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 EXHIBIT 10.34  
  
 [ "..." indicates material has been omitted pursuant to a  
 Confidential Treatment Request, which the Company has filed separately  
 with the Securities and Exchange Commission]  
  
 EntreMed-Covance Agreement  
  
 BIOPROCESSING SERVICES AGREEMENT  
  
This manufacturing services agreement dated this 7th day of July 1999 (the  
"Agreement") between EntreMed, Inc. a Delaware corporation ("Sponsor") having  
its principal place of business at 0000 Xxxxxxx Xxxxxx Xxxxx, Xxxxxxxxx, XX  
00000 and Covance Biotechnology Services Inc., a Delaware Corporation ("CBSI"),  
having its principal place of business at 6051 Xxxxxx Xxxxx Xxxx Drive, P. O.  
Xxx 00000, Xxxxxxxx Xxxxxxxx Xxxx, XX 00000-0000.  
  
WITNESSETH  
WHEREAS, CBSI provides a full range of bioprocessing services to the  
biopharmaceutical industry, including process development, fermentation, cell  
culture, separation/purification, bioanalytical chemistry, quality control,  
quality assurance, and regulatory affairs.  
  
WHEREAS, sponsor desires CBSI to perform services in accordance with the terms  
of this Agreement and the Scope of Work (as hereinafter defined) related to the  
production of the material known as Angiostatin(TM) (the "Product") and CBSI  
desires to perform such services.  
  
NOW, THEREFORE, in consideration of the above statements and other good and  
valuable consideration, the sufficiency and receipt of which are hereby  
acknowledged, the parties hereto agree as follows:  
  
  
Section 1.  
SCOPE OF WORK  
a) A detailed Scope of Work document ("Scope") to be provided by Sponsor or  
 prepared by CBSI under Sponsor's direction and approved by Sponsor will be  
 attached to this agreement as Appendix 1. CBSI will perform the service or  
 services ("Program") for Sponsor in accordance with the Scope. The Scope  
 will specify the program design, information desired, estimated duration  
 of the Program, and all other matters pertinent to completion of the  
 Program, and will be deemed a part of this Agreement and is incorporated  
 herein by reference.  
  
b) CBSI will, at Sponsor's request, consult with Sponsor in developing the  
 Program design in a manner consistent with current regulatory guidelines.  
 However, CBSI does not warrant that the Product will be safe or  
 efficacious or that the CMC section prepared as result of performing the  
 Program will satisfy all the requirements of any regulatory agencies at  
 the time of submission.  
  
c) CBSI's performance of the work will be based on technical information  
 provided by or for the Sponsor. This information will be translated into  
 development and/or manufacturing documents (development plans, batch  
 records, specifications, etc.) which will be reviewed and approved by the  
 Sponsor. These documents will form the basis upon which the work will be  
 performed.  
  
  
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 EntreMed-Covance Agreement  
  
  
Section 2.  
PROGRAM PERFORMANCE  
CBSI shall use commercially reasonable efforts to provide facilities, supplies,  
and staff necessary to complete the Program as provided in the Scope, as it may  
be modified as provided herein, and in accordance with the terms of this  
Agreement. In the event of any conflict between the Scope/Program and this  
Agreement, the terms of this Agreement shall control.  
  
CBSI will appoint a CBSI representative (the "Program Manager") to be  
responsible for the completion of the Program by CBSI. The Program Manager will  
coordinate performance of the Program with a representative designated by  
Sponsor (the "Sponsor Representative"), which representative shall have  
responsibility over all matters relating to performance of the Program on behalf  
of Sponsor. Unless otherwise agreed in the Scope, all communications between  
CBSI and the Sponsor regarding the conduct of the Program pursuant to the Scope  
shall be addressed to or routed through the Program Manager and Sponsor  
Representative, directly. CBSI may, at its option, substitute the Program  
Manager during the course of the program.  
  
Section 3.  
PROGRAM MATERIALS  
a) Sponsor will provide CBSI with sufficient amounts of raw materials or  
 other substances with which to perform the Program as specified in the  
 Scope, (the "Materials"), as well as all documentation and such other data  
 as may be available to apprise CBSI of the stability of the Materials,  
 process characteristics, proper storage, manufacturing and safety  
 requirements. Sponsor will also provide CBSI with all necessary  
 information to effect the reliable transfer of the process from the  
 Sponsor to CBSI.  
  
b) Upon completion of the Program, any remaining samples of the Materials or  
 other substances provided to CBSI will be returned to Sponsor, at  
 Sponsor's option and/or retained by CBSI in compliance with regulatory  
 requirements.  
  
Section 4.  
COMPLIANCE WITH GOVERNMENT REGULATIONS  
a) CBSI will perform the Program in accordance with the Scope, and the  
 current state of the Food and Drug Administration's current Good  
 Manufacturing Practices (cGMP's) when appropriate to do so. Subject to  
 paragraph b. of Section 4 below, CBSI will also comply in all material  
 respects with all applicable government regulatory requirements concerning  
 current Good Manufacturing Practices appropriate to the Program.  
  
b) Should such government regulatory requirements be changed, CBSI will make  
 every reasonable effort to satisfy the new requirements. In the event that  
 compliance with such new regulatory requirements necessitates a change in  
 the Scope for the Program, CBSI  
  
  
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 will submit to Sponsor a revised technical and cost proposal for Sponsor's  
 acceptance prior to making any changes in the Scope or the Program.  
  
c) In the event of a conflict in government regulations, Sponsor will  
 designate, in writing, which regulations shall be followed by CBSI in its  
 performance of the Program.  
  
Section 5.  
FACILITY VISITS  
Sponsor's representatives may visit CBSI's facility at appropriate times  
consistent with the Program to observe the progress of the Program. CBSI will  
assist Sponsor in scheduling such visits which will be in compliance with  
requirement to protect confidentiality of other clients.  
  
Section 6.  
COMPENSATION  
a) The estimated budget for the Program is as provided in the Scope (Appendix  
 1). Such budget is subject to adjustment if (1) Sponsor executes this  
 Agreement later than 30 days after the date CBSI has executed this  
 Agreement and (2) the Materials or other data or information required to  
 conduct the Program is supplied or provided more than 30 days after the  
 date CBSI has executed this Agreement.  
  
b) Sponsor shall make payments as defined in the Payment Schedule included in  
 Appendix 1. A "..." fee equal to "..." will be added to "...". The "..."  
 fee will be waived on "...". "..." charges, such as for "...", will be  
 invoiced "...". Payments are due 30 days from the date of invoice. Late  
 payments are subject to an interest charge of "...". Any payments that are  
 greater than 90 days past due constitute a breach of this Agreement unless  
 there is a dispute relative to such payments which has not yet been  
 resolved pursuant to Section 14.  
  
c) In the event that "...", "..." shall "..." for "..." at the rate of "...".  
  
Section 7.  
CHANGE ORDERS  
a) The estimated budget for the Program specified in Section 6 of this  
 Agreement and the individual budget components and time estimates  
 specified in the Scope are subject to a number of general and program  
 specific assumptions. The program specific assumptions relate to  
 the Program design and objectives, manpower requirements, timing, capital  
 expenditure requirements, if any, and other matters relating to the  
 completion of the Program as set forth in the Scope (the "Program  
 Assumptions"). CBSI also assumes that the Sponsor will cooperate and  
 perform its obligations under the Agreement and Scope in a timely manner,  
 that no event outside the control of CBSI will occur, including, without  
 limitation, the events described in Section 17, and that there are no  
 material changes to any applicable laws, rules or regulations which effect  
 the Program (the foregoing assumptions together with the Program  
 Assumptions, collectively, the "Assumptions")  
  
  
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 In the event that any of the Assumptions require modification or the  
 Program objectives cannot be achieved based on the Assumptions (each  
 being, a "Modification") then the Scope may be amended as provided in  
 paragraph b) of this Section 7.  
  
b) In the event a Modification is identified by the Sponsor or by CBSI, the  
 identifying party shall notify the other party as soon as is reasonably  
 possible. CBSI shall provide Sponsor with a Change Order containing an  
 estimate of the required Modifications to the Program budget and timeline  
 specified in the Scope within 20 business days of receiving such notice.  
 Sponsor shall use best efforts to respond in writing to such Change Order  
 promptly. If Sponsor does not approve such Change Order and has not  
 terminated the Program but wants the Program to be modified to take into  
 account the Modification, then Sponsor and CBSI shall use best efforts to  
 agree on a Change Order that is mutually acceptable. If practicable, CBSI  
 shall continue work on the Program during any such negotiations, but shall  
 not commence work with respect to the Change Order unless authorized in  
 writing.  
  
Section 8.  
CONFIDENTIAL INFORMATION/LEGAL PROCEEDINGS  
a) CBSI will not disclose, without Sponsor's written permission, any  
 information pertaining to Sponsor's Program unless such disclosure: 1) is  
 to an affiliate of CBSI who is under a similar obligation to keep such  
 information confidential; 2) is or becomes publicly available through no  
 fault of CBSI; 3) is disclosed by a third party entitled to disclose it;  
 4) is already known to CBSI as shown by its prior written records; or 5)  
 is required by any law, rule, regulation, order decision, decree, subpoena  
 or other legal process to be disclosed. If such disclosure is requested by  
 legal process, CBSI will make all reasonable efforts to notify Sponsor of  
 this request promptly prior to any disclosure to permit Sponsor to oppose  
 such disclosure by appropriate legal action.  
  
b) CBSI will not transfer any materials without Sponsor's written permission  
 to any third party unless such transfer is to an affiliate bound by the  
 terms herein and is consistent with the Program.  
  
c) If CBSI shall be obliged to provide testimony or records regarding any  
 Sponsor Program in any legal or administrative proceeding, then Sponsor  
 shall reimburse CBSI its out-of-pocket costs therefore plus an hourly fee  
 for its employees or representatives equal to the internal fully burdened  
 costs to CBSI of such employee or representative.  
  
Section 9.  
WORK PRODUCT  
a) All work outputs (e.g. reports) will be prepared on CBSI's standard format  
 unless otherwise specified in the Scope.  
  
b) Sponsor will have title to all Materials, raw data, documentation,  
 records, protocols, specimens and other reports generated as a result of  
 this Program. All such written  
  
  
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 materials will be archived by CBSI for a period of five years following  
 completion of the Program unless otherwise defined by the Program or  
 required by applicable laws or regulations. Five years after completion of  
 the Program, all of the aforementioned materials will be sent to the  
 Sponsor and a reasonable return fee will be charged. The Sponsor may elect  
 to have the materials retained in the CBSI Archives for an additional  
 period of time at a reasonable additional cost. If the Sponsor chooses to  
 have CBSI dispose of the materials, a reasonable disposal fee will be  
 charged. CBSI will continue to retain such documentation and materials as  
 required by regulations and as may be required by law, pertaining to such  
 activities as well as for archival purposes.  
  
Section 10.  
INVENTIONS, PATENTS, AND RESULTS OF THE PROGRAM  
  
Any product or product improvement inventions or discoveries, including new uses  
for product and related patent rights which arise as a result of the work  
performed by CBSI will be owned by and assigned to Sponsor and CBSI will  
cooperate with Sponsor in perfecting Sponsor's interest in such intellectual  
property. Any process or process improvement inventions or discoveries made  
solely by CBSI which arise as a result of the work performed by CBSI and related  
patent rights will be owned by CBSI. Any such process or process improvement  
inventions or discoveries and related patent rights which are made jointly by  
the parties shall be owned jointly by the parties. With respect to any invention  
or discovery not owned by Sponsor as set forth above, CBSI hereby grants to  
Sponsor an exclusive, royalty-free, paid up, perpetual, worldwide, sublicensable  
license in the field of Anti-Angiogenesis under CBSI's sole and joint inventions  
and related patent rights arising as a result of the work performed by CBSI  
hereunder in order to make, have made, use, import, sell or offer to sell  
Product.  
  
  
Section 11.  
INDEPENDENT CONTRACTOR  
CBSI shall perform the Program as an independent contractor of Sponsor and shall  
have complete and exclusive control over its facilities, equipment, employees  
and agents. Nothing in this agreement or other arrangements for which it is made  
shall constitute CBSI, or anyone furnished or used by CBSI in the performance of  
the services, as employee, joint venture, partner, or servant of Sponsor.  
  
Section 12.  
INSURANCE  
CBSI shall secure and maintain in full force and effect throughout the  
performance of the Program policies of insurance for (a) Workmen's Compensation,  
(b) General Liability, (c) Automobile Liability, and (d) Professional Liability  
having policy limits, deductibles and other terms appropriate to the conduct of  
CBSI's business in CBSI's sole and exclusive judgment. Certificates evidencing  
such insurance will be made available for examination upon request of the  
Sponsor.  
  
  
  
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Section 13.  
DEFAULT  
a) If CBSI is in default of its material obligations under this Agreement,  
 then Sponsor shall promptly notify CBSI in writing of any such default.  
 CBSI shall have a period of 45 days from the date of receipt of such  
 notice within which to cure such default; provided that if such default  
 renders the Program invalid, then CBSI, shall, at Sponsor's option, either  
 (1) repeat the Program at its cost within a time period mutually agreed to  
 by it and Sponsor or (2) refund the contract price paid by Sponsor. If  
 CBSI shall fail to cure such default within the specified cure period or  
 repeat the Program, as the case may be, then this Agreement shall, at  
 Sponsor's option, immediately terminate. In the event of such termination,  
 Sponsor's sole remedy shall be, in the case where such default has not  
 rendered the Program invalid, a reduction in the total contract price for  
 the Program in an amount equal to the difference between (1) the total  
 contract price for the Program and (2) the value of the work properly  
 performed, and, in the case where such default does render the Program  
 invalid, a refund of the contract price; provided however that under no  
 circumstance shall CBSI be liable to Sponsor in an amount that, in  
 aggregate exceeds, the contract price paid for such Program. In the event  
 that any said default is directly attributable to the grossly negligent  
 acts or omissions of CBSI, the limitation of remedies set forth in this  
 section 13 (a) shall not apply.  
  
b) If Sponsor is in default of its material obligations under this Agreement,  
 CBSI shall promptly notify Sponsor in writing of any such default. Sponsor  
 shall have a period of 45 days from the date of receipt of such notice  
 within which to cure such default; provided that if Sponsor fails to cure  
 such breach within the specified cure period, this Agreement shall, at  
 CBSI's option, immediately terminate.  
  
c) Not withstanding anything herein to the contrary, UNDER NO CIRCUMSTANCES  
 SHALL EITHER PARTY BE ENTITLED TO INCIDENTAL, INDIRECT, CONSEQUENTIAL OR  
 SPECIAL DAMAGES ARISING IN CONNECTION WITH THE DEFAULT OR BREACH OF ANY  
 OBLIGATION OF THE OTHER PARTY UNDER THIS AGREEMENT, THE SCOPE OR ANY  
 DOCUMENTS OR APPENDICES RELATED THERETO.  
  
Section 14.  
DISPUTE RESOLUTION  
a) In the event any dispute shall arise between the Sponsor and CBSI with  
 respect to any of the terms and conditions of this Agreement or the  
 Protocol; then senior executives of the Sponsor and CBSI shall meet as  
 promptly as practicable after notice of such dispute to resolve in good  
 faith such dispute.  
  
  
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b) If the Sponsor and CBSI are unable to satisfactorily resolve the dispute,  
 then such dispute shall be finally settled by an arbitrator in accordance  
 with this Section 14. The arbitration will be held in or around Raleigh,  
 North Carolina, and except as noted below, shall be conducted in  
 accordance with the rules of the American Arbitration Association by two  
 arbitrators appointed, one by each party. If the arbitrators appointed  
 cannot agree on the resolution of the dispute within sixty (60) days after  
 the dispute is submitted to them, they shall thereupon appoint a third  
 arbitrator, and if they fail to agree upon a third arbitrator within 30  
 days after a deadlock is declared by either arbitrator, a third arbitrator  
 will be appointed by the American Arbitration Association upon the request  
 of either arbitrator. The arbitrators shall have no authority to award  
 consequential, punitive or exemplary damages or to vary from or ignore the  
 terms of this Agreement and shall be bound by controlling law. Finally,  
 the parties may seek judicial intervention for emergency relief, such as  
 restraining orders and injunctions where appropriate.  
  
 Any decision by the third arbitrator and either one of the other  
 arbitrators shall be binding upon the parties and may be entered as final  
 judgment in any court having jurisdiction. The cost of any arbitration  
 proceeding shall be borne by the parties as the arbitrators shall  
 determine if the parties have not otherwise agreed. The arbitrators shall  
 render their final decision in writing to the parties.  
  
Section 15.  
INDEMNIFICATION  
  
a) CBSI shall indemnify Sponsor and its affiliates and their respective  
 officers, directors and employees from any loss, cost, damage or expense  
 (a "Loss") from any lawsuit, action, claim, demand, assessment or  
 proceeding (a "Claim") for personal injury to Program participants or  
 personal injury to any employee of Sponsor or property damage arising or  
 occurring during the conduct of the Program as a result of (i) CBSI's  
 negligence, gross negligence or intentional misconduct or inaction, or  
 (ii) CBSI's violation, non-compliance or non-performance of any terms of  
 this Agreement; provided that if such Loss or Claim arises in whole or in  
 part from Sponsor's negligence, gross negligence or intentional misconduct  
 or inaction, then the amount of the Loss that CBSI shall indemnify Sponsor  
 for pursuant to this Section 15 shall be reduced by an amount in  
 proportion to the percentage of Sponsor's responsibilities for such Loss  
 determined by a court of competent jurisdiction in a final and  
 non-appealable decision or in a binding settlement between the parties.  
  
b) Sponsor shall indemnify CBSI and its affiliates and their respective  
 officers, directors, employees and agents (the "CBSI Group") from any  
 Claim or Loss arising from or related to (i) personal injury to a  
 participant in the Program or personal injury to any employee of the CBSI  
 Group directly or indirectly caused by the raw material, Product,  
 intermediates or the Program, (ii) CBSI's performance of or involvement  
 with the raw material, the Product or its obligations under this Agreement  
 or the Scope related thereto,  
  
  
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 (iii) CBSI's performance of the Program violating or infringing on the  
 patents, trademarks, tradenames, servicemarks or copyrights of any third  
 party with respect to Product and the process to manufacture Product,  
 Product intermediates, or raw materials relating to Product, (iv) the  
 harmful or otherwise unsafe effect of the raw materials or Product,  
 including, without limitation, a Claim based upon Sponsor or any other  
 person's use, consumption, sale, distribution or marketing of any  
 substance, including the raw material or the Product, (v) the negligence,  
 gross negligence or intentional misconduct or inaction of Sponsor in the  
 performance of its obligations under this Agreement or Scope related to  
 the Program, or (vi) the Sponsor's violation, non-compliance or  
 non-performance of any of the terms of this Agreement; provided that if  
 such Loss or Claim (other than a Loss or Claim described in clause (iv)  
 hereof) arises in whole or in part from CBSI's negligence, gross  
 negligence or intentional misconduct or inaction, then the amount of such  
 Loss that Sponsor shall indemnify the CBSI Group for pursuant to this  
 Section 15 shall be reduced by an amount in proportion to the percentage  
 of CBSI's responsibilities for such Loss as determined by a court of  
 competent jurisdiction in a final and non-appealable decision or in a  
 binding settlement between the parties. Sponsor shall not indemnify the  
 CBSI Group from any Loss from any claim described in clause (iv) hereof  
 arising solely from the willful misconduct or inaction of CBSI.  
  
c) Upon receipt of notice of any Claim which may give rise to a right of  
 indemnity from the other party hereto, the party seeking indemnification  
 (the "Indemnified Party") shall give written notice thereof to the other  
 party, (the "Indemnifying Party") with a Claim for indemnity. Such Claim  
 for indemnity shall indicate the nature of the Claim and the basis  
 therefore. Promptly after a claim is made for which the Indemnified Party  
 seeks indemnity, the Indemnified Party shall permit the Indemnifying  
 Party, at its option and expense, to assume the complete defense of such  
 Claim, provided that (i) the Indemnified Party will have the right to  
 participate in the defense of any such Claim at its own cost and expense,  
 (ii) the Indemnifying Party will conduct the defense of any such Claim  
 with due regard for the business interests and potential related  
 liabilities of the Indemnified Party and (iii) the Indemnifying Party  
 will, prior to making any settlement, consult with the Indemnified Party  
 as to the terms of such settlement. The Indemnified Party shall have the  
 right, at its election, to release and hold harmless the Indemnifying  
 Party from its obligations hereunder with respect to such Claim and assume  
 the complete defense of the same in return for payment by the Indemnifying  
 Party to the Indemnified Party of the amount of the Indemnifying Party's  
 settlement offer. The Indemnifying Party will not, in defense of any such  
 Claim, except with the consent of the Indemnified Party, consent to the  
 entry of any judgment or enter into any settlement which does not include,  
 as an unconditional term thereof, the giving by the claimant or plaintiff  
 to the Indemnified Party of a release from all liability in respect  
 thereof. After notice to the Indemnified Party of the Indemnifying Party's  
 election to assume the defense of such Claim, the Indemnifying Party shall  
 be liable to the Indemnified Party for such legal or other reasonable  
 expenses subsequently incurred by the Indemnified Party in connection with  
 the defense thereof at the request of the Indemnifying Party. As to those  
 Claims with respect to which the Indemnifying Party does not elect to  
 assume control of the defense,  
  
  
  
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 the Indemnified Party will afford the Indemnifying Party an opportunity to  
 participate in such defense at the Indemnifying Party's own cost and  
 expense, and will not settle or otherwise dispose of any of the same  
 without the consent of the Indemnifying Party.  
  
Section 16.  
REPRESENTATION  
Sponsor hereby represents and warrants to CBSI that it has legal title and/or a  
valid license to the raw material, expression systems and process patents and  
the Product and that, to the best of its knowledge, CBSI's performance of the  
Program will not violate or infringe on the patents, trademarks, tradenames,  
servicemarks or copyrights of any third party.  
  
Section 17.  
FORCE MAJEURE  
Either party shall be excused from performing its respective obligations under  
this Agreement if its performance is delayed or prevented by any event beyond  
such party's reasonable control, including, but not limited to, acts of God,  
fire, explosion, weather, disease, war, insurrection, civil strife, riots,  
government action, or power failure, provided that such performance shall be  
excused only to the extent of and during such disability. Any time specified for  
completion of performance in the Scope falling due during or subsequent to the  
occurrence of any or such events shall be automatically extended for a period of  
time to recover from such disability. CBSI will promptly notify Sponsor if, by  
reason of any of the events referred to herein, CBSI is unable to meet any such  
time for performance specified in the Scope. If any part of the Program is  
invalid as a result of such disability, CBSI will, upon written request from  
Sponsor, but at Sponsor's sole cost and expense, repeat that part of the Program  
affected by the disability. If CBSI is likely to be unable to perform for a  
period in excess of 60 days then the parties agree to negotiate in good faith a  
mutually satisfactory approach to resolve the delay resulting from this  
paragraph. If the parties cannot reach a mutually satisfactory approach within  
60 days, then Sponsor shall be entitled to terminate this Agreement without  
payment of liquidated damages (Section 20).  
  
Section 18.  
ALLOCATION OF RESOURCES  
If delays in the agreed commencement or performance of the Program occur because  
of the Sponsor's inability to supply CBSI with agreed Materials or any  
information required to begin or perform the Program within 30 days of such  
agreed time, CBSI may reallocate resources being held for performance of the  
Program without incurring liability to Sponsor.  
  
Section 19.  
USE OF NAMES  
Neither party shall use the name of the other party or the names of the  
employees of the other party in any advertising or sales promotional material or  
in any publication without prior  
  
  
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written permission of such party, except Sponsor may, as required by law or  
regulatory requirements, disclose that CBSI has performed the Program.  
  
Section 20.  
TERMINATION BY SPONSOR  
a) Sponsor may at any time terminate the Program prior to completion by  
 giving 45 days written notice to CBSI. In such event CBSI shall comply  
 with such notice to terminate work on the Program and use its best efforts  
 to reduce cost to Sponsor, and Sponsor shall pay CBSI upon receipt of  
 CBSI's invoice all of its costs incurred or irrevocably obligated.  
  
c) The termination of this Agreement for any reason shall not relieve either  
 party of its obligation to the other for obligations in respect of (i)  
 confidentiality of information, (ii) consents for advertising purposes and  
 publications, (iii) indemnification and, (iv) compensation for services  
 performed.  
  
Section 21.  
ASSIGNMENT  
This Agreement shall not be assigned in whole or in part by either party without  
the prior written consent of the other, which consent shall not be unreasonably  
withheld or delayed except Sponsor may assign without consent in the event of a  
merger, acquisition, or transfer of all of its assets related to this Agreement.  
Any attempt to assign this Agreement without such consent, where required, shall  
be void and of no effect subject to the limitations on assignment herein. This  
Agreement shall be binding upon and inure to the benefit of the successors and  
assigns of the parties hereto.  
  
Section 22.  
NOTICE  
All notices to be given as required in the Agreement shall be in writing and  
shall be delivered personally, sent by telecopies, or mailed either by a  
reputable overnight carrier or first class mail, postage prepaid to the parties  
at the addresses set forth above or such other addresses as the parties may  
designate in writing. Such notice shall be effective on the date sent, if  
delivered personally or sent by telecopier, the date after delivery if sent by  
overnight carrier and on the date received if mailed first class.  
  
Section 23.  
CHOICE OF LAW  
This Agreement shall be construed and enforced in accordance with the laws of  
the State of Delaware without regard to choice of law principles.  
  
Section 24.  
WAIVER/SEVERABILITY  
No waiver of any provision of this Agreement, whether by conduct or otherwise,  
in any one or more instances shall be deemed to be or be construed as a further  
or continuing waiver of  
  
  
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 EntreMed-Covance Agreement  
  
  
any such provision, or of any other provision or condition of this Agreement. If  
any provisions hereof shall be determined to be invalid or unenforceable, the  
validity and effect of the other provisions of this Agreement shall not be  
effected thereby.  
  
Section 25.  
ENTIRE AGREEMENT; MODIFICATION/COUNTERPARTS  
This instrument, the Confidential Disclosure Agreement with an effective date of  
31 March 1998, and the Scope set forth the entire Agreement between the parties  
hereto with respect to the performance of the Program by CBSI for Sponsor and as  
such, supersedes all prior and contemporaneous negotiations, agreements,  
representations, understandings, and commitments with respect thereto and shall  
take precedence over all terms, conditions and provisions on any purchase order  
form or form of order acknowledgment or other document purporting to address the  
same subject matter. This Agreement shall not be waived, released, discharged,  
changed or modified in any manner except by an instrument signed by the duly  
authorized officers of each of the partied hereto, which instrument shall make  
specific reference to this Agreement and shall express the plan or intention to  
modify same. This Agreement may be executed in one or more counterparts each of  
which shall be deemed an original but all of which together shall constitute one  
and the same instrument.  
  
This Agreement becomes effective and binding on both parties on and as of the  
last date that the parties hereto have executed this Agreement. Should terms  
contained herein be at variance with the terms and conditions specified in  
Sponsor's written acceptance, then the terms and conditions contained herein  
take precedence.  
  
  
   
ENTREMED, INC. COVANCE BIOTECHNOLOGY SERVICES INC.  
  
By: /s/ XXXX X. XXXXXXX By: /s/ XXXX X. XXXXX  
 ----------------------- ----------------------------------  
  
Name: Xxxx X. Xxxxxxx Name: Xxxx X. Xxxxx  
 ----------------------- ----------------------------------  
  
Title: Chairman & CEO Title: President & CEO  
 ----------------------- ----------------------------------  
  
Date: July 7, 1999 Date: July 7th, 1999  
 ----------------------- ----------------------------------  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
  
 SCOPE OF WORK FOR  
 PRODUCTION OF  
 ANIMAL TOXICOLOGY  
 AND cGMP  
 ANGIOSTATIN  
  
  
  
  
 PREPARED FOR: ENTREMED, INC.  
 PREPARED BY: COVANCE BIOTECHNOLOGY SERVICES INC.  
 DATED: JULY 7, 1999  
  
  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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 XXXXXXXX 0  
  
  
  
   
XXXXXXXXXXX XXXXX XXXXX PRODUCTION OF "..." 22  
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THE ANGIOSTATIN PROJECT AND OBJECTIVES  
  
  
 UNDERSTANDING OF THE ANGIOSTATIN PROJECT  
  
 - The product is Angiostatin, a protein consisting of  
 "..."  
  
 - molecule is expressed in "..."  
  
 - production clone has been selected (Clone # "...")  
  
 - cell lines have been received at CBSI and have been  
 released for evaluation  
  
 - fermentation process is not established at the "..."  
 scale  
  
 - recovery process is not established at the "..." scale  
  
 - purification process is not established at the "..."  
 scale  
  
 - analytical methods are not established at CBSI  
  
 - stability data is not available  
  
 - product specifications are not established  
  
 - productivity is not established  
  
 - "..." of Angiostatin are required for use in toxicology  
 studies  
  
 - toxicology material will be vialed at CBSI  
  
 - "..." of Angiostatin are required for use in clinical  
 trials  
  
 - IND for Phase I clinical trials is targeted to be filed  
 "..."  
  
  
 OBJECTIVES FOR THE ANGIOSTATIN PROGRAM  
  
 CBSI recognizes the following objectives for the Angiostatin  
 program and will make all reasonable efforts to meet the  
 EntreMed's timelines.  
  
 - Provide process development services for fermentation,  
 purification, formulation and analytical protein  
 chemistry (reference pages 8-11).  
  
 - Manufacture and vial "..." of Angiostatin for "..." by  
 "...".  
  
 - Manufacture and vial "..." of Angiostatin for "..." by  
 "...".  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
 - Manufacture "..." of "..." Angiostatin for "..." by  
 "...".  
  
 - Manufacture "..." of "..." Angiostatin for "..." by  
 "...".  
  
 - Support EntreMed's regulatory strategy by preparing a  
 draft CMC section for a Phase I IND filing. EntreMed's  
 targeted date for IND filing for Phase I clinical trials  
 is "...".  
  
  
 Note: When manufacturing clinical material, CBSI will follow  
 current Good Manufacturing Practices. CBSI will manufacture  
 utilizing in process control tests to meet the specifications  
 for purity, identity and safety. CBSI does not warrant that  
 the material produced under cGMP will be biologically active.  
  
 -----------------------------------------------------------------  
 "...".  
 -----------------------------------------------------------------  
  
  
 For the Angiostatin program, CBSI will:  
  
 - Attempt to reproduce and scale up fermentation, recovery  
 and purification processes to manufacture Angiostatin  
 based on information from EntreMed. Perform development  
 work as necessary  
  
 - Transfer/Develop methodology and qualify assays for  
 in-process control (IPC), for release testing of  
 Angiostatin and for use in support of stability testing  
  
 - Prepare "..."  
  
 - Perform runs at the "..."(1) scale to determine  
 reproducibility, stability and robustness of the  
 developed fermentation, recovery and purification  
 processes  
  
 - Perform runs at the "..."(2) scale to test scalability  
 of the process  
  
 - Perform pre-production activities in preparation for  
 cGMP manufacturing including procurement, testing and  
 release of raw materials, preparation of cGMP  
 documentation, and equipment and facility set-up  
  
 - Perform "..."at the "..."(3) scale and perform  
 subsequent recovery and purification to demonstrate  
 feasibility of the process at large scale  
  
 - Perform toxicology lot production at the "..." scale and  
 subsequent purification to produce a total of "..." of  
 Angiostatin (number of runs to be determined)  
  
  
-----------------------------------  
  
 (1) "..." working volume  
  
 (2) "..." working volume  
  
 (3) "..." working volume  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
 - Perform sufficient number of clinical runs at the "..."  
 scale and perform subsequent recovery and purification  
 to obtain "..." of cGMP Angiostatin  
  
 - Perform fill/finish activities for toxicology material  
  
 - Perform Quality Control testing and Quality Assurance  
 activities in support of release of bulk-filled Phase I  
 Angiostatin  
  
 - Provide manufacturing and QC/QA reports in support of  
 the CMC section of the Phase I IND filing for  
 Angiostatin targeted for "...".  
  
  
  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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PROGRAM ASSUMPTIONS  
  
Program assumptions are listed to provide a framework by which the Program may  
proceed. If these assumptions prove to be incorrect, then alternative approaches  
will need to be considered to achieve the stated deliverables.  
  
1. The Angiostatin process will require "..." for fermentation and "..." for  
 recovery and purification (per "..." process).  
  
2. All technology transfer performs as represented by EntreMed.  
  
3. For Angiostatin, "..." will be sufficient to ensure process operation and  
 reproducibility.  
  
4. Price and timelines assume "...".  
  
5. At large-scale, "...". Starting on "...".  
  
6. Angiostatin delivery dates are of critical importance to EntreMed. The  
 program will be managed to maximize the likelihood of achieving  
 Angiostatin delivery on or before the required dates. Process development  
 activities will continue "..." to support large-scale manufacturing and to  
 optimize/improve the manufacturing process prior to transfer of the  
 process to manufacturing. Continuing process development will be in  
 parallel with manufacturing; any improvements in the manufacturing process  
 that are discovered by this parallel development work will be incorporated  
 into the manufacturing process when practicable within the constraints of  
 a cGMP environment.  
  
  
  
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 APPENDIX 1  
  
  
ANGIOSTATIN DEVELOPMENT ACTIVITIES  
  
 PLAN OF ACTION  
  
 The objective of this activity is to develop a scaleable and cGMP  
 compatible process that yields Angiostatin of appropriate quality  
 for toxicology studies and clinical trials.  
  
 - Attempt to reproduce and scale up a fermentation process for  
 Angiostatin with reference to the existing CBSI process for  
 Endostatin. Perform additional development work as necessary.  
  
 - Attempt to reproduce and scale up a recovery process for  
 Angiostatin with reference to the existing CBSI process for  
 Endostatin. Perform additional development work as necessary.  
  
 - Attempt to reproduce and scale up a purification process for  
 Angiostatin with reference to the existing CBSI process for  
 Endostatin. Perform additional development work as necessary.  
  
 - Transfer/Develop methods to assess identity, purity,  
 concentration and product-related contaminants.  
  
 CBSI will conduct appropriate Process Development efforts to specify  
 both fermentation and purification yields and control production of  
 the various species of Angiostatin.  
  
 These process development efforts include some or all activities  
 described on the following pages.  
  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
  
  
  
  
  
-------------------------------------------------------------------------------------------------------------------------------  
 FERMENTATION PD ACTIVITY ESTIMATED ESTIMATED ESTIMATED  
 NO. OF NO. OF FTE-WEEKS  
 PERSONS WEEKS  
-------------------------------------------------------------------------------------------------------------------------------  
   
"..." "..." "..." "..."  
-------------------------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
-------------------------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
-------------------------------------------------------------------------------------------------------------------------------  
TOTAL FTE-WEEKS NEEDED "..."  
-------------------------------------------------------------------------------------------------------------------------------  
  
  
  
  
  
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 21  
 [ "..." indicates material has been omitted pursuant to a  
 Confidential Treatment Request, which the Company has filed separately  
 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
  
  
  
  
  
  
--------------------------------------------------------------------------------------------------------------  
PURIFICATION PD ACTIVITY ESTIMATED ESTIMATED ESTIMATED  
 NO. OF NO. OF TOTAL  
 PERSONS WEEKS FTE-WEEKS  
--------------------------------------------------------------------------------------------------------------  
   
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
TOTAL FTE-WEEKS NEEDED "..."  
--------------------------------------------------------------------------------------------------------------  
  
  
  
  
  
--------------------------------------------------------------------------------------------------------------  
ANALYTICAL PD ACTIVITY ESTIMATED ESTIMATED ESTIMATED  
 NO. OF NO. OF TOTAL  
 PERSONS WEEKS FTE-WEEKS  
--------------------------------------------------------------------------------------------------------------  
   
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
TOTAL FTE-WEEKS NEEDED "..."  
--------------------------------------------------------------------------------------------------------------  
  
  
  
  
  
--------------------------------------------------------------------------------------------------------------  
FORMULATION PD ACTIVITY ESTIMATED ESTIMATED ESTIMATED  
 NO. OF NO. OF TOTAL  
 PERSONS WEEKS FTE-WEEKS  
--------------------------------------------------------------------------------------------------------------  
   
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
"..." "..." "..." "..."  
--------------------------------------------------------------------------------------------------------------  
TOTAL FTE-WEEKS NEEDED "..."  
--------------------------------------------------------------------------------------------------------------  
  
 FINANCIAL SUMMARY  
  
 - "..."  
  
  
  
  
  
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 22  
 [ "..." indicates material has been omitted pursuant to a  
 Confidential Treatment Request, which the Company has filed separately  
 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
  
ANGIOSTATIN MANUFACTURING RELATED ACTIVITIES  
  
 TECHNOLOGY TRANSFER  
  
 The objective of this activity is to transfer from EntreMed to CBSI  
 existing methodology and process information to obtain a complete  
 understanding of the process as it currently exists.  
  
 TECHNOLOGY TRANSFER includes the following activities:  
  
 - EntreMed will transfer existing methods and technical  
 information from the "..." and "..." regarding the  
 fermentation and purification processes and analytical  
 techniques for quantifying Angiostatin  
  
 - CBSI will verify raw materials and purchase long lead  
 time materials  
  
 - CBSI will verify equipment requirements and purchase  
 long lead time items, if any  
  
 - CBSI will identify any facility or equipment engineering  
 issues related to large-scale manufacture  
  
 - CBSI will outline the manufacturing plan that includes  
 identifying technical issues with the facility,  
 scheduling of the facility, and development of detailed  
 timelines for specific production activities, including  
 changeover  
  
 Price  
  
 "..."  
  
  
  
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 23  
 [ "..." indicates material has been omitted pursuant to a  
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 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
  
CELL BANKING AND TESTING  
  
The objective of this activity is to generate and test a cGMP Master Cell Bank  
(MCB) from a research cell bank and generate and test a Manufacturer's Working  
Cell Bank (MWCB) from the MCB.  
  
a) CBSI will receive vials of the "..." following confirmation of purity and  
 non-host contamination by "...". "..." must be "..." prior to receipt of  
 cells.  
  
b) CBSI will develop specifications for all raw materials based on  
 information provided by EntreMed. CBSI will order and release raw  
 materials according to CBSI Standard Operating Procedures.  
  
c) CBSI will generate batch records for the cell bank production activities.  
 EntreMed will review and approve all batch records prior to cell bank  
 production.  
  
d) CBSI will produce a "..." vial MCB and a "..." vial MWCB from a MCB vial.  
 CBSI Quality Group will provide support for batch record review and  
 approval, raw material release and environmental monitoring.  
  
e) CBSI will provide temporary storage for cell banks ("..." degreesC).  
 Within "..." of completion of cell banking activities, at least "..." of  
 the cell bank will be transferred for storage to a designated third party  
 approved by EntreMed.  
  
f) CBSI will perform the following tests on samples from the MCB and MWCB.  
 CBSI and EntreMed will agree to suitable acceptance criteria for these  
 tests:  
 - "..." ("...")  
 - "..." ("...")  
 - "..." ("...")  
  
g) CBSI will submit samples of the MCB and MWCB to "..." to perform the  
 following. CBSI and EntreMed will agree to suitable acceptance criteria  
 for these tests:  
 - "..." ("...")  
 - "..." ("...")  
  
h) CBSI will provide EntreMed with copies of the completed and approved batch  
 records. CBSI will retain the originals in its archives.  
  
i) "..." testing of the MCB and MWCB is not included in the scope of this  
 proposal.  
  
j) EntreMed is responsible for ensuring that the cell line supplied is  
 suitable for the intended use.  
  
Price  
 "..."  
  
 PRE-PRODUCTION ACTIVITIES  
  
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 24  
 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
  
  
 The objective of this activity is for CBSI to perform the following  
 activities in preparation for cGMP manufacturing:  
  
 - Develop and finalize process flow diagrams  
  
 - Complete engineering for processes  
  
 - Prepare specifications  
  
 - Test and release all raw materials  
  
 - Procure and release all necessary supplies  
  
 - Complete and qualify any necessary equipment  
 modifications  
  
 - Prepare a detailed list of specifications, test methods,  
 SOPs, protocols and manufacturing procedures  
  
 - Develop manufacturing procedures for implementation into  
 the CBSI Batch Record/Manufacturing Execution System  
  
 - Set up to perform small scale runs, large scale  
 demonstration runs, toxicology runs and large scale cGMP  
 runs  
  
 Price  
  
 "..."(4)  
  
 "..."  
  
  
  
  
  
-----------------------------  
  
 (4) "..."  
  
  
  
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 25  
 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
  
 LARGE SCALE "..." DEMONSTRATION RUNS  
  
 - "..." demonstration runs and subsequent purification  
 will be performed according to the procedures developed  
 including any change in methods determined to be useful  
 following "..." runs.  
  
 - Additional "..." demonstration runs may be needed if  
 unforeseen scale-up issues arise ("...").  
  
 - Records for this stage of the process will be maintained  
 using DRAFT cGMP documents (batch records and  
 formulation records).  
  
 - Analytical assays will be preformed to verify product  
 identity and quality on material from these  
 demonstration runs using appropriate assays.  
  
 - Specific goals for yield and purity will be mutually  
 agreed upon between EntreMed and CBSI based on early  
 development results, clinical needs and project  
 timelines.  
  
 The "..." scale activities will be performed in CBSI's large  
 scale manufacturing area. Each manufacturing run is expected  
 to require one week in the large-scale fermentation area and  
 one-week in the large scale purification area. Any material  
 produced during demonstration runs can be used for  
 formulation, stability and other non-clinical activities.  
  
 Price  
  
 "..."  
  
 IT IS ASSUMED THAT "..." DEMONSTRATION RUNS WILL BE SUFFICIENT TO  
 ENSURE PROCESS OPERATION AND REPRODUCIBILITY.  
  
 MILESTONE: AFTER COMPLETION OF DEMONSTRATION RUNS, CBSI AND ENTREMED  
 WILL DETERMINE THAT USEABLE ANGIOSTATIN CAN BE PRODUCED AT LARGE  
 SCALE BASED ON THE REVIEW OF DATA.  
  
 IF THE MILESTONE IS NOT ACHIEVED AFTER "..." DEMONSTRATION RUNS, THE  
 PARTIES AGREE TO MODIFY THE SCOPE TO ACCOMMODATE ADDITIONAL  
 DEVELOPMENT WORK AND DEMONSTRATION RUNS TO ACHIEVE THE MILESTONE.  
 THE COST FOR THE ADDITIONAL DEMONSTRATION RUNS IS "...".  
  
  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
  
  
 ASSAY QUALIFICATION  
  
 The objective of this activity is to perform qualification of assays  
 to assess the performance capability of the assays used in support  
 of cGMP manufacturing and stability studies.  
  
 EntreMed and CBSI will jointly determine the specific assays to be  
 used for in-process control and Angiostatin release testing. The  
 types of assays listed below will assess the identity, purity,  
 strength and homogeneity of Angiostatin. The specific testing  
 regimen will depend on the inherent properties of Angiostatin.  
  
 This table lists the assays that may be employed for  
 characterization, in-process control and release testing of  
 Angiostatin.  
  
  
  
-----------------------------------------------------------------------------------------  
 METHOD COST FOR QUALIFICATION  
-----------------------------------------------------------------------------------------  
   
 "..." "..."  
-----------------------------------------------------------------------------------------  
 "..." "..."  
-----------------------------------------------------------------------------------------  
 "..." "..."  
-----------------------------------------------------------------------------------------  
 "..." "..."  
-----------------------------------------------------------------------------------------  
 "..." "..."  
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 "..." "..."  
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 "..." "..."  
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 "..." "..."  
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 "..." "..."  
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 "..." "..."  
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 "..." "..."  
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 Price  
  
 "..."  
  
 "..."  
  
  
  
  
  
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 27  
 [ "..." indicates material has been omitted pursuant to a  
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 cGMP STABILITY STUDIES  
  
 The objective of this activity is to perform studies on clinical  
 material produced in cGMP runs. Activities include:  
  
 - Evaluate final product configuration for stability in real  
 time conditions at anticipated storage temperatures  
  
 - Perform studies that at least cover the duration of the  
 clinical trial  
  
  
 The following table/schedule illustrates a clinical trial lasting  
 "..." with expected storage at "...":  
  
  
  
-------------------------------------------------------------------------------------------------------  
 Xx0 Xx0x Xx0x Xx0x Xx0x Xx0x  
-------------------------------------------------------------------------------------------------------  
   
"..." degrees C "..." "..." "..." "..." "..." "..."  
-------------------------------------------------------------------------------------------------------  
"..." degrees C "..." "..." "..." "..." "..." "..."  
-------------------------------------------------------------------------------------------------------  
  
  
  
 CBSI will prepare a report describing the stability data for  
 Angiostatin.  
  
 The duration of cGMP stability studies depends on study design and  
 duration of clinical trial.  
  
 Price  
  
 "..."  
  
 "..."  
  
  
  
  
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 28  
 [ "..." indicates material has been omitted pursuant to a  
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 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
  
  
 REGULATORY SUPPORT SERVICES  
  
 The objective of this activity is to support the regulatory aspects  
 of manufacturing Angiostatin at the CBSI facility.  
  
 The Regulatory support segment includes the following activities:  
  
 - Prepare site documents  
  
 - Prepare scale-up/development and other reports  
  
 - Write the CMC sections for Phase I IND filing  
  
 - Respond to any questions related to manufacturing raised  
 by regulatory authorities  
  
 - Host any inspections  
  
  
 Price  
  
 "..."  
  
 "...": "..."  
  
 "..."  
  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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 PROGRAM MANAGEMENT  
  
 CBSI takes a Program Team approach to managing all manufacturing  
 projects. The Program Team would consist of a CBSI Program Manager,  
 a representative from EntreMed and CBSI representatives from process  
 development, quality and manufacturing. The Program Team would meet  
 weekly via teleconference or in person.  
  
 The Executive Committee will meet on a monthly basis (or as  
 required) to review Program progress, review budgetary progress and  
 address any outstanding issues.  
  
 The Program Manager is responsible for coordination of all technical  
 aspects of the Program, including monitoring financial and temporal  
 progress of the Program and submitting periodic reports.  
  
 CBSI will provide a Program Manager for the duration of the project.  
  
 Price  
  
 "..."  
  
  
  
  
 FILL/FINISH OF TOXICOLOGY MATERIAL  
  
 The objective of this activity is to vial Angiostatin for toxicology  
 studies.  
  
 - The fill concentration for Angiostatin toxicology  
 material will be "..." in a formulation to be mutually  
 determined.  
  
 - CBSI will perform "..." vial fills in "..." vials ("..."  
 per vial).  
  
  
 Price  
  
 "..."  
  
  
  
  
  
  
  
  
  
  
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 30  
 [ "..." indicates material has been omitted pursuant to a  
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QA RELEASE TESTING OF VIALED CLINICAL MATERIAL  
  
 The objective of this activity is to provide QC testing of vialed  
 Angiostatin for use in human clinical studies.  
  
 - Receive vialed Angiostatin from "...".  
  
 - Test vialed Angiostatin per Item Specifications to be  
 determined. Testing to be performed by CBSI QC staff.  
  
 - Provide certificate of analysis, released by QA, for  
 vialed Angiostatin.  
  
 Price  
  
 The price for this phase of the Program is "...".  
  
 "..."  
  
  
 SAMPLING OF LARGE SCALE DEMONSTRATION RUNS FOR DIAGNOSTIC PURPOSES  
  
 The objective of this activity is to allow diagnostic assessment of  
 the large scale production process for Angiostatin.  
  
 - Draw samples at appropriate process points during large  
 scale demonstration runs for diagnostic assessment of  
 Angiostatin activity  
 - Ship samples to EntreMed for diagnostic assessment  
  
 Price  
  
 The price for sampling and shipping samples is "...". "...".  
  
  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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FINANCIAL SUMMARY FOR "..." COMPONENTS OF ANGIOSTATIN MANUFACTURING RELATED  
ACTIVITIES  
  
  
  
  
  
------------------------------------------------------------------------------------------------------------  
 ANGIOSTATIN MANUFACTURING RELATED  
 ACTIVITIES "..."  
------------------------------------------------------------------------------------------------------------  
  
   
Technology Transfer "..."  
------------------------------------------------------------------------------------------------------------  
  
Cell Banking and Testing "..."  
------------------------------------------------------------------------------------------------------------  
  
Pre-Production Activities "..."  
------------------------------------------------------------------------------------------------------------  
  
Large Scale "..." Demonstration Runs "..."  
------------------------------------------------------------------------------------------------------------  
  
Assay Qualification "..."  
------------------------------------------------------------------------------------------------------------  
  
cGMP Stability Studies (for estimated "...") "..."  
------------------------------------------------------------------------------------------------------------  
  
Regulatory Support "..."  
------------------------------------------------------------------------------------------------------------  
  
Project Management "..."  
------------------------------------------------------------------------------------------------------------  
  
Fill/Finish of Toxicology Material (for estimated "...") "..."  
------------------------------------------------------------------------------------------------------------  
  
TOTAL "..."  
------------------------------------------------------------------------------------------------------------  
  
  
  
  
--------------------------------------------------------------------------------  
"...".  
--------------------------------------------------------------------------------  
  
  
  
  
  
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 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
  
  
 ANGIOSTATIN LARGE SCALE PRODUCTION OF "..."  
  
 MILESTONE: BEFORE INITIATING TOXICOLOGY MANUFACTURING, CBSI AND ENTREMED  
 WILL DETERMINE THAT USEABLE ANGIOSTATIN CAN BE PRODUCED AT LARGE SCALE  
 BASED ON THE REVIEW OF DATA FROM THE DEMONSTRATION RUNS.  
  
 TOXICOLOGY MATERIAL MANUFACTURING  
  
 The objective of this activity is to produce material for use in  
 toxicology studies and to perform demonstration runs on the  
 fermentation process.  
  
 The "..." MWCB will be used for manufacture of toxicology material.  
  
 Draft cGMP documentation as prepared during pre-production  
 activities will be used during production of toxicology material.  
  
 The Quality department will release raw materials used for the  
 manufacture of toxicology material.  
  
 CBSI will perform the appropriate number of "..." fermentation runs  
 in series with subsequent purification to produce approximately  
 "..." of Angiostatin for toxicology studies. CBSI will use its best  
 judgement to establish a manufacturing strategy in consultation with  
 EntreMed.  
  
 The Analytical Development Group will perform preliminary analysis  
 of samples using appropriate assays.  
  
 The Quality Assurance Group will not perform a formal review of  
 documentation.  
  
 Toxicology material will be released to EntreMed based on the  
 Quality Control (QC) criteria listed below:  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
  
 CBSI will provide EntreMed with copies of the documentation used  
 during toxicology production. CBSI will retain the originals in its  
 archives.  
  
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 33  
 [ "..." indicates material has been omitted pursuant to a  
 Confidential Treatment Request, which the Company has filed separately  
 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
 Estimated Price  
  
 See "FINANCIAL SUMMARY FOR ANGIOSTATIN MANUFACTURING" on pages 26-27  
 for details  
  
 Note: If EntreMed requests "...".  
  
  
  
  
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 34  
 [ "..." indicates material has been omitted pursuant to a  
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 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
  
  
 CLINICAL TRIAL MATERIAL MANUFACTURING  
  
 The objective of this activity is to produce cGMP quality material  
 for use in Phase I clinical trials.  
  
 The "..." MWCB will be used for cGMP manufacture of clinical  
 material.  
  
 cGMP documentation as prepared during pre-production activities and  
 modified during demonstration runs will be adhered to and  
 manufacturing will be performed under Quality Assurance oversight as  
 described in the Quality Function section.  
  
 CBSI will perform the appropriate number of "..." fermentation runs  
 in series with subsequent purification to produce "..." of  
 Angiostatin for clinical trials. CBSI will use its best judgement to  
 establish a manufacturing strategy in consultation with EntreMed.  
  
 Release criteria for clinical material is to be developed and agreed  
 to before clinical trial material manufacturing.  
  
  
 Note: When manufacturing clinical material, CBSI will follow current  
 Good Manufacturing Practices. By testing this material against  
 analytical specifications, CBSI will demonstrate this material meets  
 specifications for purity and contamination levels. CBSI does not  
 warrant that the material produced under cGMP will be biologically  
 active. Clinical studies will be used to determine if the material  
 is efficacious.  
  
  
 Analytical methods to verify substance identity and quality will be  
 performed by the QC department.  
  
 CBSI will provide EntreMed with copies of the completed and approved  
 batch records. All records will be in pre-approved cGMP documents  
 subject to full QA review. CBSI will retain the originals in its  
 archives.  
  
 Estimated Price  
  
 See "FINANCIAL SUMMARY FOR ANGIOSTATIN MANUFACTURING" on pages 26-27  
 for details  
  
 Note: If EntreMed requests "...".  
  
  
  
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 35  
 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
  
  
 QUALITY FUNCTION  
  
 The objective of this activity is to provide Quality Control and  
 Quality Assurance support for cGMP manufacturing activities.  
 Activities include:  
  
 - Provide support to ensure cGMP compliance of clinical material  
 production.  
  
 - Issue and maintain controlled documents such as item  
 specifications and batch records.  
  
 - Prepare certificates of analysis.  
  
 - Perform IPC and Product testing according to approved test  
 methods and specifications.  
  
 - Characterize reference standard  
  
 - Compare Angiostatin to reference standard.  
  
 - Review and approve completed production and environmental  
 control records.  
  
 - Select, qualify and/or audit vendors, if necessary  
  
  
 IPC and Product release tests may include the following methods:  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
 - "..."  
  
  
 Estimated Labor  
  
 "...".  
  
 Estimated Price  
  
 See "FINANCIAL SUMMARY FOR ANGIOSTATIN MANUFACTURING" on pages 26-27  
 for details.  
  
  
  
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 36  
 [ "..." indicates material has been omitted pursuant to a  
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 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
  
FINANCIAL SUMMARY FOR ANGIOSTATIN MANUFACTURING  
  
  
Table 1  
  
  
----------------------------------------------------------------------------------------------------------------------------  
 Assumptions Price per run  
----------------------------------------------------------------------------------------------------------------------------  
   
1. If the process requires: "..."  
 - "..." for fermentation  
 - "..." for recovery and purification  
----------------------------------------------------------------------------------------------------------------------------  
2. If the process requires: "..."  
 - "..." for fermentation  
 - MORE THAN "..." AND LESS THAN OR EQUAL TO "..." for recovery and purification  
----------------------------------------------------------------------------------------------------------------------------  
3. If the process requires: "..."  
 - LESS THAN "..." for fermentation and/or  
 - LESS THAN "..." for recovery and purification  
----------------------------------------------------------------------------------------------------------------------------  
4. If the process requires processing times greater than those indicated in 2. (above), then  
 Parties agree that the process is economically unviable and agree to discuss how best to proceed.  
----------------------------------------------------------------------------------------------------------------------------  
  
  
  
  
  
  
  
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 37  
 [ "..." indicates material has been omitted pursuant to a  
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 APPENDIX 1  
  
  
  
The price for this section will be based on "...". "...".  
  
Table 2  
  
  
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 "..." "..." "..." "..."  
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 "..." "..." "..." "..."  
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 "..." "..." "..." "..."  
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Note: If EntreMed requests "...".  
  
  
"...".  
  
--------------------------------------------------------------------------------  
"...".  
--------------------------------------------------------------------------------  
  
  
  
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 38  
 [ "..." indicates material has been omitted pursuant to a  
 Confidential Treatment Request, which the Company has filed separately  
 with the Securities and Exchange Commission]  
  
 APPENDIX 1  
  
  
  
ESTIMATED PAYMENT SCHEDULE  
  
  
  
  
  
  
----------------------------------------------------------------------------------------------------------------------  
 FINANCIAL SUMMARY PAYMENT SCHEDULE  
----------------------------------------------------------------------------------------------------------------------  
   
Angiostatin Process Development Activities "..."  
----------------------------------------------------------------------------------------------------------------------  
  
"..." Components of Angiostatin Manufacturing-Related Activites "..."  
----------------------------------------------------------------------------------------------------------------------  
  
Angiostatin Manufacturing "..."  
----------------------------------------------------------------------------------------------------------------------  
  
  
  
  
  
ACCEPTANCE SIGNATURE  
  
  
Signature below indicates acceptance of this scope of work.  
  
  
COVANCE BIOTECHNOLOGY SERVICES INC. ENTREMED, INC.  
  
  
  
By: /s/ XXXX X. XXXXX By: /s/ XXXX X. XXXXXXX  
 ------------------- --------------------  
  
Date: July 7, 1999 Date: July 7, 1999  
 ---------------------- --------------------  
  
  
  
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