defense is sought under this Agreement, pursuant to Article 11. 1 hereof, within thirty (30) days after the second Party has become aware of any fact, condition or event that said Party asserts gives rise to its right to indemnity or defense hereunder. Licensors and Cutanogen will use all reasonable efforts to cooperate fully with respect to the defense of any claim for which indemnity or defense is sought pursuant hereto.

14.2. Cutanogen shall obtain and carry in full force and effect commercial, general liability insurance which shall protect Cutanogen and Licensors with respect to events covered by Paragraph 14.1 above. Such insurance shall be written by a reputable insurance company authorized to do business in the State of Ohio, shall list UC and SHC as additional named insureds thereunder, shall be endorsed to include product liability coverage and shall require thirty (30) days written notice to be given to UC and SHC prior to any cancellation or material changes thereof. The limits of such insurance shall be not less than two million dollars ($2.000,000) per occurrence with an aggregate of five million dollars ($5,000,000) in aggregate for personal injury or death, and two million dollars ($2,000,000) per occurrence with an aggregate of five million dollars ($5,000,000) in aggregate for property damage. Cutanogen shall provide Licensors with Certificates of Insurance evidencing the same.

14.3. In the event that Cutanogen shall grant sublicenses to third parties under this Agreement, each such sublicense shall be embodied in a written document and copied to the Licensors at the time of its grant. Cutanogen hereby assumes responsibility for the performance of all obligations imposed on Sublicensees by this Agreement and all sublicenses or other grant of rights contemplated by this Agreement shall be consistent with the terms and conditions of this Agreement.

14.4. Neither this Agreement nor any of the rights or obligations hereunder may be assigned by any Party without the prior consent of the other Parties, which consent shall not be unreasonably withheld. Unless any of the other Parties provides written notice to the requesting Party within ninety (90) days of the requesting Party's request for consent hereunder of their intent to withhold consent, the consent of the other Parties hereunder shall be deemed to have been given. Notwithstanding the foregoing, Cutanogen may assign this Agreement without the Licensors' consent to any purchaser of all or substantially all of Cutanogen's business to which this Agreement relates, provided the intended assignee agrees in writing to accept all of the terms and conditions of this Agreement.

14.5. It is understood that the Licensors are subject to United States laws and regulations controlling the export of technical data, computer software, laboratory prototypes and other commodities (including *inter alia* the Arms Export Control Act as amended., and the Export Administration Act of 1979 as amended, and that their obligations hereunder are contingent on compliance with all applicable United States export laws and regulations. The transfer of certain technical data and/or commodities may require a license from the cognizant agency of the United States Government and/or written assurances by Cutanogen that Cutanogen shall not export data or commodities to certain foreign countries without prior approval of such agency. The Licensors neither represent nor warrant that a license shall not be required nor that, if required, it shall be issued. In any event, Cutanogen specifically agrees not to export or re-export any information and/or technical data and/of products in violation of any applicable USA laws and/or regulations.

14.6. This Agreement shall be construed under and interpreted under the laws of the State of Ohio. U.S.A., except that questions affecting the construction, validity and effect of any Patent shall be determined by the national law of the country in which the Patent has been granted.

14.7. In the event that any Party is prevented from performing or is unable to perform any of its obligations under this Agreement due to any act of God, fire, casualty, flood, war, strike, lockout, failure of public utilities, government regulation or the like, such Party shall give notice to the other Parties in writing promptly, and thereupon the affected Party's performance shall be excused and the time for performance shall be extended for the period of delay or inability to perform due to such *force majeure* occurrence.

14.8. The waiver of a breach of default of any provisions of this Agreement by any Party must be in written form and signed by all Parties, and shall not be construed as a waiver of any succeeding breach of the same or any other provision.

14.9. Cutanogen shall have the right to register any mark with the Patent and Trademark Office and shall own any such mark approved for inclusion on the Principal Register, or otherwise utilized by it in connection with the Product including without limitation trademarks, trade dress, symbols, designs and Product color, shape and size.

14.10. In the event that any term, provision, or covenant of this Agreement shall be determined by a court of competent jurisdiction to be invalid. illegal, or unenforceable, that term will be curtailed, limited, or deleted, but only to the extent necessary to remove such invalidity, legality, or unenforceability, and the remaining terms, provisions and covenants shall not in any way be affected or impaired thereby. Further, the Parties will agree to legally enforceable provisions to replace any term, provision or covenant determined to be invalid. illegal or unenforceable so as to put the Parties, as nearly as possible, in the same position that they would have been had such term, provision or covenant not been held invalid, illegal or unenforceable.

14.11. The article headings herein are for purposes of convenient reference only and shall not be used to construe or modify the terms written in the text of this Agreement.

14.12. The relationship between the Parties is that of independent contractors and contractee. No Party shall be deemed to be an agent of another in connection with the exercise of any rights hereunder, and none shall have any right or authority to assume or create any obligation or responsibility on behalf of another.

14.13. This Agreement contains the entire understanding of the Parties with respect to the matter contained herein. The Parties may, from time to time during the continuance of this Agreement, modify, vary or alter any of the provisions of this Agreement, but only by an instrument duly executed by authorized officials of both Parties hereto.

IN WITNESS WHEREOF the Parties hereto have caused this Agreement to be executed by their properly and duly authorized officers or representatives as of the date first above

UNIVERISTY OF CINCINNATI	CUTANOGEN CORPORATION
/s/ Norman M. Pollack	/s/ Steven Boyce
Signature	Signature
Norman M. Pollack Ph.D.	Steven Boyce
Printed Name	Printed Name
Director of Intellectual Property and University Patent Officer	Founder and President
University of Cincinnati	Title
Title	
8/24/98	5/15/98
Date	Date

SHRINERS HOSPITALS FOR CHILDREN
/s/John D. VerMass
Signature
John D. VerMass
Printed Name
President
Title
May 29, 1998
Date

Appendix A to License Agreement Among the University of Cincinnati (UC). Shriners Hospitals for Children (SHC) and Cutanogen Corporation (Cutanogen)

The undersigned, who is employed by Cutanogen as an employee, consultant or advisor and is concurrently employed by UC or SHC, has read, understood and agrees to the terms and conditions of the Agreement between UC, SHC and Cutanogen to which this Appendix A is attached. The undersigned agrees that compensation provided by Cutanogen, in whatever form provided, will be accepted in lieu of the portion of licensing revenues paid by Cutanagen that normally would be shared· with the undersigned as an inventor or co-inventor of any patent, patent application or other intellectual property licensed to Cutanogen by UC.

ACCEPTED AND AGREED TO

/s/Steven Boyce
Signature
Steven Boyce
Printed Name
UC and SHC
Concurrent Employer (UC or SHC)
5/15/98
Date

Exhibit G – Amendment to the License Agreement between Cutanogen Corporation on the one hand and the University of Cincinnati and Shriners Hospitals for Children on the other hand.

AMENDMENT TO LICENSE AGREEMENT

THIS AMENDMENT (this "Amendment") to the License Agreement, dated as of August 24, 1998 (the “License Agreement"), by and between Cutanogen Corporation, an Ohio corporation ("Cutanogen"), the University of Cincinnati ("UC") and Shriners Hospitals for Children ("SHC"), is made effective as of December 29 , 2005 ("Effective Date"). All defined terms set forth herein shall have the meanings set forth in the License Agreement, unless otherwise expressly set forth herein.

RECITALS`

WHEREAS, the Parties desire to amend certain of the provisions of the License Agreement;

NOW, THEREFORE, in consideration of the foregoing and the mutual promises and covenants hereinafter set forth, Cutanogen, UC and SHC, intending to be legally bound, hereby agree as follows:

AGREEMENT

1. Section 1.1 of the License Agreement is hereby amended in its entirety to read as follows:

1.10 "Technology" shall mean the technology embodied in the Licensed IP, including, without limitation, the technology described in the Patents, and all Improvements thereto."

2. Section 1.2 of the License Agreement is hereby amended in its entirety to read as follows:

1.16 "Patents" shall mean any patent or patent application, and any patent issuing therefrom., together with any extensions, reissues, reexaminations, substitutions, renewals, divisions, continuations and continuations-in-part thereof, all to the extent the foregoing arise or issue from any Licensed IP, including, without limitation, the following issued patents and pending applications:

1. International Publication Number WO 03/076562 AI, publication dated September 18, 2003 "Apparatus for Preparing a Biocompatible Matrix"

2. International Publication Number WO 2003/076604 A3, publication dated September 18, 2003 "Surgical Device for Skin Therapy or Testing"

3. United States Patent Number US 6,905,105 B2, patent date 06-14-05 "Apparatus for Preparing a Biocompatible Matrix.

4. United States Patent Application Publication Number US 2003/0170892 AI, publication date 09-11-03 "Surgical Device for Skin Therapy or Testing"

3. Section 1.5 of the License Agreement is hereby amended in its entirety to read as follows:

1.5 "Product" shall mean any product made, used or sold by Cutanogen and/or a Sublicensee under any Licensed IP."

4. Section 1.6 of the License Agreement is hereby amended in its entirety to read as follows:

1.6 "Process" shall mean any and all processes practiced by Cutanogen and/or a Sublicensee under any Licensed IP."

5 Section 1.20 of the License Agreement is hereby amended in its entirety to read as follows:

1.20 "Cutanogen Inventor" shall mean an inventor employed or otherwise retained (e.g., consultant) by Cutanogen; provided that if such inventor is also a UC Inventor and/or an SHC Inventor, such inventor shall only be deemed a Cutanogen Inventor to the extent that the relevant invention did not make use of the facilities, materials or other resources furnished by or through UC and/or SHC."

6. Article 1 of the License Agreement is hereby amended to add the following new Sections:

1.25 "Intellectual Property" shall mean all worldwide patents, trade secrets, know-how and all other intellectual property rights, including all applications and registrations with respect thereto, but excluding all trademarks, trade names, service marks, logos and other corporate identifiers."

1.26 "Licensed IP" shall mean all Intellectual Property owned or controlled by Licensors arising from the following:

i. UC Invention Disclosures :

UC 90-022 Casting Device for Implantable Biopolymer Substrates
UC 91-017 Lipid-enriched Skin Substitute
UC 94-038 Topical Antimicrobial Mixtures for Wound Care

ii. SHC Records of Medical Invention :

SHC Topical Nutrient Formulations for Wound Treatment, signed October 27, 1993; submitted to SHC, Tampa, November 8, 1993

SHC Cultured Skin Substitutes for Wound Treatment: Concept, Composition and Uses; signed January 14, 1997; submitted to SHC, Tampa, January 14, 1997

iii. Research and/or clinical studies conducted in whole or in part by a UC Inventor and/or SHC Inventor with respect to work initiated by Steven Boyce regarding a skin substitute with human keratinocytes and fibroblasts and covering the following subject matter:

1) regulation of cellular viability (DNA synthesis, mitochondrial metabolism) and phenotypes (epidermal barrier, basement membrane) by culture conditions (media, biophysical environment);

2) identification of molecular mediators (cytokines, extracellular matrix) of wound healing processes (angiogenesis, matrix structure);

3) regulation of melanocyte distribution (cell density) and pigment expression (melanin content) to restore normal skin color;

4) stimulation of angiogenesis by addition of human dermal microvascular endothelial cells and morphogenesis of vascular analogs;

5) regulation and automation of keratinocyte growth rates and metabolism (reduction of lactic acid and ammonia) in the Kerator bioreactor; or

6) treatment of extensive burns with cultured skin substitutes in the clinic by paired-site comparison to meshed, split-thickness skin autograft."

7. Section 2.1 of the License Agreement is hereby amended in its entirety to read as follows:

2.1 The Licensors agree to grant and hereby grant to Cutanogen an exclusive, worldwide license, with the right to grant sublicenses, under the Licensed IP (including, without limitation, the Patents) and any Improvements to make, have made, use (including, without limitation, research and develop), market, offer for sale, sell and otherwise dispose of Products and practice the Processes. Cutanogen shall have the exclusive option to extend the Term of such license on commercially reasonable terms negotiated in good faith and mutually agreed upon by the parties."

8. Except as expressly provided in this Amendment, all of the terms and conditions of the License Agreement remain in full force and effect and fully binding upon and enforceable against the Parties.

9. This Amendment may be executed in several counterparts, and all counterparts so executed shall constitute one agreement, binding on the Parties, notwithstanding that such Parties are not signatory to the same counterpart.

[Remainder of page intentionally left blank. Signatures appear on following page.]

IN WI1NESS WHEREOF, the Parties have executed this Amendment as of the Effective Date.

UNIVERSITY OF CINCINNATI
By: /s/Anne H. Chasser
Name: Anne H. Chaser
Title: Assoc. V.P. for IP

SHRINERS HOSPITALS FOR CHILDREN
By:
Name:
Title:

CUTANOGEN CORPORATION
By:
Name:
Title:

IN WITNESS WHEREOF, the Parties have executed this Amendment as of the Effective Date.

UNIVERSITY OF CINCINNATI
By:
Name:
Title:

SHRINERS HOSPITALS FOR CHILDREN
By: /s/Ralph W Semb
Name: Ralph W. Semb
Title: President

CUTANOGEN CORPORATION
By:
Name:
Title:

IN WITNESS WHEREOF, the Parties have executed this Amendment as of the Effective Date.

UNIVERSITY OF CINCINNATI
By:
Name:
Title:

SHRINERS HOSPITALS FOR CHILDREN
By:
Name:
Title:

CUTANOGEN CORPORATION
By: /s/Steven T Boyce
Name: Steven T. Boyce, PhD
Title: President

Exhibit H – Settlement Agreement and Release dated February 2, 2006 between the Shriners Hospital for Children, Cutanogen Corporation, the Shareholders of Cutanogen Corporation, and Cambrex Bio Science Walkersville, Inc.

SETTLEMENT AGREEMENT AND RELEASE

THIS SETTLEMENT AGREEMENT AND RELEASE is entered into effective as of the 2nd day of February, 2006 (the **"Effective Date"**), by and among **Shriners Hospitals for Children ("SHC"), Cutanogen Corporation ("Cutanogen"),** the **Shareholders of Cutanogen Corporation** (the **"Shareholders")** listed on **Schedule I** attached hereto. and **Cambrex Bio Science Walkersville, Inc. ("Cambrex")** .

WHEREAS, the parties deem it prudent and advisable, in lieu of spending further time and expense, to settle all disputes and claims of whatsoever kind and nature, arising out of or relating to finder's fees in connection with the acquisition of Cutanogen by Cambrex whether pursuant to the Independent Contractor Agreement dated September 1, 2003 (the **"IC Agreement"** a copy of which is attached hereto as Exhibit A and is, by reference, incorporated herein) or otherwise (**"the SHC/Cutanogen Disputes"**); and

WHEREAS. the parties desire to memorialize certain ongoing business relationships relating to the development and commercial sales of the Product (as defined in the Stock Purchase Agreement, dated as of the date hereof, by and among Cutanogen, the Shareholders and Cambrex (the **"Cutanogen Agreement"**));

NOW. THEREFORE, in consideration of the mutual and reciprocal obligations and undertakings hereinafter set forth, the parties agree as follows:

1. **Novation in Settlement of Claims under the IC Agreement** : The parties agree that the rights and obligations of SHC and Cutanogen under the IC Agreement are hereby novated and superseded by the substitution of the following agreement with respect to the payment of fees to SHC in respect of the acquisition of Cutanogen by Cambrex.

a. **Payments to SHC** : Cutanogen, the Shareholders and Cambrex agree that Cambrex is authorized and agrees to deduct from each Payment (as defined in the Cutanogen Agreement) and pay directly to SHC at 2900 Rocky Point Drive, Tampa, FL, 33607 (mailing address: Post Office Box 31356, Tampa, FL, 33631-3356) or by wire transfer of immediately available funds to an account designated by SHC, on Cutanogen's behalf, five percent (5.0%) of the amounts set forth in Article L § 1.2 of the Cutanogen Agreement if, when and as each of the Payments are made to the Shareholders or their agent, as follows. For the avoidance of doubt, the portion of each Payment payable to SHC shall be paid in U.S. currency in the amounts and as of the dates set forth below:

i. Within three (3) business days following the signing of this Agreement, Ten Thousand Dollars ($10,000) in U.S. Currency.

ii. At the Closing of the Cutanogen Agreement, Sixty-Five Thousand Dollars ($65,000) (the **"Initial Payment"**).

iii. Following the Closing Date (as defined in the Cutanogen Agreement), up to an additional Two Hundred Forty Thousand Dollars ($240,000) in five (5) separate payments upon the achievement of certain milestones (each payment, a **"Milestone Payment",** and collectively, the **"Milestone Payments"**), as follows:

1) Not later than thirty (30) days after submission (**"Milestone 1"**) to the U.S. Food and Drug Administration (**"FDA"**) of a "Humanitarian Device Exemption" application under 21 CFR Part 814 for the Product, Cambrex shall pay to SHC Thirty-Two Thousand Five Hundred Dollars ($32,500);

2) Not later than thirty (30) days after approval (**"Milestone 2"**) but the FDA of the aforementioned Product application, Cambrex shall pay to SHC Thirty-Two Thousand Five Hundred Dollars ($32,500);

3) Not later than thirty (30) days after the first commercial sale (**"Milestone 3"**) of the Product pursuant to the aforementioned application, Cambrex shall pay to SHC Fifty Thousand Dollars ($50,000) or One Hundred Fifteen thousand Dollars ($115,000) if Milestones 1 and 2 have not been achieved or Eighty-Two Thousand Five Hundred Dollars ($82,500) if Milestone 1 has been achieved but Milestone 2 has not been achieved or;

4) Not later than thirty (30) days after submission (**"Milestone 4"**) to the FDA of a §510(k) application, a Biologics License Application or a Pre-Market Approval application for the Product, Cambrex shall pay to SHC Fifty Thousand Dollars ($50,000); and

5) Not later than thirty (30) days after the approval (**"Milestone 5"**) by the FDA of such §510(k) application, Biologics License Application or Pre-Market Approval application, Cambrex shall pay to SHC Seventy-Five Thousand Dollars ($75,000).

2. **SHC Product Purchase Undertaking** . While the parties acknowledge and agree that SHC cannot commit to purchasing the Product, SHC represents that it intends to purchase from Cutanogen (or its successors or assigns), as clinical demand and budgetary considerations permit, up to twenty (20) square meters of the Product during the first year commencing with the achievement of Milestone 1 or Milestone 3, whichever occurs first (the "Initial Year"). Should SHC purchase any Product during the Initial Year, SHC's cost for such Product during such year shall be the lesser of (i) if and for so long as the federal Food and Drug Administration's ("FDA") pricing restrictions for Humanitarian Use Devices or pursuant to a Humanitarian Device Exemption apply to commercial sales of the Product, an amount equal to the allowable costs of research and development, fabrication, and distribution; or (ii) if or to the extent that no FDA pricing restrictions apply to commercial sales of the Product, an amount no less favorable than the lowest price paid by any third-party purchaser during the Initial Year other than the U.S. government. In the event of any subsequent third-party sales (other than to the U.S. government) at a lower price than the price paid by SHC during the Initial Year, prices paid by SHC for the remaining portion of the Initial Year, commencing as of the date of such third party sale, shall be adjusted such that the price per square meter of Product paid by SHC for the remaining portion of the Initial Year is equal to the lowest price per square meter of Product paid by third-party purchasers (other than the U.S. Government) during the Initial Year. Should SHC purchase at least ten (l0) square meters of the Product during the Initial Year, Cutanogen and Cambrex shall provide, at SHC's request, SHC with such sales data as may be reasonably necessary to enable SHC to audit compliance with this "most favored nation" provision. SHC's right of audit under this Section 2 shall be exercisable (i) no more than twice during the Initial Year and the six month period following the expiration of the Initial Year and (ii) no later than the expiration of the six month period following the end of the Term. All such information shall be deemed to be the confidential information of Cutanogen and Cambrex, and SHC shall not disclose such confidential information to any third party except to those employees, consultants and other representatives of SHC who have a need to know such information for purposes of conducting the audit(s). SHC and Cutanogen (or its successors or assigns) may renew the purchase undertaking set forth in this Section 2 for periods after the Initial Year on such terms as are mutually agreed, including, without limitation. tenus governing favorable pricing.

3. **SHC's Undertaking for :Multi-Site Clinical Trials of Product** : Following the Closing, in the event that Cutanogen (or its successors or assigns) chooses, at its sole discretion, to conduct site clinical trials of the Product at SHC, SHC shall conduct, and Cutanogen (or its successors or assigns) shall pay SHC for, such trials at sites and upon terms and conditions as mutually agreed. Payments to SHC shall include SHC's direct costs and indirect costs at a minimum of thirty percent (30%) of direct costs. SHC and Cutanogen (or its successors, assigns or designee(s)) will enter into a research support agreement with regard to each clinical trial in a form and with such terms and conditions as mutually agreed.

4. **Licenses** . SHC acknowledges and agrees as to SHC that the license agreement dated as of May 29, 1998, as an1ended, between SHC and the University of Cincinnati as licensors and Cutanogen as licensee (the "License Agreement") will remain in full force and effect as of and following the Closing. SHC further agrees that there are no liabilities as to SHC outstanding as of the date hereof with respect to Cutanogen's obligations under such License Agreement.

5. **Release of Cutanogen, the Shareholders and Cambrex** : Except as hereafter provided, as to Carl G. Fischer, Jr., Richard J. Kagan, John E. McCall, Kevin Yakuboff, and Glenn D.Warden (the **"Designated Shareholders"**) and subject to Section 7 hereof, in consideration of the mutual covenants and dismissals of claims herein, the receipt and sufficiency of which is hereby acknowledged, SHC, on behalf of itself, its officers, directors, shareholders. partners, members. subsidiaries, parents, divisions, agents, successors, and assigns, do hereby forever release. requite. and discharge Cutanogen, the Shareholders and Cambrex and its and their respective heirs, executors, administrators, personal representatives and assigns, officers, directors, shareholders, partners, members, subsidiaries, parents, divisions, attorneys, agents, successors, and assigns (collectively, the **"Cutanogen and Cambrex Releasors"**) from any and all suits, debts, accounts, charges, claims, demands, judgments, actions, causes of action, damages, expenses, costs, attorneys' fees, and liabilities of any kind whatsoever, whether known or unknown, suspected or unsuspected, vested or contingent, in law or in equity or otherwise, which SHC has ever had, now has, or may have against the Cutanogen and Cambrex Releasors for or on account of any matter, cause or thing whatsoever arising out of or relating to (i) the IC Agreement, the acquisition of Cutanogen by Cambrex and the SHC/Cutanogen Disputes, or (ii) a Shareholder's ownership, purchase or sale of the stock of Cutanogen or breach of any intellectual property or ethical policy of SHC; provided, however, that no Designated Shareholder shall be released, requited or discharged from any claim arising out of such Designated Shareholder's ownership, purchase or sale of the stock of Cutanogenor breach of any intellectual property or ethical policy of SHC and/or any claim for disgorgement to SHC by the Designated Shareholders of their pro rata share of the additional $14,000 consideration if and as received by the Designated Shareholders resulting from SHC's compromise of the SHC/Cutanogen Disputes.

6. **Release and Indemnification of SHC** : In consideration of the mutual covenants and dismissals of claims herein, the receipt and sufficiency of which is hereby acknowledged, the Cutanogen and Cambrex Releasors do hereby forever release, requite, and discharge SHC and its officers, directors, shareholders, partners, members, subsidiaries, parents, divisions, agents. successors, and assigns from any and all suits. debts, accounts. charges, claims, demands, judgments, actions, causes of action. damages, expenses, costs, attorneys' fees, and liabilities of any kind whatsoever, whether known or unknown, suspected or unsuspected, vested or contingent, in law or in equity or otherwise, which the Cutanogen and Cambrex Releasors have ever had, now have, or may have against SHC for or on account of any matter, cause or thing whatsoever arising out of or relating to the IC Agreement, the acquisition of Cutanogen by Cambrex and the SHC/Cutanogen Disputes or the License Agreement insofar as any such matter, cause or thing arises out of or relates to that certain Institution Research Agreement dated June 20, 2005 between The Proctor & Gamble Company, Children's Hospital Medical Center and the Skin Sciences Institute. Steven T. Boyce (**"Boyce"**) shall indemnify, defend and hold SHC and its Affiliates and each of their respective agents. employees, officers, trustees and directors (the "SHC Indemnitees") harmless from and against any liability, damage, loss, cost or expense (including reasonable attorneys fees) arising from or occurring as a result of any claim whatsoever regardless of whether such claim sounds in tort, contract, strict liability, products liability or any other legal theory against the SHC Indenmitees arising out of or relating to that certain Institution Research Agreement dated June 20, 2005, between The Proctor & Gamble Company, Children's Hospital Medical Center and the Skin Sciences Institute. This undertaking to indemnify the SHC Indemnitees is made by Boyce in his individual capacity and not on behalf of SHC as an employee or agent and Boyce waives any claim for coverage under any SHC indemnification that may otherwise be available to employees of SHC. Boyce expressly waives his right to discharge the obligation of indemnification to SHC as set forth herein under any of the United States Bankruptcy laws and the expressly agrees to not list or include the indebtedness to the SHC as set forth herein on any Chapter 7 or Chapter 13 Bankruptcy that he may file, it being the express intent of the parties that said indebtedness not be dischargeable under the Bankruptcy laws of the United States; and in the event that the waiver of dischargeability is deemed unenforceable, Boyce agrees to enter into a post-petition reaffirmation of this indemnification obligation pursuant to 11 U.S.C. § 524(c) and expressly waives the right to assert that this reaffirmation undertaking is avoidable as an executory contract.

7. **Survival:** The rights, obligations and provisions of Paragraphs One (1), Two (2), Three (3) and Four (4),the proviso in Paragraph Five (5)(ii), and the indemnification obligation in Paragraph Six (6) of this Agreement expressly survive the releases set forth herein.

8. **Entire Agreement, Governing Law:** This Agreement constitutes the entire Agreement between the parties with regard to the matters herein set forth. If any provision of this Agreement is held to be invalid, then the remainder of the Agreement shall remain in full force and effect and shall, in all respects, be interpreted, enforced and governed under the laws of the State of Ohio. Any changes in this Agreement, whether by additions, deletions, Waivers, amendments or modifications, may be made only in writing and signed by all parties.

9. **Acknowledgment of Review:** The parties to this Agreement each represent and agree that they have carefully read, reviewed and consulted with legal counsel regarding the terms and conditions of this Agreement, that they understand the terms of this Agreement, that no promise, assurance, commitment or inducement has been made or offered to him, her or it except as set forth in this Agreement, that he, she or it is executing this Agreement without reliance upon any statement or representation of the person or party released, except as set forth herein, and that he. she or it intends to and is competent to be bound by this Agreement.

10. **Confidentiality:** The parties agree that the terms of this Agreement will be kept confidential, and will not be shared with any third parties other than its and their respective parents, subsidiaries, principals, agents, employees, accountants, attorneys, reinsurers, regulators, representatives and any other individuals or entities that are entitled to receive this information by law or regulation, without either a lawful subpoena (or other process) or the written consent of the parties.

11. **Requisite Authority** : Each person signing this Agreement on behalf of SHC, Cutanogen and Cambrex represents and warrants that he has full authority to do so and represents and warrants that said party has not assigned or intended to assign any claims being released under this Agreement to any other person or entity. This Agreement will be executed in several counterparts, each of which will be deemed an original.

IN WITNESS WHEREOF, **Shriners Hospitals for Children** , **Cutanogen Corporation, the Shareholders and Cambrex Bio Science Walkersville, Inc.** , have executed this **Settlement Agreement and Release** as of the Effective Date.

Shriners Hospitals for Children
By: /s/Ralph W Semb
RALPH W. SEMB
Its: President

Cutanogen Corporation
By: /s/Steven T Boyce
Its:President

Cambrex Bio Science Walkersville, Inc.
By: /s/Shawn P. Cavanagh
Its: Senior Vice President

[COUNTERPART SIGNATURE PAGE TO THE
SETTLEMENT AGREEMENT AND RELEASE]

Shareholders:

/s/ Peter Amstein
Peter Amstein
/s/ Steven T. Boyce
Steven T. Boyce
/s/ Edward J. Carl
Edward J. Carl
/s/ Kevin J. Eastace
Kevin J. Eastace
/s/ Carl G. Fischer, Jr.
Carl G. Fischer, Jr.
/s/ Patricia B. Goodman
Patricia B. Goodman
/s/ Ken Green
Ken Green
/s/ Jay Hay
Jay Hay
/s/ Erna Hoffberger
Erna Hoffberger
/s/ Richard J. Kagan
Richard J. Kagan
/s/ Lisa Kagan
Lisa Kagan
/s/ Albert L. Klosterman
Albert L. Klosterman

[COUNTERPART SIGNATURE PAGE TO THE
SETTLEMENT AGREEMENT AND RELEASE]

/s/ Jack W. Martz
Jack W. Martz
/s/ John E. McCall
John E. McCall
/s/ Tony L. Shipley
Tony L. Shipley
/s/ Kevin Yakuboff
Kevin Yakuboff
/s/ Mark J. Buch
Mark J. Buch
/s/ Glenn D. Warden
Glenn D. Warden
/s/ William T. Nuerge
William T. Nuerge

THE EBTC Foundation
By: /s/ President & Chairman
Its: President & Chairman

EXHIBIT A

INDEPENDENT CONTRACTOR AGREEMENT

See Attached .

INDEPENDENT CONTRACTOR AGREEMENT

BETWEEN SHRINERS HOSPITALS FOR CHILDREN AND CUTANOGEN CORPORATION

THIS AGREEMENT made as of this 1 st day of September , 2003, by and between Shriners Hospitals for Children, a corporation of the State of Colorado having a place of business at 2900 Rocky Point Drive, Tampa, FL 33607 (hereinafter "Shriners"), and Cutanogen Corporation (hereinafter referred to as "CC") having an office at: 3130 Highland Avenue, Suite 3100, Cincinnati, OH 45219-2374.

WHEREAS , SHRINERS desires to enter into an independent contractor agreement with CC to facilitate greater availability of autologous cultured skin substitutes for patients of the Shriners Hospitals for Children (SHC), and all patients with burn injuries greater than 50% of the total body surface area. Shriners will seek to find a corporate partner (licensee, investor, acquirer or other joint venture partner) for CC. SHC's efforts in finding a corporate partner, licensee or investor are not exclusive and CC should continue with its independent efforts to achieve the same purpose. SHC and CC will identify to each other prospective partners or investors to explore synergies and prevent duplication of efforts on a regular basis, through monthly progress reports or other similar approach. It is therefore mutually agreed by and between the parties hereto as follows:

1 **TERM** The term of this Agreement shall commence on Sept.1, 2003 (the "Commencement Date") and expire three years from such date, unless sooner terminated or renewed as provided hereunder.

2 **DUTIES** Shriners shall use commercially-reasonable efforts to identify, follow-up with and negotiate with companies or entities that have a potential need for, or interest in CC's technology or business. However, Shriners cannot guarantee it will produce results with any such companies or entities. Prior to approaching any company or entity, Shriners will inform CC as to the company or entity's name and line of business to ensure that the potential prospect is not already in negotiations with CC. CC will confirm, bye-mail, whether or not Shriners should proceed with introducing its prospect to CC. Shriners will complete a Confidential Disclosure Agreement (CDA) with each company or entity before discussion of proprietary information or the confidential business plan of CC. Shriners will provide a copy of each CDA to CC to identify the company or entity as a business prospect. At the sole discretion of Shriners, Shriners will introduce some or all of these companies or entities to CC. As part of its duties, Shriners will also follow-up with potential prospects identified by CC and provided to Shriners. The acceptance of terms of any negotiations conducted by Shriners on behalf of CC will be at the sole discretion of CC.

3 **COMPENSATION** During the term of this Agreement, Shriners shall be paid a finder's fee of 10% of all consideration received by CC from any companies or entities that CC has either confirmed by email or requested that Shriners follow-up with, pursuant to section 2 of this Agreement that Shriners should introduce to CC, within ten days of the receipt of any consideration by CC from these parties. In the event that CC receives compensation from a Shriners-introduced or followed-up company or entity within one year after this Agreement has been terminated, then Shriners will still receive the same consideration it would have normally received had this Agreement been in effect at that time.

4 **CONFIDENTIAL INFORMATION**

a. Shriners may have already acquired and will acquire information and knowledge about the confidential affairs of CC (for this purpose including without limitation confidential information with respect to the CC's customer lists, technologies, business methodology, business techniques, promotional materials and information, and other similar matters treated by CC as confidential (the "Confidential Information")). Accordingly, Shriners covenants and agrees that during the term of this agreement and thereafter, Shriners shall not, without the prior written consent of CC, disclose to any person, other than a person to whom disclosure is reasonably necessary or appropriate in connection with the performance by Shriners of Shriners' duties hereunder, any Confidential Information obtained by Shriners while providing services to CC under this Agreement. The obligation of confidentiality shall not apply to the following:

i. information at or after such time that it is or becomes publicly available through no fault of Shriners;

ii. information that is already independently known to Shriners as shown by prior written records;

iii. information at or after such time that is disclosed to Shriners on a non- confidential basis by a third party with the legal right to do so; or

iv. information required to be released by any governmental entity with jurisdiction, provided that Shriners notifies CC prior to making such release of information.

b. Shriners shall deliver to CC or its designee at the termination of this Agreement all CC data, correspondence, memoranda, notes, records, product compositions, and other documents and all copies thereof, made, composed or received by Shriners, solely or jointly with others, that are in Shriners' possession, custody, or control at termination and that are related in any manner to the past, present, or anticipated business or any member of CC or one its subsidiaries. In this regard, Shriners hereby grants and conveys to CC all right, title, and interest in and to, including without limitation, the right to possess, print, copy, and sell or otherwise dispose of, any reports, records, papers, summaries, photographs, drawings or other documents, and writings, and copies, abstracts or summaries thereof, that may be prepared by Shriners or under its direction or that may come into his possession in any way during the term of this Agreement that relate in any manner to the past, present or anticipated business of CC.

5 **EXPENSES** CC will not be responsible for any expenses incurred by Shriners in connection with performing their duties as an independent consultant under this Agreement. Shriners will not be responsible for any expenses incurred by CC in connection with performing their duties under this Agreement.

6 **TERMINATION**

a. Either party may terminate this Agreement for any reason by giving the other party thirty (30) days written notice.

b. SHRINERS and CC each shall also have the right to terminate this Agreement immediately "For Cause". which shall include, but not be limited to, fraud, breach of fiduciary duty, conviction of a crime or like conduct.

7 **ENTIRE AGREEMENT: SURVIVAL**

a. This Agreement contains the entire agreement between the parties with respect to the transactions contemplated herein and supersedes, effective as of the date hereof, any prior agreement or understanding between SHRINERS and CC. The unenforceability of any provision of this Agreement shall not affect the enforceability of any other Provision. This Agreement, or any waiver, change, discharge or modification as sought. may not be amended except by an agreement in writing signed by CC and SHRINERS. Waiver of or failure to exercise any rights provided by this Agreement and in any respect shall not be deemed a waiver of any further or future rights. This agreement shall not in any way affect the rights or obligations of either party under the License Agreement between Cutanogen Corporation, University of Cincinnati and· Shriners Hospitals for Children dated August 24, 1998.

b. The provisions of Sections 4, 7, 10 and 11 shall survive the termination of this Agreement.

8 **ASSIGNMENT** This Agreement shall not be assigned by either party to third parties.

9 **GOVERNING LAW** This Agreement and all the amendments hereof, and waivers and consents with respect thereto shall be governed by the laws of the State of Florida, without regard to the conflicts of laws principles thereof and the parties agree that the jurisdiction shall be in Hillsborough County, Florida.

10 **NOTICE** . All notices, responses, demands or other communications under this Agreement shall be in writing and shall be deemed to have been given when:

a. Delivered by hand;

b. Sent by fax (with receipt confirmed), provided that a copy is mailed by registered or certified mail, return receipt requested; or,

c. Received by the addressee as sent be express delivery service (receipt requested) in each case to the appropriate addresses, and fax numbers as the party may designate to itself by notice to the other parties:

i. If to SHRINERS HOSPITALS FOR CHILDREN:

Shriners Hospitals for Children, 2900 Rocky Point Drive, Tampa, FL 33607
Attention: Managing Attorney
Fax: 813-281-0943

ii. If to CUTANOGEN CORPORATION:

3130 Highland Avenue, Suite 3100, Cincinnati, OH 45219-2374
Attention: Steven T. Boyce, Ph.D., President
Fax: 513-221-1891

11 **SEVERABILITY** Should any part of this Agreement for any reason be declared invalid by a court of competent jurisdiction, such decision shall not affect the validity of any remaining portion, which remaining provisions shall remain in full force and effect as if this Agreement had been executed with the invalid portion thereof eliminated, and it is hereby declared the intention of the parties that they would have executed the remaining portions of this Agreement without including any such part, parts or portions which may, for any reason, be hereafter declared invalid.

IN WITNESS WHEREOF , the undersigned have executed this agreement as of the day and year first above written.

SHRINERS HOSPITALS FOR CHILDREN
By: /s/Ralph W. Semb
President
Date: 10/9/03

CUTANOGEN CORPORATION
By: /s/Steven T. Boyce
Steven T. Boyce
President
Date:09/26/03

MANUFACTURING SERVICES AGREEMENT

This Manufacturing Services Agreement (the "Agreement") is made as of [INSERT DATE], (the "Effective Date") between Lonza Walkersville, Inc., a Delaware corporation having its principal place of business at 8830 Biggs Ford Road, Walkersville, Maryland 21793 ("LWI"), and [NAME], [a/an] [State of formation, if an entity] [corporation / partnership / limited liability company / limited liability partnership / individual], having an [office / address] at [address] ("CLIENT") (each of LWI and CLIENT, a "Party" and, collectively, the "Parties").

RECITALS

A. LWI operates a multi-client production facility located at 8830 Biggs Ford Road, Walkersville, Maryland 21793 (the "Facility").
B. CLIENT desires to have LWI produce a product containing human cells and intended for therapeutic use in humans, and LWI desires to produce such product.
C. CLIENT desires to have LWI conduct work according to individual Statement of Work, as further defined in Section 1.32 **below.**
NOW, THEREFORE, in consideration of the foregoing and the mutual promises and covenants hereinafter set forth, LWI and CLIENT, intending to be legally bound, hereby agree as follows:

AGREEMENT

1. DEFINITIONS

WHEN USED IN THIS AGREEMENT, CAPITALIZED TERMS WILL HAVE THE MEANINGS AS DEFINED BELOW AND THROUGHOUT THE AGREEMENT. UNLESS THE CONTEXT INDICATES OTHERWISE, THE SINGULAR WILL INCLUDE THE PLURAL AND THE PLURAL WILL INCLUDE THE SINGULAR.

1.1. " **ACCEPTANCE PERIOD** " SHALL HAVE THE MEANING SET FORTH IN SECTION 5.2..

1.2. " **AFFILIATE** " MEANS, WITH RESPECT TO EITHER PARTY, ANY OTHER CORPORATION OR BUSINESS ENTITY THAT DIRECTLY, OR INDIRECTLY THROUGH ONE OR MORE INTERMEDIARIES, CONTROLS, IS CONTROLLED BY OR IS UNDER COMMON CONTROL WITH SUCH PARTY. FOR PURPOSES OF THIS DEFINITION, THE TERM "CONTROL" AND, WITH CORRELATIVE MEANINGS, THE TERMS "CONTROLLED BY" AND "UNDER COMMON CONTROL WITH" MEANS DIRECT OR INDIRECT OWNERSHIP OF MORE THAN FIFTY PERCENT (50%) OF THE SECURITIES OR OTHER OWNERSHIP INTERESTS REPRESENTING THE EQUITY VOTING STOCK OR GENERAL PARTNERSHIP OR MEMBERSHIP INTEREST OF SUCH ENTITY OR THE POWER TO DIRECT OR CAUSE THE DIRECTION OF THE MANAGEMENT OR POLICIES OF SUCH ENTITY, WHETHER THROUGH THE OWNERSHIP OF VOTING SECURITIES, BY CONTRACT, OR OTHERWISE.

1.3. " **BATCH** " MEANS A SPECIFIC QUANTITY OF PRODUCT THAT IS INTENDED TO HAVE UNIFORM CHARACTER AND QUALITY, WITHIN SPECIFIED LIMITS, AND IS PRODUCED ACCORDING TO A SINGLE MANUFACTURING ORDER DURING THE SAME CYCLE OF MANUFACTURE

1.4. " **BATCH RECORD** " MEANS THE PRODUCTION RECORD PERTAINING TO A BATCH.

1.5. " **CGMP** " MEANS THE REGULATORY REQUIREMENTS FOR CURRENT GOOD MANUFACTURING PRACTICES PROMULGATED BY THE FDA UNDER 21 CFR PARTS 210 AND 211, AS AMENDED FROM TIME TO TIME.

1.6. " **CHANGE ORDER** " HAS THE MEANING SET FORTH IN SECTION 2.2.

1.7. " **CLIENT DEVELOPMENT MATERIALS** " HAS THE MEANING SET FORTH IN SECTION 2.3.

1.8. " **CLIENT INVENTIONS** " MEANS ANY KNOW-HOW OR INVENTIONS, WHETHER OR NOT PATENTABLE, CONCEIVED, DEVELOPED OR REDUCED TO PRACTICE BY CLIENT ON OR BEFORE THE EFFECTIVE DATE.

1.9. " **CLIENT MATERIALS** " MEANS THE CLIENT DEVELOPMENT MATERIALS AND THE CLIENT PRODUCTION MATERIALS.

1.10. " **CLIENT PERSONNEL** " HAS THE MEANING SET FORTH IN SECTION 4.8.1.

1.11. " **CLIENT PRODUCTION MATERIALS** " HAS THE MEANING SET FORTH IN SECTION 4.2.

1.12. " **COMMENCEMENT DATE** " MEANS THE DATE SET FORTH IN THE STATEMENT OF WORK, BASED ON A DRAFT PLAN, FOR THE COMMENCEMENT OF THE PRODUCTION OF THE PRODUCT.

1.13. " **CONFIDENTIAL INFORMATION** " HAS THE MEANING SET FORTH IN SECTION 10.1.

1.14. " **DISAPPROVAL NOTICE** " SHALL HAVE THE MEANING SET FORTH IN SECTION 5.2.2.

1.15. " **DRAFT PLAN** " SHALL HAVE THE MEANING SET FORTH IN SECTION 4.1.

1.16. " **FDA** " MEANS THE U.S. FOOD AND DRUG ADMINISTRATION, AND ANY SUCCESSOR AGENCY THEREOF.

1.17. " **FIRST STATEMENT OF WORK** " HAS THE MEANING SET FORTH IN THE DEFINITION OF STATEMENT OF WORK.

1.18. " **INTELLECTUAL PROPERTY** " MEANS ALL WORLDWIDE PATENTS, COPYRIGHTS, TRADE SECRETS, KNOW-HOW AND ALL OTHER INTELLECTUAL PROPERTY RIGHTS, INCLUDING ALL APPLICATIONS AND REGISTRATIONS WITH RESPECT THERETO, BUT EXCLUDING ALL TRADEMARKS, TRADE NAMES, SERVICE MARKS, LOGOS AND OTHER CORPORATE IDENTIFIERS.

1.19. " **LWI INVENTIONS** " MEANS ANY KNOW-HOW, MEDIA, ASSAYS, METHODS OR OTHER INVENTIONS, WHETHER OR NOT PATENTABLE, CONCEIVED, DEVELOPED OR REDUCED TO PRACTICE BY LWI: (A) ON OR BEFORE THE EFFECTIVE DATE; OR (B) IN CONNECTION WITH THE PERFORMANCE OF THE STATEMENT OF WORK OR THE DRAFT PLAN.

1.20. " **LWI OPERATING DOCUMENTS** " MEANS THE STANDARD OPERATING PROCEDURES, STANDARD MANUFACTURING PROCEDURES, RAW MATERIAL SPECIFICATIONS, PROTOCOLS, VALIDATION DOCUMENTATION, AND SUPPORTING DOCUMENTATION USED BY LWI, SUCH AS ENVIRONMENTAL MONITORING, FOR OPERATION AND MAINTENANCE OF THE FACILITY AND LWI EQUIPMENT USED IN THE PROCESS OF PRODUCING THE PRODUCT, EXCLUDING ANY OF THE FOREGOING THAT ARE UNIQUE TO THE MANUFACTURE OF PRODUCT.

1.21. " **LWI PARTIES** " HAS THE MEANING SET FORTH IN SECTION 15.2.

1.22. " **MASTER PRODUCTION RECORD** " MEANS THE DOCUMENTATION DEVELOPED BY LWI THAT CONTAINS A DETAILED DESCRIPTION OF A PROCESS AND ANY OTHER INSTRUCTIONS TO BE FOLLOWED BY LWI IN THE PRODUCTION OF A PRODUCT.

1.23. " **MATERIALS** " MEANS ALL RAW MATERIALS AND SUPPLIES TO BE USED IN THE PRODUCTION OF A PRODUCT.

1.24. " **PROCESS** " MEANS THE MANUFACTURING PROCESS FOR A PRODUCT DEVELOPED BY LWI PURSUANT TO THE TERMS OF THIS AGREEMENT.

1.25. " **PRODUCT** " HAS THE MEANING SET FORTH IN A STATEMENT OF WORK.

1.26. " **PRODUCT WARRANTIES** " MEANS THOSE WARRANTIES AS SPECIFICALLY STATED IN SECTION 5.2.2.

1.27. " **PRODUCTION TERM** " SHALL HAVE THE MEANING SET FORTH IN SECTION 4.4.

1.28. " **QUALITY AGREEMENT** " MEANS THE QUALITY AGREEMENT ENTERED INTO BY THE PARTIES SIMULTANEOUSLY WITH THE EXECUTION HEREOF RELATING TO A PRODUCT.

1.29. " **REGULATORY APPROVAL** " MEANS THE APPROVAL BY THE FDA TO MARKET AND SELL THE PRODUCT IN THE UNITED STATES.

1.30. " **SOP** " MEANS A STANDARD OPERATING PROCEDURE.

1.31. " **SPECIFICATIONS** " MEANS THE PRODUCT SPECIFICATIONS SET FORTH IN THE STATEMENT OF WORK OR AS MODIFIED BY THE PARTIES IN CONNECTION WITH THE PRODUCTION OF A PARTICULAR BATCH OF PRODUCT HEREUNDER.

1.32. " **STATEMENT OF WORK** " MEANS A PLAN TO DEVELOP A PROCESS OR PRODUCT THAT IS ATTACHED HERETO AS APPENDIX A OR LATER BECOMES ATTACHED THROUGH AN AMENDMENT BY THE PARTIES. THE FIRST STATEMENT OF WORK, WHICH IS ATTACHED HERETO, IS NUMBERED APPENDIX A-1 AND IS HEREBY INCORPORATED AND MADE A PART OF THIS AGREEMENT (THE " **FIRST STATEMENT OF WORK** "). IT IS CONTEMPLATED THAT EACH SEPARATE PROJECT SHALL HAVE ITS OWN STATEMENT OF WORK. AS EACH SUBSEQUENT STATEMENT OF WORK IS AGREED TO BY THE PARTIES, EACH SHALL STATE THAT IT IS TO BE INCORPORATED AND MADE A PART OF THIS AGREEMENT AND SHALL BE CONSECUTIVELY NUMBERED AS A-2, A-3, ETC.

1.33. " **TECHNOLOGY TRANSFER** " MEANS THE TRANSFER OF DOCUMENTATION, SPECIFICATIONS, AND PRODUCTION PROCESS BY CLIENT TO LWI FOR THE DEVELOPMENT OF THE MASTER PRODUCTION RECORD FOR THE MANUFACTURING OF THE PRODUCT SPECIFICALLY FOR THE CLIENT.

1.34. " **THIRD PARTY** " MEANS ANY PARTY OTHER THAN LWI, CLIENT OR THEIR RESPECTIVE AFFILIATES.

2. STATEMENTS OF WORK - PROCESS AND PRODUCT DEVELOPMENT; TECHNOLOGY TRANSFER; PROCESS OR PRODUCT MANUFACTURE

2.1 STATEMENT OF WORK . PRIOR TO PERFORMING ANY PROCESS OR PRODUCT DEVELOPMENT, TECHNOLOGY TRANSFER, OR PROCESS OR PRODUCT MANUFACTURE, THE PARTIES WILL COLLABORATE TO DEVELOP A STATEMENT OF WORK, DESCRIBING THE ACTIVITIES TO BE PERFORMED BY THE PARTIES, OR TO BE SUBCONTRACTED BY LWI TO THIRD PARTIES. ONCE AGREED TO BY THE PARTIES, THE STATEMENT OF WORK SHALL BE EXECUTED BY EACH OF THE PARTIES AND APPENDED HERETO AS PART OF APPENDIX A. IN THE EVENT OF A CONFLICT BETWEEN THE TERMS AND CONDITIONS OF THIS AGREEMENT AND ANY STATEMENT OF WORK, THE TERMS AND CONDITIONS OF THIS AGREEMENT SHALL CONTROL.

2.2 MODIFICATION OF STATEMENT OF WORK . SHOULD CLIENT WANT TO CHANGE A STATEMENT OF WORK OR TO INCLUDE ADDITIONAL SERVICES TO BE PROVIDED BY LWI, CLIENT MAY PROPOSE TO LWI AN AMENDMENT TO THE STATEMENT OF WORK WITH THE DESIRED CHANGES OR ADDITIONAL SERVICES (" **CHANGE ORDER** "). IF LWI DETERMINES THAT IT HAS THE RESOURCES AND CAPABILITIES TO ACCOMMODATE SUCH CHANGE ORDER, LWI WILL PREPARE A MODIFIED VERSION OF THE STATEMENT OF WORK REFLECTING SUCH CHANGE ORDER (INCLUDING, WITHOUT LIMITATION, ANY CHANGES TO THE ESTIMATED TIMING, ESTIMATED CHARGES OR SCOPE OF A PROJECT) AND WILL SUBMIT SUCH MODIFIED VERSION OF THE STATEMENT OF WORK TO CLIENT FOR REVIEW AND COMMENT. THE MODIFIED STATEMENT OF WORK SHALL BE BINDING ON THE PARTIES ONLY IF IT REFERS TO THIS AGREEMENT, STATES THAT IT IS TO BE MADE A PART THEREOF, AND IS SIGNED BY BOTH PARTIES. WHEREAFTER SUCH MODIFIED VERSION OF THE STATEMENT OF WORK WILL BE DEEMED TO HAVE REPLACED THE PRIOR VERSION OF THE STATEMENT OF WORK. NOTWITHSTANDING THE FOREGOING, IF A MODIFIED VERSION OF THE STATEMENT OF WORK IS NOT AGREED TO BY BOTH PARTIES, THE EXISTING STATEMENT OF WORK SHALL REMAIN IN EFFECT.

2.3 CLIENT DELIVERABLES . WITHIN THE TIME PERIOD SPECIFIED IN A STATEMENT OF WORK, CLIENT WILL PROVIDE LWI WITH (A) THE MATERIALS LISTED IN THE STATEMENT OF WORK FOR WHICH CLIENT IS RESPONSIBLE FOR DELIVERING TO LWI, AND ANY HANDLING INSTRUCTIONS, PROTOCOLS, SOPS AND OTHER DOCUMENTATION NECESSARY TO MAINTAIN THE PROPERTIES OF SUCH MATERIALS FOR THE PERFORMANCE OF THE STATEMENT OF WORK, AND (B) ANY PROTOCOLS, SOPS AND OTHER INFORMATION AND DOCUMENTATION IN POSSESSION OR CONTROL OF CLIENT AND NECESSARY FOR THE PERFORMANCE OF THE STATEMENT OF WORK, AND FOR THE PREPARATION OF THE MASTER PRODUCTION RECORD IN CONFORMANCE WITH CGMP, INCLUDING, WITHOUT LIMITATION, PROCESS INFORMATION, SOPS, DEVELOPMENT DATA AND REPORTS, QUALITY CONTROL ASSAYS, RAW MATERIAL SPECIFICATIONS (INCLUDING VENDOR, GRADE AND SAMPLING/TESTING REQUIREMENTS), PRODUCT AND SAMPLE PACKING AND SHIPPING INSTRUCTIONS, AND PRODUCT SPECIFIC CLEANING AND DECONTAMINATION INFORMATION, (COLLECTIVELY, THE " **CLIENT DEVELOPMENT MATERIALS** ").

2.4 PERFORMANCE BY LWI . SUBJECT TO THE PROVISION BY CLIENT OF THE CLIENT DEVELOPMENT MATERIALS PURSUANT TO SECTION 2.3

, LWI WILL USE COMMERCIALLY REASONABLE EFFORTS TO PERFORM, DIRECTLY OR, SUBJECT TO THE TERMS OF THE STATEMENT OF WORK OR APPROVAL BY CLIENT (SUCH APPROVAL NOT TO BE UNREASONABLY WITHHELD), THROUGH A THIRD PARTY CONTRACTOR, THE WORK DESCRIBED IN A STATEMENT OF WORK IN A PROFESSIONAL AND WORKMANLIKE MANNER IN ACCORDANCE WITH THE TERMS OF THIS AGREEMENT. LWI WILL USE COMMERCIALLY REASONABLE EFFORTS PROMPTLY TO NOTIFY CLIENT OF ANY MATERIAL DELAYS THAT ARISE DURING THE PERFORMANCE OF THE STATEMENT OF WORK.

3. TECHNOLOGY TRANSFER

3.1 BASED ON THE INFORMATION PROVIDED BY CLIENT AND INCLUDING PROCESS CHANGES DEVELOPED BY LWI PURSUANT TO ANY APPLICABLE STATEMENT OF WORK, LWI WILL PREPARE THE MASTER PRODUCTION RECORD FOR THE PROCESS IN ACCORDANCE WITH THE SCHEDULE SET FORTH IN THE STATEMENT OF WORK. CLIENT WILL INFORM LWI OF ANY SPECIFIC REQUIREMENTS CLIENT MAY HAVE RELATING TO THE MASTER PRODUCTION RECORD, INCLUDING, WITHOUT LIMITATION, ANY INFORMATION OR PROCEDURES CLIENT WISHES TO HAVE INCORPORATED THEREIN. IF LWI INTENDS TO INCLUDE IN THE MASTER PRODUCTION RECORD THE USE OF ANY ASSAY, MEDIUM, OR OTHER TECHNOLOGY THAT IS NOT COMMERCIALLY AVAILABLE, LWI WILL INFORM CLIENT OF SUCH INTENTION AND THE PARTIES WILL MEET TO DISCUSS AND ATTEMPT TO AGREE IN GOOD FAITH ON THE TERMS OF USE OF SUCH NON-COMMERCIALLY AVAILABLE MATERIALS OR TECHNOLOGY IN THE PROCESS.

3.2 CLIENT WILL COOPERATE WITH LWI TO ASSIST LWI TO DEVELOP THE MASTER PRODUCTION RECORD AND PROCESS, INCLUDING, WITHOUT LIMITATION, BY PROVIDING LWI WITH ADDITIONAL INFORMATION AND PROCEDURES AS MAY BE REQUIRED TO CREATE THE MASTER PRODUCTION RECORD, PROCESS, AND/OR ANY OF THE FOLLOWING: (I) MANUFACTURING PROCESS INFORMATION, SOPS, DEVELOPMENT REPORTS, (II) QUALITY CONTROL ASSAYS, (III) RAW MATERIAL SPECIFICATIONS (INCLUDING VENDOR, GRADE AND SAMPLING/TESTING REQUIREMENTS), (IV) PRODUCT AND SAMPLE PACKING AND SHIPPING INSTRUCTIONS, (V) PRODUCT SPECIFIC CLEANING AND DECONTAMINATION INFORMATION.

3.3 LWI WILL DELIVER A DRAFT VERSION OF THE MASTER PRODUCTION RECORD TO CLIENT FOR ITS REVIEW AND APPROVAL IN ACCORDANCE WITH THE SCHEDULE SET FORTH IN THE STATEMENT OF WORK. CLIENT WILL NOTIFY LWI IN WRITING OF ANY OBJECTIONS IT HAS TO THE DRAFT MASTER PRODUCTION RECORD, AND UPON SUCH NOTIFICATION, REPRESENTATIVES OF LWI AND CLIENT WILL MEET PROMPTLY TO RESOLVE SUCH OBJECTIONS. UPON CLIENT'S WRITTEN ACCEPTANCE OF THE DRAFT MASTER PRODUCTION RECORD, OR IN THE EVENT THAT CLIENT DOES NOT SUBMIT A WRITTEN NOTICE SETTING FORTH CLIENT'S OBJECTIONS TO THE DRAFT MASTER PRODUCTION RECORD WITHIN TEN (10) DAYS FOLLOWING RECEIPT OF SUCH DRAFT BY CLIENT, SUCH DRAFT WILL BE DEEMED APPROVED BY CLIENT.

3.4 THE PROCESS, MASTER PRODUCTION RECORD, SPECIFICATIONS, AND ANY IMPROVEMENTS OR MODIFICATIONS THERETO DEVELOPED DURING THE TERM OF THIS AGREEMENT, BUT EXCLUDING ANY LWI OPERATING DOCUMENTS, LWI INVENTIONS OR LWI CONFIDENTIAL INFORMATION INCLUDED IN ANY OF THE FOREGOING, WILL BE DEEMED CLIENT CONFIDENTIAL INFORMATION AND SUBJECT TO THE PROVISIONS SET FORTH IN ARTICLE 10

. CLIENT SHALL BE PERMITTED TO USE THE PROCESS AND/OR THE MASTER PRODUCTION RECORD TO MANUFACTURE AND SELL PRODUCT; PROVIDED, HOWEVER, THAT IF THE PROCESS AND/OR THE MASTER PRODUCTION RECORD INCORPORATES OR CONTAINS ANY LWI INTELLECTUAL PROPERTY OR LWI CONFIDENTIAL INFORMATION, PRIOR TO ANY DISCLOSURE OF SUCH LWI INTELLECTUAL PROPERTY OR LWI CONFIDENTIAL INFORMATION TO, OR USE BY, A THIRD PARTY MANUFACTURER, CLIENT SHALL OBTAIN LWI'S WRITTEN CONSENT TO SUCH DISCLOSURE.

4. MANUFACTURE OF PRODUCT; ORDER PROCESS; DELIVERIES

4.1 DRAFT PLAN . TOGETHER WITH THE DRAFT VERSION OF THE MASTER PRODUCTION RECORD DESCRIBED IN SECTION 3.3 ABOVE, LWI WILL DELIVER TO CLIENT FOR REVIEW AND COMMENT, A PROPOSED DRAFT PLAN DESCRIBING THE ACTIVITIES TO BE PERFORMED BY LWI, OR TO BE SUBCONTRACTED BY LWI TO THIRD PARTIES, IN THE PRODUCTION OF A PRODUCT (THE " **DRAFT PLAN** "). ONCE LWI DELIVERS TO CLIENT THE PROPOSED DRAFT PLAN, THE PARTIES WILL MEET TO DECIDE WHETHER TO ISSUE A NEW STATEMENT OF WORK PURSUANT TO SECTION 2.1

, OR TO MODIFY AN EXISTING STATEMENT OF WORK PURSUANT TO SECTION 2.2
, BASED ON THAT DRAFT PLAN AND ANY AGREED UPON MODIFICATIONS.

4.2 CLIENT DELIVERABLES. WITHIN ANY TIME PERIOD SPECIFIED IN THE DRAFT PLAN AND AGREED TO IN ANY APPLICABLE STATEMENT OF WORK, CLIENT WILL PROVIDE LWI WITH (A) THE MATERIALS LISTED IN THE STATEMENT OF WORK REQUIRED TO BE SUPPLIED BY CLIENT FOR THE PRODUCTION OF THE PRODUCT, AND ANY HANDLING INSTRUCTIONS, PROTOCOLS, SOPS AND OTHER DOCUMENTATION NECESSARY TO MAINTAIN THE PROPERTIES OF SUCH MATERIALS FOR THE PERFORMANCE OF THE DRAFT PLAN (COLLECTIVELY, THE " **CLIENT PRODUCTION MATERIALS** ").

4.3 COMMENCEMENT DATE . THE STATEMENT OF WORK BASED ON A DRAFT PLAN WILL INCLUDE A COMMENCEMENT DATE AGREED UPON BY THE PARTIES.

4.4 MANUFACTURE BY LWI . DURING THE TIME PERIOD SPECIFIED IN ANY STATEMENT OF WORK DURING WHICH PRODUCT WILL BE MANUFACTURED (THE " **PRODUCTION TERM** "), LWI WILL USE COMMERCIALLY REASONABLE EFFORTS TO MANUFACTURE, PACKAGE, SHIP, HANDLE QUALITY ASSURANCE AND QUALITY CONTROL FOR THE PRODUCT, ALL AS SET FORTH IN THE STATEMENT OF WORK, AND TO DELIVER TO CLIENT THE QUANTITIES OF PRODUCT REQUESTED BY CLIENT IN THE STATEMENT OF WORK, ALL IN ACCORDANCE WITH THE TERMS SET FORTH IN SECTION 4.5

BELOW.

4.5 PACKAGING AND SHIPPING . LWI WILL PACKAGE AND LABEL THE PRODUCT FOR SHIPMENT IN ACCORDANCE WITH THE MASTER PRODUCTION RECORD AND LWI'S STANDARD PRACTICES IN EFFECT AT THE TIME OF PERFORMANCE BY LWI. LWI WILL SHIP THE PRODUCT FOB SHIPPING POINT DELIVERED AT THE FACILITY TO A COMMON CARRIER DESIGNATED BY CLIENT TO LWI IN WRITING NOT LESS THAN TEN DAYS PRIOR TO THE APPLICABLE DELIVERY DATE UNLESS OTHERWISE AGREED TO IN A STATEMENT OF WORK. CLIENT WILL PROVIDE TO LWI ITS ACCOUNT NUMBER WITH THE SELECTED CARRIER AND WILL PAY FOR ALL SHIPPING COSTS IN CONNECTION WITH EACH SHIPMENT OF PRODUCT. EACH SHIPMENT WILL BE ACCOMPANIED BY THE DOCUMENTATION LISTED IN THE DRAFT PLAN. LWI WILL USE COMMERCIALLY REASONABLE EFFORTS TO DELIVER EACH SHIPMENT OF PRODUCT TO CLIENT ON THE REQUESTED DELIVERY DATE FOR SUCH SHIPMENT. LWI WILL PROMPTLY NOTIFY CLIENT IF LWI REASONABLY BELIEVES THAT IT WILL BE UNABLE TO MEET A DELIVERY DATE. CLIENT SHALL BE REQUIRED TO TAKE DELIVERY OF A BATCH OF PRODUCT WITHIN THIRTY (30) DAYS AFTER ACCEPTANCE OF SUCH BATCH IN ACCORDANCE WITH SECTION 5.2 (THE "DELIVERY PERIOD").

4.6 QUALITY AGREEMENT . UPON THE DECISION TO MANUFACTURE A PRODUCT ACCORDING TO A DRAFT PLAN, THE PARTIES SHALL ENTER INTO A SEPARATE QUALITY AGREEMENT, IN THE FORM ATTACHED HERETO, SETTING FORTH THE TERMS FOR PRODUCT QUALITY, QUANTITY, PRICE, AND ANY OTHER TERMS NECESSARY FOR SUCH AGREEMENTS. SUCH QUALITY AGREEMENT SHALL BE SEPARATELY APPENDED TO THIS AGREEMENT.

4.7 RECORDS . LWI WILL MAINTAIN ACCURATE RECORDS FOR THE PRODUCTION OF THE PRODUCT, AS REQUIRED BY APPLICABLE LAWS AND REGULATIONS. LWI WILL RETAIN POSSESSION OF THE MASTER PRODUCTION RECORD, ALL BATCH RECORDS AND LWI OPERATING DOCUMENTS, AND WILL MAKE COPIES THEREOF AVAILABLE TO CLIENT UPON CLIENT'S REQUEST AND AT CLIENT'S EXPENSE. LWI OPERATING DOCUMENTS WILL REMAIN LWI CONFIDENTIAL INFORMATION. CLIENT WILL HAVE THE RIGHT TO USE AND REFERENCE ANY OF THE FOREGOING IN CONNECTION WITH A FILING FOR REGULATORY APPROVAL OF THE PRODUCT OR AS OTHERWISE AUTHORIZED BY THE AGREEMENT.

4.8 CLIENT ACCESS .

4.8.1 CLIENT'S EMPLOYEES AND AGENTS (INCLUDING ITS INDEPENDENT CONTRACTORS) (COLLECTIVELY, " **CLIENT PERSONNEL** ") MAY PARTICIPATE IN THE PRODUCTION OF THE PRODUCT ONLY IN SUCH CAPACITIES AS MAY BE APPROVED IN WRITING IN ADVANCE BY LWI. CLIENT PERSONNEL WORKING AT THE FACILITY ARE REQUIRED TO COMPLY WITH LWI'S OPERATING DOCUMENTS AND ANY OTHER APPLICABLE LWI FACILITY AND/OR SAFETY POLICIES. FOR THE AVOIDANCE OF DOUBT, CLIENT PERSONNEL MAY NOT PHYSICALLY PARTICIPATE IN THE PRODUCTION OR MANUFACTURE OF ANY PRODUCT THAT MAY BE USED IN OR ON HUMANS.

4.8.2 CLIENT PERSONNEL WORKING AT THE FACILITY WILL BE AND REMAIN EMPLOYEES OF CLIENT, AND CLIENT WILL BE SOLELY RESPONSIBLE FOR THE PAYMENT OF COMPENSATION FOR SUCH CLIENT PERSONNEL (INCLUDING APPLICABLE FEDERAL, STATE AND LOCAL WITHHOLDING, FICA AND OTHER PAYROLL TAXES, WORKERS' COMPENSATION INSURANCE, HEALTH INSURANCE, AND OTHER SIMILAR STATUTORY AND FRINGE BENEFITS). CLIENT COVENANTS AND AGREES TO MAINTAIN WORKERS' COMPENSATION BENEFITS AND EMPLOYERS' LIABILITY INSURANCE AS REQUIRED BY APPLICABLE FEDERAL AND MARYLAND LAWS WITH RESPECT TO ALL CLIENT PERSONNEL WORKING AT THE FACILITY.

4.8.3 CLIENT WILL PAY FOR THE ACTUAL COST OF REPAIRING OR REPLACING TO ITS PREVIOUS STATUS (TO THE EXTENT THAT LWI DETERMINES, IN ITS REASONABLE JUDGMENT, THAT REPAIRS CANNOT BE ADEQUATELY EFFECTED) ANY PROPERTY OF LWI DAMAGED OR DESTROYED BY CLIENT PERSONNEL, PROVIDED CLIENT SHALL NOT BE LIABLE FOR REPAIR OR REPLACEMENT COSTS RESULTING FROM ORDINARY WEAR AND TEAR.

4.8.4 CLIENT PERSONNEL VISITING OR HAVING ACCESS TO THE FACILITY WILL ABIDE BY LWI STANDARD POLICIES, OPERATING PROCEDURES AND THE SECURITY PROCEDURES ESTABLISHED BY LWI. CLIENT WILL BE LIABLE FOR ANY BREACHES OF SECURITY BY CLIENT PERSONNEL. IN ADDITION, CLIENT WILL REIMBURSE LWI FOR THE COST OF ANY LOST SECURITY CARDS ISSUED TO CLIENT PERSONNEL, AT THE RATE OF $50 PER SECURITY CARD. ALL CLIENT PERSONNEL WILL AGREE TO ABIDE BY LWI POLICIES AND SOPS ESTABLISHED BY LWI, AND WILL SIGN AN APPROPRIATE CONFIDENTIALITY AGREEMENT.

4.8.5 CLIENT WILL INDEMNIFY AND HOLD HARMLESS LWI FROM AND AGAINST ANY AND ALL LOSSES, DAMAGES, LIABILITIES, COSTS AND EXPENSES (INCLUDING REASONABLE ATTORNEYS' FEES AND EXPENSES) ARISING OUT OF ANY INJURIES SUFFERED BY CLIENT PERSONNEL WHILE AT THE FACILITY OR ELSEWHERE, EXCEPT TO THE EXTENT CAUSED BY THE GROSS NEGLIGENCE OR WILLFUL MISCONDUCT ON THE PART OF ANY LWI PARTY.

4.9 **DISCLAIMERS** . CLIENT ACKNOWLEDGES AND AGREES THAT LWI PARTIES WILL NOT ENGAGE IN ANY PRODUCT REFINEMENT OR DEVELOPMENT OF THE PRODUCT, OTHER THAN AS EXPRESSLY SET FORTH IN THIS AGREEMENT AND THE STATEMENT OF WORK. CLIENT ACKNOWLEDGES AND AGREES THAT LWI PARTIES HAVE NOT PARTICIPATED IN THE INVENTION OR TESTING OF ANY PRODUCT, AND HAVE NOT EVALUATED ITS SAFETY OR SUITABILITY FOR USE IN HUMANS OR OTHERWISE.

5. **PRODUCT WARRANTIES; ACCEPTANCE AND REJECTION OF PRODUCTS**

5.1 **PRODUCT WARRANTIES** . LWI WARRANTS THAT ANY PRODUCT MANUFACTURED BY LWI PURSUANT TO THIS AGREEMENT, AT THE TIME OF DELIVERY PURSUANT TO SECTION 4.5

: (A) CONFORMS TO THE SPECIFICATIONS; (B) WAS MANUFACTURED IN ACCORDANCE WITH THE MASTER PRODUCTION RECORD; AND (C) WAS MANUFACTURED IN ACCORDANCE WITH CGMP.

5.2 **APPROVAL OF SHIPMENT** .

5.2.1 WHEN THE PRODUCT ORDERED BY CLIENT IS READY FOR DELIVERY, LWI WILL NOTIFY CLIENT AND SUPPLY CLIENT WITH THE REQUIRED DOCUMENTATION SET FORTH IN THE DRAFT PLAN.

5.2.2 WITHIN TEN (10) CALENDAR DAYS AFTER CLIENT'S RECEIPT OF SUCH DOCUMENTATION REGARDING SUCH PRODUCT (THE " **ACCEPTANCE PERIOD** "), CLIENT SHALL DETERMINE BY REVIEW OF SUCH DOCUMENTATION WHETHER OR NOT THE GIVEN BATCH CONFORMS TO THE PRODUCT WARRANTIES SET FORTH IN SECTION 5.1 ABOVE (" **PRODUCT WARRANTIES** "). IF CLIENT ASSERTS THAT THE PRODUCT DOES NOT COMPLY WITH THE PRODUCT WARRANTIES SET FORTH IN SECTION 5.1

ABOVE, CLIENT WILL DELIVER TO LWI, IN ACCORDANCE WITH THE NOTICE PROVISIONS SET FORTH IN SECTION 17.4 HEREOF, WRITTEN NOTICE OF DISAPPROVAL (THE " **DISAPPROVAL NOTICE** ") OF SUCH PRODUCT, STATING IN REASONABLE DETAIL THE BASIS FOR SUCH ASSERTION OF NON-COMPLIANCE WITH THE PRODUCT WARRANTIES. IF A VALID DISAPPROVAL NOTICE IS RECEIVED BY LWI DURING THE ACCEPTANCE PERIOD, THEN LWI AND CLIENT WILL PROVIDE ONE ANOTHER WITH ALL RELATED PAPERWORK AND RECORDS (INCLUDING, BUT NOT LIMITED TO, QUALITY CONTROL TESTS) RELATING TO BOTH THE PRODUCTION OF THE PRODUCT AND THE DISAPPROVAL NOTICE. IF A VALID DISAPPROVAL NOTICE IS NOT RECEIVED DURING THE ACCEPTANCE PERIOD, THE PRODUCT WILL BE DEEMED ACCEPTED AND READY FOR SHIPMENT. UPON ACCEPTANCE, THE PRODUCT SHALL BE DELIVERED TO CLIENT, AND CLIENT SHALL ACCEPT DELIVERY THEREOF, WITHIN 10-DAYS AFTER SUCH ACCEPTANCE. TITLE AND RISK OF LOSS TO SUCH PRODUCT SHALL PASS TO CLIENT AT THE TIME OF DELIVERY TO THE COMMON CARRIER PURSUANT TO SECTION 4.5.

5.3 **DISPUTE RESOLUTION** . LWI AND CLIENT WILL ATTEMPT TO RESOLVE ANY DISPUTE REGARDING THE CONFORMITY OF A SHIPMENT OF PRODUCT WITH THE PRODUCT WARRANTIES. IF SUCH DISPUTE CANNOT BE SETTLED WITHIN 30 DAYS OF THE SUBMISSION BY EACH PARTY OF SUCH RELATED PAPERWORK AND RECORDS TO THE OTHER PARTY, AND IF THE PRODUCT IS ALLEGED NOT TO CONFORM WITH THE PRODUCT WARRANTIES SET FORTH IN SECTION 5.1

(A), THEN CLIENT WILL SUBMIT A SAMPLE OF THE BATCH OF THE DISPUTED SHIPMENT TO AN INDEPENDENT TESTING LABORATORY OF RECOGNIZED REPUTE SELECTED BY CLIENT AND APPROVED BY LWI (SUCH APPROVAL NOT TO BE UNREASONABLY WITHHELD) FOR ANALYSIS, UNDER QUALITY ASSURANCE APPROVED PROCEDURES, OF THE CONFORMITY OF SUCH SHIPMENT OF PRODUCT WITH THE SPECIFICATIONS. THE COSTS ASSOCIATED WITH SUCH ANALYSIS BY SUCH INDEPENDENT TESTING LABORATORY WILL BE PAID BY THE PARTY WHOSE ASSESSMENT OF THE CONFORMITY OF THE SHIPMENT OF PRODUCT WITH THE SPECIFICATIONS WAS MISTAKEN.

5.4 REMEDIES FOR NON-CONFORMING PRODUCT .

5.4.1 IN THE EVENT THAT THE PARTIES AGREE, OR AN INDEPENDENT TESTING LABORATORY DETERMINES, PURSUANT TO SECTION 5.3, THAT A BATCH OF PRODUCT MATERIALLY FAILS TO CONFORM TO THE PRODUCT WARRANTIES DUE TO THE FAILURE OF: (A) LWI PERSONNEL PROPERLY TO EXECUTE THE MASTER PRODUCTION RECORD, (B) LWI PERSONNEL TO COMPLY WITH CGMP, OR (C) THE FACILITY UTILITIES, THEN, AT CLIENT'S REQUEST, LWI WILL PRODUCE FOR CLIENT SUFFICIENT QUANTITIES OF PRODUCT TO REPLACE THE NON-CONFORMING PORTION OF SUCH BATCH OF PRODUCT (THE " **PRODUCTION RERUN** "), IN ACCORDANCE WITH THE PROVISIONS OF THIS AGREEMENT AND AT NO ADDITIONAL COST TO CLIENT.

5.4.2 IN THE EVENT THAT THE PARTIES AGREE, OR AN INDEPENDENT TESTING LABORATORY DETERMINES, PURSUANT TO SECTION 5.3, THAT A BATCH OF PRODUCT MATERIALLY FAILS TO CONFORM TO THE PRODUCT WARRANTIES FOR ANY REASON OTHER THAN AS SET FORTH IN SECTION 5.4.1

, THEN LWI SHALL HAVE NO LIABILITY TO CLIENT WITH RESPECT TO SUCH BATCH AND LWI WILL, AT CLIENT'S REQUEST, PRODUCE FOR CLIENT A PRODUCTION RERUN AT CLIENT'S EXPENSE.

5.4.3 CLIENT ACKNOWLEDGES AND AGREES THAT ITS SOLE REMEDY WITH RESPECT TO THE FAILURE OF PRODUCT TO CONFORM WITH ANY OF THE PRODUCT WARRANTIES IS AS SET FORTH IN THIS SECTION 5.4, AND IN FURTHERANCE THEREOF, CLIENT HEREBY WAIVES ALL OTHER REMEDIES AT LAW OR IN EQUITY REGARDING THE FOREGOING CLAIMS.

6. DAMAGE OR DESTRUCTION OF MATERIALS AND/OR PRODUCT

6.1 REMEDIES . IF DURING THE MANUFACTURE OF PRODUCT PURSUANT TO THIS AGREEMENT, PRODUCT AND/OR MATERIALS ARE DESTROYED OR DAMAGED BY LWI PERSONNEL, AND SUCH DAMAGE OR DESTRUCTION RESULTED FROM LWI'S FAILURE TO EXECUTE THE PROCESS IN CONFORMITY WITH THE MASTER PRODUCTION RECORD, THEN, EXCEPT AS PROVIDED IN SECTION 6.2

BELOW, LWI, AS SOON AS IT IS COMMERCIALLY PRACTICABLE TO DO SO, WILL PROVIDE CLIENT WITH ADDITIONAL PRODUCT PRODUCTION TIME EQUAL TO THE ACTUAL TIME LOST BECAUSE OF THE DESTRUCTION OR DAMAGE OF THE PRODUCT AND/OR MATERIALS AND WILL REPLACE SUCH PRODUCT AND/OR MATERIALS AT NO ADDITIONAL COST TO CLIENT. CLIENT ACKNOWLEDGES AND AGREES THAT ITS SOLE REMEDY WITH RESPECT TO DAMAGED OR DESTROYED MATERIALS AND/OR PRODUCT (EXCEPT FOR THE NON-CONFORMITY OF SHIPPED PRODUCT DESCRIBED IN SECTION 5) IS AS SET FORTH IN THIS SECTION 6.1
, AND IN FURTHERANCE THEREOF, CLIENT HEREBY WAIVES ALL OTHER REMEDIES AT LAW OR IN EQUITY REGARDING THE FOREGOING CLAIMS.

6.2 LIMITATIONS . NOTWITHSTANDING ANYTHING TO THE CONTRARY SET FORTH IN THE PRECEDING SECTION 6.1, IF DURING THE MANUFACTURE OF PRODUCT PURSUANT TO THIS AGREEMENT, PRODUCT OR MATERIALS ARE DESTROYED OR DAMAGED BY LWI PERSONNEL WHILE LWI PERSONNEL WERE ACTING AT THE DIRECTION OF CLIENT PERSONNEL, THEN LWI WILL HAVE NO LIABILITY TO CLIENT AS THE RESULT OF SUCH DESTRUCTION OR DAMAGE.

7. STORAGE OF MATERIALS

7.1 PRE-PRODUCTION . LWI WILL STORE AT THE EXPENSE OF CLIENT ANY CLIENT MATERIALS, EQUIPMENT OR OTHER PROPERTY DELIVERED PURSUANT TO THE STATEMENT OF WORK OR THE DRAFT PLAN TO THE FACILITY BY CLIENT MORE THAN 30 DAYS PRIOR TO THE COMMENCEMENT DATE. THE STORAGE RATES WILL BE SET FORTH IN THE STATEMENT OF WORK AND MAY BE AMENDED FROM TIME TO TIME BY LWI. NO STORAGE FEES WILL BE CHARGED DURING THE PERIOD STARTING 30 DAYS PRIOR TO THE COMMENCEMENT DATE AND ENDING UPON THE EXPIRATION OR TERMINATION OF THE PRODUCTION TERM.

7.2 POST-PRODUCTION . LWI WILL STORE AT THE FACILITY FREE OF CHARGE ANY IN–PROCESS MATERIALS, CLIENT MATERIALS, EQUIPMENT AND OTHER CLIENT PROPERTY (OTHER THAN PRODUCT MANUFACTURED HEREUNDER) THAT REMAINS AT THE FACILITY ON THE DATE OF EXPIRATION OR TERMINATION OF THE PRODUCTION TERM (COLLECTIVELY " **REMAINING CLIENT PROPERTY** "), FOR UP TO 15 CALENDAR DAYS. IF CLIENT HAS NOT PROVIDED ANY INSTRUCTIONS AS TO THE SHIPMENT OR OTHER DISPOSITION OF REMAINING CLIENT PROPERTY PRIOR TO THE EXPIRATION OF SUCH FIFTEEN (15)-DAY PERIOD, LWI MAY, IN ITS SOLE DISCRETION, DESTROY SUCH REMAINING CLIENT PROPERTY, OR CONTINUE TO STORE SUCH REMAINING CLIENT PROPERTY AT THE FACILITY OR ELSEWHERE. IN THE EVENT THAT LWI CONTINUES TO STORE SUCH REMAINING CLIENT PROPERTY, CLIENT WILL PAY TO LWI A STORAGE CHARGE AT LWI'S THEN-STANDARD STORAGE RATES FOR THE PERIOD BEGINNING ON THE SIXTEENTH (16TH) DAY AFTER THE EXPIRATION OR TERMINATION OF THE PRODUCTION TERM THROUGH THE DATE THAT THE STORAGE TERMINATES.

7.3 PRODUCT . NOTWITHSTANDING THE FOREGOING, IF CLIENT FAILS TO TAKE DELIVERY OF A PRODUCT WITHIN THE APPLICABLE DELIVERY PERIOD AS REQUIRED BY SECTION 4.5, CLIENT WILL PAY TO LWI A STORAGE CHARGE AT THREE TIMES LWI'S THEN STANDARD STORAGE RATE, WHICH SHALL BEGIN ACCRUING ON THE FIRST DAY FOLLOWING THE EXPIRATION OF THE APPLICABLE DELIVERY PERIOD.

8. REGULATORY MATTERS

8.1 PERMITS AND APPROVALS . DURING THE PRODUCTION TERM, LWI WILL USE COMMERCIALLY REASONABLE EFFORTS TO MAINTAIN ANY LICENSES, PERMITS AND APPROVALS NECESSARY FOR THE MANUFACTURE OF THE PRODUCT IN THE FACILITY. LWI WILL PROMPTLY NOTIFY CLIENT IF LWI RECEIVES NOTICE THAT ANY SUCH LICENSE, PERMIT, OR APPROVAL IS OR MAY BE REVOKED OR SUSPENDED.

8.2 INSPECTIONS/QUALITY AUDIT BY CLIENT . UP TO TWO TIMES DURING THE PRODUCTION TERM AND UPON NOT LESS THAN 30 DAYS' PRIOR WRITTEN NOTICE, LWI WILL PERMIT CLIENT TO INSPECT AND AUDIT THE PARTS OF THE FACILITY WHERE THE MANUFACTURE OF THE PRODUCT IS CARRIED OUT IN ORDER TO ASSESS LWI'S COMPLIANCE WITH CGMP, AND TO DISCUSS ANY RELATED ISSUES WITH LWI'S MANAGEMENT PERSONNEL. CLIENT PERSONNEL ENGAGED IN SUCH INSPECTION WILL ABIDE BY THE TERMS AND CONDITIONS SET FORTH IN SECTIONS 4.8.4

AND 10.

8.3 INSPECTIONS BY REGULATORY AGENCIES . LWI WILL ALLOW REPRESENTATIVES OF ANY REGULATORY AGENCY TO INSPECT THE RELEVANT PARTS OF THE FACILITY WHERE THE MANUFACTURE OF THE PRODUCT IS CARRIED OUT AND TO INSPECT THE MASTER PRODUCTION RECORD AND BATCH RECORDS TO VERIFY COMPLIANCE WITH CGMP AND OTHER PRACTICES OR REGULATIONS AND WILL PROMPTLY NOTIFY CLIENT OF THE SCHEDULING OF ANY SUCH INSPECTION RELATING TO THE MANUFACTURE OF PRODUCT. LWI WILL PROMPTLY SEND TO CLIENT A COPY OF ANY REPORTS, CITATIONS, OR WARNING LETTERS RECEIVED BY CLIENT IN CONNECTION WITH AN INSPECTION OF A REGULATORY AGENCY TO THE EXTENT SUCH DOCUMENTS RELATE TO OR AFFECT THE MANUFACTURE OF THE PRODUCT.

9. FINANCIAL TERMS

9.1 PAYMENTS . CLIENT WILL MAKE PAYMENTS TO LWI IN THE AMOUNTS AND ON THE DATES SET FORTH IN THE STATEMENT OF WORK. IN THE EVENT THAT CLIENT HAS NOT PAID AN INVOICE WITHIN THIRTY (30) BUSINESS DAYS OF THE APPLICABLE DUE DATE (AS ESTABLISHED BY SECTION 9.3), CLIENT'S FAILURE SHALL BE CONSIDERED A MATERIAL BREACH UNDER SECTION 14.2, SUBJECT TO THE CURE PROVISIONS SET FORTH THEREIN. FURTHER, IN ADDITION TO ALL OTHER REMEDIES AVAILABLE TO LWI, IN THE EVENT THAT CLIENT HAS NOT PAID AN INVOICE WITHIN SIXTY (60) BUSINESS DAYS OF THE APPLICABLE DUE DATE (AS ESTABLISHED BY SECTION 9.3), LWI MAY ELECT TO SUSPEND THE PROVISION OF ALL OR A PORTION OF THE SERVICES UNDER THIS AGREEMENT, PROVIDED THAT CLIENT SHALL REMAIN LIABLE FOR ALL FEES OWED PURSUANT TO THE STATEMENT OF WORK DURING ANY SUCH SUSPENSION.

9.2 SECURITY DEPOSIT . THE SECURITY DEPOSIT, AS DEFINED IN THE STATEMENT OF WORK, WILL BE RETURNED TO CLIENT WITHIN 60 DAYS AFTER THE DATE OF EXPIRATION OR TERMINATION OF THIS AGREEMENT, IF CLIENT HAS PAID ALL FEES, CHARGES, OR OTHER PAYMENTS DUE IN CONNECTION WITH CHARGES INCURRED PRIOR TO THE EXPIRATION OR TERMINATION OF THIS AGREEMENT, INCLUDING, BUT NOT LIMITED TO, CHARGES FOR LOST, DESTROYED, STOLEN OR DAMAGED PROPERTY OF LWI (ALL SUCH FEES, CHARGES, OR OTHER PAYMENTS BEING CALLED " **OBLIGATIONS** "). IF ANY OBLIGATIONS REMAIN OUTSTANDING AFTER THE DATE OF EXPIRATION OR TERMINATION OF THIS AGREEMENT, THEN LWI SHALL BE ENTITLED TO APPLY THE SECURITY DEPOSIT AGAINST THE PAYMENT OF SUCH OBLIGATIONS. THE AMOUNT OF THE SECURITY DEPOSIT REMAINING, IF ANY, AFTER SUCH APPLICATION WILL BE RETURNED TO CLIENT. CLIENT SHALL REMAIN LIABLE TO LWI FOR ANY DEFICIENCIES REMAINING AFTER THE APPLICATION OF THE SECURITY DEPOSIT AGAINST THE OBLIGATIONS.

9.3 INVOICES . WITHIN 30 DAYS OF THE END OF EACH MONTH DURING WHICH CHARGES WERE INCURRED, LWI WILL PROVIDE CLIENT WITH AN INVOICE SETTING FORTH A DETAILED ACCOUNT OF ANY FEES, EXPENSES, OR OTHER PAYMENTS PAYABLE BY CLIENT UNDER THIS AGREEMENT FOR THE PRECEDING MONTH. THE AMOUNTS SET FORTH IN EACH SUCH INVOICE WILL BE DUE AND PAYABLE WITHIN 30 DAYS OF RECEIPT OF SUCH INVOICE BY CLIENT.

9.4 TAXES . CLIENT AGREES THAT IT IS RESPONSIBLE FOR AND WILL PAY ANY SALES, USE OR OTHER TAXES (THE " **TAXES** ") RESULTING FROM LWI'S PRODUCTION OF PRODUCT UNDER THIS AGREEMENT (EXCEPT FOR INCOME OR PERSONAL PROPERTY TAXES PAYABLE BY LWI). TO THE EXTENT NOT PAID BY CLIENT, CLIENT WILL INDEMNIFY AND HOLD HARMLESS THE LWI PARTIES FROM AND AGAINST ANY AND ALL PENALTIES, FEES, EXPENSES AND COSTS WHATSOEVER IN CONNECTION WITH THE FAILURE BY CLIENT TO PAY THE TAXES. LWI WILL NOT COLLECT ANY SALES AND USE TAXES FROM CLIENT IN CONNECTION WITH THE PRODUCTION OF ANY PRODUCT HEREUNDER IF CLIENT PROVIDES TO LWI THE APPROPRIATE VALID EXEMPTION CERTIFICATES.

9.5 INTEREST . ANY FEE, CHARGE OR OTHER PAYMENT DUE TO LWI BY CLIENT UNDER THIS AGREEMENT THAT IS NOT PAID WITHIN 30 DAYS AFTER IT IS DUE WILL ACCRUE INTEREST ON A DAILY BASIS AT A RATE OF 1.5% PER MONTH (OR THE MAXIMUM LEGAL INTEREST RATE ALLOWED BY APPLICABLE LAW, IF LESS) FROM AND AFTER SUCH DATE.

9.6 METHOD OF PAYMENT . ALL PAYMENTS TO LWI HEREUNDER BY CLIENT WILL BE IN UNITED STATES CURRENCY AND WILL BE BY CHECK, WIRE TRANSFER, MONEY ORDER, OR OTHER METHOD OF PAYMENT APPROVED BY LWI. BANK INFORMATION FOR WIRE TRANSFERS IS AS FOLLOWS:

MAILING ADDRESS FOR WIRE TRANSFER PAYMENTS:
[TO BE PROVIDED]

9.7 COST ADJUSTMENTS . AFTER THE FIRST ANNIVERSARY OF THE EFFECTIVE DATE, LWI MAY ANNUALLY ADJUST THE VARIOUS COSTS AND RATES SET FORTH IN THE STATEMENT OF WORK ATTACHED HERETO TO REFLECT CHANGES IN THE COST OF MATERIALS AND/OR LABOR RATE PAID BY LWI IN CONNECTION WITH THE PRODUCTION OF PRODUCT UNDER THIS AGREEMENT; PROVIDED, HOWEVER, THAT ANY INCREASE IN LABOR RATES SHALL NOT EXCEED ANY PERCENTAGE INCREASE IN THE US CONSUMER PRICE INDEX FOR THE MOST RECENTLY PUBLISHED PERCENTAGE CHANGE FOR THE 12-MONTH PERIOD PRECEDING THE APPLICABLE CONTRACT ANNIVERSARY DATE. LWI AGREES TO PROVIDE CLIENT WITH WRITTEN NOTICE OF ANY SUCH COST ADJUSTMENT.

10. CONFIDENTIAL INFORMATION

10.1 DEFINITION . " **CONFIDENTIAL INFORMATION** " MEANS ALL TECHNICAL, SCIENTIFIC AND OTHER KNOW-HOW AND INFORMATION, TRADE SECRETS, KNOWLEDGE, TECHNOLOGY, MEANS, METHODS, PROCESSES, PRACTICES, FORMULAS, INSTRUCTIONS, SKILLS, TECHNIQUES, PROCEDURES, SPECIFICATIONS, DATA, RESULTS AND OTHER MATERIAL, PRE-CLINICAL AND CLINICAL TRIAL RESULTS, MANUFACTURING PROCEDURES, TEST PROCEDURES AND PURIFICATION AND ISOLATION TECHNIQUES, AND ANY TANGIBLE EMBODIMENTS OF ANY OF THE FOREGOING, AND ANY SCIENTIFIC, MANUFACTURING, MARKETING AND BUSINESS PLANS, ANY FINANCIAL AND PERSONNEL MATTERS RELATING TO A PARTY OR ITS PRESENT OR FUTURE PRODUCTS, SALES, SUPPLIERS, CUSTOMERS, EMPLOYEES, INVESTORS OR BUSINESS, THAT HAS BEEN DISCLOSED BY OR ON BEHALF OF SUCH PARTY TO THE OTHER PARTY EITHER IN CONNECTION WITH THE DISCUSSIONS AND NEGOTIATIONS PERTAINING TO THIS AGREEMENT OR IN THE COURSE OF PERFORMING THIS AGREEMENT. WITHOUT LIMITING THE FOREGOING, THE TERMS OF THIS AGREEMENT WILL BE DEEMED "CONFIDENTIAL INFORMATION" AND WILL BE SUBJECT TO THE TERMS AND CONDITIONS SET FORTH IN THIS ARTICLE 10

.

10.2 EXCLUSIONS . NOTWITHSTANDING THE FOREGOING SECTION 10.1

, ANY INFORMATION DISCLOSED BY A PARTY TO THE OTHER PARTY WILL NOT BE DEEMED "CONFIDENTIAL INFORMATION" TO THE EXTENT THAT SUCH INFORMATION:

(A) AT THE TIME OF DISCLOSURE IS IN THE PUBLIC DOMAIN;

(B) BECOMES PART OF THE PUBLIC DOMAIN, BY PUBLICATION OR OTHERWISE, THROUGH NO FAULT OF THE PARTY RECEIVING SUCH INFORMATION;

(C) AT THE TIME OF DISCLOSURE IS ALREADY IN POSSESSION OF THE PARTY WHO RECEIVED SUCH INFORMATION, AS ESTABLISHED BY CONTEMPORANEOUS WRITTEN RECORDS;

(D) IS LAWFULLY PROVIDED TO A PARTY, WITHOUT RESTRICTION AS TO CONFIDENTIALITY OR USE, BY A THIRD PARTY LAWFULLY ENTITLED TO POSSESSION OF SUCH CONFIDENTIAL INFORMATION; OR

(E) IS INDEPENDENTLY DEVELOPED BY A PARTY WITHOUT USE OF OR REFERENCE TO THE OTHER PARTY'S CONFIDENTIAL INFORMATION, AS ESTABLISHED BY CONTEMPORANEOUS WRITTEN RECORDS.

10.3 DISCLOSURE AND USE RESTRICTION . EXCEPT AS EXPRESSLY PROVIDED HEREIN, THE PARTIES AGREE THAT FOR THE TERM OF THE AGREEMENT AND THE FIVE-YEAR PERIOD FOLLOWING ANY TERMINATION OF THE AGREEMENT, EACH PARTY AND ITS AFFILIATES WILL KEEP COMPLETELY CONFIDENTIAL AND WILL NOT PUBLISH OR OTHERWISE DISCLOSE ANY CONFIDENTIAL INFORMATION OF THE OTHER PARTY, ITS AFFILIATES OR SUBLICENSEES, EXCEPT IN ACCORDANCE WITH SECTION 10.4. NEITHER PARTY WILL USE CONFIDENTIAL INFORMATION OF THE OTHER PARTY EXCEPT AS NECESSARY TO PERFORM ITS OBLIGATIONS OR TO EXERCISE ITS RIGHTS UNDER THIS AGREEMENT.

10.4 PERMITTED DISCLOSURES . EACH RECEIVING PARTY AGREES TO (I) INSTITUTE AND MAINTAIN SECURITY PROCEDURES TO IDENTIFY AND ACCOUNT FOR ALL COPIES OF CONFIDENTIAL INFORMATION OF THE DISCLOSING PARTY AND (II) LIMIT DISCLOSURE OF THE DISCLOSING PARTY'S CONFIDENTIAL INFORMATION TO ITS U.S. AND EUROPEAN AFFILIATES AND EACH OF ITS AND THEIR RESPECTIVE OFFICERS, DIRECTORS, EMPLOYEES, AGENTS, CONSULTANTS AND INDEPENDENT CONTRACTORS HAVING A NEED TO KNOW SUCH CONFIDENTIAL INFORMATION FOR PURPOSES OF THIS AGREEMENT; PROVIDED THAT SUCH U.S. AND EUROPEAN AFFILIATES AND EACH OF ITS AND THEIR RESPECTIVE OFFICERS, DIRECTORS, EMPLOYEES, AGENTS, CONSULTANTS AND INDEPENDENT CONTRACTORS ARE INFORMED OF THE TERMS OF THIS AGREEMENT AND ARE SUBJECT TO OBLIGATIONS OF CONFIDENTIALITY, NON-DISCLOSURE AND NON-USE SIMILAR TO THOSE SET FORTH HEREIN.

10.5 GOVERNMENT-REQUIRED DISCLOSURE . IF A DULY CONSTITUTED GOVERNMENT AUTHORITY, COURT OR REGULATORY AGENCY ORDERS THAT A PARTY HERETO DISCLOSE INFORMATION SUBJECT TO AN OBLIGATION OF CONFIDENTIALITY UNDER THIS AGREEMENT, SUCH PARTY SHALL COMPLY WITH THE ORDER, BUT SHALL NOTIFY THE OTHER PARTY AS SOON AS POSSIBLE, SO AS TO PROVIDE THE SAID PARTY AN OPPORTUNITY TO APPLY TO A COURT OF RECORD FOR RELIEF FROM THE ORDER.

10.6 PUBLICITY . NEITHER PARTY WILL REFER TO, DISPLAY OR USE THE OTHER'S NAME, TRADEMARKS OR TRADE NAMES CONFUSINGLY SIMILAR THERETO, ALONE OR IN CONJUNCTION WITH ANY OTHER WORDS OR NAMES, IN ANY MANNER OR CONNECTION WHATSOEVER, INCLUDING ANY PUBLICATION, ARTICLE, OR ANY FORM OF ADVERTISING OR PUBLICITY, EXCEPT WITH THE PRIOR WRITTEN CONSENT OF THE OTHER PARTY.

11. INTELLECTUAL PROPERTY

11.1 OWNERSHIP .

11.1.1 AS BETWEEN THE PARTIES, CLIENT SHALL OWN ANY AND ALL INVENTIONS OR DISCOVERIES THAT ARE (I) MADE, CONCEIVED OR REDUCED TO PRACTICE IN THE COURSE OF OR RESULTING FROM THIS AGREEMENT BY EITHER PARTY ALONE OR THE PARTIES JOINTLY AND (II) APPLICABLE SPECIFICALLY ONLY TO THE PRODUCT OR THE PROCESS (" **CLIENT NEW IP** "). LWI HEREBY ASSIGNS TO CLIENT ALL OF LWI'S RIGHT, TITLE AND INTEREST IN AND TO SUCH CLIENT NEW IP.

11.1.2 AS BETWEEN THE PARTIES, LWI SHALL OWN ANY AND ALL INVENTIONS OR DISCOVERIES THAT ARE (I) MADE, CONCEIVED OR REDUCED TO PRACTICE IN THE COURSE OF OR RESULTING FROM THIS AGREEMENT BY LWI AND (II) CAPABLE OF BEING APPLIED TO PRODUCTS OR PROCESSES OTHER THAN OR IN ADDITION TO THE PRODUCT OR THE PROCESS, AND (III) RELATES GENERALLY TO LWI'S BUSINESS OF PRODUCING BIOLOGICAL MATERIALS (" **LWI NEW IP** "). CLIENT HEREBY ASSIGNS TO LWI ALL OF CLIENT'S RIGHT, TITLE AND INTEREST IN AND TO SUCH LWI NEW IP.

11.2 LICENSE GRANTS .

11.2.1 DURING THE TERM OF THIS AGREEMENT, CLIENT HEREBY GRANTS TO LWI A FULLY PAID, NON-EXCLUSIVE LICENSE UNDER ANY AND ALL CLIENT INTELLECTUAL PROPERTY THAT IS NECESSARY FOR LWI TO PERFORM ITS OBLIGATIONS UNDER THIS AGREEMENT FOR THE SOLE AND LIMITED PURPOSE OF LWI'S PERFORMANCE OF ITS OBLIGATIONS UNDER THIS AGREEMENT, INCLUDING, WITHOUT LIMITATION, THE DEVELOPMENT OF THE PROCESS AND THE MANUFACTURE OF PRODUCT FOR CLIENT.

11.2.2 LWI HEREBY GRANTS TO CLIENT AN IRREVOCABLE, FULLY PAID, NON-EXCLUSIVE LICENSE, WITH THE RIGHT TO GRANT AND AUTHORIZE SUBLICENSES, UNDER ANY AND ALL (I) LWI INTELLECTUAL PROPERTY (INCLUDING LWI NEW IP) THAT LWI INCORPORATES INTO THE PROCESS, TO MAKE, HAVE MADE, USE, SELL, OFFER FOR SALE, HAVE SOLD AND IMPORT THE PRODUCT, AND (II) KNOW-HOW INCLUDED IN THE LWI NEW IP AND NOT CLAIMED IN A PATENT OR PATENT APPLICATION, TO USE FOR ANY PURPOSE.

11.3 FURTHER ASSURANCES . EACH PARTY AGREES TO TAKE ALL NECESSARY AND PROPER ACTS, AND WILL CAUSE ITS EMPLOYEES, AFFILIATES, CONTRACTORS, AND CONSULTANTS TO TAKE SUCH NECESSARY AND PROPER ACTS, TO EFFECTUATE THE OWNERSHIP PROVISIONS SET FORTH IN THIS ARTICLE 11.

11.4 PROSECUTION OF PATENTS .

11.4.1 LWI WILL HAVE THE SOLE RIGHT AND DISCRETION TO FILE, PROSECUTE AND MAINTAIN PATENT APPLICATIONS AND PATENTS CLAIMING LWI INVENTIONS AT LWI'S EXPENSE. CLIENT WILL COOPERATE WITH LWI TO FILE, PROSECUTE AND MAINTAIN PATENT APPLICATIONS AND PATENTS CLAIMING LWI INVENTIONS, AND WILL HAVE THE RIGHT TO REVIEW AND PROVIDE COMMENTS TO LWI RELATING TO SUCH PATENT APPLICATIONS AND PATENTS.

11.4.2 CLIENT WILL HAVE THE SOLE RIGHT AND DISCRETION TO FILE, PROSECUTE AND MAINTAIN PATENT APPLICATIONS AND PATENTS CLAIMING CLIENT INVENTIONS AT CLIENT'S EXPENSE. LWI WILL COOPERATE WITH CLIENT TO FILE, PROSECUTE AND MAINTAIN PATENT APPLICATIONS AND PATENTS CLAIMING CLIENT INVENTIONS, AND WILL HAVE THE RIGHT TO REVIEW AND PROVIDE COMMENTS TO CLIENT RELATING TO SUCH PATENT APPLICATIONS AND PATENTS.

12. REPRESENTATIONS AND WARRANTIES

12.1 BY CLIENT . CLIENT HEREBY REPRESENTS AND WARRANTS TO LWI THAT, TO THE BEST OF ITS KNOWLEDGE, (I) IT HAS THE REQUISITE INTELLECTUAL PROPERTY AND LEGAL RIGHTS RELATED TO THE CLIENT DELIVERABLES AND THE PRODUCT TO AUTHORIZE THE PERFORMANCE OF LWI'S OBLIGATIONS UNDER THIS AGREEMENT, AND (II) THE PERFORMANCE OF THE STATEMENT OF WORK AND THE PRODUCTION BY LWI OF THE PRODUCT AS CONTEMPLATED IN THIS AGREEMENT WILL NOT GIVE RISE TO A POTENTIAL CAUSE OF ACTION BY A THIRD PARTY AGAINST LWI FOR INFRINGEMENT OR ANOTHER VIOLATION OF INTELLECTUAL PROPERTY RIGHTS. SUCH REPRESENTATION AND WARRANTY WILL NOT APPLY TO ANY PRODUCTION EQUIPMENT SUPPLIED BY LWI.

12.2 BY LWI . LWI HEREBY REPRESENTS AND WARRANTS TO CLIENT THAT, TO THE BEST OF ITS KNOWLEDGE, (I) IT HAS THE REQUISITE INTELLECTUAL PROPERTY RIGHTS IN ITS EQUIPMENT AND FACILITY TO BE ABLE TO PERFORM ITS OBLIGATIONS UNDER THIS AGREEMENT, AND (II) THAT LWI'S USE OF ITS EQUIPMENT AND FACILITY AS CONTEMPLATED IN THIS AGREEMENT WILL NOT GIVE RISE TO A POTENTIAL CAUSE OF ACTION BY A THIRD PARTY AGAINST CLIENT FOR INFRINGEMENT OR ANOTHER VIOLATION OF INTELLECTUAL PROPERTY RIGHTS.

13. DISCLAIMER; LIMITATION OF LIABILITY

13.1 DISCLAIMER . EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS AGREEMENT, LWI MAKES NO REPRESENTATIONS AND GRANTS NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, WITH RESPECT TO THE PRODUCTS, MATERIALS, AND SERVICES PROVIDED UNDER THIS AGREEMENT, AND LWI SPECIFICALLY DISCLAIMS ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE WITH RESPECT TO SUCH PRODUCTS, MATERIALS, OR SERVICES.

13.2 DISCLAIMER OF CONSEQUENTIAL DAMAGES . IN NO EVENT SHALL EITHER PARTY BE LIABLE TO THE OTHER OR ANY OF ITS AFFILIATES FOR ANY CONSEQUENTIAL, INCIDENTAL, INDIRECT, SPECIAL, PUNITIVE OR EXEMPLARY DAMAGES (INCLUDING, WITHOUT LIMITATION, LOST PROFITS, BUSINESS OR GOODWILL) SUFFERED OR INCURRED BY SUCH OTHER PARTY OR ITS AFFILIATES IN CONNECTION WITH THIS AGREEMENT, EVEN IF ADVISED OF THE POSSIBILITY OF SUCH DAMAGES .

13.3 LIMITATION OF LIABILITY . BOTH PARTIES HEREBY AGREE THAT TO THE FULLEST EXTENT PERMITTED BY LAW, LWI'S LIABILITY TO CLIENT, FOR ANY AND ALL INJURIES, CLAIMS, LOSSES, EXPENSES, OR DAMAGES, WHATSOEVER, ARISING OUT OF OR IN ANY WAY RELATED TO THIS AGREEMENT FROM ANY CAUSE OR CAUSES, INCLUDING, BUT NOT LIMITED TO, NEGLIGENCE, ERRORS, OMISSIONS OR STRICT LIABILITY, SHALL NOT EXCEED THE TOTAL CHARGES PAID BY CLIENT TO LWI DURING THE 12 (TWELVE) MONTHS PRECEDING THE EVENT GIVING RISE TO LIABILITY. TO THE EXTENT THAT THIS CLAUSE CONFLICTS WITH ANY OTHER CLAUSE, THIS CLAUSE SHALL TAKE PRECEDENCE OVER SUCH CONFLICTING CLAUSE. IF APPLICABLE LAW PREVENTS ENFORCEMENT OF THIS CLAUSE, THEN THIS CLAUSE SHALL BE DEEMED MODIFIED TO PROVIDE THE MAXIMUM PROTECTION FOR LWI AS IS ALLOWABLE UNDER APPLICABLE LAW.

14. TERM AND TERMINATION

14.1 TERM . THE TERM OF THIS AGREEMENT WILL COMMENCE ON THE EFFECTIVE DATE AND WILL CONTINUE UNTIL THE FIFTH ANNIVERSARY OF THE EFFECTIVE DATE UNLESS TERMINATED PRIOR TO THAT TIME OR EXTENDED BY THE PARTIES.

14.2 TERMINATION FOR MATERIAL BREACH . EITHER PARTY MAY TERMINATE THIS AGREEMENT, BY WRITTEN NOTICE TO THE OTHER PARTY, FOR ANY MATERIAL BREACH OF THIS AGREEMENT BY THE OTHER PARTY, IF SUCH BREACH IS NOT CURED WITHIN THIRTY (30) DAYS AFTER THE BREACHING PARTY RECEIVES WRITTEN NOTICE OF SUCH BREACH FROM THE NON-BREACHING PARTY; PROVIDED, HOWEVER, THAT IF SUCH BREACH IS NOT CAPABLE OF BEING CURED WITHIN SUCH THIRTY-DAY PERIOD AND THE BREACHING PARTY HAS COMMENCED AND DILIGENTLY CONTINUED ACTIONS TO CURE SUCH BREACH WITHIN SUCH THIRTY-DAY PERIOD, EXCEPT IN THE CASE OF A PAYMENT DEFAULT, THE CURE PERIOD SHALL BE EXTENDED TO 180 DAYS, SO LONG AS THE BREACHING PARTY IS MAKING DILIGENT EFFORTS TO DO SO. SUCH TERMINATION SHALL BE EFFECTIVE UPON EXPIRATION OF SUCH CURE PERIOD.

14.3 TERMINATION BY NOTICE .

14.3.1 WITHOUT CAUSE . AFTER THE FIRST ANNIVERSARY OF THE EFFECTIVE DATE, EITHER PARTY MAY TERMINATE THIS AGREEMENT BY PROVIDING WRITTEN NOTICE OF TERMINATION NOT LESS THAN SIX MONTHS IN ADVANCE OF THE DATE OF TERMINATION. FOR THE AVOIDANCE OF DOUBT, IN THE EVENT OF TERMINATION BY CLIENT UNDER THIS SECTION 14.3.1, CLIENT SHALL, AT MINIMUM, REMAIN LIABLE FOR ALL FEES OWED PURSUANT TO ANY OUTSTANDING STATEMENT OF WORK DURING SUCH SIX-MONTH PERIOD.

14.3.2 TERMINATION OF CLINICAL TRIALS . EITHER PARTY MAY TERMINATE THIS AGREEMENT IF SUCH PARTY RECEIVES NOTICE THAT THE PRODUCTION OF PRODUCT HEREUNDER OR THE CLINICAL TRIALS FOR WHICH PRODUCT IS BEING PRODUCED HEREUNDER HAVE BEEN OR WILL BE SUSPENDED OR TERMINATED BY THE FDA (OR OTHER REGULATORY AUTHORITY) BY PROVIDING WRITTEN NOTICE OF TERMINATION NOT LESS THAN 2 MONTHS IN ADVANCE OF THE DATE OF TERMINATION. FOR THE AVOIDANCE OF DOUBT, IN THE EVENT OF TERMINATION BY CLIENT UNDER THIS SECTION 14.3.2, CLIENT SHALL, AT MINIMUM, REMAIN LIABLE FOR ALL FEES OWED PURSUANT TO ANY OUTSTANDING STATEMENT OF WORK DURING SUCH TWO-MONTH PERIOD.

14.4 TERMINATION BY INSOLVENCY . EITHER PARTY MAY TERMINATE THIS AGREEMENT UPON NOTICE TO THE OTHER PARTY, UPON (A) THE DISSOLUTION, TERMINATION OF EXISTENCE, LIQUIDATION OR BUSINESS FAILURE OF THE OTHER PARTY; (B) THE APPOINTMENT OF A CUSTODIAN OR RECEIVER FOR THE OTHER PARTY WHO HAS NOT BEEN TERMINATED OR DISMISSED WITHIN NINETY (90) DAYS OF SUCH APPOINTMENT; (C) THE INSTITUTION BY THE OTHER PARTY OF ANY PROCEEDING UNDER NATIONAL, FEDERAL OR STATE BANKRUPTCY, REORGANIZATION, RECEIVERSHIP OR OTHER SIMILAR LAWS AFFECTING THE RIGHTS OF CREDITORS GENERALLY OR THE MAKING BY SUCH PARTY OF A COMPOSITION OR ANY ASSIGNMENT FOR THE BENEFIT OF CREDITORS UNDER ANY NATIONAL, FEDERAL OR STATE BANKRUPTCY, REORGANIZATION, RECEIVERSHIP OR OTHER SIMILAR LAW AFFECTING THE RIGHTS OF CREDITORS GENERALLY, WHICH PROCEEDING IS NOT DISMISSED WITHIN NINETY (90) DAYS OF FILING. ALL RIGHTS AND LICENSES GRANTED PURSUANT TO THIS AGREEMENT ARE, AND SHALL OTHERWISE BE DEEMED TO BE, FOR PURPOSES OF SECTION 365(N) OF TITLE 11 OF THE UNITED STATES CODE, LICENSES OF RIGHTS OF “INTELLECTUAL PROPERTY” AS DEFINED THEREIN.

14.5 EFFECTS OF TERMINATION .

14.5.1 ACCRUED RIGHTS . TERMINATION OF THIS AGREEMENT FOR ANY REASON WILL BE WITHOUT PREJUDICE TO ANY RIGHTS THAT WILL HAVE ACCRUED TO THE BENEFIT OF A PARTY PRIOR TO SUCH TERMINATION. SUCH TERMINATION WILL NOT RELIEVE A PARTY OF OBLIGATIONS THAT ARE EXPRESSLY INDICATED TO SURVIVE THE TERMINATION OF THIS AGREEMENT.

14.5.2 DISPOSITION OF REMAINING CLIENT PROPERTY AND CONFIDENTIAL INFORMATION . UPON TERMINATION OR EXPIRATION OF THIS AGREEMENT, LWI WILL STORE ANY REMAINING CLIENT PROPERTY AS SET FORTH IN SECTION 7.2

AND, AT CLIENT'S OPTION, RETURN OR DESTROY ANY CLIENT CONFIDENTIAL INFORMATION IN THE POSSESSION OR CONTROL OF LWI. LIKEWISE, CLIENT WILL, AT LWI'S OPTION, RETURN OR DESTROY ANY LWI CONFIDENTIAL INFORMATION IN THE POSSESSION OR CONTROL OF CLIENT. NOTWITHSTANDING THE FOREGOING PROVISIONS: (I) LWI MAY RETAIN AND PRESERVE, AT ITS SOLE COST AND EXPENSE, SAMPLES AND STANDARDS OF EACH PRODUCT FOLLOWING TERMINATION OR EXPIRATION OF THIS AGREEMENT SOLELY FOR USE IN DETERMINING LWI'S RIGHTS AND OBLIGATIONS HEREUNDER; AND (II) EACH PARTY MAY RETAIN A SINGLE COPY OF THE OTHER PARTY'S CONFIDENTIAL INFORMATION FOR DOCUMENTATION PURPOSES ONLY AND WHICH SHALL REMAIN SUBJECT TO THE OBLIGATIONS OF NONUSE AND CONFIDENTIALITY SET FORTH IN THIS AGREEMENT.

14.5.3 SECURITY DEPOSITS . UPON ANY TERMINATION OF THIS AGREEMENT BY LWI PURSUANT TO SECTION 14.2, LWI WILL HAVE THE RIGHT TO RETAIN THE FULL AMOUNT OF ANY SECURITY DEPOSIT PAID TO LWI PURSUANT TO A STATEMENT OF WORK, WITHOUT LIMITING ANY OF ITS RIGHTS IN LAW OR IN EQUITY UNDER THIS AGREEMENT.

14.5.4 SURVIVAL . SECTIONS 1, 3.4, 4.9, 7.2, 10, 11, 13, 14.4, 15, 16 AND 17 OF THIS AGREEMENT, TOGETHER WITH ANY APPENDICES REFERENCED THEREIN, WILL SURVIVE ANY EXPIRATION OR TERMINATION OF THIS AGREEMENT.

15. INDEMNIFICATION

15.1 INDEMNIFICATION OF CLIENT . LWI WILL INDEMNIFY CLIENT, ITS AFFILIATES, AND THEIR RESPECTIVE DIRECTORS, OFFICERS, EMPLOYEES AND AGENTS, AND DEFEND AND HOLD EACH OF THEM HARMLESS, FROM AND AGAINST ANY AND ALL LOSSES, DAMAGES, LIABILITIES, COSTS AND EXPENSES (INCLUDING REASONABLE ATTORNEYS' FEES AND EXPENSES) IN CONNECTION WITH ANY AND ALL LIABILITY SUITS, INVESTIGATIONS, CLAIMS OR DEMANDS (COLLECTIVELY, " **LOSSES** ") TO THE EXTENT SUCH LOSSES ARISE OUT OF OR RESULT FROM ANY CLAIM, LAWSUIT OR OTHER ACTION OR THREAT BY A THIRD PARTY ARISING OUT OF: (A) ANY MATERIAL BREACH BY LWI OF THIS AGREEMENT, OR (B) THE GROSS NEGLIGENCE OR WILLFUL MISCONDUCT ON THE PART OF ONE OR MORE OF THE LWI PARTIES IN PERFORMING ANY ACTIVITY CONTEMPLATED BY THIS AGREEMENT, EXCEPT FOR THOSE LOSSES FOR WHICH CLIENT HAS AN OBLIGATION TO INDEMNIFY THE LWI PARTIES PURSUANT TO SECTION 15.2, AS TO WHICH LOSSES EACH PARTY WILL INDEMNIFY THE OTHER TO THE EXTENT OF THEIR RESPECTIVE LIABILITY FOR THE LOSSES.

15.2 INDEMNIFICATION OF LWI . CLIENT WILL INDEMNIFY LWI AND ITS AFFILIATES, AND THEIR RESPECTIVE DIRECTORS, OFFICERS, EMPLOYEES AND AGENTS (THE " **LWI PARTIES** "), AND DEFEND AND HOLD EACH OF THEM HARMLESS, FROM AND AGAINST ANY AND ALL LOSSES TO THE EXTENT SUCH LOSSES ARISE OUT OF OR RESULT FROM ANY CLAIM, LAWSUIT OR OTHER ACTION OR THREAT BY A THIRD PARTY ARISING OUT OF: (A) ANY MATERIAL BREACH BY CLIENT OF THIS AGREEMENT, (B) THE USE OR SALE OF PRODUCTS, EXCEPT TO THE EXTENT SUCH LOSSES ARISE OUT OF OR RESULT FROM A BREACH BY LWI OF THE PRODUCT WARRANTIES, (C) THE GROSS NEGLIGENCE OR WILLFUL MISCONDUCT ON THE PART OF CLIENT OR ITS AFFILIATES IN PERFORMING ANY ACTIVITY CONTEMPLATED BY THIS AGREEMENT, OR (D) THE USE OR PRACTICE BY LWI OF ANY PROCESS, INVENTION OR OTHER INTELLECTUAL PROPERTY SUPPLIED BY CLIENT TO LWI UNDER THIS AGREEMENT, EXCEPT FOR THOSE LOSSES FOR WHICH LWI HAS AN OBLIGATION TO INDEMNIFY CLIENT PURSUANT TO SECTION 15.1, AS TO WHICH LOSSES EACH PARTY WILL INDEMNIFY THE OTHER TO THE EXTENT OF THEIR RESPECTIVE LIABILITY FOR THE LOSSES.

15.3 INDEMNIFICATION PROCEDURE .

15.3.1 AN " **INDEMNITOR** " MEANS THE INDEMNIFYING PARTY. AN " **INDEMNITEE** " MEANS THE INDEMNIFIED PARTY, ITS AFFILIATES, AND THEIR RESPECTIVE DIRECTORS, OFFICERS, EMPLOYEES AND AGENTS.

15.3.2 AN INDEMNITEE WHICH INTENDS TO CLAIM INDEMNIFICATION UNDER SECTION 15.1 OR SECTION 15.2 HEREOF SHALL PROMPTLY NOTIFY THE INDEMNITOR IN WRITING OF ANY CLAIM, LAWSUIT OR OTHER ACTION IN RESPECT OF WHICH THE INDEMNITEE, ITS AFFILIATES, OR ANY OF THEIR RESPECTIVE DIRECTORS, OFFICERS, EMPLOYEES AND AGENTS INTEND TO CLAIM SUCH INDEMNIFICATION. THE INDEMNITEE SHALL PERMIT, AND SHALL CAUSE ITS AFFILIATES AND THEIR RESPECTIVE DIRECTORS, OFFICERS, EMPLOYEES AND AGENTS TO PERMIT, THE INDEMNITOR, AT ITS DISCRETION, TO SETTLE ANY SUCH CLAIM, LAWSUIT OR OTHER ACTION AND AGREES TO THE COMPLETE CONTROL OF SUCH DEFENSE OR SETTLEMENT BY THE INDEMNITOR; PROVIDED, HOWEVER, THAT IN ORDER FOR THE INDEMNITOR TO EXERCISE SUCH RIGHTS, SUCH SETTLEMENT SHALL NOT ADVERSELY AFFECT THE INDEMNITEE'S RIGHTS UNDER THIS AGREEMENT OR IMPOSE ANY OBLIGATIONS ON THE INDEMNITEE IN ADDITION TO THOSE SET FORTH HEREIN. NO SUCH CLAIM, LAWSUIT OR OTHER ACTION SHALL BE SETTLED WITHOUT THE PRIOR WRITTEN CONSENT OF THE INDEMNITOR AND THE INDEMNITOR SHALL NOT BE RESPONSIBLE FOR ANY LEGAL FEES OR OTHER COSTS INCURRED OTHER THAN AS PROVIDED HEREIN. THE INDEMNITEE, ITS AFFILIATES AND THEIR RESPECTIVE DIRECTORS, OFFICERS, EMPLOYEES AND AGENTS SHALL COOPERATE FULLY WITH THE INDEMNITOR AND ITS LEGAL REPRESENTATIVES IN THE INVESTIGATION AND DEFENSE OF ANY CLAIM, LAWSUIT OR OTHER ACTION COVERED BY THIS INDEMNIFICATION, ALL AT THE REASONABLE EXPENSE OF THE INDEMNITOR. THE INDEMNITEE SHALL HAVE THE RIGHT, BUT NOT THE OBLIGATION, TO BE REPRESENTED BY COUNSEL OF ITS OWN SELECTION AND EXPENSE.

15.4 INSURANCE . CLIENT WILL MAINTAIN, AT ALL TIMES DURING THE TERM OF THIS AGREEMENT AND FOR FIVE YEARS THEREAFTER, A PRODUCTS LIABILITY INSURANCE POLICY (THE " **INSURANCE POLICY** "), WITH A PER OCCURRENCE LIMIT OF AT LEAST FIVE MILLION DOLLARS ($5,000,000) AND AN AGGREGATE LIMIT OF AT LEAST FIVE MILLION DOLLARS ($5,000,000), AND WILL PROVIDE A CERTIFICATE OF INSURANCE TO LWI THAT THE INSURANCE POLICY HAS BEEN ENDORSED TO DESIGNATE LWI AS AN ADDITIONAL INSURED. CLIENT WILL MAINTAIN THE INSURANCE POLICY WITH AN INSURANCE COMPANY HAVING A MINIMUM AM BEST RATING OF A AND THAT IS LICENSED TO DO BUSINESS IN THE STATE OF MARYLAND. CLIENT WILL PROVIDE LWI WITH AT LEAST 30 DAYS' WRITTEN NOTICE PRIOR TO TERMINATION OF SUCH INSURANCE POLICY.

16. ADDITIONAL COVENANTS

16.1 NON-SOLICITATION . DURING THE TERM OF THIS AGREEMENT AND FOR TWO (2) YEARS THEREAFTER, EACH OF THE PARTIES AGREES NOT TO SEEK TO INDUCE OR SOLICIT ANY EMPLOYEE OF THE OTHER PARTY OR ITS AFFILIATES TO DISCONTINUE HIS OR HER EMPLOYMENT WITH THE OTHER PARTY OR ITS AFFILIATE IN ORDER TO BECOME AN EMPLOYEE OR AN INDEPENDENT CONTRACTOR OF THE SOLICITING PARTY OR ITS AFFILIATE; PROVIDED, HOWEVER, THAT NEITHER PARTY SHALL BE IN VIOLATION OF THIS SECTION 16.1 AS A RESULT OF MAKING A GENERAL SOLICITATION FOR EMPLOYEES OR INDEPENDENT CONTRACTORS. FOR THE AVOIDANCE OF DOUBT, THE PUBLICATION OF AN ADVERTISEMENT SHALL NOT CONSTITUTE SOLICITATION OR INDUCEMENT.

16.2 COMMERCIAL SCALE MANUFACTURE . IN THE EVENT THAT CLIENT DESIRES TO COMMENCE COMMERCIAL SCALE MANUFACTURE OF PRODUCT, THE PARTIES AGREE TO NEGOTIATE FOR THE PROVISION OF SUCH MANUFACTURING SERVICES TO CLIENT BY LWI.

17. MISCELLANEOUS

17.1 INDEPENDENT CONTRACTORS . EACH OF THE PARTIES IS AN INDEPENDENT CONTRACTOR AND NOTHING HEREIN CONTAINED SHALL BE DEEMED TO CONSTITUTE THE RELATIONSHIP OF PARTNERS, JOINT VENTURERS, NOR OF PRINCIPAL AND AGENT BETWEEN THE PARTIES. NEITHER PARTY SHALL AT ANY TIME ENTER INTO, INCUR, OR HOLD ITSELF OUT TO THIRD PARTIES AS HAVING AUTHORITY TO ENTER INTO OR INCUR, ON BEHALF OF THE OTHER PARTY, ANY COMMITMENT, EXPENSE, OR LIABILITY WHATSOEVER.

17.2 FORCE MAJEURE . NEITHER PARTY SHALL BE IN BREACH OF THIS AGREEMENT IF THERE IS ANY FAILURE OF PERFORMANCE UNDER THIS AGREEMENT (EXCEPT FOR PAYMENT OF ANY AMOUNTS DUE UNDER THIS AGREEMENT) OCCASIONED BY ANY REASON BEYOND THE CONTROL AND WITHOUT THE FAULT OR NEGLIGENCE OF THE PARTY AFFECTED THEREBY, INCLUDING, WITHOUT LIMITATION, AN ACT OF GOD, FIRE, FLOOD, ACT OF GOVERNMENT OR STATE, WAR, CIVIL COMMOTION, INSURRECTION, ACTS OF TERRORISM, EMBARGO, SABOTAGE, A VIRAL, BACTERIAL OR MYCOPLASMAL CONTAMINATION WHICH CAUSES A SHUTDOWN OF THE FACILITY, PREVENTION FROM OR HINDRANCE IN OBTAINING ENERGY OR OTHER UTILITIES, A SHORTAGE OF RAW MATERIALS OR OTHER NECESSARY COMPONENTS, LABOR DISPUTES OF WHATEVER NATURE, OR ANY OTHER REASON BEYOND THE CONTROL AND WITHOUT THE FAULT OR NEGLIGENCE OF THE PARTY AFFECTED THEREBY (A " **FORCE MAJEURE EVENT** "). SUCH EXCUSE SHALL CONTINUE AS LONG AS THE FORCE MAJEURE EVENT CONTINUES. UPON CESSATION OF SUCH FORCE MAJEURE EVENT, THE AFFECTED PARTY SHALL PROMPTLY RESUME PERFORMANCE UNDER THIS AGREEMENT AS SOON AS IT IS COMMERCIALLY REASONABLE FOR THE PARTY TO DO SO. EACH PARTY AGREES TO GIVE THE OTHER PARTY PROMPT WRITTEN NOTICE OF THE OCCURRENCE OF ANY FORCE MAJEURE EVENT, THE NATURE THEREOF, AND THE EXTENT TO WHICH THE AFFECTED PARTY WILL BE UNABLE TO FULLY PERFORM ITS OBLIGATIONS UNDER THIS AGREEMENT. EACH PARTY FURTHER AGREES TO USE COMMERCIALLY REASONABLE EFFORTS TO CORRECT THE FORCE MAJEURE EVENT AS QUICKLY AS PRACTICABLE (PROVIDED THAT IN NO EVENT SHALL A PARTY BE REQUIRED TO SETTLE ANY LABOR DISPUTE) AND TO GIVE THE OTHER PARTY PROMPT WRITTEN NOTICE WHEN IT IS AGAIN FULLY ABLE TO PERFORM SUCH OBLIGATIONS.

17.3 CONDEMNATION . IF THE FACILITY IS CONDEMNED OR TAKEN AS A RESULT OF THE EXERCISE OF THE POWER OF EMINENT DOMAIN OR WILL BE CONVEYED TO A GOVERNMENTAL AGENCY HAVING POWER OF EMINENT DOMAIN UNDER THE THREAT OF THE EXERCISE OF SUCH POWER (ANY OF THE FOREGOING, A " **CONDEMNATION** "), THEN THIS AGREEMENT WILL TERMINATE AS OF THE DATE ON WHICH TITLE TO THE FACILITY VESTS IN THE AUTHORITY SO EXERCISING OR THREATENING TO EXERCISE SUCH POWER AND CLIENT WILL NOT HAVE ANY RIGHT TO THE CONDEMNATION PROCEEDS.

17.4 NOTICES . ANY NOTICE REQUIRED OR PERMITTED TO BE GIVEN UNDER THIS AGREEMENT BY ANY PARTY SHALL BE IN WRITING AND SHALL BE (A) DELIVERED PERSONALLY, (B) SENT BY REGISTERED MAIL, RETURN RECEIPT REQUESTED, POSTAGE PREPAID, (C) SENT BY A NATIONALLY-RECOGNIZED COURIER SERVICE GUARANTEEING NEXT-DAY OR SECOND DAY DELIVERY, CHARGES PREPAID, OR (D) DELIVERED BY FACSIMILE (WITH DOCUMENTED EVIDENCE OF TRANSMISSION), TO THE ADDRESSES OR FACSIMILE NUMBERS OF THE OTHER PARTY SET FORTH BELOW, OR AT SUCH OTHER ADDRESSES AS MAY FROM TIME TO TIME BE FURNISHED BY SIMILAR NOTICE BY ANY PARTY. THE EFFECTIVE DATE OF ANY NOTICE UNDER THIS AGREEMENT SHALL BE THE DATE OF RECEIPT BY THE RECEIVING PARTY.

IF TO LWI :
LONZA WALKERSVILLE, INC.
ATTN: VICE PRESIDENT, CELL THERAPY BIOSERVICE
8830 BIGGS FORD ROAD
WALKERSVILLE, MARYLAND 21793
FAX: (301) 845-6099

WITH A COPY TO:
ASSISTANT GENERAL COUNSEL
LONZA AMERICA, INC.
90 BOROLINE ROAD
ALLENDALE, NJ 07401
FAX: (201) 696-3589

IF TO CLIENT :
<INSERT FULL LEGAL NAME OF CLIENT COMPANY>
ATTN: <INSERT APPROPRIATE NAME>
<INSERT STREET ADDRESS>
<INSERT CITY, STATE AND ZIP CODE>
FAX: <INSERT FAX NUMBER>

EITHER PARTY MAY CHANGE ITS ADDRESS FOR NOTICE BY GIVING NOTICE THEREOF IN THE MANNER SET FORTH IN THIS SECTION 17.4.

17.5 ENTIRE AGREEMENT; AMENDMENTS . THIS AGREEMENT, INCLUDING THE APPENDICES ATTACHED HERETO AND REFERENCED HEREIN, CONSTITUTES THE FULL UNDERSTANDING OF THE PARTIES AND A COMPLETE AND EXCLUSIVE STATEMENT OF THE TERMS OF THEIR AGREEMENT WITH RESPECT TO THE SPECIFIC SUBJECT MATTER HEREOF AND SUPERSEDES ALL PRIOR AGREEMENTS AND UNDERSTANDINGS, ORAL AND WRITTEN, AMONG THE PARTIES WITH RESPECT TO THE SUBJECT MATTER HEREOF. NO TERMS, CONDITIONS, UNDERSTANDINGS OR AGREEMENTS PURPORTING TO AMEND, MODIFY OR VARY THE TERMS OF THIS AGREEMENT (INCLUDING ANY APPENDIX HERETO) SHALL BE BINDING UNLESS HEREAFTER MADE IN A WRITTEN INSTRUMENT REFERENCING THIS AGREEMENT AND SIGNED BY EACH OF THE PARTIES.

17.6 GOVERNING LAW . THIS AGREEMENT WILL BE GOVERNED BY AND CONSTRUED IN ACCORDANCE WITH THE INTERNAL LAWS OF THE STATE OF DELAWARE, WITHOUT GIVING EFFECT TO ITS CONFLICTS OF LAWS PROVISIONS.

17.7 COUNTERPARTS . THIS AGREEMENT AND ANY AMENDMENT HERETO MAY BE EXECUTED IN ANY NUMBER OF COUNTERPARTS, EACH OF WHICH SHALL FOR ALL PURPOSES BE DEEMED AN ORIGINAL AND ALL OF WHICH SHALL CONSTITUTE THE SAME INSTRUMENT. THIS AGREEMENT SHALL BE EFFECTIVE UPON FULL EXECUTION BY FACSIMILE OR ORIGINAL, AND A FACSIMILE SIGNATURE SHALL BE DEEMED TO BE AND SHALL BE AS EFFECTIVE AS AN ORIGINAL SIGNATURE.

17.8 SEVERABILITY . IF ANY PART OF THIS AGREEMENT SHALL BE FOUND TO BE INVALID OR UNENFORCEABLE UNDER APPLICABLE LAW IN ANY JURISDICTION, SUCH PART SHALL BE INEFFECTIVE ONLY TO THE EXTENT OF SUCH INVALIDITY OR UNENFORCEABILITY IN SUCH JURISDICTION, WITHOUT IN ANY WAY AFFECTING THE REMAINING PARTS OF THIS AGREEMENT IN THAT JURISDICTION OR THE VALIDITY OR ENFORCEABILITY OF THE AGREEMENT AS A WHOLE IN ANY OTHER JURISDICTION. IN ADDITION, THE PART THAT IS INEFFECTIVE SHALL BE REFORMED IN A MUTUALLY AGREEABLE MANNER SO AS TO AS NEARLY APPROXIMATE THE INTENT OF THE PARTIES AS POSSIBLE.

17.9 TITLES AND SUBTITLES . ALL HEADINGS, TITLES AND SUBTITLES USED IN THIS AGREEMENT (INCLUDING ANY APPENDIX HERETO) ARE FOR CONVENIENCE ONLY AND ARE NOT TO BE CONSIDERED IN CONSTRUING OR INTERPRETING ANY TERM OR PROVISION OF THIS AGREEMENT (OR ANY APPENDIX HERETO).

17.10 EXHIBITS . ALL "RECITALS", "DEFINITIONS", EXHIBITS AND APPENDICES REFERRED TO HEREIN FORM AN INTEGRAL PART OF THIS AGREEMENT AND ARE INCORPORATED INTO THIS AGREEMENT BY SUCH REFERENCE.

17.11 PRONOUNS . WHERE THE CONTEXT REQUIRES, (I) ALL PRONOUNS USED HEREIN WILL BE DEEMED TO REFER TO THE MASCULINE, FEMININE OR NEUTER GENDER AS THE CONTEXT REQUIRES, AND (II) THE SINGULAR CONTEXT WILL INCLUDE THE PLURAL AND VICE VERSA.

17.12 ASSIGNMENT . THIS AGREEMENT SHALL BE BINDING UPON THE SUCCESSORS AND ASSIGNS OF THE PARTIES AND THE NAME OF A PARTY APPEARING HEREIN SHALL BE DEEMED TO INCLUDE THE NAMES OF ITS SUCCESSORS AND ASSIGNS. NEITHER PARTY MAY ASSIGN ITS INTEREST UNDER THIS AGREEMENT WITHOUT THE PRIOR WRITTEN CONSENT OF THE OTHER PARTY, SUCH CONSENT NOT TO BE UNREASONABLY WITHHELD. ANY PERMITTED ASSIGNMENT OF THIS AGREEMENT BY EITHER PARTY WILL BE CONDITIONED UPON THAT PARTY'S PERMITTED ASSIGNEE AGREEING IN WRITING TO COMPLY WITH ALL THE TERMS AND CONDITIONS CONTAINED IN THIS AGREEMENT. ANY PURPORTED ASSIGNMENT WITHOUT A REQUIRED CONSENT SHALL BE VOID. NO ASSIGNMENT SHALL RELIEVE ANY PARTY OF RESPONSIBILITY FOR THE PERFORMANCE OF ANY OBLIGATION THAT ACCRUED PRIOR TO THE EFFECTIVE DATE OF SUCH ASSIGNMENT.

17.13 WAIVER . THE FAILURE OF ANY PARTY AT ANY TIME OR TIMES TO REQUIRE PERFORMANCE OF ANY PROVISION OF THIS AGREEMENT (INCLUDING ANY APPENDIX HERETO) WILL IN NO MANNER AFFECT ITS RIGHTS AT A LATER TIME TO ENFORCE THE SAME. NO WAIVER BY ANY PARTY OF ANY TERM, PROVISION OR CONDITION CONTAINED IN THIS AGREEMENT (INCLUDING ANY APPENDIX HERETO), WHETHER BY CONDUCT OR OTHERWISE, IN ANY ONE OR MORE INSTANCES, SHALL BE DEEMED TO BE OR CONSTRUED AS A FURTHER OR CONTINUING WAIVER OF ANY SUCH TERM, PROVISION OR CONDITION OR OF ANY OTHER TERM, PROVISION OR CONDITION OF THIS AGREEMENT (INCLUDING ANY APPENDIX HERETO).

17.14 DISPUTE RESOLUTION . IF THE PARTIES ARE UNABLE TO RESOLVE A DISPUTE, DESPITE ITS GOOD FAITH EFFORTS, EITHER PARTY MAY REFER THE DISPUTE TO THE CHIEF EXECUTIVE OFFICER (OR OTHER DESIGNEE) OF EACH PARTY. IN THE EVENT THAT NO AGREEMENT IS REACHED BY THE CHIEF EXECUTIVE OFFICERS (OR OTHER DESIGNEES) WITH RESPECT TO SUCH DISPUTE WITHIN THIRTY (30) DAYS AFTER ITS REFERRAL TO THEM, EITHER PARTY MAY PURSUE ANY AND ALL REMEDIES AVAILABLE AT LAW OR IN EQUITY.

17.15 NO PRESUMPTION AGAINST DRAFTER . FOR PURPOSES OF THIS AGREEMENT, CLIENT HEREBY WAIVES ANY RULE OF CONSTRUCTION THAT REQUIRES THAT AMBIGUITIES IN THIS AGREEMENT (INCLUDING ANY APPENDIX HERETO) BE CONSTRUED AGAINST THE DRAFTER.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, THE PARTIES HAVE EXECUTED THIS AGREEMENT AS OF THE DATE LAST SIGNED BY THE PARTIES HERETO.

	[INSERT NAME OF CLIENT]
Date	By: Name: Title:
	LONZA WALKERSVILLE, INC.
Date	By: Name: Title:

APPENDIX A
STATEMENT OF WORK

TO BE ATTACHED

APPENDIX B
QUALITY AGREEMENT

TO BE ATTACHED

EXHIBIT J – STOCK PURCHASE AGREEMENT

STOCK PURCHASE AGREEMENT
DATED AS OF [_____]
BETWEEN
REGENICIN , INC.
[“PURCHASER”]
AND
LONZA WALKERSVILLE, INC.
[“COMPANY”]
WITH RESPECT TO ALL OUTSTANDING CAPITAL STOCK OF THE
CUTANOGEN CORPORATION
(“CUTANOGEN”)

STOCK PURCHASE AGREEMENT

THIS STOCK PURCHASE AGREEMENT, DATED AS OF [_____] (THIS " AGREEMENT "), IS BETWEEN REGENICIN, INC., A NEVADA CORPORATION (" PURCHASER "), AND LONZA WALKERSVILLE, INC., A DELAWARE CORPORATION (THE " COMPANY "). CERTAIN TERMS USED IN THIS AGREEMENT WITHOUT DEFINITION SHALL HAVE THEIR MEANINGS AS DEFINED IN SECTION 8.11 .

W I T N E S S E T H :

WHEREAS, THE COMPANY OWNS ALL OF THE ISSUED AND OUTSTANDING CAPITAL STOCK OF CUTANOGEN (REFERRED TO HEREIN AS THE " CUTANOGEN SHARES ");

WHEREAS, CUTANOGEN IS ENGAGED IN THE RESEARCH AND DEVELOPMENT OF PRODUCTS USED IN THE LIFE SCIENCES INDUSTRY (“CUTANOGEN BUSINESS”);

WHEREAS, THE PARTIES HAVE ENTERED INTO A KNOW-HOW LICENSE AND STOCK PURCHASE AGREEMENT, DATED JUNE 30, 2009 (THE “LICENSE AND SPA”);

WHEREAS, UPON THE OCCURRENCE OF CERTAIN EVENTS DELINEATED IN THE LICENSE AND SPA, THE COMPANY DESIRES TO SELL, AND PURCHASER DESIRES TO PURCHASE, THE CUTANOGEN SHARES ON THE TERMS AND SUBJECT TO THE CONDITIONS SET FORTH IN THIS AGREEMENT;

NOW, THEREFORE, IN CONSIDERATION OF THE REPRESENTATIONS, WARRANTIES, COVENANTS AND AGREEMENTS CONTAINED IN THIS AGREEMENT, AND INTENDING TO BE LEGALLY BOUND HEREBY, PURCHASER AND THE COMPANY HEREBY AGREE AS FOLLOWS:

ARTICLE I
SALE OF SHARES AND CLOSING

SECTION 1.1 PURCHASE AND SALE

. THE COMPANY AGREES TO SELL TO PURCHASER, AND PURCHASER AGREES TO PURCHASE FROM THE COMPANY, ALL OF THE RIGHT, TITLE AND INTEREST OF THE COMPANY IN AND TO THE CUTANOGEN SHARES AT THE CLOSING ON THE TERMS AND SUBJECT TO THE CONDITIONS SET FORTH IN THIS AGREEMENT.

(B) COMPANY ACKNOWLEDGES RECEIPT OF TWO MILLION DOLLARS ($2,000,000) FROM PURCHASER AS THE AGGREGATE PURCHASE PRICE FOR THE CUTANOGEN SHARES IN ACCORDANCE WITH PARAGRAPH 6.2 OF THE LICENSE AND SPA, TO WHICH THIS AGREEMENT IS ATTACHED. THE PARTIES AGREE THAT (I) COMPANY WILL RETAIN THE EXCLUSIVE RIGHT TO MANUFACTURE THE PERMADERM PRODUCT LINE AT A CUSTOMARY MARGIN LEVEL AS MORE DEFINITIVELY SET FORTH IN THE FORM OF AGREEMENT (“ MANUFACTURING AGREEMENT ”) ATTACHED HERETO AS EXHIBIT 1.2B AND PURCHASER WILL BE RESPONSIBLE FOR GAINING REGULATORY APPROVAL OF PERMADERM AND ALL ASSOCIATED EXPENSES INCLUDING THOSE WHICH COMPANY MIGHT INCUR UNDER THE MANUFACTURING AGREEMENT; AND (II) IN ADDITION, COMPANY WILL RETAIN THE DISTRIBUTION RIGHTS FOR THE COLLAGEN SPONGE, WHICH IS THE TISSUE ENGINEERED MATRIX OF PERMADERM. UNDER SUCH DISTRIBUTION AGREEMENT COMPANY WILL KEEP 15% OF THE COLLAGEN SPONGE SALE PRICE AS A LOGISTICS/DISTRIBUTION FEE. ADDITIONALLY, ANY REMAINING PROFIT FROM THE SALE OF THE SPONGE TO A THIRD PARTY WILL BE SPLIT EQUALLY BETWEEN THE PARTIES. THE DISTRIBUTION AGREEMENT WILL CONTAIN A LIST OF THOSE ENTITIES WHICH WILL NOT BE INCLUDED AS PART OF ITS DISTRIBUTION RIGHTS. NOTWITHSTANDING THE ABOVE, IN ORDER TO EFFECTUATE THESE RIGHTS TO BE RETAINED BY COMPANY, PURCHASER WILL PROVIDE COMPANY WITH A WORLDWIDE, TRANSFERABLE, NON-REVOCABLE LICENSE ENABLING COMPANY TO PERFORM SUCH TASKS.

SECTION 1.2 CLOSING

. THE CLOSING OF THE PURCHASE AND SALE OF THE CUTANOGEN SHARES PURSUANT TO THIS AGREEMENT (THE " CLOSING ") SHALL TAKE PLACE AT 10:00 A.M. (NEW YORK TIME) ON A DATE TO BE SPECIFIED BY THE PARTIES (THE " CLOSING DATE "), WHICH DATE SHALL BE NO LATER THAN THE SECOND (2 ND) BUSINESS DAY AFTER THE ACHIEVEMENT OF CERTAIN MILESTONES INCLUDED IN THE LICENSE AND SPA AND SATISFACTION OR WAIVER OF THE CONDITIONS SET FORTH IN ARTICLE V (OTHER THAN THOSE CONDITIONS THAT BY THEIR NATURE ARE TO BE SATISFIED AT THE CLOSING, BUT SUBJECT TO THE SATISFACTION OR WAIVER OF THOSE CONDITIONS AT SUCH TIME), AT THE OFFICES OF LONZA INC., 90 BOROLINE ROAD, ALLENDALE, NJ 07401, UNLESS ANOTHER TIME, DATE OR PLACE IS AGREED TO IN WRITING BY THE PARTIES HERETO. AT THE CLOSING, THE COMPANY WILL ASSIGN AND TRANSFER TO PURCHASER ALL OF COMPANY'S RIGHT, TITLE AND INTEREST IN AND TO THE CUTANOGEN SHARES BY DELIVERING TO PURCHASER CERTIFICATES REPRESENTING THE CUTANOGEN SHARES, IN GENUINE AND UNALTERED FORM, DULY ENDORSED IN BLANK OR ACCOMPANIED BY DULY EXECUTED STOCK POWERS ENDORSED IN BLANK, WITH REQUISITE STOCK TRANSFER TAX STAMPS, IF ANY, ATTACHED. AT THE CLOSING, THERE SHALL ALSO BE DELIVERED TO THE COMPANY AND PURCHASER THE CERTIFICATES AND OTHER INSTRUMENTS TO BE DELIVERED UNDER ARTICLE V .

SECTION 1.3 FURTHER ASSURANCES; POST-CLOSING COOPERATION

.

(A) SUBJECT TO THE TERMS AND CONDITIONS OF THIS AGREEMENT, AT ANY TIME OR FROM TIME TO TIME AFTER THE CLOSING, EACH OF THE PARTIES HERETO SHALL EXECUTE AND DELIVER SUCH OTHER DOCUMENTS AND INSTRUMENTS, PROVIDE SUCH MATERIALS AND INFORMATION AND TAKE SUCH OTHER ACTIONS AS MAY REASONABLY BE NECESSARY, PROPER OR ADVISABLE, TO THE EXTENT PERMITTED BY LAW, TO FULFILL ITS OBLIGATIONS UNDER THIS AGREEMENT.

(B) FOLLOWING THE CLOSING, EACH PARTY WILL AFFORD THE OTHER PARTY, ITS COUNSEL AND ITS ACCOUNTANTS, DURING NORMAL BUSINESS HOURS, REASONABLE ACCESS TO THE BOOKS, RECORDS, PERSONNEL FILES, PAYROLL FILES AND OTHER DATA RELATING TO THE CUTANOGEN BUSINESS IN ITS POSSESSION WITH RESPECT TO PERIODS PRIOR TO THE CLOSING AND THE RIGHT TO MAKE COPIES AND EXTRACTS THEREFROM, TO THE EXTENT THAT SUCH ACCESS MAY BE REASONABLY REQUIRED BY THE REQUESTING PARTY IN CONNECTION WITH (I) THE PREPARATION OF TAX RETURNS, (II) THE DETERMINATION OR ENFORCEMENT OF RIGHTS AND OBLIGATIONS UNDER THIS AGREEMENT, (III) COMPLIANCE WITH THE REQUIREMENTS OF ANY GOVERNMENTAL AUTHORITY, (IV) IN CONNECTION WITH ANY ACTUAL OR THREATENED ACTION OR PROCEEDING OR (V) THE DETERMINATION OF PENSION OR OTHER BENEFITS. FURTHER, EACH PARTY AGREES FOR A PERIOD EXTENDING SIX (6) YEARS AFTER THE CLOSING DATE NOT TO DESTROY OR OTHERWISE DISPOSE OF ANY SUCH BOOKS, RECORDS, PERSONNEL FILES, PAYROLL FILES AND OTHER DATA UNLESS SUCH PARTY SHALL FIRST OFFER IN WRITING TO SURRENDER SUCH BOOKS, RECORDS, PERSONNEL FILES, PAYROLL FILES AND OTHER DATA TO THE OTHER PARTY AND SUCH OTHER PARTY SHALL NOT AGREE IN WRITING TO TAKE POSSESSION THEREOF DURING THE SIXTY (60) DAY PERIOD AFTER SUCH OFFER IS MADE.

(C) IF, IN ORDER PROPERLY TO PREPARE ITS TAX RETURNS, OTHER DOCUMENTS OR REPORTS REQUIRED TO BE FILED WITH GOVERNMENTAL AUTHORITIES OR ITS FINANCIAL STATEMENTS OR TO FULFILL ITS OBLIGATIONS HEREUNDER, IT IS NECESSARY THAT A PARTY BE FURNISHED WITH ADDITIONAL INFORMATION, DOCUMENTS OR RECORDS RELATING TO THE CUTANOGEN BUSINESS NOT REFERRED TO IN PARAGRAPH (B) ABOVE, AND SUCH INFORMATION, DOCUMENTS OR RECORDS ARE IN POSSESSION OR CONTROL OF THE OTHER PARTY, SUCH OTHER PARTY AGREES TO USE ITS REASONABLE BEST EFFORTS TO FURNISH OR MAKE AVAILABLE SUCH INFORMATION, DOCUMENTS OR RECORDS (OR COPIES THEREOF) AT THE RECIPIENT'S REQUEST, COST AND EXPENSE.

(D) NOTWITHSTANDING ANYTHING TO THE CONTRARY CONTAINED IN THIS SECTION, IF THE PARTIES ARE IN AN ADVERSARIAL RELATIONSHIP IN LITIGATION OR ARBITRATION, THE FURNISHING OF INFORMATION, DOCUMENTS OR RECORDS IN ACCORDANCE WITH ANY PROVISION OF THIS SECTION 1.4 SHALL BE SUBJECT TO APPLICABLE RULES RELATING TO DISCOVERY.

ARTICLE II
REPRESENTATIONS AND WARRANTIES OF THE COMPANY

THE COMPANY REPRESENTS AND WARRANTS TO PURCHASER THAT:

SECTION 2.1 ORGANIZATION AND STANDING

.

(A) COMPANY IS A CORPORATION OR OTHER ORGANIZATION VALIDLY EXISTING AND IN GOOD STANDING UNDER THE LAWS OF ITS JURISDICTION OF INCORPORATION OR ORGANIZATION. COMPANY IS DULY LICENSED OR QUALIFIED TO DO BUSINESS AND IS IN GOOD STANDING IN EACH JURISDICTION IN WHICH THE NATURE OF THE BUSINESS CONDUCTED BY IT OR THE CHARACTER OR LOCATION OF THE PROPERTIES AND ASSETS OWNED OR LEASED OR HELD UNDER LICENSE BY IT MAKES SUCH LICENSING OR QUALIFICATION NECESSARY, EXCEPT WHERE THE FAILURE TO BE SO LICENSED, QUALIFIED OR IN GOOD STANDING WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO IMPAIR IN ANY MATERIAL RESPECT THE ABILITY OF COMPANY TO PERFORM ITS OBLIGATIONS HEREUNDER OR PREVENT OR MATERIALLY DELAY CONSUMMATION OF THE CUTANOGEN TRANSACTION.

(B) CUTANOGEN IS A CORPORATION OR OTHER ORGANIZATION VALIDLY EXISTING AND IN GOOD STANDING UNDER THE LAWS OF THE JURISDICTION OF ITS INCORPORATION OR ORGANIZATION.

SECTION 2.2 CAPITALIZATION

. (A) (A) ALL THE OUTSTANDING SHARES OF CAPITAL STOCK OF, OR OTHER EQUITY INTERESTS IN, CUTANOGEN ARE DULY AUTHORIZED, HAVE BEEN VALIDLY ISSUED, ARE FULLY PAID, NONASSESSABLE AND FREE OF PREEMPTIVE RIGHTS, AND ARE OWNED DIRECTLY BY COMPANY FREE AND CLEAR OF ALL LIENS, PLEDGES, SECURITY INTERESTS AND TRANSFER RESTRICTIONS, EXCEPT FOR SUCH TRANSFER RESTRICTIONS OF GENERAL APPLICABILITY AS MAY BE PROVIDED UNDER APPLICABLE SECURITIES LAWS AND RULES AND REGULATIONS PROMULGATED THEREUNDER (" LIENS "). THE DELIVERY OF CERTIFICATES AT THE CLOSING REPRESENTING THE CUTANOGEN SHARES IN THE MANNER PROVIDED IN SECTION 1.3 WILL TRANSFER TO PURCHASER GOOD AND VALID TITLE TO THE CUTANOGEN SHARES, FREE AND CLEAR OF ALL LIENS OTHER THAN LIENS CREATED OR SUFFERED TO EXIST BY PURCHASER.

(B) THERE ARE NO OUTSTANDING CONTRACTUAL OBLIGATIONS OF THE COMPANY OR ANY OF ITS SUBSIDIARIES (I) RESTRICTING THE TRANSFER OF, (II) AFFECTING THE VOTING RIGHTS OF, (III) REQUIRING THE SALE, ISSUANCE OR OTHER DISPOSITION OF, OR THE REPURCHASE, REDEMPTION OR DISPOSITION OF, OR CONTAINING ANY RIGHT OF FIRST REFUSAL WITH RESPECT TO, (IV) REQUIRING THE REGISTRATION FOR SALE OF, OR (V) GRANTING ANY PREEMPTIVE OR ANTI-DILUTIVE RIGHT WITH RESPECT TO, ANY SHARES OF CAPITAL STOCK OF, OR OTHER EQUITY INTERESTS IN, CUTANOGEN.

SECTION 2.3 AUTHORITY; NONCONTRAVENTION; VOTING REQUIREMENTS

.

(A) THE COMPANY HAS ALL NECESSARY CORPORATE POWER AND AUTHORITY TO EXECUTE AND DELIVER THIS AGREEMENT AND, SUBJECT TO OBTAINING THE COMPANY STOCKHOLDER AUTHORIZATION, TO PERFORM ITS OBLIGATIONS HEREUNDER AND TO CONSUMMATE THE CUTANOGEN TRANSACTION. THE EXECUTION, DELIVERY AND PERFORMANCE BY THE COMPANY OF THIS AGREEMENT, HAS BEEN DULY AUTHORIZED AND APPROVED BY THE BOARD OF DIRECTORS OF COMPANY, AND EXCEPT FOR OBTAINING THE COMPANY STOCKHOLDER AUTHORIZATION, NO OTHER CORPORATE ACTION ON THE PART OF ANY OF COMPANY IS NECESSARY TO AUTHORIZE THE EXECUTION, DELIVERY AND PERFORMANCE BY THE COMPANY OF THIS AGREEMENT. THIS AGREEMENT HAS BEEN DULY EXECUTED AND DELIVERED BY THE COMPANY AND, ASSUMING DUE AUTHORIZATION, EXECUTION AND DELIVERY HEREOF BY PURCHASER, CONSTITUTES A LEGAL, VALID AND BINDING OBLIGATION OF THE COMPANY, ENFORCEABLE AGAINST THE COMPANY IN ACCORDANCE WITH ITS TERMS, EXCEPT THAT SUCH ENFORCEABILITY (I) MAY BE LIMITED BY BANKRUPTCY, INSOLVENCY, FRAUDULENT TRANSFER, REORGANIZATION, MORATORIUM AND OTHER SIMILAR LAWS OF GENERAL APPLICATION AFFECTING OR RELATING TO THE ENFORCEMENT OF CREDITORS' RIGHTS GENERALLY AND (II) IS SUBJECT TO GENERAL PRINCIPLES OF EQUITY, WHETHER CONSIDERED IN A PROCEEDING AT LAW OR IN EQUITY (THE " BANKRUPTCY AND EQUITY EXCEPTION ").

(B) THE COMPANY BOARD, AT A MEETING DULY CALLED AND HELD, HAS OR WILL HAVE (I) APPROVED AND DECLARED ADVISABLE THIS AGREEMENT AND DIRECTED THAT THIS AGREEMENT BE SUBMITTED TO THE HOLDERS OF SHARES OF COMPANY COMMON STOCK FOR THEIR AUTHORIZATION.

(C) THE EXECUTION AND DELIVERY OF THIS AGREEMENT BY THE COMPANY , WILL NOT (I) CONFLICT WITH OR VIOLATE ANY PROVISION OF THE CERTIFICATE OF INCORPORATION OR BYLAWS (OR OTHER COMPARABLE ORGANIZATION DOCUMENTS) OR (II) ASSUMING THAT THE AUTHORIZATIONS, CONSENTS AND APPROVALS REFERRED TO IN SECTION 2.4 AND THE COMPANY STOCKHOLDER AUTHORIZATION ARE OBTAINED AND THE FILINGS REFERRED TO IN SECTION 2.4 ARE MADE, (X) VIOLATE ANY LAW, JUDGMENT, WRIT OR INJUNCTION OF ANY GOVERNMENTAL AUTHORITY APPLICABLE TO THE COMPANY OR ANY OF ITS SUBSIDIARIES OR (Y) VIOLATE OR CONSTITUTE A DEFAULT UNDER ANY OF THE TERMS, CONDITIONS OR PROVISIONS OF ANY LOAN OR CREDIT AGREEMENT, DEBENTURE, NOTE, BOND, MORTGAGE, INDENTURE, DEED OF TRUST, LEASE, CONTRACT OR OTHER AGREEMENT (EACH, A " CONTRACT ") TO WHICH THE COMPANY OR ANY OF ITS SUBSIDIARIES IS A PARTY, EXCEPT, IN THE CASE OF CLAUSE (II), FOR SUCH VIOLATIONS OR DEFAULTS AS WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO HAVE A MATERIAL ADVERSE EFFECT OR TO IMPAIR IN ANY MATERIAL RESPECT THE ABILITY OF COMPANY TO PERFORM ITS OBLIGATIONS HEREUNDER.

SECTION 2.4 GOVERNMENTAL APPROVALS

. EXCEPT FOR (I) A POSSIBLE FILING WITH THE SWISS STOCK EXCHANGE (“SWX”), (II) FILINGS REQUIRED UNDER, AND COMPLIANCE WITH OTHER APPLICABLE REQUIREMENTS OF, THE HSR ACT AND (III) FILINGS REQUIRED UNDER, AND COMPLIANCE WITH OTHER APPLICABLE REQUIREMENTS OF, NON-U.S. LAWS INTENDED TO PROHIBIT, RESTRICT OR REGULATE ACTIONS OR TRANSACTIONS HAVING THE PURPOSE OR EFFECT OF MONOPOLIZATION, RESTRAINT OF TRADE, HARM TO COMPETITION OR EFFECTUATING FOREIGN INVESTMENT (COLLECTIVELY, " FOREIGN ANTITRUST LAWS "), NO CONSENTS OR APPROVALS OF, OR FILINGS, DECLARATIONS OR REGISTRATIONS WITH, ANY GOVERNMENTAL AUTHORITY ARE NECESSARY FOR THE EXECUTION AND DELIVERY OF THIS AGREEMENT BY THE COMPANY, OTHER THAN SUCH CONSENTS, APPROVALS, FILINGS, DECLARATIONS OR REGISTRATIONS THAT, IF NOT OBTAINED, MADE OR GIVEN, WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO HAVE A MATERIAL ADVERSE EFFECT OR TO IMPAIR IN ANY MATERIAL RESPECT THE ABILITY OF THE COMPANY TO PERFORM ITS OBLIGATIONS HEREUNDER.

SECTION 2.5 INTELLECTUAL PROPERTY

.

(A) AS USED HEREIN: (I) " INTELLECTUAL PROPERTY " MEANS ALL U.S. AND FOREIGN (A) TRADEMARKS, SERVICE MARKS, TRADE NAMES, INTERNET DOMAIN NAMES, DESIGNS, LOGOS AND SLOGANS, TOGETHER WITH GOODWILL, REGISTRATIONS AND APPLICATIONS RELATING TO THE FOREGOING (" TRADEMARKS "), (B) PATENTS AND PENDING PATENT APPLICATIONS, INVENTION DISCLOSURE STATEMENTS, AND ANY AND ALL DIVISIONS, CONTINUATIONS, CONTINUATIONS-IN-PART, REISSUES, REEXAMINATIONS AND EXTENSIONS THEREOF, ANY COUNTERPARTS CLAIMING PRIORITY THEREFROM AND LIKE STATUTORY RIGHTS (" PATENTS "), (C) REGISTERED AND UNREGISTERED COPYRIGHTS (INCLUDING THOSE IN SOFTWARE) AND REGISTRATIONS AND APPLICATIONS TO REGISTER THE SAME (" COPYRIGHTS "), (D) CONFIDENTIAL TECHNOLOGY, KNOW-HOW, INVENTIONS, PROCESSES, FORMULAE, ALGORITHMS, MODELS AND METHODOLOGIES (" TRADE SECRETS ") AND (E) DATABASES AND COMPILATIONS, INCLUDING ANY AND ALL ELECTRONIC DATA AND ELECTRONIC COLLECTIONS OF DATA; (II) " IP LICENSES " MEANS ANY LICENSE OR SUBLICENSE RIGHTS IN OR TO ANY INTELLECTUAL PROPERTY; AND (III) " SOFTWARE " MEANS ALL COMPUTER PROGRAMS, INCLUDING ANY AND ALL SOFTWARE IMPLEMENTATIONS OF ALGORITHMS, MODELS AND METHODOLOGIES WHETHER IN SOURCE CODE OR OBJECT CODE FORM, AND ALL DOCUMENTATION, INCLUDING USER MANUALS AND TRAINING MATERIALS, RELATED TO ANY OF THE FOREGOING. A LIST OF ANY INTELLECTUAL PROPERTY IS ATTACHED HERETO AS EXHIBIT 2.5A.

(B) EXCEPT AS WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO RESULT IN A MATERIAL ADVERSE EFFECT, CUTANOGEN OWNS OR POSSESSES APPROPRIATE LICENSES OR OTHER LEGAL RIGHTS TO USE, SELL OR LICENSE ALL CUTANOGEN INTELLECTUAL PROPERTY.

(C) EXCEPT AS WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO HAVE A MATERIAL ADVERSE EFFECT, ALL TRADEMARK REGISTRATIONS AND APPLICATIONS FOR REGISTRATION, PATENTS ISSUED OR PENDING AND COPYRIGHT REGISTRATIONS AND APPLICATIONS FOR REGISTRATION INCLUDED IN THE CUTANOGEN INTELLECTUAL PROPERTY ARE VALID AND SUBSISTING, IN FULL FORCE AND EFFECT AND HAVE NOT LAPSED, EXPIRED OR BEEN ABANDONED (SUBJECT TO THE VULNERABILITY OF A REGISTRATION FOR TRADEMARKS TO CANCELLATION FOR LACK OF USE), AND, TO THE KNOWLEDGE OF THE COMPANY, ARE NOT THE SUBJECT OF ANY OPPOSITION FILED WITH THE UNITED STATES PATENT AND TRADEMARK OFFICE OR ANY OTHER INTELLECTUAL PROPERTY REGISTRY.

(D) TO THE KNOWLEDGE OF THE COMPANY, THE CONDUCT OF THE CUTANOGEN BUSINESS DOES NOT INFRINGE, MISAPPROPRIATE, OR OTHERWISE VIOLATE ANY INTELLECTUAL PROPERTY RIGHTS OF ANY THIRD PARTY.

(E) TO THE KNOWLEDGE OF THE COMPANY, NO THIRD PARTY IS INFRINGING, MISAPPROPRIATING, DILUTING OR VIOLATING ANY CUTANOGEN INTELLECTUAL PROPERTY.

SECTION 2.6 BROKERS AND OTHER ADVISORS

. NO BROKER, INVESTMENT BANKER, FINANCIAL ADVISOR OR OTHER PERSON IS ENTITLED TO ANY BROKER'S, FINDER'S, FINANCIAL ADVISOR'S OR OTHER SIMILAR FEE OR COMMISSION, OR THE REIMBURSEMENT OF EXPENSES, IN CONNECTION WITH THE TRANSACTION CONTEMPLATED HEREIN.

SECTION 2.7 NO OTHER REPRESENTATIONS OR WARRANTIES

. EXCEPT FOR THE REPRESENTATIONS AND WARRANTIES MADE BY THE COMPANY IN THIS ARTICLE II OR PURSUANT TO THE CERTIFICATES TO BE DELIVERED PURSUANT TO SECTION 5.2(A) , NEITHER THE COMPANY NOR ANY OTHER PERSON MAKES ANY REPRESENTATION OR WARRANTY WITH RESPECT TO CUTANOGEN OR, NOTWITHSTANDING THE DELIVERY OR DISCLOSURE TO PURCHASER OR ANY OF ITS AFFILIATES OR REPRESENTATIVES OF ANY DOCUMENTATION, FORECASTS OR OTHER INFORMATION WITH RESPECT TO ANY ONE OR MORE OF THE FOREGOING.

ARTICLE III
REPRESENTATIONS AND WARRANTIES OF PURCHASER

PURCHASER REPRESENTS AND WARRANTS TO THE COMPANY THAT:

SECTION 3.1 ORGANIZATION AND STANDING

. PURCHASER IS A CORPORATION VALIDLY EXISTING AND IN GOOD STANDING UNDER THE LAWS OF THE STATE OF **NEVADA.** PURCHASER IS DULY LICENSED OR QUALIFIED TO DO BUSINESS AND IS IN GOOD STANDING IN EACH JURISDICTION IN WHICH THE NATURE OF THE BUSINESS CONDUCTED BY IT OR THE CHARACTER OR LOCATION OF THE PROPERTIES AND ASSETS OWNED OR LEASED OR HELD UNDER LICENSE BY IT MAKES SUCH LICENSING OR QUALIFICATION NECESSARY, EXCEPT WHERE THE FAILURE TO BE SO LICENSED, QUALIFIED OR IN GOOD STANDING WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO IMPAIR IN ANY MATERIAL RESPECT THE ABILITY OF PURCHASER TO PERFORM ITS OBLIGATIONS HEREUNDER OR PREVENT OR MATERIALLY DELAY CONSUMMATION OF THE TRANSACTION.

SECTION 3.2 AUTHORITY; NONCONTRAVENTION

(A) PURCHASER HAS ALL NECESSARY CORPORATE POWER AND AUTHORITY TO EXECUTE AND DELIVER THIS AGREEMENT, TO PERFORM ITS OBLIGATIONS HEREUNDER AND TO CONSUMMATE THE TRANSACTION. THE EXECUTION, DELIVERY AND PERFORMANCE BY PURCHASER OF THIS AGREEMENT, AND THE CONSUMMATION BY PURCHASER OF THE TRANSACTION, HAVE BEEN DULY AUTHORIZED AND APPROVED BY ITS BOARD OF DIRECTORS, AND NO OTHER CORPORATE ACTION ON THE PART OF PURCHASER IS NECESSARY TO AUTHORIZE THE EXECUTION, DELIVERY AND PERFORMANCE BY PURCHASER OF THIS AGREEMENT AND THE CONSUMMATION BY IT OF THE TRANSACTION. THIS AGREEMENT HAS BEEN DULY EXECUTED AND DELIVERED BY PURCHASER AND, ASSUMING DUE AUTHORIZATION, EXECUTION AND DELIVERY HEREOF BY THE COMPANY, CONSTITUTES A LEGAL, VALID AND BINDING OBLIGATION OF PURCHASER, ENFORCEABLE AGAINST PURCHASER IN ACCORDANCE WITH ITS TERMS, SUBJECT TO THE BANKRUPTCY AND EQUITY EXCEPTION.

(B) NEITHER THE EXECUTION AND DELIVERY OF THIS AGREEMENT BY PURCHASER, NOR THE CONSUMMATION BY PURCHASER OF THE TRANSACTION, NOR COMPLIANCE BY PURCHASER WITH ANY OF THE TERMS OR PROVISIONS HEREOF, WILL (I) CONFLICT WITH OR VIOLATE ANY PROVISION OF THE CERTIFICATE OF INCORPORATION OR BYLAWS OF PURCHASER OR (II) ASSUMING THAT THE AUTHORIZATIONS, CONSENTS AND APPROVALS REFERRED TO IN SECTION 3.3 ARE OBTAINED AND THE FILINGS REFERRED TO IN SECTION 3.3 ARE MADE, (X) VIOLATE ANY LAW, JUDGMENT, WRIT OR INJUNCTION OF ANY GOVERNMENTAL AUTHORITY APPLICABLE TO PURCHASER OR ANY OF ITS SUBSIDIARIES, OR (Y) VIOLATE OR CONSTITUTE A DEFAULT UNDER ANY OF THE TERMS, CONDITIONS OR PROVISIONS OF ANY CONTRACT TO WHICH PURCHASER OR ANY OF ITS SUBSIDIARIES IS A PARTY, EXCEPT, IN THE CASE OF CLAUSE (II), FOR SUCH VIOLATIONS OR DEFAULTS AS WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO IMPAIR THE ABILITY OF PURCHASER TO PERFORM ITS OBLIGATIONS HEREUNDER OR PREVENT OR MATERIALLY DELAY CONSUMMATION OF THE TRANSACTION.

(C) NO VOTE OF THE HOLDERS OF ANY CLASS OR SERIES OF PURCHASER'S CAPITAL STOCK OR OTHER SECURITIES IS NECESSARY FOR THE CONSUMMATION BY PURCHASER OF THE TRANSACTION.

SECTION 3.3 GOVERNMENTAL APPROVALS

. NO CONSENTS OR APPROVALS OF, OR FILINGS, DECLARATIONS OR REGISTRATIONS WITH, ANY GOVERNMENTAL AUTHORITY ARE NECESSARY FOR THE EXECUTION, DELIVERY AND PERFORMANCE OF THIS AGREEMENT BY PURCHASER, OTHER THAN SUCH OTHER CONSENTS, APPROVALS, FILINGS, DECLARATIONS OR REGISTRATIONS THAT, IF NOT OBTAINED, MADE OR GIVEN, WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO IMPAIR IN ANY MATERIAL RESPECT THE ABILITY OF PURCHASER TO PERFORM ITS OBLIGATIONS HEREUNDER OR PREVENT OR MATERIALLY DELAY CONSUMMATION OF THE TRANSACTION.

SECTION 3.4 INFORMATION SUPPLIED

. ANY INFORMATION SUPPLIED BY PURCHASER TO COMPANY WILL NOT CONTAIN ANY UNTRUE STATEMENT OF A MATERIAL FACT OR OMIT TO STATE ANY MATERIAL FACT REQUIRED TO BE STATED THEREIN.

SECTION 3.5 CAPITAL RESOURCES

. PURCHASER HAS, OR WILL HAVE PRIOR TO THE CLOSING, CASH, AVAILABLE LINES OF CREDIT OR OTHER SOURCES OF IMMEDIATELY AVAILABLE FUNDS IN AN AMOUNT SUFFICIENT TO PAY ALL FEES AND EXPENSES PAYABLE BY PURCHASER. TO THE EXTENT THAT PURCHASER IS FINANCING ALL OR A PORTION OF THE TRANSACTION THROUGH PROCEEDS RECEIVED FROM DEBT FINANCING PROVIDED BY THIRD PARTIES, PRIOR TO THE EXECUTION AND DELIVERY OF THIS AGREEMENT PURCHASER HAS FURNISHED TO THE COMPANY FULLY EXECUTED COPIES OF THE DEBT COMMITMENT LETTERS RELATING TO SUCH FINANCING WITH CONDITIONS PRECEDENT NO MORE RESTRICTIVE THAN THE CONDITIONS TO CLOSING CONTAINED IN THIS AGREEMENT. AS OF THE DATE HEREOF AND AFTER COMMUNICATING WITH THE INSTITUTIONS PROVIDING SUCH DEBT FINANCING, PURCHASER KNOWS OF NO FACTS OR CIRCUMSTANCES (OTHER THAN ANY THAT ARISE AS A RESULT OF A BREACH BY THE COMPANY OF THIS AGREEMENT) THAT ARE REASONABLY LIKELY TO RESULT IN ANY OF THE CONDITIONS SET FORTH IN SUCH COMMITMENT LETTERS NOT BEING SATISFIED.

SECTION 3.6 LEGAL PROCEEDINGS

. AS OF THE DATE HEREOF, THERE IS NO PENDING OR, TO THE KNOWLEDGE OF PURCHASER, THREATENED ACTION OR PROCEEDING AGAINST OR RELATING TO PURCHASER OR ANY OF ITS SUBSIDIARIES, NOR IS THERE ANY INJUNCTION, ORDER, JUDGMENT, RULING OR DECREE IMPOSED UPON PURCHASER OR ANY OF ITS SUBSIDIARIES, IN EACH CASE, BY OR BEFORE ANY GOVERNMENTAL AUTHORITY, THAT WOULD, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO IMPAIR IN ANY MATERIAL RESPECT THE ABILITY OF PURCHASER TO PERFORM ITS OBLIGATIONS HEREUNDER.

SECTION 3.7 BROKERS AND OTHER ADVISORS

. NO BROKER, INVESTMENT BANKER, FINANCIAL ADVISOR OR OTHER PERSON IS ENTITLED TO ANY BROKER'S, FINDER'S, FINANCIAL ADVISOR'S OR OTHER SIMILAR FEE OR COMMISSION, OR THE REIMBURSEMENT OF EXPENSES, IN CONNECTION WITH THE TRANSACTION BASED UPON ARRANGEMENTS MADE BY OR ON BEHALF OF PURCHASER OR ANY OF ITS SUBSIDIARIES.

SECTION 3.8 NO RELIANCE

. NOTWITHSTANDING ANYTHING CONTAINED IN THIS AGREEMENT TO THE CONTRARY, PURCHASER ACKNOWLEDGES AND AGREES THAT (A) NEITHER THE COMPANY NOR ANY PERSON ON BEHALF OF THE COMPANY IS MAKING ANY REPRESENTATIONS OR WARRANTIES WHATSOEVER, EXPRESS OR IMPLIED, BEYOND THOSE EXPRESSLY MADE BY THE COMPANY IN ARTICLE II , AND (B) PURCHASER HAS NOT BEEN INDUCED BY, OR RELIED UPON, ANY REPRESENTATIONS, WARRANTIES OR STATEMENTS (WRITTEN OR ORAL), WHETHER EXPRESS OR IMPLIED, MADE BY ANY PERSON, THAT ARE NOT EXPRESSLY SET FORTH IN ARTICLE II OF THIS AGREEMENT. WITHOUT LIMITING THE GENERALITY OF THE FOREGOING, PURCHASER ACKNOWLEDGES THAT NO REPRESENTATIONS OR WARRANTIES ARE MADE WITH RESPECT TO ANY PROJECTIONS, FORECASTS, ESTIMATES, BUDGETS OR INFORMATION AS TO PROSPECTS WITH RESPECT TO THE CUTANOGEN BUSINESS THAT MAY HAVE BEEN MADE AVAILABLE TO PURCHASER OR ANY OF ITS REPRESENTATIVES.

ARTICLE IV
ADDITIONAL COVENANTS AND AGREEMENTS

SECTION 4.1 REASONABLE BEST EFFORTS

(A) SUBJECT TO THE TERMS AND CONDITIONS OF THIS AGREEMENT, EACH OF THE COMPANY AND PURCHASER SHALL COOPERATE WITH THE OTHER AND USE (AND SHALL CAUSE THEIR RESPECTIVE SUBSIDIARIES TO USE) THEIR RESPECTIVE REASONABLE BEST EFFORTS, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, TO PROMPTLY (I) TAKE, OR CAUSE TO BE TAKEN, ALL ACTIONS, AND DO, OR CAUSE TO BE DONE, ALL THINGS, NECESSARY, PROPER OR ADVISABLE TO CAUSE THE CONDITIONS TO CLOSING TO BE SATISFIED AS PROMPTLY AS PRACTICABLE AND TO CONSUMMATE AND MAKE EFFECTIVE, IN THE MOST EXPEDITIOUS MANNER PRACTICABLE, THE TRANSACTION, INCLUDING PREPARING AND FILING PROMPTLY AND FULLY ALL DOCUMENTATION TO EFFECT ALL NECESSARY FILINGS, NOTICES, PETITIONS, STATEMENTS, REGISTRATIONS, SUBMISSIONS OF INFORMATION, APPLICATIONS AND OTHER DOCUMENTS (INCLUDING ANY REQUIRED OR RECOMMENDED FILINGS UNDER APPLICABLE ANTITRUST LAWS), AND (II) OBTAIN ALL APPROVALS, CONSENTS, REGISTRATIONS, PERMITS, AUTHORIZATIONS AND OTHER CONFIRMATIONS FROM ANY GOVERNMENTAL AUTHORITY OR THIRD PARTY NECESSARY, PROPER OR ADVISABLE TO CONSUMMATE THE TRANSACTION. FOR PURPOSES HEREOF, " ANTITRUST LAWS " MEANS THE SHERMAN ACT, AS AMENDED, THE CLAYTON ACT, AS AMENDED, THE HSR ACT, THE FEDERAL TRADE COMMISSION ACT, AS AMENDED, ALL APPLICABLE FOREIGN ANTITRUST LAWS AND ALL OTHER APPLICABLE LAWS ISSUED BY A GOVERNMENTAL AUTHORITY THAT ARE DESIGNED OR INTENDED TO PROHIBIT, RESTRICT OR REGULATE ACTIONS HAVING THE PURPOSE OR EFFECT OF MONOPOLIZATION OR RESTRAINT OF TRADE OR LESSENING OF COMPETITION THROUGH MERGER OR ACQUISITION.

(B) EACH OF THE COMPANY AND PURCHASER SHALL USE ITS REASONABLE BEST EFFORTS TO (I) COOPERATE IN ALL RESPECTS WITH EACH OTHER IN CONNECTION WITH ANY FILING OR SUBMISSION WITH A GOVERNMENTAL AUTHORITY IN CONNECTION WITH THE TRANSACTION AND IN CONNECTION WITH ANY INVESTIGATION OR OTHER INQUIRY BY OR BEFORE A GOVERNMENTAL AUTHORITY RELATING TO THE TRANSACTION, INCLUDING ANY PROCEEDING INITIATED BY A PRIVATE PARTY, AND (II) KEEP THE OTHER PARTY INFORMED IN ALL MATERIAL RESPECTS AND ON A REASONABLY TIMELY BASIS OF ANY MATERIAL COMMUNICATION RECEIVED BY SUCH PARTY FROM, OR GIVEN BY SUCH PARTY TO, THE FEDERAL TRADE COMMISSION, THE ANTITRUST DIVISION OF THE DEPARTMENT OF JUSTICE, OR ANY OTHER GOVERNMENTAL AUTHORITY AND OF ANY MATERIAL COMMUNICATION RECEIVED OR GIVEN IN CONNECTION WITH ANY PROCEEDING BY A PRIVATE PARTY, IN EACH CASE REGARDING THE TRANSACTION. SUBJECT TO APPLICABLE LAWS RELATING TO THE EXCHANGE OF INFORMATION, EACH OF THE PARTIES HERETO SHALL HAVE THE RIGHT TO REVIEW IN ADVANCE, AND TO THE EXTENT PRACTICABLE EACH WILL CONSULT THE OTHER ON, ALL THE INFORMATION RELATING TO THE OTHER PARTY AND ITS SUBSIDIARIES, AS THE CASE MAY BE, THAT APPEARS IN ANY FILING MADE WITH, OR WRITTEN MATERIALS SUBMITTED TO, ANY THIRD PARTY AND/OR ANY GOVERNMENTAL AUTHORITY IN CONNECTION WITH THE TRANSACTION.

(C) IN FURTHERANCE AND NOT IN LIMITATION OF THE COVENANTS OF THE PARTIES CONTAINED IN THIS SECTION 4.5 , EACH OF THE COMPANY AND PURCHASER SHALL USE ITS REASONABLE BEST EFFORTS TO RESOLVE SUCH OBJECTIONS, IF ANY, AS MAY BE ASSERTED BY A GOVERNMENTAL AUTHORITY OR OTHER PERSON WITH RESPECT TO THE TRANSACTION. WITHOUT LIMITING ANY OTHER PROVISION HEREOF, PURCHASER AND THE COMPANY SHALL EACH USE ITS REASONABLE BEST EFFORTS TO (I) AVOID THE ENTRY OF, OR TO HAVE VACATED OR TERMINATED, ANY DECREE, ORDER OR JUDGMENT THAT WOULD RESTRAIN, PREVENT OR DELAY THE CONSUMMATION OF THE TRANSACTION, INCLUDING BY DEFENDING THROUGH LITIGATION ON THE MERITS ANY CLAIM ASSERTED IN ANY COURT BY ANY PERSON, AND (II) AVOID OR ELIMINATE EACH AND EVERY IMPEDIMENT UNDER ANY ANTITRUST LAW THAT MAY BE ASSERTED BY ANY GOVERNMENTAL AUTHORITY WITH RESPECT TO THE TRANSACTION SO AS TO ENABLE THE CONSUMMATION OF THE TRANSACTION TO OCCUR AS SOON AS REASONABLY POSSIBLE INCLUDING, IN THE CASE OF PURCHASER, BY TAKING ALL SUCH ACTIONS, INCLUDING (X) PROPOSING, NEGOTIATING, COMMITTING TO AND EFFECTING, BY CONSENT DECREE, HOLD SEPARATE ORDER, OR OTHERWISE, THE SALE, DIVESTITURE OR DISPOSITION OF SUCH ASSETS OR BUSINESSES OF PURCHASER (OR ANY OF ITS SUBSIDIARIES) AND (Y) OTHERWISE TAKING OR COMMITTING TO TAKE ACTIONS THAT LIMIT PURCHASER OR ITS SUBSIDIARIES' FREEDOM OF ACTION WITH RESPECT TO, OR ITS ABILITY TO RETAIN, ONE OR MORE OF ITS, OR ITS SUBSIDIARIES', BUSINESSES, PRODUCT LINES OR ASSETS, IN EACH CASE, AS MAY BE REQUIRED IN ORDER TO AVOID THE ENTRY OF, OR TO EFFECT THE DISSOLUTION OF, ANY INJUNCTION, TEMPORARY RESTRAINING ORDER OR OTHER ORDER IN ANY ACTION OR PROCEEDING, WHICH WOULD OTHERWISE HAVE THE EFFECT OF PREVENTING OR MATERIALLY DELAYING THE CONSUMMATION OF THE TRANSACTION.

SECTION 4.2 PUBLIC ANNOUNCEMENTS

. THE INITIAL PRESS RELEASE WITH RESPECT TO THE EXECUTION OF THIS AGREEMENT SHALL BE A JOINT PRESS RELEASE TO BE REASONABLY AGREED UPON BY PURCHASER AND THE COMPANY. THEREAFTER, NEITHER THE COMPANY NOR PURCHASER SHALL ISSUE OR CAUSE THE PUBLICATION OF ANY PRESS RELEASE OR OTHER PUBLIC ANNOUNCEMENT (TO THE EXTENT NOT PREVIOUSLY ISSUED OR MADE IN ACCORDANCE WITH THIS AGREEMENT) WITH RESPECT TO THIS AGREEMENT OR THE TRANSACTION WITHOUT THE PRIOR CONSENT OF THE OTHER PARTY (WHICH CONSENT SHALL NOT BE UNREASONABLY WITHHELD, CONDITIONED OR DELAYED), EXCEPT AS MAY BE REQUIRED BY LAW, APPLICABLE FIDUCIARY DUTIES OR BY ANY APPLICABLE LISTING AGREEMENT WITH THE SWX AS DETERMINED IN THE GOOD FAITH JUDGMENT OF THE PARTY PROPOSING TO MAKE SUCH RELEASE (IN WHICH CASE SUCH PARTY SHALL NOT ISSUE OR CAUSE THE PUBLICATION OF SUCH PRESS RELEASE OR OTHER PUBLIC ANNOUNCEMENT WITHOUT PRIOR CONSULTATION WITH THE OTHER PARTY TO THE EXTENT REASONABLY PRACTICABLE).

SECTION 4.3 ACCESS TO INFORMATION; CONFIDENTIALITY

. SUBJECT TO APPLICABLE LAWS RELATING TO THE EXCHANGE OF INFORMATION, THE COMPANY SHALL AFFORD TO PURCHASER REASONABLE ACCESS DURING NORMAL BUSINESS HOURS TO THE OFFICERS, EMPLOYEES, ACCOUNTANTS, PROPERTIES, BOOKS, CONTRACTS AND RECORDS OF THE COMPANY RELATING TO THE CUTANOGEN BUSINESS, AND THE COMPANY SHALL FURNISH PROMPTLY TO PURCHASER OTHER INFORMATION CONCERNING THE CUTANOGEN BUSINESS AS PURCHASER MAY REASONABLY REQUEST; PROVIDED , HOWEVER , THAT THE COMPANY SHALL NOT BE OBLIGATED TO PROVIDE SUCH ACCESS OR INFORMATION IF THE COMPANY DETERMINES, IN ITS REASONABLE JUDGMENT, THAT DOING SO WOULD VIOLATE APPLICABLE LAW OR A CONTRACT OR OBLIGATION OF CONFIDENTIALITY OWING TO A THIRD PARTY OR JEOPARDIZE THE PROTECTION OF AN ATTORNEY-CLIENT PRIVILEGE. UNTIL THE CLOSING DATE, THE INFORMATION PROVIDED PURSUANT TO THIS AGREEMENT WILL BE SUBJECT TO THE TERMS OF THE CONFIDENTIALITY AGREEMENT, DATED AS OF **[_____]** , BETWEEN PURCHASER AND THE COMPANY (AS IT MAY BE AMENDED FROM TIME TO TIME, THE " CONFIDENTIALITY AGREEMENT "), WHICH SHALL SURVIVE THE TERMINATION OF THIS AGREEMENT IN ACCORDANCE WITH THE TERMS OF THE CONFIDENTIALITY AGREEMENT.

SECTION 4.4 NOTIFICATION OF CERTAIN MATTERS

. THE COMPANY SHALL GIVE PROMPT NOTICE TO PURCHASER, AND PURCHASER SHALL GIVE PROMPT NOTICE TO THE COMPANY, OF (I) ANY NOTICE OR OTHER COMMUNICATION RECEIVED BY SUCH PARTY FROM ANY GOVERNMENTAL AUTHORITY IN CONNECTION WITH THE TRANSACTION OR FROM ANY PERSON ALLEGING THAT THE CONSENT OF SUCH PERSON IS OR MAY BE REQUIRED IN CONNECTION WITH THE TRANSACTION, AND (II) ANY ACTIONS OR PROCEEDINGS COMMENCED OR, TO SUCH PARTY'S KNOWLEDGE, THREATENED AGAINST, RELATING TO OR INVOLVING OR OTHERWISE AFFECTING SUCH PARTY OR ANY OF ITS SUBSIDIARIES WHICH, IN THE CASE OF EITHER CLAUSE (I) OR (II), WOULD REASONABLY BE EXPECTED TO HAVE A MATERIAL ADVERSE EFFECT OR PREVENT OR MATERIALLY DELAY CONSUMMATION OF THE TRANSACTION.

SECTION 4.5 FEES AND EXPENSES

. EXCEPT AS PROVIDED IN SECTION 7.3 , ALL FEES AND EXPENSES INCURRED IN CONNECTION WITH THIS AGREEMENT AND THE TRANSACTION SHALL BE PAID BY THE PARTY INCURRING SUCH FEES OR EXPENSES, WHETHER OR NOT THE TRANSACTION ARE CONSUMMATED.

ARTICLE V
CONDITIONS

SECTION 5.1 CONDITIONS TO THE OBLIGATIONS OF EACH PARTY

. THE RESPECTIVE OBLIGATIONS OF EACH PARTY HERETO TO CONSUMMATE THE TRANSACTION SHALL BE SUBJECT TO THE SATISFACTION (OR WAIVER, IF PERMISSIBLE UNDER APPLICABLE LAW) ON OR PRIOR TO THE CLOSING DATE OF THE FOLLOWING CONDITIONS:

(A) THE COMPANY STOCKHOLDER AUTHORIZATION SHALL HAVE BEEN OBTAINED.

(B) NO LAW, INJUNCTION, JUDGMENT OR RULING ENACTED, PROMULGATED, ISSUED, ENTERED, AMENDED OR ENFORCED BY ANY GOVERNMENTAL AUTHORITY (COLLECTIVELY, THE " RESTRAINTS ") SHALL BE IN EFFECT ENJOINING, RESTRAINING, PREVENTING OR PROHIBITING CONSUMMATION OF THE TRANSACTION OR MAKING THE CONSUMMATION OF THE TRANSACTION ILLEGAL.

(C) ALL CONSENTS, APPROVALS AND ACTIONS OF, FILINGS WITH AND NOTICES TO ANY GOVERNMENTAL AUTHORITY REQUIRED OF PURCHASER, THE COMPANY OR ANY OF THEIR RESPECTIVE SUBSIDIARIES TO CONSUMMATE THE TRANSACTION, THE FAILURE OF WHICH TO BE OBTAINED OR TAKEN WOULD BE REASONABLY EXPECTED TO HAVE A MATERIAL ADVERSE EFFECT OR AN ADVERSE EFFECT ON THE ABILITY OF PURCHASER AND THE COMPANY TO CONSUMMATE THE TRANSACTION, SHALL HAVE BEEN OBTAINED; PROVIDED THAT NO SUCH CONSENT, APPROVAL, ACTION, FILING OR NOTICE UNDER THE FOREIGN ANTITRUST LAWS SHALL BE A CONDITION TO EITHER PARTY'S OBLIGATIONS TO CONSUMMATE THE TRANSACTION. WITHOUT LIMITING THE FOREGOING, ANY APPLICABLE WAITING PERIOD UNDER THE HSR ACT (AND ANY EXTENSION THEREOF) SHALL HAVE EXPIRED OR TERMINATED.

(D) THE PURCHASER SHALL HAVE DELIVERED A FULLY EXECUTED ORIGINAL COPY OF EACH OF (I) THE CONSULTING AGREEMENT (" CONSULTING AGREEMENT ") DATED FEBRUARY 2, 2006 BETWEEN STEVEN T. BOYCE AND CAMBREX BIOSCIENCE WALKERSVILLE, INC. AND (II) THE STOCK PURCHASE AGREEMENT (" SPA ") DATED FEBRUARY 2, 2006 BETWEEN CERTAIN SELLERS AND CAMBREX BIOSCIENCE WALKERSVILLE, INC. REGARDING THE SALE OF CUTANOGEN REFLECTING AN ASSIGNMENT OF BOTH AGREEMENTS TO PURCHASER. ADDITIONALLY, THE SPA SHALL BE REVISED SO THAT SUCH ASSIGNMENT ALLOWS COMPANY TO HAVE NO LIABILITY UNDER SAID SPA.

(E) THE ACHIEVEMENT OF CERTAIN MILESTONES INCLUDED IN THE LICENSE AND SPA.

SECTION 5.2 CONDITIONS TO THE OBLIGATIONS OF PURCHASER

. THE OBLIGATIONS OF PURCHASER TO CONSUMMATE THE TRANSACTION SHALL BE SUBJECT TO THE SATISFACTION (OR WAIVER, IF PERMISSIBLE UNDER APPLICABLE LAW) ON OR PRIOR TO THE CLOSING DATE OF THE FOLLOWING CONDITIONS:

(A) EACH OF THE REPRESENTATIONS AND WARRANTIES OF THE COMPANY SET FORTH IN THIS AGREEMENT SHALL BE TRUE AND CORRECT AT AND AS OF THE CLOSING DATE AS IF MADE ON SUCH DATE (OTHER THAN THOSE REPRESENTATIONS AND WARRANTIES THAT ADDRESS MATTERS ONLY AS OF A PARTICULAR DATE, WHICH SHALL BE TRUE AND CORRECT AS OF SUCH DATE), EXCEPT (X) FOR CHANGES PERMITTED BY THIS AGREEMENT OR (Y) WHERE THE FAILURE OF ANY SUCH REPRESENTATION OR WARRANTY TO BE TRUE AND CORRECT (WITHOUT GIVING EFFECT TO ANY LIMITATION AS TO "MATERIALITY" OR " MATERIAL ADVERSE EFFECT" SET FORTH THEREIN) WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO HAVE A MATERIAL ADVERSE EFFECT; AND PURCHASER SHALL HAVE RECEIVED A CERTIFICATE OF AN EXECUTIVE OFFICER OF THE COMPANY TO THAT EFFECT.

(B) THE COMPANY SHALL HAVE PERFORMED OR COMPLIED WITH IN ALL MATERIAL RESPECTS ALL AGREEMENTS AND COVENANTS REQUIRED BY THIS AGREEMENT TO BE PERFORMED OR COMPLIED WITH BY IT ON OR PRIOR TO THE CLOSING DATE; AND PURCHASER SHALL HAVE RECEIVED A CERTIFICATE OF AN EXECUTIVE OFFICER OF THE COMPANY TO THAT EFFECT.

SECTION 5.3 CONDITIONS TO THE OBLIGATIONS OF THE COMPANY

THE OBLIGATIONS OF THE COMPANY TO CONSUMMATE THE TRANSACTION SHALL BE SUBJECT TO THE SATISFACTION (OR WAIVER, IF PERMISSIBLE UNDER APPLICABLE LAW) ON OR PRIOR TO THE CLOSING DATE OF THE FOLLOWING CONDITIONS:

(A) EACH OF THE REPRESENTATIONS AND WARRANTIES OF PURCHASER SET FORTH IN THIS AGREEMENT SHALL BE TRUE AND CORRECT AT AND AS OF THE CLOSING DATE AS IF MADE ON SUCH DATE, EXCEPT WHERE THE FAILURE OF ANY SUCH REPRESENTATION OR WARRANTY TO BE TRUE AND CORRECT WOULD NOT, INDIVIDUALLY OR IN THE AGGREGATE, REASONABLY BE EXPECTED TO IMPAIR THE ABILITY OF PURCHASER TO PERFORM ITS OBLIGATIONS HEREUNDER OR PREVENT OR MATERIALLY DELAY CONSUMMATION OF THE TRANSACTION; AND THE COMPANY SHALL HAVE RECEIVED A CERTIFICATE OF AN EXECUTIVE OFFICER OF PURCHASER TO THAT EFFECT.

(B) PURCHASER SHALL HAVE PERFORMED OR COMPLIED WITH IN ALL MATERIAL RESPECTS ALL AGREEMENTS AND COVENANTS REQUIRED BY THIS AGREEMENT TO BE PERFORMED OR COMPLIED WITH BY IT ON OR PRIOR TO THE CLOSING DATE; AND THE COMPANY SHALL HAVE RECEIVED A CERTIFICATE OF AN EXECUTIVE OFFICER OF PURCHASER TO THAT EFFECT.

SECTION 5.4 FRUSTRATION OF CLOSING CONDITIONS

NEITHER THE COMPANY NOR PURCHASER MAY RELY ON THE FAILURE OF ANY CONDITION SET FORTH IN SECTION 5.1 , 5.2 OR 5.3 , AS THE CASE MAY BE, TO BE SATISFIED IF SUCH FAILURE WAS CAUSED BY SUCH PARTY'S FAILURE TO USE REASONABLE BEST EFFORTS TO CONSUMMATE THE TRANSACTION, TO THE EXTENT REQUIRED BY AND SUBJECT TO SECTION 4.4 AND THE OTHER APPLICABLE PROVISIONS OF ARTICLE IV .

ARTICLE VI
TAX MATTERS

SECTION 6.1 TAX FILINGS

.

(A) AFTER THE CLOSING, PURCHASER SHALL PREPARE AND FILE, OR CAUSE TO BE PREPARED AND FILED, ON BEHALF OF CUTANOGEN ALL CUTANOGEN TAX RETURNS (IF NECESSARY), AND PAY (OR CAUSE TO BE PAID) ALL TAXES SHOWN DUE ON SUCH TAX RETURNS.

(B) TO THE EXTENT PERMITTED BY APPLICABLE LAW OR ADMINISTRATIVE PRACTICE OF ANY TAXING AUTHORITY, ANY TRANSACTIONS INVOLVING CUTANOGEN THAT ARE NOT IN THE ORDINARY COURSE OF BUSINESS OCCURRING ON THE CLOSING DATE BUT AFTER THE CLOSING SHALL BE REPORTED ON PURCHASER'S CONSOLIDATED UNITED STATES FEDERAL INCOME TAX RETURN TO THE EXTENT PERMITTED BY TREASURY REGULATION §1.1502-76(B)(1)(II)(B).

(C) PURCHASER AND THE COMPANY AGREE TO FURNISH OR CAUSE TO BE FURNISHED TO EACH OTHER, AND EACH AT ITS OWN EXPENSE, AS PROMPTLY AS PRACTICABLE, SUCH INFORMATION (INCLUDING ACCESS TO BOOKS AND RECORDS) AND ASSISTANCE, INCLUDING MAKING EMPLOYEES AVAILABLE ON A MUTUALLY CONVENIENT BASIS TO PROVIDE ADDITIONAL INFORMATION AND EXPLANATIONS OF ANY MATERIAL PROVIDED RELATING TO CUTANOGEN, AS IS REASONABLY NECESSARY FOR THE FILING OF ANY TAX RETURNS, FOR THE PREPARATION FOR ANY AUDIT AND FOR THE PROSECUTION OR DEFENSE OF ANY ACTION OR PROCEEDING RELATING TO ANY ADJUSTMENT OR PROPOSED ADJUSTMENT WITH RESPECT TO TAXES. PURCHASER SHALL RETAIN IN ITS POSSESSION, AND SHALL PROVIDE THE COMPANY REASONABLE ACCESS TO (INCLUDING THE RIGHT TO MAKE COPIES OF), SUCH SUPPORTING BOOKS AND RECORDS AND ANY OTHER MATERIALS THAT THE COMPANY MAY SPECIFY WITH RESPECT TO MATTERS RELATING TO TAXES FOR ANY TAXABLE PERIOD ENDING ON OR PRIOR TO OR WHICH INCLUDES THE CLOSING DATE UNTIL THE RELEVANT STATUTE OF LIMITATIONS HAS EXPIRED. AFTER SUCH TIME, PURCHASER MAY DISPOSE OF SUCH MATERIAL; PROVIDED , THAT PRIOR TO SUCH DISPOSITION PURCHASER SHALL GIVE THE COMPANY A REASONABLE OPPORTUNITY AT ITS EXPENSE TO TAKE POSSESSION OF SUCH MATERIALS.

(D) NEITHER PURCHASER NOR ANY AFFILIATE OR SUCCESSOR OF PURCHASER SHALL AMEND, REFILE OR OTHERWISE MODIFY ANY TAX RETURN RELATING IN WHOLE OR IN PART TO CUTANOGEN WITH RESPECT TO ANY TAXABLE YEAR OR PERIOD ENDING ON OR BEFORE DECEMBER 31, 2007, WITHOUT THE PRIOR WRITTEN CONSENT OF THE COMPANY.

SECTION 6.2 CERTAIN OTHER TAXES

. ALL TRANSFER, DOCUMENTARY, SALES, USE, STAMP, REGISTRATION AND OTHER SUCH TAXES AND FEES (INCLUDING ANY PENALTIES AND INTEREST) INCURRED IN CONNECTION WITH THIS AGREEMENT, IF ANY, SHALL BE PAID 50% BY PURCHASER AND 50% BY THE COMPANY, AND THE PARTY OBLIGATED UNDER APPLICABLE LAW TO FILE ALL NECESSARY TAX RETURNS AND OTHER DOCUMENTATION WITH RESPECT TO ANY SUCH TRANSFER, DOCUMENTARY, SALES, USE, STAMP, REGISTRATION AND OTHER TAXES AND FEES, SHALL FILE SUCH TAX RETURNS OR OTHER DOCUMENTATION AND, IF REQUIRED BY APPLICABLE LAW, THE OTHER PARTY WILL, AND WILL CAUSE ITS AFFILIATES TO, JOIN IN THE EXECUTION OF ANY SUCH TAX RETURNS AND OTHER DOCUMENTATION AND WILL COOPERATE WITH THE OTHER PARTY TO TAKE SUCH COMMERCIALLY REASONABLE ACTIONS AS WILL MINIMIZE OR REDUCE THE AMOUNT OF SUCH TAXES OR FEES.

SECTION 6.3 TAX AUDITS.

(A) THE COMPANY SHALL HAVE THE SOLE RIGHT (BUT NOT THE OBLIGATION) TO REPRESENT THE INTERESTS OF CUTANOGEN IN ANY AUDIT OR ADMINISTRATIVE OR COURT PROCEEDING RELATING TO (I) TAXES DESCRIBED IN SECTION 6.1(A) AND (II) WITH RESPECT TO ALL OTHER TAXES, TAXES FOR TAXABLE PERIODS ENDING ON OR BEFORE DECEMBER 31, 2007 AND, IN EACH CASE, THE COMPANY SHALL HAVE THE RIGHT TO EMPLOY COUNSEL OF ITS CHOICE AT ITS EXPENSE.

(B) PURCHASER SHALL HAVE THE SOLE RIGHT TO REPRESENT THE INTERESTS OF CUTANOGEN IN ALL OTHER AUDITS OR ADMINISTRATIVE OR COURT PROCEEDINGS RELATING TO TAXES.

(C) THE COMPANY, ON THE ONE HAND, AND PURCHASER, ON THE OTHER HAND, SHALL NOT ENTER INTO ANY COMPROMISE OR AGREE TO SETTLE ANY CLAIM PURSUANT TO ANY TAX AUDIT OR PROCEEDING WHICH WOULD ADVERSELY AFFECT THE OTHER PARTY WITHOUT THE WRITTEN CONSENT OF THE OTHER PARTY.

SECTION 6.4 INDEMNIFICATION.

AFTER THE CLOSING DATE, PURCHASER SHALL, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, INDEMNIFY AND HOLD HARMLESS THE COMPANY AND ITS AFFILIATES FROM AND AGAINST ANY AND ALL TAX LOSSES ARISING OUT OF OR RELATING TO ANY TAXES OF CUTANOGEN.

SECTION 6.5 REFUNDS

. ANY REFUNDS OF TAXES (TOGETHER WITH ANY INTEREST WITH RESPECT THERETO) PAID TO OR IN RESPECT OF CUTANOGEN (INCLUDING ANY AMOUNTS CREDITED AGAINST INCOME TAX TO WHICH PURCHASER, ITS AFFILIATES) AND THAT RELATE TO TAXES FOR WHICH THE COMPANY IS RESPONSIBLE PURSUANT TO THIS ARTICLE VI SHALL BE FOR THE ACCOUNT OF THE COMPANY. PURCHASER SHALL PAY OVER TO THE COMPANY ANY SUCH REFUND OR THE AMOUNT OF ANY SUCH CREDIT (IN EACH CASE, TOGETHER WITH ANY INTEREST WITH RESPECT THERETO) WITHIN FIFTEEN (15) DAYS AFTER RECEIPT OR ENTITLEMENT THERETO. PURCHASER SHALL, IF THE COMPANY SO REQUESTS AND AT THE COMPANY'S EXPENSE, PREPARE, EXECUTE AND FILE ANY CLAIMS FOR REFUNDS OR CREDITS, TO WHICH THE COMPANY IS ENTITLED UNDER THIS SECTION. PURCHASER SHALL PERMIT THE COMPANY TO CONTROL THE PROSECUTION OF ANY SUCH REFUND.

SECTION 6.6 CERTAIN ELECTIONS AND OTHER TAX MATTERS

(A) AT THE COMPANY'S REQUEST, PURCHASER SHALL MAKE OR JOIN IN MAKING ANY ELECTIONS UNDER SECTION 338 OF THE CODE (AND ANY COMPARABLE ELECTION UNDER ANY RELEVANT STATE OR LOCAL LAW) (A " SECTION 338 ELECTION ") WITH RESPECT TO THE PURCHASE AND SALE OF THE CUTANOGEN SHARES. IN NO EVENT SHALL PURCHASER MAKE A SECTION 338 ELECTION WITH RESPECT TO CUTANOGEN WITHOUT THE PRIOR WRITTEN CONSENT OF THE COMPANY. IF THE COMPANY SHALL DECIDE TO MAKE ONE OR MORE SECTION 338 ELECTIONS, IT SHALL NOTIFY PURCHASER IN WRITING OF SUCH DECISION WITHIN SIXTY (60) DAYS AFTER THE CLOSING DATE. IF, PURSUANT TO THIS SECTION, THE COMPANY DETERMINES TO MAKE A SECTION 338 ELECTION, THE COMPANY SHALL PROPOSE AN ALLOCATION OF THE APPLICABLE PURCHASE PRICE (WHICH, FOR THIS PURPOSE, SHALL INCLUDE ANY LIABILITIES PROPERLY TAKEN INTO ACCOUNT FOR PURPOSES OF DETERMINING THE PURCHASE PRICE UNDER CODE SECTION 338) IN ACCORDANCE WITH CODE SECTION 1060 AND THE TREASURY REGULATIONS PROMULGATED THEREUNDER (AND ANY SIMILAR PROVISION OF STATE, LOCAL OR FOREIGN LAW, AS APPROPRIATE), AND SHALL NOTIFY PURCHASER IN WRITING OF SUCH PROPOSED PURCHASE PRICE ALLOCATION WITHIN THIRTY (30) DAYS FOLLOWING DELIVERY OF THE NOTIFICATION OF THE COMPANY'S DECISION TO MAKE A SECTION 338 ELECTION. THE PARTIES SHALL COOPERATE IN GOOD FAITH TO AGREE ON AN ALLOCATION OF THE PURCHASE PRICE AND, ONCE AGREED TO, THE ALLOCATION SHALL BE BINDING ON THE PARTIES (THE " ALLOCATION "). ADDITIONALLY, THE PARTIES AGREE TO SHARE EQUALLY THE TOTAL BENEFIT RECEIVED OR ACHIEVED BY THE PARTIES AS A RESULT OF SUCH SECTION 338 ELECTION. IF THE PARTIES CANNOT AGREE UPON THE ALLOCATION WITHIN THIRTY (30) DAYS FOLLOWING THE COMPANY'S DELIVERY OF ITS PROPOSED ALLOCATION TO PURCHASER, THE PARTIES SHALL SUBMIT ANY DISPUTES TO THREE (3) INDEPENDENT ACCOUNTANTS. THE INDEPENDENT ACCOUNTANTS SHALL FINALLY AND CONCLUSIVELY RESOLVE ANY DISPUTED MATTERS IN ACCORDANCE WITH CODE SECTION 1060 WITHIN THIRTY (30) DAYS FOLLOWING RECEIPT OF THE SUBMISSION. PURCHASER AND THE COMPANY SHALL REPORT AND FILE TAX RETURNS (INCLUDING BUT NOT LIMITED TO INTERNAL REVENUE SERVICE FORM 8594) IN ALL RESPECTS AND FOR ALL PURPOSES CONSISTENT WITH THE ALLOCATION. NEITHER PURCHASER NOR THE COMPANY SHALL TAKE ANY POSITION (WHETHER IN AUDITS, TAX RETURNS OR OTHERWISE) THAT IS INCONSISTENT WITH THE ALLOCATION UNLESS REQUIRED TO DO SO BY APPLICABLE LAW. WITHIN 180 DAYS FOLLOWING THE CLOSING, THE COMPANY SHALL DELIVER TO PURCHASER IRS FORM 8023 (OR APPLICABLE SUCCESSOR FORM) FOR WHICH A SECTION 338 ELECTION IS MADE, FULLY EXECUTED BY THE COMPANY OR OTHER APPLICABLE SELLERS PURSUANT TO THE REQUIREMENTS STATED THEREIN.

(B) IT IS THE INTENTION OF THE PARTIES TO TREAT ANY INDEMNITY PAYMENT MADE UNDER THIS ARTICLE VI AS AN ADJUSTMENT TO THE PURCHASE PRICE FOR ALL FEDERAL, STATE, LOCAL AND FOREIGN TAX PURPOSES, AND THE PARTIES AGREE TO FILE THEIR TAX RETURNS ACCORDINGLY.

(C) AT LEAST FIVE (5) BUSINESS DAYS PRIOR TO THE CLOSING, THE COMPANY SHALL DELIVER TO PURCHASER A SCHEDULE SETTING FORTH THE ALLOCATION OF THE PURCHASE PRICE, WHICH ALLOCATION SHALL BE BINDING ON THE PARTIES.

ARTICLE VII
INDEMNIFICATION

SECTION 7.1 INDEMNIFICATION BY THE COMPANY

. FOLLOWING THE CLOSING, EXCEPT WITH RESPECT TO TAXES (WHICH SHALL BE GOVERNED EXCLUSIVELY BY ARTICLE VI), , THE COMPANY SHALL, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, INDEMNIFY, DEFEND AND HOLD HARMLESS PURCHASER, EACH AFFILIATE OF PURCHASER AND EACH OF THEIR RESPECTIVE DIRECTORS, OFFICERS, SUCCESSORS AND ASSIGNS (THE " PURCHASER INDEMNITEES ") FROM AND AGAINST ANY AND ALL LOSSES SUFFERED OR INCURRED BY ANY OF THE PURCHASER INDEMNITEES ARISING OUT OF OR RESULTING FROM THE BREACH OF ANY REPRESENTATION OR WARRANTY MADE BY COMPANY IN ARTICLE II OF THIS AGREEMENT. ALL SUCH REPRESENTATIONS AND WARRANTIES WILL SURVIVE THE CLOSING AND REMAIN IN FULL FORCE AND EFFECT FOR A PERIOD OF NINETY (90) DAYS FOLLOWING THE CLOSING DATE.

SECTION 7.2 INDEMNIFICATION BY PURCHASER

. FOLLOWING THE CLOSING, EXCEPT WITH RESPECT TO TAXES (WHICH SHALL BE GOVERNED EXCLUSIVELY BY ARTICLE VI), PURCHASER SHALL, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, INDEMNIFY, DEFEND AND HOLD HARMLESS THE COMPANY, EACH AFFILIATE OF THE COMPANY AND EACH OF THEIR RESPECTIVE DIRECTORS, OFFICERS, EMPLOYEES, SUCCESSORS AND ASSIGNS (THE " COMPANY INDEMNITEES ") FROM AND AGAINST ANY AND ALL LOSSES SUFFERED OR INCURRED BY ANY OF THE COMPANY INDEMNITEES ARISING OUT OF OR RESULTING FROM ANY CUTANOGEN LIABILITY (INCLUDING, WITHOUT LIMITATION, ARISING OUT OF THE FAILURE OF PURCHASER OR CUTANOGEN TO PAY, PERFORM OR OTHERWISE DISCHARGE WHEN DUE ANY SUCH CUTANOGEN LIABILITY), WHETHER ARISING PRIOR TO, ON OR AFTER THE CLOSING. THIS INDEMNITY SHALL ALSO APPLY IN THE EVENT OF THE PURCHASER'S BREACH OF ANY REPRESENTATION OR WARRANTY THAT IT HAS MADE IN ARTICLE III OF THIS AGREEMENT. ALL SUCH REPRESENTATIONS AND WARRANTIES WILL SURVIVE THE CLOSING AND REMAIN IN FULL FORCE AND EFFECT FOR A PERIOD OF NINETY (90) DAYS FOLLOWING THE CLOSING DATE.

SECTION 7.3 LIMITATIONS ON INDEMNIFICATION OBLIGATIONS

. THE AMOUNT WHICH ANY PARTY (AN " INDEMNIFYING PARTY ") IS OR MAY BE REQUIRED TO PAY TO ANY OTHER PARTY (AN " INDEMNITEE ") PURSUANT TO SECTION 7.1 OR SECTION 7.2 SHALL BE REDUCED (INCLUDING, WITHOUT LIMITATION, RETROACTIVELY) BY ANY INSURANCE PROCEEDS OR OTHER AMOUNT ACTUALLY RECOVERED BY OR ON BEHALF OF SUCH INDEMNITEE, IN REDUCTION OF THE RELATED LOSS. IF AN INDEMNITEE SHALL HAVE RECEIVED THE PAYMENT REQUIRED BY THIS AGREEMENT FROM AN INDEMNIFYING PARTY IN RESPECT OF ANY LOSS AND SHALL SUBSEQUENTLY ACTUALLY RECEIVE INSURANCE PROCEEDS OR OTHER AMOUNTS IN RESPECT OF SUCH LOSS, THEN SUCH INDEMNITEE SHALL PAY TO SUCH INDEMNIFYING PARTY A SUM EQUAL TO THE AMOUNT OF SUCH INSURANCE PROCEEDS OR OTHER AMOUNTS ACTUALLY RECEIVED (UP TO BUT NOT IN EXCESS OF THE AMOUNT OF ANY INDEMNITY PAYMENT MADE HEREUNDER). AN INSURER WHO WOULD OTHERWISE BE OBLIGATED TO PAY ANY CLAIM SHALL NOT BE RELIEVED OF THE RESPONSIBILITY WITH RESPECT THERETO, OR, SOLELY BY VIRTUE OF THE INDEMNIFICATION PROVISIONS HEREOF, HAVE ANY SUBROGATION RIGHTS WITH RESPECT THERETO, IT BEING EXPRESSLY UNDERSTOOD AND AGREED THAT NO INSURER OR ANY OTHER THIRD PARTY SHALL BE ENTITLED TO A "WINDFALL" (I.E. , A BENEFIT THEY WOULD NOT BE ENTITLED TO RECEIVE IN THE ABSENCE OF THE INDEMNIFICATION PROVISIONS) BY VIRTUE OF THE INDEMNIFICATION PROVISIONS HEREOF.

SECTION 7.4 PROCEDURES FOR INDEMNIFICATION OF THIRD PARTY CLAIMS

. PROCEDURES FOR INDEMNIFICATION OF THIRD PARTY CLAIMS SHALL BE AS FOLLOWS:

(A) IF AN INDEMNITEE SHALL RECEIVE NOTICE OR OTHERWISE LEARN OF THE ASSERTION BY A PERSON (INCLUDING, WITHOUT LIMITATION, ANY GOVERNMENTAL AUTHORITY) WHO IS NOT A PARTY TO THIS AGREEMENT OF ANY CLAIM OR OF THE COMMENCEMENT BY ANY SUCH PERSON OF ANY ACTION OR PROCEEDING (A " THIRD PARTY CLAIM ") WITH RESPECT TO WHICH AN INDEMNIFYING PARTY MAY BE OBLIGATED TO PROVIDE INDEMNIFICATION PURSUANT TO SECTION 7.1 OR SECTION 7.2 , SUCH INDEMNITEE SHALL GIVE SUCH INDEMNIFYING PARTY WRITTEN NOTICE THEREOF PROMPTLY AFTER BECOMING AWARE OF SUCH THIRD PARTY CLAIM; PROVIDED THAT THE FAILURE OF ANY INDEMNITEE TO GIVE NOTICE AS PROVIDED IN THIS SECTION 7.4(A) SHALL NOT RELIEVE THE RELATED INDEMNIFYING PARTY OF ITS OBLIGATIONS UNDER THIS ARTICLE VII , EXCEPT TO THE EXTENT THAT SUCH INDEMNIFYING PARTY IS PREJUDICED BY SUCH FAILURE TO GIVE NOTICE. SUCH NOTICE SHALL DESCRIBE THE THIRD PARTY CLAIM IN REASONABLE DETAIL AND, IF ASCERTAINABLE, SHALL INDICATE THE AMOUNT (ESTIMATED IF NECESSARY) OF THE LOSS THAT HAS BEEN OR MAY BE SUSTAINED BY SUCH INDEMNITEE.

(B) AN INDEMNIFYING PARTY MAY ELECT TO DEFEND OR TO SEEK TO SETTLE OR COMPROMISE, AT SUCH INDEMNIFYING PARTY'S OWN EXPENSE AND BY SUCH INDEMNIFYING PARTY'S OWN COUNSEL, ANY THIRD PARTY CLAIM. WITHIN THIRTY (30) DAYS AFTER THE RECEIPT OF NOTICE FROM AN INDEMNITEE IN ACCORDANCE WITH SECTION 7.4(A) (OR SOONER, IF THE NATURE OF SUCH THIRD PARTY CLAIM SO REQUIRES), THE INDEMNIFYING PARTY SHALL NOTIFY THE INDEMNITEE WHETHER THE INDEMNIFYING PARTY WILL ASSUME RESPONSIBILITY FOR DEFENDING SUCH THIRD PARTY CLAIM. AFTER NOTICE FROM AN INDEMNIFYING PARTY TO AN INDEMNITEE OF ITS ELECTION TO ASSUME THE DEFENSE OF A THIRD PARTY CLAIM, SUCH INDEMNIFYING PARTY SHALL NOT BE LIABLE TO SUCH INDEMNITEE UNDER THIS ARTICLE VII FOR ANY LEGAL OR OTHER EXPENSES (EXCEPT EXPENSES APPROVED IN ADVANCE BY THE INDEMNIFYING PARTY) SUBSEQUENTLY INCURRED BY SUCH INDEMNITEE IN CONNECTION WITH THE DEFENSE THEREOF; PROVIDED THAT IF THE DEFENDANTS IN ANY SUCH CLAIM INCLUDE BOTH THE INDEMNIFYING PARTY AND ONE OR MORE INDEMNITEES AND IN ANY INDEMNITEE'S REASONABLE JUDGMENT A CONFLICT OF INTEREST BETWEEN ONE OR MORE OF SUCH INDEMNITEES AND SUCH INDEMNIFYING PARTY EXISTS IN RESPECT OF SUCH CLAIM, SUCH INDEMNITEES SHALL HAVE THE RIGHT TO EMPLOY SEPARATE COUNSEL TO REPRESENT SUCH INDEMNITEES AND IN THAT EVENT THE REASONABLE FEES AND EXPENSES OF SUCH SEPARATE COUNSEL (BUT NOT MORE THAN ONE SEPARATE COUNSEL REASONABLY SATISFACTORY TO THE INDEMNIFYING PARTY) SHALL BE PAID BY SUCH INDEMNIFYING PARTY. IF AN INDEMNIFYING PARTY ELECTS NOT TO ASSUME RESPONSIBILITY FOR DEFENDING A THIRD PARTY CLAIM, OR FAILS TO NOTIFY AN INDEMNITEE OF ITS ELECTION AS PROVIDED IN THIS SECTION 7.4(B) , SUCH INDEMNITEE MAY DEFEND OR (SUBJECT TO THE REMAINDER OF THIS SECTION 7.4(B) AND SECTION 7.4(D)) SEEK TO COMPROMISE OR SETTLE SUCH THIRD PARTY CLAIM AT THE EXPENSE OF THE INDEMNIFYING PARTY. NEITHER AN INDEMNIFYING PARTY NOR AN INDEMNITEE SHALL CONSENT TO ENTRY OF ANY JUDGMENT OR ENTER INTO ANY SETTLEMENT OF ANY THIRD PARTY CLAIM WHICH DOES NOT INCLUDE AS AN UNCONDITIONAL TERM THEREOF THE GIVING BY THE CLAIMANT OR PLAINTIFF TO SUCH INDEMNITEE, IN THE CASE OF A CONSENT OR SETTLEMENT BY AN INDEMNIFYING PARTY, OR THE INDEMNIFYING PARTY, IN THE CASE OF A CONSENT OR SETTLEMENT BY THE INDEMNITEE, OF A WRITTEN RELEASE FROM ALL LIABILITY IN RESPECT TO SUCH THIRD PARTY CLAIM.

(C) IF AN INDEMNIFYING PARTY CHOOSES TO DEFEND OR TO SEEK TO COMPROMISE OR SETTLE ANY THIRD PARTY CLAIM, THE RELATED INDEMNITEE SHALL MAKE AVAILABLE TO SUCH INDEMNIFYING PARTY ANY PERSONNEL OR ANY BOOKS, RECORDS OR OTHER DOCUMENTS WITHIN ITS CONTROL OR WHICH IT OTHERWISE HAS THE ABILITY TO MAKE AVAILABLE THAT ARE NECESSARY OR APPROPRIATE FOR SUCH DEFENSE, SETTLEMENT OR COMPROMISE, AND SHALL OTHERWISE COOPERATE IN THE DEFENSE, SETTLEMENT OR COMPROMISE OF SUCH THIRD PARTY CLAIM.

(D) NOTWITHSTANDING ANYTHING IN THIS SECTION 7.4 TO THE CONTRARY, NEITHER AN INDEMNIFYING PARTY NOR AN INDEMNITEE MAY SETTLE OR COMPROMISE ANY CLAIM OVER THE OBJECTION OF THE OTHER; PROVIDED , HOWEVER , THAT CONSENT TO SETTLEMENT OR COMPROMISE SHALL NOT BE UNREASONABLY WITHHELD, CONDITIONED OR DELAYED. IF AN INDEMNIFYING PARTY NOTIFIES THE RELATED INDEMNITEE IN WRITING OF SUCH INDEMNIFYING PARTY'S DESIRE TO SETTLE OR COMPROMISE A THIRD PARTY CLAIM ON THE BASIS SET FORTH IN SUCH NOTICE (PROVIDED THAT SUCH SETTLEMENT OR COMPROMISE INCLUDES AS AN UNCONDITIONAL TERM THEREOF THE GIVING BY THE CLAIMANT OR PLAINTIFF OF A WRITTEN RELEASE OF THE INDEMNITEE FROM ALL LIABILITY IN RESPECT THEREOF) AND THE INDEMNITEE SHALL NOTIFY THE INDEMNIFYING PARTY IN WRITING THAT SUCH INDEMNITEE DECLINES TO ACCEPT ANY SUCH SETTLEMENT OR COMPROMISE, SUCH INDEMNITEE MAY CONTINUE TO CONTEST SUCH THIRD PARTY CLAIM, FREE OF ANY PARTICIPATION BY SUCH INDEMNIFYING PARTY, AT SUCH INDEMNITEE'S SOLE EXPENSE. IN SUCH EVENT, THE OBLIGATION OF SUCH INDEMNIFYING PARTY TO SUCH INDEMNITEE WITH RESPECT TO SUCH THIRD PARTY CLAIM SHALL BE EQUAL TO (I) THE COSTS AND EXPENSES OF SUCH INDEMNITEE PRIOR TO THE DATE SUCH INDEMNIFYING PARTY NOTIFIES SUCH INDEMNITEE OF THE OFFER TO SETTLE OR COMPROMISE (TO THE EXTENT SUCH COSTS AND EXPENSES ARE OTHERWISE INDEMNIFIABLE HEREUNDER) PLUS (II) THE LESSER OF (X) THE AMOUNT OF ANY OFFER OF SETTLEMENT OR COMPROMISE WHICH SUCH INDEMNITEE DECLINED TO ACCEPT AND (Y) THE ACTUAL OUT-OF-POCKET AMOUNT SUCH INDEMNITEE IS OBLIGATED TO PAY SUBSEQUENT TO SUCH DATE AS A RESULT OF SUCH INDEMNITEE'S CONTINUING TO PURSUE SUCH THIRD PARTY CLAIM.

(E) IN THE EVENT OF PAYMENT BY AN INDEMNIFYING PARTY TO ANY INDEMNITEE IN CONNECTION WITH ANY THIRD PARTY CLAIM, SUCH INDEMNIFYING PARTY SHALL, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, BE SUBROGATED TO AND SHALL STAND IN THE PLACE OF SUCH INDEMNITEE AS TO ANY EVENTS OR CIRCUMSTANCES IN RESPECT OF WHICH SUCH INDEMNITEE MAY HAVE ANY RIGHT OR CLAIM RELATING TO SUCH THIRD PARTY CLAIM AGAINST ANY CLAIMANT OR PLAINTIFF ASSERTING SUCH THIRD PARTY CLAIM OR AGAINST ANY OTHER PERSON. SUCH INDEMNITEE SHALL COOPERATE WITH SUCH INDEMNIFYING PARTY IN A REASONABLE MANNER, AND AT THE COST AND EXPENSE OF SUCH INDEMNIFYING PARTY, IN PROSECUTING ANY SUBROGATED RIGHT OR CLAIM.

SECTION 7.5 OTHER PROCEDURES FOR INDEMNIFICATION

(A) ANY CLAIM ON ACCOUNT OF A LOSS WHICH DOES NOT RESULT FROM A THIRD PARTY CLAIM SHALL BE ASSERTED BY WRITTEN NOTICE GIVEN BY THE INDEMNITEE TO THE RELATED INDEMNIFYING PARTY. SUCH INDEMNIFYING PARTY SHALL HAVE A PERIOD OF THIRTY (30) DAYS AFTER THE RECEIPT OF SUCH NOTICE WITHIN WHICH TO RESPOND THERETO. IF SUCH INDEMNIFYING PARTY DOES NOT RESPOND WITHIN SUCH THIRTY (30) DAY PERIOD, SUCH INDEMNIFYING PARTY SHALL BE DEEMED TO HAVE REFUSED TO ACCEPT RESPONSIBILITY TO MAKE PAYMENT. IF SUCH INDEMNIFYING PARTY DOES NOT RESPOND WITHIN SUCH THIRTY (30) DAY PERIOD OR REJECTS SUCH CLAIM IN WHOLE OR IN PART, SUCH INDEMNITEE SHALL BE FREE TO PURSUE SUCH REMEDIES AS MAY BE AVAILABLE TO SUCH PARTY UNDER THIS AGREEMENT OR UNDER APPLICABLE LAW.

(B) IN ADDITION TO ANY ADJUSTMENTS REQUIRED PURSUANT TO SECTION 7.3 , IF THE AMOUNT OF ANY LOSS SHALL, AT ANY TIME SUBSEQUENT TO THE PAYMENT REQUIRED BY THIS AGREEMENT, BE REDUCED BY RECOVERY, SETTLEMENT OR OTHERWISE, THE AMOUNT OF SUCH REDUCTION, LESS ANY EXPENSES INCURRED IN CONNECTION THEREWITH, SHALL PROMPTLY BE REPAID BY THE INDEMNITEE TO THE INDEMNIFYING PARTY.

SECTION 7.6 REMEDIES CUMULATIVE

. THE REMEDIES PROVIDED IN THIS ARTICLE VII SHALL BE CUMULATIVE AND SHALL NOT PRECLUDE ASSERTION BY AN INDEMNITEE OF ANY OTHER RIGHTS OR THE SEEKING ANY AND ALL OTHER REMEDIES AGAINST ANY INDEMNIFYING PARTY.

SECTION 7.7 SURVIVAL OF INDEMNITIES

. THE OBLIGATIONS OF EACH OF THE PARTIES UNDER THIS ARTICLE VII SHALL SURVIVE THE SALE OR OTHER TRANSFER BY IT OF ANY ASSETS OR BUSINESSES OR THE ASSIGNMENT BY IT OF ANY LIABILITIES WITH RESPECT TO ANY LOSS OF THE OTHER RELATED TO SUCH ASSETS, BUSINESSES OR LIABILITIES.

SECTION 7.8 LIMITATION OF LIABILITY

. IN NO EVENT SHALL AN INDEMNIFYING PARTY BE LIABLE UNDER THIS ARTICLE VII FOR ANY SPECIAL, CONSEQUENTIAL, INDIRECT, INCIDENTAL OR PUNITIVE DAMAGES OR LOST PROFITS, HOWEVER CAUSED AND ON ANY THEORY OF LIABILITY (INCLUDING, WITHOUT LIMITATION, NEGLIGENCE) ARISING IN ANY WAY OUT OF THIS ARTICLE VII , WHETHER OR NOT SUCH PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES; PROVIDED , HOWEVER , THAT THE FOREGOING LIMITATIONS SHALL NOT LIMIT EACH PARTY'S INDEMNIFICATION OBLIGATIONS FOR LIABILITIES TO THIRD PARTIES AS SET FORTH IN THIS ARTICLE VII .

ARTICLE VIII
MISCELLANEOUS

SECTION 8.1 SURVIVAL OF REPRESENTATIONS, WARRANTIES AND AGREEMENTS

THE REPRESENTATIONS AND WARRANTIES CONTAINED HEREIN OR IN ANY OTHER WRITING DELIVERED PURSUANT HERETO, AS WELL AS ANY COVENANT OR AGREEMENT OF THE PARTIES THAT BY ITS TERMS CONTEMPLATES PERFORMANCE EXCLUSIVELY PRIOR TO THE CLOSING DATE, SHALL SURVIVE UNTIL (BUT NOT BEYOND) THE CLOSING DATE. NOTHING IN THIS PARAGRAPH SHALL LIMIT ANY COVENANT OR AGREEMENT OF THE PARTIES THAT BY ITS TERMS CONTEMPLATES PERFORMANCE IN WHOLE OR IN PART AFTER THE CLOSING DATE.

SECTION 8.2 AMENDMENT OR SUPPLEMENT

AT ANY TIME PRIOR TO THE CLOSING DATE, THIS AGREEMENT MAY BE AMENDED OR SUPPLEMENTED IN ANY AND ALL RESPECTS, WHETHER BEFORE OR AFTER AUTHORIZATION OF THE TRANSACTION BY THE HOLDERS OF COMPANY COMMON STOCK, BY WRITTEN AGREEMENT OF THE PARTIES HERETO, BY ACTION TAKEN BY THEIR RESPECTIVE BOARDS OF DIRECTORS; PROVIDED , HOWEVER , THAT FOLLOWING THE COMPANY STOCKHOLDER AUTHORIZATION, THERE SHALL BE NO AMENDMENT OR CHANGE TO THE PROVISIONS HEREOF WHICH BY LAW OR IN ACCORDANCE WITH THE RULES OF ANY RELEVANT STOCK EXCHANGE WOULD REQUIRE FURTHER APPROVAL BY THE HOLDERS OF COMPANY COMMON STOCK WITHOUT SUCH APPROVAL.

SECTION 8.3 EXTENSION OF TIME, WAIVER, ETC

AT ANY TIME PRIOR TO THE CLOSING DATE, ANY PARTY MAY, SUBJECT TO APPLICABLE LAW, (A) WAIVE ANY INACCURACIES IN THE REPRESENTATIONS AND WARRANTIES OF THE OTHER PARTY HERETO, (B) EXTEND THE TIME FOR THE PERFORMANCE OF ANY OF THE OBLIGATIONS OR ACTS OF THE OTHER PARTY HERETO OR (C) WAIVE COMPLIANCE BY ANY OTHER PARTY WITH ANY OF THE AGREEMENTS CONTAINED HEREIN OR, EXCEPT AS OTHERWISE PROVIDED HEREIN, WAIVE ANY OF SUCH PARTY'S CONDITIONS; PROVIDED THAT AFTER THE COMPANY STOCKHOLDER AUTHORIZATION IS OBTAINED, THERE MAY NOT BE ANY EXTENSION OR WAIVER OF THIS AGREEMENT OR ANY PORTION THEREOF WHICH, BY LAW OR IN ACCORDANCE WITH THE RULES OF ANY RELEVANT STOCK EXCHANGE, REQUIRES FURTHER APPROVAL BY SUCH STOCKHOLDERS. NOTWITHSTANDING THE FOREGOING, NO FAILURE OR DELAY BY THE COMPANY OR PURCHASER IN EXERCISING ANY RIGHT HEREUNDER SHALL OPERATE AS A WAIVER THEREOF NOR SHALL ANY SINGLE OR PARTIAL EXERCISE THEREOF PRECLUDE ANY OTHER OR FURTHER EXERCISE THEREOF OR THE EXERCISE OF ANY OTHER RIGHT HEREUNDER. ANY AGREEMENT ON THE PART OF A PARTY HERETO TO ANY SUCH EXTENSION OR WAIVER SHALL BE VALID ONLY IF SET FORTH IN AN INSTRUMENT IN WRITING SIGNED ON BEHALF OF SUCH PARTY.

SECTION 8.4 ASSIGNMENT

NEITHER THIS AGREEMENT NOR ANY OF THE RIGHTS, INTERESTS OR OBLIGATIONS HEREUNDER SHALL BE ASSIGNED, IN WHOLE OR IN PART, BY ANY OF THE PARTIES WITHOUT THE PRIOR WRITTEN CONSENT OF THE OTHER PARTY; PROVIDED THAT SUCH CONSENT SHALL NOT BE REQUIRED (A) FOR ASSIGNMENTS AND TRANSFERS BY OPERATION OF LAW AND (B) IN THE EVENT THE COMPANY ASSIGNS ANY OR ALL OF ITS RIGHTS, INTERESTS AND OBLIGATIONS HEREUNDER TO A PERSON WITH WHOM THE COMPANY MERGES OR TO WHOM THE COMPANY SELLS ALL OR SUBSTANTIALLY ALL OF ITS ASSETS OR TO AN AFFILIATE OF COMPANY. SUBJECT TO THE PRECEDING SENTENCE, THIS AGREEMENT SHALL BE BINDING UPON, INURE TO THE BENEFIT OF, AND BE ENFORCEABLE BY, THE PARTIES HERETO AND THEIR RESPECTIVE SUCCESSORS AND PERMITTED ASSIGNS. ANY PURPORTED ASSIGNMENT NOT PERMITTED UNDER THIS SECTION SHALL BE NULL AND VOID.

SECTION 8.5 COUNTERPARTS

THIS AGREEMENT MAY BE EXECUTED IN COUNTERPARTS (EACH OF WHICH SHALL BE DEEMED TO BE AN ORIGINAL BUT BOTH OF WHICH TAKEN TOGETHER SHALL CONSTITUTE ONE AND THE SAME AGREEMENT) AND SHALL BECOME EFFECTIVE WHEN ONE OR MORE COUNTERPARTS HAVE BEEN SIGNED BY EACH OF THE PARTIES AND DELIVERED TO THE OTHER PARTY.

SECTION 8.6 ENTIRE AGREEMENT; NO THIRD PARTY BENEFICIARIES

THIS AGREEMENT, TOGETHER WITH THE SCHEDULES, THE DISCLOSURE LETTER AND THE CONFIDENTIALITY AGREEMENT, (A) CONSTITUTES THE ENTIRE AGREEMENT, AND SUPERSEDES ALL OTHER PRIOR AGREEMENTS AND UNDERSTANDINGS, BOTH WRITTEN AND ORAL, BETWEEN THE PARTIES, OR ANY OF THEM, WITH RESPECT TO THE SUBJECT MATTER HEREOF AND THEREOF AND (B) ARE NOT INTENDED TO AND SHALL NOT CONFER UPON ANY PERSON OTHER THAN THE PARTIES HERETO ANY RIGHTS OR REMEDIES HEREUNDER.

SECTION 8.7 GOVERNING LAW; SUBMISSION TO JURISDICTION; APPOINTMENT OF AGENT FOR SERVICE OF PROCESS; WAIVER OF JURY TRIAL.

(A) THIS AGREEMENT SHALL BE GOVERNED BY, AND CONSTRUED IN ACCORDANCE WITH, THE LAWS OF THE STATE OF NEW JERSEY, WITHOUT REGARD TO PRINCIPLES OF CONFLICT OF LAWS THAT WOULD REQUIRE THE APPLICATION OF THE LAWS OF ANOTHER JURISDICTION. THE PARTIES HERETO HEREBY DECLARE THAT IT IS THEIR INTENTION THAT THIS AGREEMENT SHALL BE REGARDED AS MADE UNDER THE LAWS OF THE STATE OF NEW JERSEY AND THAT THE LAWS OF SAID STATE SHALL BE APPLIED IN INTERPRETING ITS PROVISIONS IN ALL CASES WHERE LEGAL INTERPRETATION SHALL BE REQUIRED. EACH OF THE PARTIES HERETO HEREBY IRREVOCABLY AND UNCONDITIONALLY AGREES (I) TO BE SUBJECT TO THE JURISDICTION OF THE COURTS OF THE STATE OF NEW JERSEY AND OF THE FEDERAL COURTS SITTING IN THE STATE OF NEW JERSEY.

(B) THE PARTIES HERETO HEREBY AGREE TO BRING ALL ACTIONS AND PROCEEDINGS ARISING OUT OF OR RELATING TO THIS AGREEMENT IN THE COURTS OF THE STATE OF NEW JERSEY, AND THE PARTIES IRREVOCABLY WAIVE, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, THE DEFENSE OF AN INCONVENIENT FORUM TO THE MAINTENANCE OF ANY SUCH ACTION OR PROCEEDING. THE PARTIES HERETO AGREE THAT A FINAL JUDGMENT IN ANY SUCH ACTION OR PROCEEDING SHALL BE CONCLUSIVE AND MAY BE ENFORCED IN OTHER JURISDICTIONS BY SUIT ON THE JUDGMENT OR IN ANY OTHER MANNER PROVIDED BY APPLICABLE LAW.

(C) **EACH OF THE PARTIES HERETO HEREBY IRREVOCABLY WAIVES ANY AND ALL RIGHTS TO TRIAL BY JURY IN ANY ACTION OR PROCEEDING ARISING OUT OF OR RELATED TO THIS AGREEMENT.**

SECTION 8.8 SPECIFIC ENFORCEMENT

. THE PARTIES AGREE THAT IRREPARABLE DAMAGE WOULD OCCUR IN THE EVENT THAT ANY OF THE PROVISIONS OF THIS AGREEMENT WERE NOT PERFORMED IN ACCORDANCE WITH THEIR SPECIFIC TERMS OR WERE OTHERWISE BREACHED. IT IS ACCORDINGLY AGREED THAT THE PARTIES SHALL, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, BE ENTITLED TO AN INJUNCTION OR INJUNCTIONS TO PREVENT BREACHES OF THIS AGREEMENT AND TO ENFORCE SPECIFICALLY THE TERMS AND PROVISIONS OF THIS AGREEMENT IN THE CHANCERY COURT OF THE STATE OF DELAWARE, WITHOUT BOND OR OTHER SECURITY BEING REQUIRED, THIS BEING IN ADDITION TO ANY OTHER REMEDY TO WHICH THEY ARE ENTITLED AT LAW OR IN EQUITY.

SECTION 8.9 NOTICES

ALL NOTICES, REQUESTS AND OTHER COMMUNICATIONS TO ANY PARTY HEREUNDER SHALL BE IN WRITING AND SHALL BE DEEMED GIVEN IF DELIVERED PERSONALLY, FACSIMILED (WHICH IS CONFIRMED) OR SENT BY OVERNIGHT COURIER (PROVIDING PROOF OF DELIVERY) TO THE PARTIES AT THE FOLLOWING ADDRESSES:

IF TO PURCHASER, TO: _____
ATTENTION: _____

WITH A COPY (WHICH SHALL NOT CONSTITUTE NOTICE) TO: _____

ATTENTION: _____

IF TO THE COMPANY, TO: **[COMPANY]**

_____

ATTENTION: _____

WITH A COPY (WHICH SHALL NOT CONSTITUTE NOTICE) TO:

OR SUCH OTHER ADDRESS OR FACSIMILE NUMBER AS SUCH PARTY MAY HEREAFTER SPECIFY FOR THE PURPOSE BY NOTICE TO THE OTHER PARTY HERETO. ALL SUCH NOTICES, REQUESTS AND OTHER COMMUNICATIONS SHALL BE DEEMED RECEIVED ON THE DATE OF RECEIPT BY THE RECIPIENT THEREOF IF RECEIVED PRIOR TO 5 P.M. IN THE PLACE OF RECEIPT AND SUCH DAY IS A BUSINESS DAY IN THE PLACE OF RECEIPT. OTHERWISE, ANY SUCH NOTICE, REQUEST OR COMMUNICATION SHALL BE DEEMED NOT TO HAVE BEEN RECEIVED UNTIL THE NEXT SUCCEEDING BUSINESS DAY IN THE PLACE OF RECEIPT.

SECTION 8.10 SEVERABILITY

IF ANY TERM OR OTHER PROVISION OF THIS AGREEMENT IS DETERMINED BY A COURT OF COMPETENT JURISDICTION TO BE INVALID, ILLEGAL OR INCAPABLE OF BEING ENFORCED BY ANY RULE OF LAW OR PUBLIC POLICY, ALL OTHER TERMS, PROVISIONS AND CONDITIONS OF THIS AGREEMENT SHALL NEVERTHELESS REMAIN IN FULL FORCE AND EFFECT. UPON SUCH DETERMINATION THAT ANY TERM OR OTHER PROVISION IS INVALID, ILLEGAL OR INCAPABLE OF BEING ENFORCED, THE PARTIES HERETO SHALL NEGOTIATE IN GOOD FAITH TO MODIFY THIS AGREEMENT SO AS TO EFFECT THE ORIGINAL INTENT OF THE PARTIES AS CLOSELY AS POSSIBLE TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW IN AN ACCEPTABLE MANNER TO THE END THAT THE TRANSACTION IS FULFILLED TO THE EXTENT POSSIBLE.

SECTION 8.11 DEFINITIONS

(A) AS USED IN THIS AGREEMENT, THE FOLLOWING TERMS HAVE THE MEANINGS ASCRIBED THERETO BELOW:

" ACTION OR PROCEEDING " SHALL MEAN ANY ACTION, SUIT, PROCEEDING, ARBITRATION OR GOVERNMENTAL AUTHORITY INVESTIGATION.

" AFFILIATE " SHALL MEAN, AS TO ANY PERSON, ANY OTHER PERSON THAT DIRECTLY OR INDIRECTLY CONTROLS, OR IS CONTROLLED BY, OR IS UNDER COMMON CONTROL WITH, SUCH PERSON. FOR THIS PURPOSE, "CONTROL" (INCLUDING, WITH ITS CORRELATIVE MEANINGS, "CONTROLLED BY" AND "UNDER COMMON CONTROL WITH") SHALL MEAN THE POSSESSION, DIRECTLY OR INDIRECTLY, OF THE POWER TO DIRECT OR CAUSE THE DIRECTION OF MANAGEMENT OR POLICIES OF A PERSON, WHETHER THROUGH THE OWNERSHIP OF SECURITIES OR PARTNERSHIP OR OTHER OWNERSHIP INTERESTS, BY CONTRACT OR OTHERWISE.

" CUTANOGEN LIABILITY " SHALL MEAN ANY LIABILITY RELATING TO, ARISING OUT OF OR RESULTING FROM ANY ACTION, INACTION, EVENT, OMISSION, CONDITION, FACT OR CIRCUMSTANCE OCCURRING OR EXISTING PRIOR TO, ON OR AFTER THE CLOSING, IN EACH CASE TO THE EXTENT SUCH LIABILITY RELATES TO, ARISES OUT OF OR RESULTS FROM ANY OF THE ASSETS OR PROPERTY OF CUTANOGEN.

" MATERIAL ADVERSE EFFECT " SHALL MEAN ANY CHANGE, EVENT OR OCCURRENCE WHICH HAS A MATERIAL ADVERSE EFFECT ON THE CUTANOGEN BUSINESS WHEN TAKEN AS A WHOLE, OTHER THAN CHANGES, EVENTS, OCCURRENCES OR EFFECTS ARISING OUT OF, RESULTING FROM OR ATTRIBUTABLE TO (I) CHANGES IN CONDITIONS IN THE UNITED STATES OR GLOBAL ECONOMY OR CAPITAL OR FINANCIAL MARKETS GENERALLY, INCLUDING CHANGES IN INTEREST OR EXCHANGE RATES, (II) CHANGES IN GENERAL LEGAL, REGULATORY, POLITICAL, ECONOMIC OR BUSINESS CONDITIONS OR CHANGES IN GENERALLY ACCEPTED ACCOUNTING PRINCIPLES THAT, IN EACH CASE, GENERALLY AFFECT INDUSTRIES IN WHICH CUTANOGEN CONDUCTS BUSINESS, PROVIDED THAT SUCH CHANGES DO NOT AFFECT CUTANOGEN IN A DISPROPORTIONATE MANNER.

" TRANSACTION " REFERS COLLECTIVELY TO THIS AGREEMENT AND THE TRANSACTIONS CONTEMPLATED HEREBY TO TAKE PLACE ON THE CLOSING DATE, INCLUDING THE PURCHASE AND SALE OF THE CUTANOGEN SHARES.

" BUSINESS DAY " SHALL MEAN A DAY EXCEPT A SATURDAY, A SUNDAY OR OTHER DAY ON WHICH THE SEC OR BANKS IN THE CITY OF NEW YORK ARE AUTHORIZED OR REQUIRED BY LAW TO BE CLOSED.

" CODE " SHALL MEAN THE INTERNAL REVENUE CODE OF 1986, AS AMENDED.

" COMPANY BOARD " SHALL MEAN THE BOARD OF DIRECTORS OF THE COMPANY OR ANY DULY CONSTITUTED COMMITTEE THEREOF WHICH HAS BEEN GIVEN THE AUTHORITY TO ACT IN THE NAME, PLACE AND STEAD OF THE BOARD OF DIRECTORS OF THE COMPANY WITH RESPECT TO THIS AGREEMENT, THE TRANSACTION AND THE TRANSACTIONS CONTEMPLATED THEREBY.

" COMPANY COMMON STOCK " SHALL MEAN THE VOTING COMMON STOCK, $0.10 PAR VALUE, OF THE COMPANY.

" COMPANY LIABILITY " SHALL MEAN ANY LIABILITY OF THE COMPANY.

" GAAP " SHALL MEAN GENERALLY ACCEPTED ACCOUNTING PRINCIPLES IN THE UNITED STATES.

" GOVERNMENTAL AUTHORITY " SHALL MEAN ANY GOVERNMENT, COURT, REGULATORY OR ADMINISTRATIVE AGENCY, COMMISSION OR AUTHORITY OR OTHER GOVERNMENTAL INSTRUMENTALITY, FEDERAL, STATE OR LOCAL, DOMESTIC, FOREIGN OR MULTINATIONAL.

" HSR ACT " SHALL MEAN THE HART-SCOTT-RODINO ANTITRUST IMPROVEMENTS ACT OF 1976, AS AMENDED.

" INDEBTEDNESS " OF ANY PERSON MEANS ALL OBLIGATIONS OF SUCH PERSON (I) FOR BORROWED MONEY, (II) EVIDENCED BY NOTES, BONDS, DEBENTURES OR SIMILAR INSTRUMENTS, (III) UNDER CAPITAL LEASES AND (IV) IN THE NATURE OF GUARANTEES OF THE OBLIGATIONS DESCRIBED IN CLAUSES (I) THROUGH (III) ABOVE OF ANY OTHER PERSON.

" INSURANCE PROCEEDS " SHALL MEAN THOSE MONIES (I) RECEIVED BY AN INSURED FROM AN INSURANCE CARRIER OR (II) PAID BY AN INSURANCE CARRIER ON BEHALF OF THE INSURED, IN EITHER CASE NET OF ANY APPLICABLE PREMIUM ADJUSTMENTS, RETROSPECTIVELY RATED PREMIUM ADJUSTMENTS, DEDUCTIBLES, RETENTIONS OR COSTS PAID BY SUCH INSURED.

" KNOWLEDGE " SHALL MEAN, IN THE CASE OF EITHER THE COMPANY OR PURCHASER, THE ACTUAL KNOWLEDGE, AS OF THE DATE OF THIS AGREEMENT, OF ANY OF THE EXECUTIVE OFFICERS OF SUCH PARTY.

" LIABILITIES " SHALL MEAN ANY AND ALL DEBTS, LIABILITIES AND OBLIGATIONS, WHETHER ACCRUED OR FIXED, ABSOLUTE OR CONTINGENT, MATURED OR UNMATURED, RESERVED OR UNRESERVED, OR DETERMINED OR DETERMINABLE, INCLUDING, WITHOUT LIMITATION, THOSE ARISING UNDER ANY LAW, CLAIM, DEMAND, ACTION OR PROCEEDING, WHETHER ASSERTED OR UNASSERTED, OR JUDGMENT, WRIT OR INJUNCTION OF ANY GOVERNMENTAL AUTHORITY, AND THOSE ARISING UNDER ANY CONTRACT, ARRANGEMENT, COMMITMENT OR UNDERTAKING OR ANY FINES, DAMAGES OR EQUITABLE RELIEF WHICH MAY BE IMPOSED AND INCLUDING, WITHOUT LIMITATION, ALL COSTS AND EXPENSES RELATED THERETO.

" LOSS " SHALL MEAN ANY AND ALL CLAIMS, ACTIONS, CAUSES OF ACTION, LIABILITIES, LOSSES, DAMAGES, AND REASONABLE OUT-OF-POCKET EXPENSES AND COSTS.

" PERSON " SHALL MEAN AN INDIVIDUAL, A CORPORATION, A LIMITED LIABILITY COMPANY, A PARTNERSHIP, AN ASSOCIATION, A TRUST OR ANY OTHER ENTITY, INCLUDING A GOVERNMENTAL AUTHORITY.

" SUBSIDIARY " WHEN USED WITH RESPECT TO ANY PARTY, SHALL MEAN ANY CORPORATION, LIMITED LIABILITY COMPANY, PARTNERSHIP, ASSOCIATION, TRUST OR OTHER ENTITY OF WHICH SECURITIES OR OTHER OWNERSHIP INTERESTS REPRESENTING MORE THAN 50% OF THE EQUITY AND MORE THAN 50% OF THE ORDINARY VOTING POWER (OR, IN THE CASE OF A PARTNERSHIP, MORE THAN 50% OF THE GENERAL PARTNERSHIP INTERESTS) ARE, AS OF SUCH DATE, OWNED BY SUCH PARTY OR ONE OR MORE SUBSIDIARIES OF SUCH PARTY OR BY SUCH PARTY AND ONE OR MORE SUBSIDIARIES OF SUCH PARTY.

" TAXING AUTHORITY " MEANS ANY GOVERNMENTAL AUTHORITY AND ANY OTHER QUASI-GOVERNMENTAL OR NON-GOVERNMENTAL BODY ADMINISTERING, REGULATING OR HAVING GENERAL RESPONSIBILITY FOR THE IMPOSITION OF ANY TAX.

SECTION 8.12 INTERPRETATION.

(A) THE TABLE OF CONTENTS AND HEADINGS CONTAINED IN THIS AGREEMENT ARE FOR REFERENCE PURPOSES ONLY AND SHALL NOT AFFECT IN ANY WAY THE MEANING OR INTERPRETATION OF THIS AGREEMENT. WHENEVER THE WORDS " INCLUDE ", " INCLUDES " OR " INCLUDING " ARE USED IN THIS AGREEMENT, THEY SHALL BE DEEMED TO BE FOLLOWED BY THE WORDS " WITHOUT LIMITATION ". THE WORDS " HEREOF ", " HEREIN " AND " HEREUNDER " AND WORDS OF SIMILAR IMPORT WHEN USED IN THIS AGREEMENT SHALL REFER TO THIS AGREEMENT AS A WHOLE AND NOT TO ANY PARTICULAR PROVISION OF THIS AGREEMENT. ALL TERMS DEFINED IN THIS AGREEMENT SHALL HAVE THE DEFINED MEANINGS WHEN USED IN ANY DOCUMENT MADE OR DELIVERED PURSUANT HERETO UNLESS OTHERWISE DEFINED THEREIN. THE DEFINITIONS CONTAINED IN THIS AGREEMENT ARE APPLICABLE TO THE SINGULAR AS WELL AS THE PLURAL FORMS OF SUCH TERMS AND TO THE MASCULINE AS WELL AS TO THE FEMININE AND NEUTER GENDERS OF SUCH TERM. ANY AGREEMENT, INSTRUMENT OR STATUTE DEFINED OR REFERRED TO HEREIN OR IN ANY AGREEMENT OR INSTRUMENT THAT IS REFERRED TO HEREIN MEANS SUCH AGREEMENT, INSTRUMENT OR STATUTE AS FROM TIME TO TIME AMENDED, MODIFIED OR SUPPLEMENTED, INCLUDING (IN THE CASE OF AGREEMENTS OR INSTRUMENTS) BY WAIVER OR CONSENT AND (IN THE CASE OF STATUTES) BY SUCCESSION OF COMPARABLE SUCCESSOR STATUTES AND REFERENCES TO ALL ATTACHMENTS THERETO AND INSTRUMENTS INCORPORATED THEREIN. REFERENCES TO A PERSON ARE ALSO TO ITS PERMITTED SUCCESSORS AND

ASSIGNS.

(B) THE PARTIES HERETO HAVE PARTICIPATED JOINTLY IN THE NEGOTIATION AND DRAFTING OF THIS AGREEMENT AND, IN THE EVENT AN AMBIGUITY OR QUESTION OF INTENT OR INTERPRETATION ARISES, THIS AGREEMENT SHALL BE CONSTRUED AS JOINTLY DRAFTED BY THE PARTIES HERETO AND NO PRESUMPTION OR BURDEN OF PROOF SHALL ARISE FAVORING OR DISFAVORING ANY PARTY BY VIRTUE OF THE AUTHORSHIP OF ANY PROVISION OF THIS AGREEMENT.

IN WITNESS WHEREOF, THE PARTIES HERETO HAVE CAUSED THIS AGREEMENT TO BE DULY EXECUTED AND DELIVERED AS OF THE DATE FIRST ABOVE WRITTEN.

REGENICIN, INC.
By:
Name:
Title:

LONZA WALKERSVILLE, INC.
By:
Name:
Title: