EXHIBIT 12  
  
  
CONFIDENTIAL PORTIONS OF THIS EXHIBIT HAVE BEEN OMITTED PURSUANT TO REGULATION  
240.25B-2B OF THE SECURITIES EXCHANGE ACT OF 1934. [\*] INDICATES OMITTED  
MATERIAL THAT IS THE SUBJECT OF A CONFIDENTIAL TREATMENT REQUEST AND IS FILED  
SEPARATELY WITH THE COMMISSION.  
  
THIS AGREEMENT is made this day of January 2000 between:  
  
(1) AVECIA LIMITED acting through its LifeScience Molecules business whose  
 registered office is at Xxxxxxx Xxxxx, Xxxxxxxx, Xxxxxxxxxx, X0 0XX,  
 Xxxxxxx ("AVECIA");  
  
(2) RIBOZYME PHARMACEUTICALS INCORPORATED of 0000 Xxxxxxxxxx Xxxxx, Xxxxxxx,  
 Xxxxxxxx 00000, XXX ("RPI").  
  
WHEREAS  
  
(A) AVECIA has experience and knowledge with regard to the manufacture of  
 oligonucleotides and intermediates for preparation of oligonucleotides,  
 process scale-up and GMP (as defined below).  
  
(B) RPI is carrying out research and development work in relation to certain  
 ribozymes.  
  
(C) It is intended that AVECIA will carry out a development programme upon and  
 subject to the terms and conditions of this Agreement with a view to  
 scaling up the process for production of such ribozymes and carrying out  
 initial production of such ribozymes as set out in Part II of this  
 Agreement and carrying out such production on behalf of RPI as set out in  
 Part III of this Agreement.  
  
NOW IT IS HEREBY AGREED AS FOLLOWS:  
  
  
 PART I - DEFINITIONS AND INTERPRETATION  
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1. Headings and Definitions  
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 1.1 In this Agreement, the following terms and expressions shall have the  
 following meanings:  
  
 Angiozyme means RPI's proprietary anti-angiogenesis ribozyme  
 compound being jointly developed with Chiron  
 Corporation. Angiozyme is also designated as  
 Angiozyme.(TM)  
  
 S-1  
  
  
 Anti-HCV means RPI's proprietary anti-hepatitis c virus Ribozyme  
 ribozyme compound being jointly developed with Xxx  
 Lilly & Company. Anti-HCV Ribozyme is also designated  
 as Heptazyme.  
  
 Collaborator means any of Chiron Corporation, Xxx Xxxxx & Company or  
 other corporate partner of RPI who is collaborating  
 with RPI to develop and commercialise a Product  
 manufactured under this Agreement, or any licensee of  
 RPI who is developing and commercialising a Product  
 manufactured under this Agreement. "Collaborators"  
 shall mean more than one of them.  
  
 Confidential means any information disclosed by RPI to AVECIA  
 Information pursuant to the Technology Transfer, and any technical  
 and commercial information relating to the Programme  
 and any other information of a confidential nature  
 disclosed (whether disclosed in writing, verbally, by  
 way of sample or by any other means and whether  
 directly or indirectly) by either party ("the  
 Disclosing Party") to the other ("the Receiving  
 Party"), including and without limitation any  
 information relating to the Disclosing Party's business  
 affairs.  
  
 GMP means current good manufacturing practices (as provided  
 for, respectively, in the Rules governing Medicinal  
 Products in the European Community Volume 4 (Guide to  
 Good Manufacturing Practice for Medicinal Products) and  
 by the US Food and Drug Administration as set out in  
 21CFR210 and 21CFR211, as amended from time to time)  
 the responsibilities of each party in respect of which  
 for each Product shall be agreed and defined in the  
 Quality Agreement, and shall be consistent with the  
 interpretation for Active Pharmaceutical Intermediates  
 in guidance documents provided by the Federal Drug  
 Administration and the International Conference on  
 Harmonisation.  
  
 Effective Date means 13/th/ December 1999.  
  
 Intellectual means all know-how, inventions, discoveries, Property  
 devices, data, patents, designs, copyrights, or other  
 industrial or intellectual property in all applications  
 therefor.  
  
 S-2  
  
  
 JRC means the joint review committee provided for in Clause  
 4 and Schedule 2.  
  
  
 Nominated means a contract manufacturer nominated by RPI to  
 Manufacturer carry out manufacture of the Product(s) on RPI's behalf  
 and which has agreed to enter into confidentiality  
 undertakings with AVECIA pursuant to Clause 12.4 below.  
  
 Process means the process for production of the Product(s) as  
 developed during the Programme.  
  
 Product means, unless stated specifically, Angiozyme, Anti-HCV  
 Ribozyme or such other Ribozyme product agreed by the  
 parties. "Products" shall be a reference to such  
 Ribozymes taken together.  
  
 Product means the specification designated by RPI for each of  
 Specification the Product(s) and as set out and  
 determined by the analytical test methods in the  
 Quality Agreement.  
  
 Programme means the programme for development of the Process  
 (including the Technology Transfer) referred to in  
 Clause 2 and more specifically detailed in Schedule 1.  
  
 Quality means the agreement made between AVECIA and  
 Agreement RPI in respect of each Product, the terms of which  
 shall be agreed by the JRC prior to commencement of  
 manufacture and supply of each Product on a case by  
 case basis. A draft of the Quality Agreement is  
 attached as Schedule 3.  
  
 Ribozyme means a ribonucleic acid-based molecule able to cause  
 catalytic cleavage of itself or another molecule  
 independent of protein.  
  
 Technical means the agreement made between AVECIA and  
 Agreement RPI, the terms of which shall be agreed by the JRC,  
 detailing the process information and analytical  
 methods to be communicated to AVECIA during the  
 Technology Transfer. A draft of the Technical Agreement  
 is attached as Schedule 4.  
  
 Technology means the communication by RPI of technical  
 Transfer information, including processes and analytical  
 methods, relating to the Products to AVECIA as may be  
 required  
  
 S-4  
  
  
 by AVECIA to carry out the Programme and as  
 further set forth in the Technical Agreement.  
  
 1.2 The headings of the several sections of this Agreement are intended  
 for convenience of reference only and are not intended to be a part of  
 or to affect the meaning or interpretation of this Agreement.  
  
 1.3 References to recitals, clauses, paragraphs and Schedules are to  
 recitals, clauses and paragraphs of and Schedules to this Agreement.  
 The Schedules and any attachments form part of this Agreement and  
 shall have the same force and effect as if expressly set out in the  
 body of the Agreement and any reference to the Agreement shall include  
 the Schedules and any attachments.  
  
  
 PART II - THE PROGRAMME  
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2. Performance of the Programme  
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 2.1 The Technology Transfer shall be deemed to have commenced on the  
 Effective Date. During the Technology Transfer, RPI shall give all  
 appropriate technical assistance reasonably requested by AVECIA in  
 relation to the Technology Transfer.  
  
 2.2 AVECIA will carry out the work as detailed in the Programme (as may be  
 amended from time to time in writing by the JRC).  
  
 2.3 Subject to Clause 4.2 below, the Programme has four stages as set out  
 below and as more specifically detailed in Schedule 1 ("Stage(s)"),  
 provided that AVECIA shall, at all times during any Stage, have the  
 flexibility to carry out the requirements of the Programme in such  
 manner and at such times as AVECIA shall see fit and at its sole  
 discretion and subject to the overall supervision of the JRC and the  
 provisions of Clause 4.  
  
 Stages in Programme  
  
 Stage Description  
 ----- -----------  
  
 1 Technology Transfer of process and analytical methods  
 2 Process development - deprotection and purification scale-up  
 of the Products as determined by the JRC  
 3 preparation of GMP manufacturing documentation  
 4 Process scale up - GMP manufacture of 1kg of a mutually  
 agreed Product  
  
 S-5  
  
  
 2.4 The process information and analytical methods to be communicated to  
 AVECIA during the Technology Transfer shall be agreed and detailed in  
 the Technical Agreement. Stage 2 of the Programme shall commence when  
 the JRC confirms that the Technology Transfer is complete according to  
 the verification protocol (set forth in the Quality Agreement) to  
 ensure such information has been received and correctly interpreted.  
  
 2.5 Stage 3 of the Programme shall not commence until:  
  
 (a) the identity of the first Product to be produced during Stage 4  
 using the Process is confirmed;  
  
 (b) the analytical methods for the Products have been transferred  
 from RPI to AVECIA; and  
  
 (c) the JRC confirms AVECIA's ability to manufacture the Product to  
 be produced during Stage 4 using the Process.  
  
 2.6 For the avoidance of doubt, any time periods specified in Schedule 1  
 shall be indicative only unless provided for specifically in this  
 Clause 2.  
  
 2.7 AVECIA shall be responsible for obtaining all raw materials and  
 reagents in order to produce the Product, including solvents, gases,  
 amidites and other laboratory consumables and the solid support, to be  
 utilised in conjunction with synthesis of a Product during the  
 Programme.  
  
 2.8 For the avoidance of doubt, it shall not be considered a breach of  
 this Agreement by AVECIA if an objective of the Programme is not  
 achieved:  
  
 (a) so long as AVECIA uses reasonable commercial and technical  
 diligence and makes good faith efforts to perform its obligations  
 to the fullest extent, and any failure to meet an objective of  
 the Programme shall not relieve RPI of its obligations to make  
 payment in accordance with Clause 3; or  
  
 (b) due to delay caused or contributed to by RPI.  
  
3. Payment for the Programme and First Kilogram of Product  
 -------------------------------------------------------  
  
 Subject to Clauses 4.2 and 13 below, RPI shall pay to AVECIA the following  
 sums at the time stated:  
  
 (a) on signature of this Agreement by both parties: [ \* ]; and  
  
 (b) upon receipt of Product by RPI but subject to Clause 4.5 below: [ \* ]  
 per gram of Product manufactured to the Product Specification during  
 Stage 4 of the  
  
 S-6  
  
  
 Programme and available for delivery to RPI by AVECIA (subject to a  
 maximum of [ \* ]for up to one kilogram of the Product manufactured  
 during stage 4 of the Programme unless otherwise agreed under Clause  
 5.3 below).  
  
 For the avoidance of doubt, a gram of Product shall mean a gram of nucleic  
 acid material which meets the Product Specification, net of any  
 accompanying salts, water or other residual solvents.  
  
4. Reporting, Variation and Completion of the Programme  
 ----------------------------------------------------  
  
 4.1 The Programme and the progress by AVECIA under the Programme shall be  
 supervised by the JRC which shall be established within the period of  
 30 days following the date of this Agreement. Such supervision by the  
 JRC shall take place in accordance with the provisions set out in  
 Schedule 2.  
  
 4.2 The parties may agree to alter the Programme either to extend the  
 projected duration of any of the Stages or to change any of the work  
 contained in any of the Stages provided that the parties shall first  
 agree in writing the terms of such extension and alteration of the  
 Programme including any amended payment terms.  
  
 4.3 The parties shall conduct regular information exchange on at least two  
 (2) weekly intervals by telephone or in a manner to be agreed by the  
 JRC, provided that where AVECIA considers that, for the purposes of  
 optimising or improving the Process, revisions or changes in methods  
 should be undertaken by AVECIA during the performance of the  
 Programme, AVECIA shall notify the JRC without delay of the reasons  
 therefor and the actions which it proposes to take.  
  
 4.4 Completion of the Programme will be deemed to have occurred when the  
 quantity of Product specified in Stage 4 has been manufactured in  
 accordance with the Product Specification and has been made available  
 for delivery to RPI pursuant to Clause 5 below.  
  
 4.5 RPI shall pay to AVECIA within thirty (30) days of the completion of  
 the Programme any sums required to be paid pursuant to Clause 3 above  
 which may remain outstanding at the completion of the Programme.  
 Notwithstanding the foregoing, and subject to Clause 13, in respect of  
 the Product held by AVECIA pursuant to Clause 5.1(a), RPI shall not be  
 obligated to make any payments to AVECIA pursuant to Clause 3(b) prior  
 to 1/st/ January 2001, unless RPI requests delivery of the Product  
 prior to 1/st/ January 2001, in which case RPI shall make payments to  
 AVECIA for the quantity of Product requested by RPI within 30 days of  
 the date of the invoice for the Product.  
  
 S-7  
  
  
5. Delivery of First Kilogram of Product under Stage 4  
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 5.1(a) Manufacture of the one kilogram (1kg) of the Product specified in  
 Stage 4 shall take place on the date(s) agreed by the parties.  
 AVECIA shall hold such manufactured Product in stock at its  
 facilities and at its expense under the terms of the Quality  
 Agreement, including the storage and stability instructions  
 provided by RPI to AVECIA. Any Product so held by AVECIA shall be  
 deemed to have been delivered and any risk shall immediately pass  
 to RPI, except insofar as any damage occurs to the Product as a  
 result of the negligence of AVECIA.  
  
 (b) Avecia shall use its best endeavours to deliver one kilogram  
 (1kg) of Product as specified in Stage 4. However, if AVECIA  
 shall manufacture at least [ \* ] and up to [ \* ], RPI shall be  
 obliged to purchase all such Product from AVECIA during 2000  
 subject to Clause 5.3 below. Subject to the foregoing, during  
 2000 AVECIA shall deliver quantities of Product at RPI's request  
 from time to time, such request not to be for less than 250 grams  
 of Product.  
  
 5.2 In the event that only a portion of the Product produced during  
 Stage 4 is delivered to RPI, RPI shall be responsible only to pay  
 for the quantity of the Product delivered.. If the quantity of  
 the Product supplied by AVECIA is less than [ \* ], then AVECIA  
 agrees to synthesise sufficient Product in order to supply the  
 shortfall quantity of Product to RPI, and the price for such  
 shortfall quantity shall be no more than that paid by RPI for the  
 initial delivered quantity. In the event that AVECIA then  
 produces more than the 1 kilogram (1kg) of Product specified in  
 Stage 4, the provisions of Clause 5.3 shall apply.  
  
 5.3 In the event that AVECIA produces more than the 1 kilogram (1kg)  
 of Product specified in Xxxxx 0, XXX agrees to purchase such  
 additional quantity up to a maximum of [ \* ] at a price to be  
 negotiated in good faith by the parties. Such agreed price shall  
 be less than [ \* ] per gram and shall be determined according to  
 the yield and price matrix attached as Schedule 5 hereto. In the  
 event that AVECIA produces more than [ \* ] of the Product, RPI  
 shall have an option, but not an obligation, to purchase such  
 additional quantity of the Product at its sole discretion at a  
 price per gram which does not exceed the price per gram paid for  
 the additional [ \* ] of the Product.  
  
 5.4 Avecia will arrange for shipment and insurance of the Product  
 produced during Stage 4 of the Programme to RPI as directed by  
 RPI at RPI's cost and expense. The Products will be shipped and  
 packaged by Avecia in accordance with RPI's shipping and  
 packaging instructions as may be agreed from time to time.  
 Deliveries will be made FOB Avecia's Grangemouth facility  
 (Incoterms 2000) and will be shipped to RPI's address as set  
 forth in this Agreement, or as otherwise directed by RPI in  
 writing. Risk and title in respect of all Product  
  
 S-8  
  
  
 supplied to RPI under this Agreement shall pass on delivery at  
 AVECIA's Grangemouth facility.  
  
6. Intellectual Property arising during the term of this Agreement  
 ---------------------------------------------------------------  
  
 6.1 Pre-Existing and Independently Developed Intellectual Property.  
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 Subject to the obligations of confidentiality contained in Clause 12  
 below and subject to Clause 6.2 below, each party shall be entitled to  
 apply for registrations of its Intellectual Property provided that  
 nothing in this Agreement shall affect the ownership by either party  
 of any Intellectual Property owned or in the possession of that party  
 at the date of this Agreement, or Intellectual Property developed  
 independently of this Agreement by any employee of that party without  
 reference to any of the Confidential Information disclosed by the  
 other party.  
  
 6.2 Ownership.  
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 (a) All rights in patents, inventions, processes, discoveries,  
 biological samples and other research materials and any other  
 novel or valuable information reflected in any medium which  
 arises or is created during the course of this Agreement shall be  
 the property of the creating party. The Parties shall promptly  
 report to each other any inventions, discoveries, biological  
 samples or other research materials made to the Process or to the  
 Products under the Agreement.  
  
 (b) Intellectual Property, whether or not patentable, which may arise  
 under this Agreement and made solely by an employee or agent of  
 RPI shall be owned by RPI ("RPI Inventions").  
  
 (c) Intellectual Property, whether or not patentable, made jointly by  
 an employee or agent of RPI and AVECIA shall be jointly owned  
 ("Joint Inventions").  
  
 (d) Intellectual Property, whether or not patentable, which may arise  
 under this Agreement and made solely by an employee or agent of  
 AVECIA shall be owned by AVECIA ("AVECIA Inventions").  
  
 (e) Inventorship will be determined according to applicable patent  
 law.  
  
 (f) AVECIA and RPI shall promptly disclose to each other in writing  
 each invention and discovery conceived and/or reduced to practice  
 under this Agreement.  
  
 (g) Intellectual Property arising from this Agreement and in the  
 possession of a party shall be treated as having been disclosed  
 to that party by the  
  
 S-9  
  
  
 party owning such Intellectual Property pursuant to this Clause  
 6.2, and the expressions "Disclosing Party" and "Receiving Party"  
 defined and used in connection with the obligations of  
 confidentiality contained in Clause 12 shall be construed  
 accordingly.  
  
 (h) In the event of a Joint Invention, RPI and AVECIA, and any wholly  
 owned group company of either, shall each be entitled to work  
 under such joint invention, but otherwise no sub-licensing shall  
 be permitted without the written consent of the joint inventor,  
 such consent not to be unreasonably withheld or delayed.  
  
 6.3 Limited Licence to carry out the activities under this Agreement.  
 -----------------------------------------------------------------  
 Each party grants to the other a limited, non-exclusive, royalty-free  
 licence to do all things necessary in order to carry out the  
 obligations and responsibilities under this Agreement under its  
 Intellectual Property (whether pre-existing Intellectual Property  
 under Clause 6.1 above or Intellectual Property arising as a result of  
 the Agreement under Clause 6.2(b) or (d) above). Such licence shall  
 expire at the completion of the Agreement and shall not be  
 transferable or sub-licensable.  
  
 6.4 Maintenance of Patents.  
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 (a) Subject to Clauses 6.1 and 6.4(e), RPI shall be responsible for  
 filing, prosecuting and maintaining patent applications and  
 resulting patents, if any, on RPI Inventions and on any Joint  
 Inventions insofar as they do not relate to synthesis or  
 manufacture of oligonucleotides other than Ribozymes.  
  
 (b) Subject to Clauses 6.1 and 6.4(e), AVECIA shall be responsible  
 for filing, prosecuting and maintaining patent applications and  
 resulting patents, if any, on AVECIA Inventions or on any Joint  
 Inventions relating to synthesis or manufacture of  
 oligonucleotides other than Ribozymes.  
  
 (c) Reasonable patent expenses for any Joint Invention will be shared  
 equally by the Parties, and reimbursed promptly upon presentation  
 of an invoice by the filing party.  
  
 (d) The non-filing party shall have the right to review and comment  
 in a timely manner on any such patent filings (applications and  
 response to office actions) prior to submission to the relevant  
 patent offices. Each party shall be solely responsible for  
 filing, prosecuting and maintaining patent applications and  
 resulting patents on any invention owned solely by it.  
  
 S-10  
  
  
 (e) Each of AVECIA and RPI shall solely own its respective technology  
 and any technology or other technology developed solely by it and  
 each shall be responsible for filing, prosecuting and monitoring  
 patent applications and resulting patents, if any, related  
 thereto.  
  
 6.5 Reservation of All Other Rights. Except as expressly set forth in  
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 this Agreement, nothing contained herein shall be construed as to  
 create any right to:  
  
 (a) AVECIA in any Intellectual Property of RPI or any other  
 proprietary technology (whether pre-existing Intellectual  
 Property under Clause 6.1 above or Intellectual Property arising  
 as a result of this Agreement under Clause 6.2(b)) of RPI  
 including, without limitation, any of RPI's patent rights  
 relating to the design, synthesis, delivery, development,  
 testing, use and sale of Ribozymes; or  
  
 (b) RPI in AVECIA Intellectual Property or any other proprietary  
 technology (whether pre-existing Intellectual Property under  
 Clause 6.1 above or Intellectual Property arising as a result of  
 this Agreement under Clause 6.2(d))of AVECIA.  
  
 PART III - SUBSEQUENT MANUFACTURE OF THE PRODUCT  
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7. Sale and Purchase  
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 7.1 Minimum Order. Unless this Agreement has been terminated under  
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 Clauses 13 or 21 below, RPI agrees that, following completion of the  
 Programme, it shall purchase a minimum of [ \* ] of the Products in  
 aggregate ("the Product Minimum") from AVECIA during the calendar  
 years 2000 to 2002, pursuant to the pricing and delivery provisions  
 contained in Clauses 7.2 and 7.3 below.  
  
 7.2 Price for Product. The parties shall negotiate in good faith the  
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 pricing schedule for the Products, on a per gram basis, to be  
 manufactured by AVECIA following completion of the Programme prior to  
 the manufacture of each order of Product. An example of the pricing  
 schedule is attached as Schedule 5 hereto. The price for quantities of  
 Products manufactured by Avecia following completion of the Programme  
 shall be based on:  
  
 (a) yields achieved dependent upon usage of raw materials; and on  
  
 (b) order volume, provided that for individual orders of less than  
 500 grams of Product the price per gram for such Product shall  
 not exceed [ \* ] of the per gram price for Product(s) ordered  
 for delivery in multiples of 500 grams or more.  
  
 S-11  
  
  
 7.3 Delivery Schedule. The parties shall agree on a schedule for  
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 delivery of Products by AVECIA to RPI ("the Delivery Schedule"). The  
 minimum order shall be 500 grams of Product except as otherwise  
 agreed subject to the pricing provisions of Clause 7.2 above.  
  
 7.4 Delivery. AVECIA will arrange for shipment and insurance of the  
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 Products ordered for delivery to RPI at RPI's direction and at RPI's  
 cost and expense. The Products will be shipped and packaged by  
 AVECIA in accordance with RPI's shipping and packaging instructions  
 as may be agreed from time to time. Deliveries will be made FOB  
 Avecia's Grangemouth facility (Incoterms 2000) and will be shipped  
 to RPI's address as set forth in this Agreement, or as otherwise  
 directed by RPI in writing. Risk and title in respect of all Product  
 supplied to RPI under this Agreement shall pass on delivery at  
 AVECIA's Grangemouth facility  
  
 7.5 Delivery Quantities  
 -------------------  
  
 (a) In the event that AVECIA delivers less than [ \* ]of the amount of  
 Product required to be delivered pursuant to the delivery schedule  
 agreed under Clause 7.3 above, RPI shall, subject to Clause 8, pay  
 AVECIA for the actual amount of Product delivered. Avecia shall  
 synthesise sufficient Product to complete the order and will supply  
 this to RPI and the price for such completion quantity shall be no  
 more, on a per gram basis, than that paid by RPI for the initial  
 delivered quantity under that order. For the avoidance of doubt, if  
 AVECIA delivers [ \* ] of the amount of Product, RPI shall, subject  
 to Clause 8, be obligated to pay AVECIA only for the [ \* ] of the  
 Product delivered.  
  
 (b) In the event that Avecia manufactures Product in quantities  
 exceeding the amount ordered for delivery under the delivery  
 schedule, RPI agrees to purchase upto [ \* ] of the order volume at a  
 price to be negotiated in good faith by the parties in respect of  
 the additional [ \* ], according to the yield and price matrix  
 attached as Schedule 5, but such amount shall not cost more per gram  
 than for the said amount ordered In the event AVECIA produces more  
 than [ \* ] of the Product, RPI shall have an option, but no  
 obligation, to purchase such additional quantity of the Product at  
 its sole discretion at a price per gram not to exceed the price per  
 gram paid for the additional quantity of the Product.  
  
 7.6 Delay in Delivery. In the event that the AVECIA delivers any  
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 Product later than four weeks from the date of delivery set out in  
 the Delivery Schedule other than as a result of Force Majeure as set  
 out in Xxxxxx 00, XXX shall be entitled to a five per cent reduction  
 in the price of the Product delivered one month late and to an  
 additional ten per cent reduction in price for each of the next two  
 complete month's delay thereafter. In the event AVECIA is unable to  
 deliver the Product within three months from the date set out in the  
 Delivery Schedule, then RPI shall have the option to either  
 terminate the Agreement pursuant to  
  
 S-12  
  
  
 Clause 13.3(b) or to manufacture or have manufactured by a Nominated  
 Manufacturer the Product. In the event RPI chooses the latter  
 option, then in order to satisfy RPI's requirement for that quantity  
 of the Product ordered, AVECIA, subject to Clause 12, agrees (i) to  
 make a good faith effort to provide, at no cost to RPI or to a  
 Nominated Manufacturer, the technical information necessary for such  
 manufacture of the Product; and (ii) to grant to RPI or a Nominated  
 Manufacturer a personal, royalty free licence under AVECIA's  
 relevant Intellectual Property to enable RPI or such Nominated  
 Manufacturer to undertake the manufacture of the Product7.7 Invoices  
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 and Payment Terms. AVECIA shall issue an invoice at the price agreed  
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 under Clause 7.2, as adjusted pursuant to Clause 7.6 if relevant,  
 above in respect of each shipment of the Product to RPI on despatch  
 by AVECIA of the Product for delivery to RPI. RPI shall pay all such  
 invoices in full within thirty days from the date of invoice,  
 provided that RPI shall not have rejected such delivery of Product  
 under Clause 8.1. In the event that payment is made by RPI before  
 any Product is examined by RPI pursuant to Clause 8.2, AVECIA will  
 reimburse RPI for the price of such Product if it is found that the  
 Product does not meet the Product Specification.  
  
 7.8 Responsibility for Raw Materials. AVECIA shall be responsible for  
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 obtaining all raw materials and reagents in order to produce the  
 Product, including solvents, gases, amidites and other laboratory  
 consumables and the solid support, to be utilised in conjunction  
 with synthesis of a Product.  
  
 7.9 Third Party Price Notice. After a period of [ \* ] from signature  
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 of this Agreement, RPI shall be entitled to give AVECIA written  
 notice if a third party under a supply agreement with RPI of at  
 least three years duration is able to supply identical products in  
 identical volumes to RPI at a price which is at least ten per cent  
 lower than the price for the Products agreed under Clause 7.2 above  
 ("Third Party Price Notice"). RPI and AVECIA shall meet to discuss  
 the position and if agreement on price is not reached within 30 days  
 of receipt of such Third Party Notice, then RPI may purchase the  
 quantity so offered from the third party and the amounts of such  
 Products purchased shall be construed as falling within the amounts  
 of Products to be delivered according to the Product Minimum  
 referred to in Clause 7.1. RPI shall not be obliged to divulge the  
 identity of such third party, but at the request of AVECIA shall in  
 lieu provide satisfactory evidence, signed by an independent notary  
 public certifying the genuineness of the competitive offer.  
  
 7.10 Non-use of RPI's Intellectual Property. Other than as provided in  
 --------------------------------------  
 this Agreement, AVECIA agrees that it will not use for its internal  
 purpose or for third parties any Intellectual Property of RPI  
 (whether pre-existing Intellectual Property under Clause 6.1 above  
 or Intellectual Property arising as a result of this Agreement under  
 Clause 6.2(b) above) or Confidential Information acquired under this  
 Agreement.  
  
 S-13  
  
  
8. Quality of the Product  
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 8.1 The Product manufactured and delivered by AVECIA to RPI under Clause 7  
 above shall conform to the Product Specification for such Product.  
  
 8.2 RPI shall examine all Product delivered to it pursuant to this  
 Agreement in accordance with the methods of analysis set out in the  
 Quality Agreement for such Product. RPI shall notify AVECIA of any  
 failure of the Product to meet the Product Specification within [ \* ]  
 days of receipt of the relevant Product. RPI shall be entitled to  
 reject any Product which does not meet the Product Specification  
 ("Rejected Product")  
  
 8.3 (a) RPI will return any Rejected Product to AVECIA and, if AVECIA  
 agrees with RPI's notification of failure, AVECIA shall replace  
 the Rejected Product at no additional cost to RPI within [ \* ]  
 days of receiving notice from RPI under Clause 8.2 or on a new  
 delivery date as mutually agreed to in writing by the Parties.  
  
 (b) In the event AVECIA is unable to replace the Rejected Product  
 within such time, RPI shall be entitled to exercise its Standby  
 Rights (as set out in Clause 9.1 below) to enable RPI or a  
 Nominated Manufacturer to manufacture sufficient Product to  
 replace the Rejected Product, and AVECIA, subject to Clause 12,  
 agrees to make a good faith effort to provide, at no cost to RPI  
 or to a Nominated Manufacturer, the technical information  
 necessary for such manufacture of the Product. In addition,  
 AVECIA will reimburse to RPI that element of the reasonable cost  
 of the Product manufactured by the Nominated Manufacturer which  
 is in excess of the price which RPI would have had to pay to  
 AVECIA. The amounts of such Products manufactured by the  
 Nominated Manufacturer shall be construed as falling within the  
 amounts of Product to be purchased by RPI in accordance with the  
 Product Minimum in Clause 7.1 above.  
  
 (c) If AVECIA disagrees with RPI's notification of failure the JRC  
 shall consider the matter and in the event no agreement is then  
 reached, the parties shall jointly appoint an expert to determine  
 whether the Product is a Rejected Product, and the costs and fees  
 of the expert shall be borne by the losing party. During the  
 period of dispute resolution under this Clause 8.3(c):-  
  
 (i) If RPI requests AVECIA to resynthesise the quantity of the  
 Rejected Product, AVECIA shall in good faith resynthesise  
 the  
  
 S-14  
  
  
 Product and deliver it to RPI within [ \* ] of receiving  
 such a request from RPI. Subject to Xxxxxx 0, XXX will  
 make payment for the resynthesised quantity within [ \* ]  
 of delivery. If the dispute is resolved in favour of  
 AVECIA, RPI agrees to purchase from AVECIA both batches of  
 the Product, and such additional quantity of the Product  
 resynthesised by AVECIA shall not count towards the  
 Product Minimum. If the dispute is resolved in favour of  
 RPI, RPI will make payment only for the resynthesised  
 Product.  
  
 (ii) In the event AVECIA is unable to replace the Rejected  
 Product within the time stated in Clause 8.3(c)(i) above,  
 RPI shall be entitled to exercise its Standby Rights (as  
 set out in Clause 9.1 below) to enable RPI or a Nominated  
 Manufacturer to manufacture sufficient Product to replace  
 the Rejected Product, and AVECIA, subject to Clause 12,  
 agrees (i) to make a good faith effort to provide to RPI  
 or to a Nominated Manufacturer, at RPI's cost, the  
 technical information necessary for such manufacture of  
 the Product; and (ii) to grant to RPI or a Nominated  
 Manufacturer a personal, royalty free licence under  
 AVECIA's relevant Intellectual Property to enable RPI or  
 such Nominated Manufacturer to undertake such manufacture.  
 If the dispute is resolved in favour of AVECIA, RPI agrees  
 to purchase from AVECIA the entire amount of the Product  
 in dispute and to make immediate payment, and any  
 additional quantity of the Product manufactured by RPI or  
 its Nominated Manufacturer shall not count toward the  
 Product Minimum. If the dispute is resolved in favour of  
 RPI, AVECIA will reimburse to RPI that element of the  
 reasonable cost of the Product manufactured by the  
 Nominated Manufacturer which is in excess of the price  
 which RPI would have had to pay to AVECIA, together with  
 any costs paid by RPI in respect of the transfer of the  
 technical information by AVECIA, and the originally  
 ordered quantity of the Product shall be construed as  
 falling within the amount of Product to be purchased by  
 RPI in accordance with the Product Minimum.  
  
 (iii) If RPI does not request AVECIA to resynthesise the  
 Rejected Product, then AVECIA shall not be required to  
 start the resynthesis until the dispute is resolved or  
 until RPI make such a request, whichever is the sooner.  
 For the avoidance of doubt, no act or omission of RPI  
 under this Sub-clause 8.3(c)(iii) shall cause the Product  
 Minimum to be reduced by the amount of the Rejected  
 Product.  
  
 S-15  
  
  
 8.4 In the absence of notification that the Product does not meet the  
 Product Specification within the period set out in Clause 8.1 above,  
 the relevant consignment of the Product shall be deemed to have been  
 accepted by RPI in full compliance with the Product Specification.  
  
  
9. Licence under AVECIA Intellectual Property to Manufacture the Product  
 ---------------------------------------------------------------------  
  
 9.1 If AVECIA is unable to meet the delivery requirements set out in the  
 Delivery Schedule agreed under Clause 7.3 above, then subject to  
 Clause 12, AVECIA shall grant to RPI or a Nominated Manufacturer a  
 personal licence on reasonable commercial terms under AVECIA's  
 relevant Intellectual Property to enable RPI or such Nominated  
 Manufacturer to undertake the manufacture of Products, in order to  
 satisfy its requirements for Products ("Standby Rights"). In the  
 event that RPI wishes to exercise its Standby Rights, RPI will provide  
 Avecia with written notice thereof in advance of such exercise and,  
 subject to Clause 8, the volume of products manufactured under the  
 Standby Rights will be subtracted from the Product Minimum.  
  
 9.2 Manufacture of Products in excess of Product Minimum. In the event  
 ----------------------------------------------------  
 that RPI's requirements for delivery of the Product over the period  
 from 1/st/ January 2000 to 31/st/ December 2002, as set out in the  
 Delivery Schedule, are in excess of the Product Minimum, then provided  
 that RPI shall purchase the greater of the Product Minimum or [ \* ] of  
 its total requirements for delivery of the Product from AVECIA, RPI  
 shall have the ability to exercise its Standby Rights for manufacture  
 of the balance of the Product required during such period. AVECIA, at  
 its cost, shall have the right to have an independent third party  
 certify RPI's delivery requirements each twelve months within the  
 above said period, subject to Clause 12.  
  
 9.3 Any royalty payable under the licence granted as a result of the  
 exercise of the Standby Rights shall be dependent upon the volume of  
 Products to be manufactured by AVECIA on behalf of RPI and shall not  
 exceed [ \* ]of the selling price of Products made by such a Nominated  
 Manufacturer. Neither RPI nor the Nominated Manufacturer, shall be  
 obligated to make any payments to AVECIA for the exercise of Standby  
 Rights pursuant to Clause 7.6 or pursuant to Clause 8.3 unless the  
 dispute is resolved in AVECIA's favour.  
  
 9.4 Without prejudice to Clause 13.5, upon the expiry or termination of  
 this Agreement, RPI may request a licence under AVECIA's Intellectual  
 Property, and the parties will negotiate in good faith the commercial  
 terms of such royalty bearing licence.  
  
  
 PART IV - GENERAL TERMS  
 -----------------------  
  
 S-16  
  
  
10. Quality Agreements  
 ------------------  
  
 AVECIA and RPI shall enter into a quality agreement in respect of each  
 Product on a case by case basis, the terms of which shall be agreed by the  
 JRC prior to manufacture and supply of each Product.  
  
  
11. Warranties, Liability and Indemnity  
 -----------------------------------  
  
 11.1 Intellectual Property Warranty and Indemnity  
 --------------------------------------------  
  
 (a) Each party warrants to the other that:  
  
 (i) it has the necessary right and authority to enter into this  
 Agreement and that to the best of its knowledge at the date  
 of this Agreement it is the rightful owner or licensee of  
 all of its Intellectual Property; and  
  
 (ii) to the best of its knowledge at the date of this Agreement,  
 the use of Intellectual Property made available by it to the  
 other party pursuant to this Agreement for the purposes set  
 out in this Agreement will not infringe the Intellectual  
 Property of a third party.  
  
 (b) Subject to Clause 11.5, each party ("the Indemnifying Party")  
 will indemnify and hold harmless the other ("the Indemnified  
 Party") against any and all liability, loss, damages, costs,  
 legal costs, professional and other expenses whatsoever incurred  
 or suffered by Indemnified Party in respect of any claim or  
 action that the use of the Indemnifying Party's Intellectual  
 Property by the Indemnified Party in its performance of this  
 Agreement infringes the Intellectual Property of any third party  
 (an "Intellectual Property Infringement") provided that the  
 Indemnified Party:  
  
 (i) gives notice to the Indemnifying Party of any Intellectual  
 Property Infringement forthwith on becoming aware of the  
 same;  
  
 (ii) gives the Indemnifying Party the sole conduct of the defence  
 to any claim or action in respect of Intellectual Property  
 Infringement and does not at any time admit liability or  
 otherwise settle or compromise or attempt to settle or  
 compromise the said claim or action except upon the express  
 instructions of the Indemnifying Party; and  
  
 S-17  
  
  
 (iii) acts in accordance with the reasonable instructions of the  
 Indemnifying Party and gives the Indemnifying Party such  
 assistance as it shall reasonably require in respect of  
 the conduct of such defence.  
  
 11.2 Liability for the Products. Liability in respect of any Product  
 --------------------------  
 delivered to RPI and not rejected by RPI within the period set out in  
 Clause 8.2 above (including, without limitation, the use to which it  
 is put) following delivery to RPI of such Product shall rest solely  
 on RPI and RPI shall indemnify AVECIA against any liability, loss,  
 damages, costs, legal costs, professional and other expenses  
 whatsoever incurred or suffered by AVECIA arising out of or in  
 respect of such Product following its delivery to RPI including,  
 without limitation, RPI's use of the Product following delivery.  
  
 11.3 Liability for Manufacture of the Products. Liability in respect of  
 -----------------------------------------  
 manufacture of the Products, whether by use or operation of the  
 Process (or any part of the Process) or otherwise, by RPI or by a  
 Nominated manufacturer on behalf of RPI shall rest solely on RPI. RPI  
 shall indemnify AVECIA against any liability, loss, damages, costs,  
 legal costs, professional and other expenses whatsoever incurred or  
 suffered by AVECIA arising out of or in respect of manufacture of the  
 Products, whether use or operation of the Process (or any part of the  
 Process) or otherwise by RPI or by a Nominated Manufacturer on behalf  
 of RPI.  
  
 11.4 Limit on AVECIA's Liability. Subject to the unlimited liability  
 ---------------------------  
 provisions of Clause 11.1, AVECIA's total liability (whether for  
 breach of contract, negligence, breach of statutory duty and/or other  
 tort, or otherwise):  
  
 (a) in connection with or as a result of the work carried out during  
 the Programme shall be limited to the aggregate amount received  
 by AVECIA from RPI under this Agreement at the time such  
 liability arises; or  
  
 (b) in connection with the manufacture of the Product pursuant to  
 Part III of this Agreement shall in no event exceed the purchase  
 price paid by RPI for the ordered quantity of Product in respect  
 of which the claim is made or liability has arisen.  
  
 11.5 No liability for consequential loss. Neither party shall be liable to  
 -----------------------------------  
 the other for any indirect, consequential or special loss, loss of  
 profits or damage howsoever arising.  
  
 11.6 No exclusion of liability for personal injury. Nothing in this  
 ---------------------------------------------  
 Agreement shall remove or limit the liability of either party in  
 respect of death or personal  
  
 S-18  
  
  
 injury arising out of the negligence or wilful default of that party  
 its servants or agents.  
  
12. Confidentiality  
 ---------------  
  
 12.1 In consideration of the Disclosing Party disclosing the Confidential  
 Information to the Receiving Party, the Receiving Party hereby  
 undertakes to maintain confidential all such Confidential Information  
 and it will accordingly not directly or indirectly disclose any of  
 the Confidential Information in whole or in part, other than under  
 Clause 12.4 below. For the purposes of this Clause 12, Intellectual  
 Property arising from the Programme and in the possession of a party  
 shall be treated as having been disclosed to that party by the party  
 owning such Intellectual Property pursuant to Clause 6.2 above, and  
 the expressions "Disclosing Party" and "Receiving Party" shall be  
 construed accordingly.  
  
 12.2 The foregoing restrictions on the Receiving Party shall not apply to  
 any Confidential Information which:  
  
 (a) the Receiving Party can prove was already in its possession and  
 at its free disposal before the disclosure hereunder to it;  
  
 (b) is hereafter disclosed to, purchased or otherwise legally  
 acquired by the Receiving Party by or from a third party who has  
 not derived it directly or indirectly from the Disclosing Party;  
  
 (c) is or becomes available to the public whether in printed  
 publications or otherwise through no act or default on the part  
 of the Receiving Party or its agents or employees; or  
  
 (d) the Receiving Party can prove to the reasonable satisfaction of  
 the Disclosing Party has been developed independently of the  
 Programme by any employee of the Receiving Party without  
 reference to any of the Confidential Information disclosed by  
 the Disclosing Party.  
  
 12.3 In order to secure the obligations set out in this Clause 12 the  
 Receiving Party agrees to exercise every reasonable precaution to  
 prevent and restrain the unauthorised disclosure and use of  
 information subject to confidentiality, including restricting access  
 to such information to such of its employees as are bound to keep  
 such information confidential and need to have such access for the  
 purpose of this Agreement.  
  
 12.4 The Receiving Party may disclose Confidential Information: (i) in the  
 case of AVECIA to Avecia Inc., 0000 Xxxxx Xxxx, XX Xxx 00000,  
 Xxxxxxxxxx, XX 00000-0000 and to Boston Biosystems Inc. of 00X  
 Xxxxxxx Xxxxxx, Xxxxxxx,  
  
 X-00  
  
  
 Xxxxxxxxxxxxx; and (ii) in the case of RPI to its Nominated  
 Manufacturer(s) (each a "Permitted Recipient"), provided that the  
 Receiving Party shall procure that prior to such disclosure each  
 Permitted Recipient to which Confidential Information is to be  
 disclosed is made aware of the obligations contained in this  
 Agreement and enters into confidentiality obligations in  
 substantially the same terms as those contained in this Agreement  
 directly with the Disclosing Party.  
  
 12.5 The provisions of this Clause 12 shall survive termination or expiry  
 of this Agreement and shall continue for a period of 10 years from  
 the date of that termination or expiry.  
  
 12.6 The parties shall remain bound by the obligations in the Mutual  
 Confidentiality Agreement signed by them and dated 23/rd/ December  
 1998, but in the event of any conflict between the terms of that  
 Mutual Confidentiality Agreement and the terms of this Agreement, the  
 latter shall prevail.  
  
13. Duration and Termination  
 ------------------------  
  
 13.1 Duration. This Agreement and the Programme shall be deemed to have  
 --------  
 commenced on the Effective Date and shall continue (unless terminated  
 in accordance with the provisions of Clauses 13.2, 13.3, 13.4 or 21)  
 until the expiry of the period of three years from the date of  
 commencement of manufacture of the Product pursuant to Part III of  
 this Agreement following completion of the Programme.  
  
 13.2 (A) Termination by mutual agreement. Subject to Clause 13.5 below,  
 -------------------------------  
 this Agreement may be terminated by mutual agreement at any time  
 prior to completion of the Programme in the event that both  
 parties agree that the Programme is not technically feasible.  
  
 (B) Termination for technical non-feasibility. Subject to Clause 13.5  
 below, this Agreement may be terminated by either party on or  
 after 1 January 2001 if it has not been agreed that the Programme  
 is technically feasible in respect of the Product Specification,  
 quantity and timeframe.  
  
 13.3 Termination by RPI. Subject to Clause 13.5 below, RPI may terminate  
 ------------------  
 this Agreement in the following ways:  
  
 (a) by [ \* ] written notice to AVECIA if RPI is unable to, or  
 elects not to, pursue development of any of the Products;  
  
 (b) forthwith upon written notice if Avecia has been unable to  
 deliver the Product within [ \* ] of the date for delivery  
 of such Product specified in the Delivery Schedule or, in  
 respect of the kilogramme of the Product  
  
 S-20  
  
  
 ordered under the Programme, on or before [ \* ] for reasons  
 not relating to technical feasibility as referred to in  
 Clauses 13.2(A) and 13.2(B)  
  
 (c) forthwith if AVECIA is in breach of this Agreement (other  
 than under Clause 13.3(b) above) and AVECIA does not  
 rectify such breach within [ \* ] of receipt of written  
 notice from RPI requiring rectification of the breach,  
 provided that it is intended that the parties will discuss  
 any alleged breach and its remediation as soon as it is  
 known; or  
  
 (d) forthwith upon written notice if AVECIA has a liquidator,  
 receiver, manager receiver or administrator appointed, or  
 ceases to continue trading or is unable to pay debts as  
 defined in Section 227 of the Insolvency Xxx 0000 (England  
 and Wales).  
  
 13.4 Termination by AVECIA. Subject to Clause 13.5 below, AVECIA may  
 ---------------------  
 terminate this Agreement in the following ways:  
  
 (a) forthwith if RPI is in breach of this Agreement (other than  
 under Clause 13.3(b) above) and RPI does not rectify such  
 breach within [ \* ] of receipt of written notice from  
 AVECIA requiring rectification of the breach, provided that  
 it is intended that the parties will discuss any alleged  
 breach and its remediation as soon as it is known; or  
  
 (b) forthwith upon written notice if RPI has a liquidator,  
 receiver, manager receiver or administrator appointed, or  
 ceases to continue trading or is unable to pay debts as  
 defined in Section 227 of the Insolvency Act 1986 (England  
 and Wales), or equivalent occurs in the USA or any other  
 jurisdiction in which RPI is incorporated or resident.  
  
 13.5 Consequences of Termination. Termination under Clauses 13.2 -  
 ---------------------------  
 13.4 above shall have one or more of the following consequences  
 according to the table set out below:  
  
 A RPI shall pay to AVECIA all sums payable up to the date of  
 termination but not yet paid, together with all reasonable  
 costs already incurred by AVECIA at the date of termination  
 or costs incurred by AVECIA after termination which could  
 not reasonably be avoided.  
  
 B The parties shall agree upon a sum payable by RPI in  
 respect of work done by AVECIA under the Programme for  
 which monies have not yet become payable under Clause 3  
 above and in the absence of agreement upon such sum the  
 provisions of Clause 26 shall apply.  
  
 S-21  
  
  
 C Any moneys paid by RPI to AVECIA up to the date of  
 termination shall be non-refundable, subject to D below  
 where applicable.  
  
 D Termination of this Agreement prior to the commencement of  
 Stage 3 of the Programme can only take place if agreed by  
 the JRC. In such event, AVECIA shall reimburse to RPI  
 within 30 days of the date of termination, a proportion of  
 the [ \* ]received from RPI under Clause 3(a) as follows:  
  
 (i) termination prior to completion of Stage 1 - [ \* ]  
 (ii) termination between Stages 1 and 2 - [ \* ]; or  
 (iii) termination between Stages 2 and 3 - [ \* ]  
  
 E AVECIA shall grant to RPI or a Nominated Manufacturer (at  
 RPI's option), a royalty-free, non-exclusive world-wide  
 licence under AVECIA's Intellectual Property including any  
 AVECIA Invention arising under Clause 6.2(d) above  
 necessary for RPI or a Nominated Manufacturer (at RPI's  
 option) to manufacture Products identified for manufacture  
 under this Agreement Any such licence granted under this  
 Clause 13.5(E) shall expire at such time asa quantity of  
 Product is manufactured which fulfills the Product Minimum  
 requirement in Clause 7.1, plus any amount ordered by RPI  
 and accepted by AVECIA, and in this respect RPI will  
 provide, or procure its Nominated Manufacturer to provide,  
 all necessary manufacturing information and records to  
 Avecia:  
  
 F Any licence granted under Clauses 6.3, 9.1 or 9.2 shall  
 terminate.  
  
 G RPI shall purchase all quantities of Product ordered by RPI  
 and manufactured by AVECIA but not yet delivered to RPI,  
 including any quantity of Product held by AVECIA pursuant  
 to Clause 5.1(a), at the price agreed under Clause 7.2  
 above.  
  
 Termination Clauses and Consequences  
  
 Clause Consequences  
 ------ ------------  
 Clause 13.2 A [ \* ]  
 Clause 13.2B [ \* ]  
 Clause 13.3 (a) [ \* ]  
 Clause 13.3 (b) [ \* ]  
 Clause 13.3 (c) [ \* ]  
 Clause 13.3 (d) [ \* ]  
 Clause 13.4 (a) [ \* ]  
 Clause 13.4 (b) [ \* ]  
  
 \* In the event of termination under Clause 13.2 , the amount to  
 be paid to AVECIA shall not exceed [ \* ]  
  
 S-22  
  
  
 \*\* In the event of termination under Clause 13.2 only, the  
 amount to be repaid by AVECIA to RPI shall be limited to  
 [ \* ] of the [ \* ] received from RPI under Clause 3(a)  
 irrespective of the Stage in the Programme at which  
 termination takes effect.  
  
 \*\*\* In the event of termination under Clause 13.3(a) only, the  
 amount payable by RPI to AVECIA under Clause 13.5 A for costs  
 incurred by AVECIA after termination which could not  
 reasonably be avoided, shall not exceed [ \* ]  
  
 13.6 Termination or expiry of this Agreement, for whatever reason,  
 shall not prejudice the acquired rights of either party.  
  
 13.7 For the avoidance of doubt, it shall not be considered a breach  
 of this Agreement if an objective of the Programme is not  
 achieved so long as AVECIA uses all reasonable commercial  
 endeavours to perform its obligations.  
  
 13.8 The provisions of Clauses 3, 6.2, 6.4, 6.5, 9, 11, 12, 13.7 - 26  
 shall survive the termination or expiry of this Agreement. In the  
 event that RPI or any Nominated Manufacturer breaches any of the  
 surviving clauses of this Agreement, any licence granted as a  
 result of the operation of consequence E under Clause 13.5 above  
 shall terminate.  
  
 14. Payment  
 -------  
  
 All amounts payable to AVECIA under this Agreement shall be paid in US  
 Dollars in accordance with the following details:-  
  
 [ \* ]  
  
 S-23  
  
  
 15. Announcements And Publicity  
 ---------------------------  
  
  
 15.1 Subject to Clause 15.2, the parties agree that neither of them  
 will make any official press release, announcement or other  
 formal publicity relating to the transactions which are the  
 subject of this Agreement, or any ancillary matter, including  
 without limitation use the name of the other in any form of  
 advertising or public promotion, without first obtaining in each  
 case the prior written consent of the other party (which consent  
 will not be unreasonably withheld), except as required by law.  
  
 15.2 The parties agree that any publication, abstract or patent  
 application resulting from this Agreement will be sent to the  
 other at least 60 days prior to filing or submission for prior  
 approval. The authorship on any publication and/or abstract will  
 be based on mutual agreement between the parties or as deemed  
 scientifically appropriate. A publication resulting from this  
 Agreementwill be delayed or prohibited if, in the reasonable  
 opinion of the other party, it will be necessary to delay or  
 prohibit such publication in order to file or procure patent  
 application or rights protection in respect of any invention or  
 discovery arising from this Agreement.Notwithstanding the  
 foregoing, AVECIA shall have no right to publish or disclose to a  
 third party, any information relating to the Products without the  
 prior written permission of RPIunless such information falls  
 within any of the exceptions in Clause 12.2.  
  
16. Assignment and Transfer  
 -----------------------  
  
 16.1 This Agreement shall inure to the benefit of, and be binding  
 upon, the successors and assignees of the parties. This Agreement  
 may not be assigned or transferred by either of the parties  
 hereto without the prior written consent of the other, which will  
 not be unreasonably withheld; provided, however, that either  
 party may assign or transfer its rights and obligations under  
 this Agreement to an affiliate of that party or a successor to  
 all or substantially all of its assets or business relating to  
 this Agreement, whether by sale, merger, operation of law or  
 otherwise by giving written notice to the other party.  
  
 16.2 AVECIA may transfer this Agreement to any entity which AVECIA may  
 establish to undertake its contract manufacturing of Product,  
 provided that AVECIA owns or controls at least 50% of the voting  
 stock of such entity and such transfer is pre-approved by RPI.  
  
17. Variation  
 ---------  
  
 No variation or amendment of this Agreement shall bind either party unless  
 made in writing in the English language and agreed to in writing by duly  
 authorised officers of both parties.  
  
 S-24  
  
  
18. Illegality  
 ----------  
  
 If any provision of this Agreement is agreed by the parties to be illegal  
 void or unenforceable under any law that is applicable hereto or if any  
 court of competent jurisdiction in a final decision so determines, this  
 Agreement shall continue in force save that such provision shall be deemed  
 to be excised herefrom with effect from the date of such agreement or  
 decision or such earlier date as the parties may agree.  
  
19. Waiver  
 ------  
  
 A failure by either party hereto to exercise or enforce any rights  
 conferred upon it by this Agreement shall not be deemed to be a waiver of  
 any such rights or operate so as to bar the exercise or enforcement thereof  
 at any subsequent time or times.  
  
20. Notices  
 -------  
  
 20.1 All notices, instructions and other communications given hereunder  
 or in connection herewith shall be in writing. Any such notice,  
 instruction or communication shall be sent either (i) by registered  
 or certified mail, return receipt requested, postage prepaid, or  
 (ii) via a reputable nationwide overnight courier service, in each  
 case to the address set forth below. Any such notice, instruction or  
 communication shall be deemed to have been delivered upon receipt.  
  
 If made to RPI, all notices shall be addressed to:  
 Ribozyme Pharmaceuticals, Inc.  
 0000 Xxxxxxxxxx Xxxxx  
 Xxxxxxx, XX 00000  
 Attention: Vice President Corporate Development  
 Tel: (000) 000-0000  
 Fax: (000) 000-0000  
 with a copy to:  
 Rothgerber, Xxxxxxx and Xxxxx  
 0000 00xx Xxxxxx, Xxxxx 0000  
 Xxxxxx, XX 00000  
 Attention: Xxxxxxx X. Xxxxx III, Esq.  
 Tel: (000) 000-0000  
 Fax: (000) 000-0000  
  
 If made to AVECIA, all notices shall be addressed to:  
 Avecia Limited  
 Xxxxxxx Xxxxx  
 Xxxxxxxx, Xxxxxxxxxx, X0 0XX  
 Attention: Vice-President, LifeScience Molecules  
 Business  
  
 S-25  
  
  
 Tel: 0000 000 0000  
 Fax: 0000 000 0000  
 with a copy to:  
 Legal Affairs Department  
 Avecia Limited  
 Hexagon House  
 Blackley, Manchester, M9 8ZS  
 Attention: Company Secretary  
 Tel: 0000 000 0000  
 Fax: 0000 000 0000  
  
 or, in each case, to such other address as may be specified in  
 writing to the other parties.  
  
 20.2 Any party may give any notice, instruction or communication in  
 connection with this Agreement using any other means (including  
 personal delivery, telecopy or ordinary mail), but no such notice,  
 instruction or communication shall be deemed to have been delivered  
 unless and until it is actually received by the party to whom it was  
 sent. Any party may change the address to which notices,  
 instructions or communications are to be delivered by giving the  
 other parties to this Agreement notice thereof in the manner set  
 forth in this Clause 20.  
  
21. Force Majeure  
 -------------  
  
 Neither party shall be liable to the other party in any manner whatsoever  
 for any failure or delay in performing its obligations under this Agreement  
 if and to the extent, and for the duration, that such is due to force  
 majeure, which expression for the purposes of this Agreement means any  
 cause beyond the reasonable control of the party in question which for the  
 avoidance of doubt and without prejudice to the generality of the  
 foregoing shall include governmental actions, war, riots, civil commotion,  
 fire, flood, epidemic, labour disputes (excluding labour disputes involving  
 the work force or any part thereof of the party in question, restraints or  
 delays affecting shipping or carriers, inability or delay in obtaining  
 supplies of adequate or suitable materials and act of God. Without  
 prejudice to Clause 13.1, any said failure or delay shall not give either  
 party the right to terminate this Agreement except, and to the extent that  
 such force majeure continues for a period exceeding three months.  
 Termination as a result of Force Majeure shall give rise to consequences  
 [ \* ] as set out in the table at Clause 13.5.  
  
22. Good Faith and Duty to Mitigate  
 -------------------------------  
  
 22.1 Each of the parties shall at all times act in good faith in carrying  
 out the terms of this Agreement.  
  
 S-26  
  
  
 22.2 Each of the parties shall use all reasonable endeavours to mitigate  
 any costs, losses or expenses due to be incurred or suffered by the  
 other party in connection with the performance or non-performance of  
 this Agreement.  
  
 23. Further Assurances  
 ------------------  
  
 At any time or from time to time on and after the Effective Date,  
 each of AVECIA and RPI shall at the request, cost and expense of  
 the other:  
  
 (a) deliver to the other such records, data or other documents  
 consistent with the provisions of this Agreement;  
  
 (b) execute, and deliver or cause to be delivered, all such  
 assignments, consents, documents or further instruments of  
 transfer or licence required by this Agreement; and  
  
 (c) take or cause to be taken all such other actions, as may  
 reasonably be deemed necessary or desirable in order to obtain  
 the full benefits of this Agreement and the transactions  
 contemplated hereby.  
  
  
 24. Maintenance of Records and Right to Inspect Manufacturing  
 ---------------------------------------------------------  
  
 24.1 AVECIA agrees to maintain good records of sufficient detail to  
 allow the critical examination of all the data and the analysis  
 documentation in a form that is Food and Drug Administration  
 compliant (collectively, "Records"). Records, including those  
 associated with lots produced, must be kept and maintained  
 safely for at least two (2) years by AVECIA. Prior to disposal  
 of these Records, AVECIA agrees to give RPI the option of  
 transferring the Records and their use to RPI. If AVECIA is no  
 longer in the contract oligonucleotide synthesis business, then  
 RPI shall have the right to immediately obtain and use all  
 Records including the Drug Master File related to the  
 production of the Product covered by this Agreement.  
  
 24.2 Upon RPI's written request, AVECIA will allow RPI and/or its  
 Collaborator(s) to review its GMP processes and procedures as  
 such processes relate to bulk drug and the preparation of  
 Product. Such audit shall be subject to the confidentiality  
 provisions of Clause 12. Such reviews shall occur as soon as  
 reasonably practical. RPI and/or its Collaborator(s) shall have  
 the right to inspect all manufacturing and testing facilities  
 and operations (including third parties) to assure compliance  
 with GMP requirements and regulatory commitments. AVECIA will  
 assure compliance with regulatory commitments and will correct  
 any deficiencies prior to manufacturing of any Product  
 contemplated under this Agreement, subject to any provisions  
 set out in the Technical Agreement or any Quality Agreement.  
 AVECIA will promptly  
  
 S-27  
  
  
 notify RPI of any regulatory inspections and  
 inquiry/communications which involve a Product and give RPI an  
 opportunity to assist AVECIA in responding to any such  
 inquires.  
  
 25. Entire Agreement  
 ----------------  
  
 25.1 This Agreement contains the entire agreement between the parties  
 and supersedes any previous agreements relating to this  
 Agreement and any understandings between the parties with  
 respect thereto, and may not be modified except by an instrument  
 in writing signed by the duly authorised representatives of the  
 parties.  
  
 25.2 In the event of any conflict between the Agreement and the  
 Schedules, then the former takes precedence .  
  
 26. Law and Jurisdiction  
 --------------------  
  
 26.1 This Agreement is governed by and shall be construed and  
 interpreted in accordance with the laws of the US State of  
 Delaware.  
  
 26.2 The parties shall meet as soon as possible to discuss and to  
 attempt to resolve all matters not specifically provided for in  
 this Agreement or in the constitution of the JRC and which  
 require a decision and all differences, disputes or  
 disagreements which may arise out of or in connection with this  
 Agreement or the JRC. If the parties are unable to resolve any  
 such matter or dispute then it shall be referred to the Vice-  
 President, Life Science Molecules business and the RPI Vice  
 President Corporate Development, who shall meet within thirty  
 (30) days of being requested to do so and shall in good faith  
 attempt to resolve the matter or dispute.  
  
 26.3 The parties agree to refer any matter or dispute which is not  
 able to be resolved pursuant to Clause 26.2 to the Centre for  
 Dispute Resolution ("CEDR") in London, England in an attempt to  
 settle the same in good faith by Alternative Dispute Resolution  
 ("ADR"). The site for ADR shall be London, England, if initiated  
 by RPI and Boulder, Colorado, if initiated by Avecia.  
  
 26.4 Neither of the parties shall be deemed to be precluded from  
 taking such interim formal steps as may be considered necessary  
 to protect such party's position while the procedures referred  
 to in Clauses 26.2 and 26.3 are pursued.  
  
 26.5 In the event that the matter or dispute remains unresolved by  
 such ADR procedure within thirty days of commencement of such  
 procedure, then the parties shall be at liberty to take such  
 other proceedings (as defined below) as they think fit.  
  
 S-28  
  
  
 26.6 Except as provided for in Clauses 26.2, 26.3 and 26.4, in  
 relation to any legal action or proceedings to enforce this  
 Agreement or arising out of in connection with this Agreement  
 ("proceedings") each of the parties irrevocably submits to the  
 exclusive jurisdiction of the Delaware Courts if initiated by  
 RPI and Denver Courts if initiated by Avecia .  
  
 27. Counterparts  
 ------------  
  
 This Agreement may be executed in counterparts, each of which shall be  
 deemed an original, but all of which together shall constitute one and  
 the same instrument.  
  
 28. Independent Contractor  
 ----------------------  
  
 Nothing in this Agreement shall create, or be deemed to create, a  
 partnership or the relationship of principal and agent or employer and  
 employee between the parties. Each party agrees to perform under this  
 Agreement solely as an independent contractor.  
  
 29. Representation by Counsel. The parties acknowledge that each of them  
 -------------------------  
 has been represented by counsel in connection with the negotiation and  
 drafting of this Agreement and that no rule of strict construction  
 should be applied to either of them as the drafter of all or any part  
 of this Agreement.  
  
 S-29  
  
  
IN WITNESS whereof, the authorised representatives of the parties have executed  
this Agreement on the date first above written.  
  
  
SIGNED for and on behalf of AVECIA LIMITED  
  
Signature .........................  
  
Name .........................  
  
Position .........................  
  
  
SIGNED for and on behalf of RIBOZYME PHARMACEUTICALS INCORPORATED  
  
  
Signature .........................  
  
Name Xxxxx Xxxxxxx  
Position Vice President, Corporate Development.  
  
 S-30  
  
  
 SCHEDULE 1  
 ----------  
  
 The Programme  
 -------------  
  
  
 PROPOSAL  
  
  
  
 PROCESS SCALE UP and GMP MANUFACTURE of OLIGONUCLEOTIDE  
 Angiozyme  
  
 for  
  
 Ribozyme Pharmaceutical Inc.  
  
  
Date Prepared: December 1999  
  
  
Proposal No: PP.050 Version 3  
  
  
Author: Xxxx X. Xxxxxxx, Commercial Development Manager  
  
  
  
  
  
  
  
  
 ABBREVIATIONS  
  
 If needed  
  
 S-1  
  
  
  
  
CONTENTS  
 PAGE  
   
1. Project Objective 4  
  
2. Project Scope 4  
  
3. Molecule Description 4  
  
4. Project Plan 5  
  
4.1 Technology Transfer of Process and Analytical Methods  
4.2 Process Development - Deprotection and Purification scale up of Products  
 as determined by the JRC.  
4.3 Preparation of GMP Manufacturing Documentation  
4.4 Process Scale Up - GMP Manufacture of Kilo 1 mutually agreed  
 Product.  
  
5. Summary Reports / Regulatory Submission 8  
5.1 Preparation of Development Reports  
5.2 of documentation  
  
6. Packaging and Despatch 8  
  
Appendix 1. Technology Transfer Plan including Oligo Pilot II production 9  
Appendix 2. Provisional Product Specifications 10  
Appendix 3. Development Quality Standard 11  
Appendix 3.2 GMP Quality Standard 12  
Appendix 4 Draft Quality Agreement 13  
  
  
 S-2  
  
  
1. PROJECT OBJECTIVE  
  
This proposal describes technology transfer, process development, process scale  
up and manufacture of 1 kg of mutually agreed product.  
  
The data generated from the technology transfer and scale up program is meant to  
provide a degree of assurance that the process detailed in the Batch  
Manufacturing Instructions will produce product suitable for use in clinical  
trials.  
  
The sequence of the oligonucleotide is described below.  
  
  
2. PROJECT SCOPE  
  
The project will consist of five stages:  
  
\* Technology Transfer of Process and Analytical Methods  
\* Process Development - Deprotection and Purification scale up of the ribozyme  
\* products as determined by the JRC  
\* Preparation of GMP Manufacture Documentation  
\* Process Scale Up - GMP Manufacture of Kilo 1 of a mutually agreed product  
  
  
Prior to the start of the project and bi-weekly following initiation, a joint  
review committee(JRC) composed of members from RPI and Avecia LSM will meet. A  
full review of all work completed will be presented, the project plan and  
specifications reviewed, and project progression agreed.  
  
Throughout the project any changes made to the work detailed in the proposal  
will be jointly agreed with RPI, managed and documented in accordance with  
Avecia LSM's project management procedures.  
  
Stability studies are not currently within the scope of this project. If  
required they will be the subject of a separate quotation.  
  
  
3. MOLECULE DESCRIPTION:  
  
The oligonucleotide product is classified as Active Pharmaceutical Ingredient  
"Ribozyme Sequence in Here"  
Provisional Specifications listed in Appendix 2.  
  
  
4. PROJECT PLAN  
  
4.1 TECHNOLOGY TRANSFER OF PROCESS AND ANALYTICAL METHODS  
  
RPI has generated experience in the manufacture of ribozymes and it is  
recognised that this knowledge must be transferred to Avecia LSM manufacturing  
personnel in order for the supply of products to commence. A Technology  
transfer plan/agreement will be agreed. This document will detail the  
activities, information requirement, success criteria and timetable for  
technology transfer of the manufacturing process and the analytical methods.  
  
It is anticipated that RPI will provide Avecia with the following information:  
\* Raw material suppliers, specifications and testing procedures  
\* RPI and [ \* ] Process description and process equipment specifications  
\* Details of in-process tests and specifications  
\* Toxicological information on the oligonucleotide  
\* Analytical Methods(final product and intermediates) and supporting  
 documentation(reagent requirements, equipment etc.)  
\* Reference samples  
  
 S-3  
  
  
The Technology Transfer project will be conducted in four phases:  
\* Information transfer and definition of Initial process  
\* Analytical methods technical transfer at Avecia LSM  
\* Oligo Pilot II production of development material at Avecia LSM, utilising  
 RPI's current process parameters  
\* Technical clearance to manufacture  
  
--------------------------------------------------------------------------------  
Time Requirement [ \* ]  
--------------------------------------------------------------------------------  
Quality Standard Development (Appendix 3)  
--------------------------------------------------------------------------------  
Facility Multi Use Development Facility-Grangemouth  
--------------------------------------------------------------------------------  
  
4.2 PROCESS DEVELOPMENT - DEPROTECTION AND PURIFICATION  
 SCALE UP OF THE PRODUCTS AS DETERMINED BY THE JRC.  
Deprotection  
  
The aim of this stage is to evaluate the deprotection process and provide a  
recommended route for the large scale GMP manufacture in the form of a Process  
Description.  
  
The Deprotection process development will start with a full review and analysis  
of samples and records generated during the technology transfer stage.  
Conditions will be defined which provide material of the appropriate purity in a  
reproducible manner.  
  
During large scale manufacture there will be opportunities to further  
investigate the cleavage mixture, time course and reaction temperature.  
  
  
  
Purification  
  
  
The aim of this stage is to evaluate the purification process and provide a  
recommended route for the large scale GMP manufacture in the form of a Process  
Description.  
  
The Purification process development will start with a full review and analysis  
of samples and records generated during the technology transfer stage.  
Procedures to ensure consistent column loading will be defined. Chromatography  
gradient and flow rate will be further investigated.  
  
Samples obtained from the OPII production runs at Avecia LSM will be utilised  
to gain full understanding of the purification parameters. The material will be  
loaded on small scale Biotage rig, with a view of extrapolating the data to the  
large scale Biotage rig in the Grangemouth Pharmaceutical Manufacturing  
Facility.  
  
These investigations will have the following objectives:  
\* Define procedures to ensure consistent column loading  
\* Investigate the impact of variation in column gradient and flow rate  
\* investigate impact of increased column loading, with a view to increasing  
 throughput  
  
  
--------------------------------------------------------------------------------  
Time Requirement [ \* ]  
--------------------------------------------------------------------------------  
Quality Standard Development (Appendix 3)  
--------------------------------------------------------------------------------  
Facility Multi Use Development Facility-Grangemouth  
--------------------------------------------------------------------------------  
  
 S-4  
  
  
4.3 PREPARATION OF GMP BATCH MANUFACTURING  
 DOCUMENTATION  
  
  
Product specific Process Instructions (provisional Batch Manufacturing  
Instructions) for oligonucleotide product will be written based on the work  
carried out during the scale up studies.  
  
--------------------------------------------------------------------------------  
Time Requirement [ \* ]  
--------------------------------------------------------------------------------  
  
4.4 PROCESS SCALE UP - GMP MANUFACTURE OF KILO 1 MUTUALLY AGREED PRODUCT.  
  
Avecia LSM will carry out the GMP manufacture of mutually agreed Product at the  
range of [ \* ] on the Oligo Process. The objective of the scale up program  
is to demonstrate the process described in the process description produces  
material of the required quality and specification.  
  
Avecia LSM will manufacture the scale up batches to the agreed specification  
using the Process instructions, material generated from this stage will be  
suitable for use in toxicology and human clinical trials.  
  
Avecia LSM will manufacture 1kg oligonucleotide to the agreed specification  
following the Process Instructions and documented analytical methods.  
  
The manufacture program following oligonucleotide assembly will proceed only if  
there is agreement by the joint review committee that the process for  
deprotection and purification, as detailed in the process instructions, can  
operate efficiently at scales above [ \* ]. If it is deemed that this  
process is insufficient to produce the quality and quantity of oligonucleotide  
product RPI require, than the decision will be made to continue scale up  
development work.  
  
Note: Further development may be required in the GMP phase, this work will be  
documented and all changes subject to QA approval.  
  
The Oligonucleotide will be supplied in a form agreed upon by both parties.  
  
A Certificate of Analysis will be supplied.  
  
Avecia LSM will retain a sample of product (exact amount to be agreed) for use  
as retention material and in further analytical studies.  
  
--------------------------------------------------------------------------------  
Time Requirement [ \* ]  
--------------------------------------------------------------------------------  
Quality Standard GMP (Appendix 3.2)  
--------------------------------------------------------------------------------  
Facility Pharmaceutical Manufacturing Facility-Grangemouth  
--------------------------------------------------------------------------------  
  
5. SUMMARY REPORTS / REGULATORY SUBMISSION  
  
5.1 Preparation of Development Reports  
  
  
Avecia LSM will compile interim reports at each stage of the process development  
programme and following GMP manufacture.  
  
The reports will be retained in the Avecia LSM QA Archives.  
  
--------------------------------------------------------------------------------  
Time Requirement Within [ \* ] weeks of each stage completion  
--------------------------------------------------------------------------------  
  
 S-5  
  
  
5.2 Preparation of Documentation  
  
If required Avecia LSM will provide information to support RPI's regulatory  
submissions.  
  
--------------------------------------------------------------------------------  
Time Requirement [ \* ]  
--------------------------------------------------------------------------------  
  
  
6. PACKAGING AND DESPATCH  
  
Specification of primary packaging of the oligonucleotide to be agreed.  
  
7. COSTING  
  
8. TIMELINES  
  
 S-6  
  
  
 SCHEDULE 2  
 ----------  
  
 Joint Review Committee (JRC)  
 ----------------------------  
  
1. Purpose  
 -------  
  
1.1 The purpose of the JRC is to be responsible for co-ordinating and  
 supervising the implementation of the Programme.  
  
1.2 The JRC is to assist in ensuring that lines of communications are  
 established and maintained between the parties and to this end shall be  
 responsible for nominating a representative in both parties who shall be  
 the main but not sole point of contact for the other party.  
  
1.3 It shall be the responsibility of the JRC to circulate copies of all  
 reports and information that it receives from one party to the other  
 without delay.  
  
1.4 The JRC is to be the primary arena for the settlement of any disagreements  
 between the parties relating to the interpretation and implementation of  
 the Programme.  
  
2. Period of Existence  
 -------------------  
  
 The JRC shall remain in being until whichever is the earlier of the  
 completion of the Programme or the termination of the Agreement.  
  
3. Membership  
 ----------  
  
3.1 The JRC shall have four members including the Chairman. Two members  
 including the Chairman shall be appointed in writing by AVECIA and two  
 members shall be appointed in writing by RPI.  
  
3.2 It is envisaged that the members of the JRC appointed by each party shall  
 vary with regard to their particular disciplines dependent on the  
 particular stage reached in the Programme. Either party may invite further  
 representatives with appropriate skills to attend meetings of the JRC in a  
 non-voting capacity.  
  
3.3 Either party may at any stage change a representative member on the JRC by  
 giving written notice of such change to the other party.  
  
4. Meetings  
 --------  
  
4.1 The initial meeting of the JRC shall take place within the period of sixty  
 (60) days following the date of this Agreement at AVECIA Grangemouth,  
 Scotland or RPI, Boulder.  
  
4.2 Subsequent meetings of the JRC shall be held every two (2) months  
 alternating between Boulder, and Grangemouth, Scotland if not otherwise  
 agreed by the JRC.  
  
4.3 If for any reason following the agreement of the Programme either party  
 wishes a meeting of the JRC to be held between the regular two (2) monthly  
 meetings, it may arrange such meeting on giving at least fifteen (15) days'  
 notice in writing to the other party, such meeting shall be held at the  
 offices of the party not requesting the meeting.  
  
5. Procedure at Meetings  
 ---------------------  
  
5.1 The Chairman of the JRC shall be responsible for preparing and circulating  
 an agenda for any meeting of the JRC at least ten (10) days prior to the  
 meeting (which agenda shall include any item considered important by either  
 party) and appointing a secretary for such meeting, who need not be a  
 representative member of the Committee, who shall be responsible for the  
 preparation and circulation of minutes of the meeting within thirty (30)  
 days of the conclusion of such meeting.  
  
 S-7  
  
  
5.2 Any resolution put to the JRC must, to be passed, be accepted by at least  
 three (3) members of the JRC present in person.  
  
5.3 Each representative of the JRC shall have one vote. The Chairman shall not  
 have a second or casting vote.  
  
5.4 Any dispute which cannot be resolved by the JRC shall so far as it comes  
 within the ambit of section 1.4 above be dealt with according to the  
 provisions of such section, any other dispute shall be dealt with in  
 accordance with clause 26 of the Agreement.  
  
6. Amendment to JRC Constitution  
 -----------------------------  
  
6.1 The JRC may amend its rules set out herein provided that a resolution  
 amending such rules is circulated in writing thirty (30) days prior to the  
 meeting and such resolution is passed in accordance with Section 5.2.  
  
 S-8  
  
  
 SCHEDULE 3  
 ----------  
  
 Quality Agreement  
 -----------------  
  
  
Draft QA Agreement  
  
  
  
The attached agreement is a draft template which has yet to be discussed with  
RPI's QA representatives. It's format and content may change as a result of  
these discussions. It is included as part of this proposal to define the set of  
assumptions that have been made in the preparation of this proposal.  
  
 S-9  
  
  
 Avecia LSM  
  
  
  
 Quality Assurance Agreement between Avecia LSM and RPI for the Technology  
 Transfer and Manufacture of Angiozyme  
  
  
  
Issued By: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 Avecia LSM QA Manager  
  
  
Approved By: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 RPI Manufacturing Director  
  
  
Approved By: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 RPI QA Director  
  
  
Approved By: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 Avecia Grangemouth Works QA Manager  
  
  
  
Approved By: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 Avecia LSM Commercial Manager  
  
  
  
  
  
  
  
Revision Summary  
  
 S-10  
  
  
Contents  
  
  
  
1. Introduction  
  
2. Background information on Angiozyme  
  
3. Responsible personnel  
  
4. Communication  
  
5. Technology Transfer  
  
6. Quality Assurance  
  
7. Purchasing, supply and testing of raw materials and packaging  
  
8. Manufacturing Facility  
  
9. Manufacture  
  
10. Sampling, testing and release of bulk active pharmaceutical ingredient  
  
11. Control and supply of samples  
  
12. Transport and Distribution  
  
13. Complaints and recall  
  
14. Safety, Health and Environment  
  
15. Stability  
  
16. Validation  
  
17. Subcontracting  
  
18. Deviations and Change Control  
  
19. Documentation and Archiving  
  
20. Regulatory  
  
 S-11  
  
  
1. Introduction  
  
 The purpose of this agreement is to ensure that the responsibilities of RPI  
 and Avecia LifeScience Molecules in the Technology Transfer and subsequent  
 manufacture of Angiozyme are clearly defined. This is to ensure that  
 misunderstandings are avoided, which could lead to a product or work of  
 unsatisfactory quality.  
  
 The agreement will address the following:-  
  
 \* Roles and responsibilities in ensuring that Avecia LSM complies with cGMP  
 and other relevant legislation.  
 \* Responsibility for the release of Angiozyme active pharmaceutical  
 ingredient for further processing for use in humans.  
 \* Agreement on access to Avecia LSM facilities for RPI's personnel.  
 \* Arrangements for changes or amendments to aspects of this agreement.  
 Channels of communication.  
 \* Supply of relevant information following a regulatory inspection, which  
 may impact on the continued supply of the product.  
  
  
 The agreement addresses the initial issues surrounding the technology  
 transfer of RPI's manufacturing process to Avecia LSM and then focuses on  
 the Quality Assurance issues surrounding the ongoing supply of Angiozyme to  
 GMP for human use.  
  
  
2. Background information on Angiozyme  
  
 Angiozyme is a........  
 It will be supplied to RPI as a powder in bulk form and subsequently  
 formulated under the control of RPI.  
  
 It is currently in Phase .. clinical trials for the treatment of ..........  
  
 As the drug product progresses through clinical trials, it is the  
 responsibility of RPI to inform Avecia LSM and to initiate a joint review of  
 the contents of this technical agreement, to ensure that the quality  
 standards described within it still meet the requirements of the regulators.  
  
 Responsible Personnel  
  
 S-12  
  
  
  
  
 XXX Avecia  
   
Commercial [ \* ]  
  
Technology Manager [ \* ] [ \* ]  
  
Manufacturing Technology [ \* ]  
Transfer  
  
Production [ \* ]  
  
Analytical Technology Transfer [ \* ]  
  
Analytical [ \* ]  
  
Quality Assurance [ \* ] [ \* ]  
 [ \* ]  
  
Facility and Plant Commissioning  
 [ \* ]  
  
Safety, Health and Environment  
  
Regulatory [ \* ] [ \* ]  
  
  
Document Controller [ \* ] [ \* ]  
  
  
  
4. Communication  
  
 S-13  
  
  
 The commercial representatives of each company will be informed of supply or  
 receipt of documents and of the occurrence of meetings or visits.  
  
4.1 Documents  
  
 The document control representatives from each company will be responsible  
 for the supply or receipt of documents.  
 All inter-company document transfers will be logged.  
 The document controller in receipt of a document will formally acknowledge  
 receipt.  
 The document controller shall maintain a centralised archive of all  
 documents received, with copies disseminated to appropriate team members in  
 a controlled manner.  
 All documents will be numbered and, if appropriate, version controlled.  
 The document controller will be responsible for recalling documents that  
 have been replaced with new versions.  
  
4.2 Review meetings  
  
 Meetings should be held between functional nominees as appropriate to ensure  
 smooth transfer of information and progress on actions.  
  
  
 5. Technology Transfer  
  
 The manufacturing and analytical Technology transfer activities associated  
 with this project are covered in more detail in the following documents:-  
  
 Manufacturing Technology Transfer Plan for Angiozyme  
 Analytical Technology Transfer Plan for Angiozyme  
  
 These activities will follow the general framework outlined below:-  
  
  
5.1 Initiation  
  
 Agree aims of the Technology transfer and the criteria for successful  
 transfer.  
 Identify information required from each side prior to initial manufacture.  
 Establish review milestones to ensure transfer is proceeding smoothly.  
  
  
5.2 Initial Manufacture  
  
 Agree Technical support arrangements between RPI and Avecia LSM.  
  
5.3 Validation  
  
 S-14  
  
  
 Establish responsibilities for all aspects of validation. See also section  
 17. below.  
  
5.4 Completion  
  
 Agree documents required and who approves against pre-agreed objectives.  
  
  
 6. Quality Assurance  
  
 Avecia shall manufacture Angiozyme to the best of its knowledge in  
 compliance with GMP as detailed in the 'Guidance for Industry;  
 Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients'  
 Draft Guidance, March 1998, published by the FDA.  
  
 RPI shall confirm their satisfaction with the compliance level applied by  
 Avecia LSM at audit.  
  
 Findings from audit(s) will be communicated in writing to Avecia LSM and any  
 corrective actions mutually agreed between representatives from the 2  
 companies. In the event of a difference in interpretation of the required  
 quality standard, the view taken by RPI will be accepted by Avecia, provided  
 this standard is not below that recommended by Avecia. If it is a  
 significantly higher standard than recommended by Avecia, then the 2 parties  
 will meet and agree by negotiation how the situation should be managed.  
  
  
 7. Purchasing, supply and testing of raw materials and packaging  
  
 RPI will provide Avecia LSM with a materials listing for the manufacture of  
 Angiozyme, together with purchasing specifications. RPI will inform Avecia  
 of any changes in these specifications as they occur.  
  
 Avecia LSM will purchase materials to the specifications provided by RPI.  
 RPI will specify the suppliers for the critical raw materials (amidites and  
 CPG) in agreement with Avecia. Avecia will be responsible for selecting its  
 own suppliers for non-critical reagents. Avecia LSM will take responsibility  
 for all testing and clearance of raw materials used in the manufacture of  
 Angiozyme, on completion of the technology transfer of appropriate test  
 methods from RPI.  
  
 RPI shall confirm the suitability of Avecia's vendor certification and raw  
 material testing and sampling procedures at audit.  
  
  
 8. Manufacturing Facility  
  
 Avecia LSM and RPI will jointly conduct a risk assessment of any differences  
 between the Avecia and RPI manufacturing facilities and how they are  
 operated.  
  
 S-15  
  
  
 The process will be operated under class 100,000 conditions, with additional  
 protection provided for the later stages of the process, which may be  
 especially vulnerable to microbial contamination. Details of this additional  
 protection will be jointly discussed and agreed between representatives of  
 the 2 companies.  
  
 [ \* ]  
  
 The facility and equipment will be qualified and cleaned prior to initial  
 manufacture in accordance with Avecia's procedures.  
  
 RPI will audit the manufacturing facility, equipment and supporting  
 documentation prior to initial manufacture to assess their suitability for  
 use.  
  
 Findings from the audit will be communicated to Avecia in writing and any  
 corrective actions mutually agreed.  
  
  
  
 9. Manufacturing  
  
 The manufacturing process will be the subject of a formal Technology  
 transfer programme between RPI and Avecia (see section 5 above)  
  
 RPI will provide Avecia with full details of the existing manufacturing  
 process, including, in process tests and specifications for both the  
 intermediates and the active pharmaceutical ingredient (if available)  
  
 Avecia will establish the existing process in the development laboratories  
 in PTD and then conduct an experimental program to scale the process up for  
 transfer to the manufacturing facility within Grangemouth Works. RPI will be  
 kept fully informed of the experimental program and of any proposed  
 modifications to the process, which will be approved by representatives from  
 both companies.  
  
 Avecia will prepare formal process instructions for manufacture to the  
 scaled up process. RPI Technical and QA representatives will review this  
 documentation and any comments shall be incorporated by Avecia.  
  
 All specifications will be formally accepted and agreed between RPI and  
 Avecia personnel and subject to change control.  
  
 In addition to the documents described above, RPI shall either provide the  
 following, or pre-approve proposals from Avecia LSM:-  
  
 Format and content of the Certificate of analysis  
  
 S-16  
  
  
 Labelling requirements  
 Definition of a batch  
 Lot or batch numbering system  
 Sampling plans  
 Sampling methods  
  
  
10. Sampling, testing and release of active pharmaceutical ingredient  
  
 On completion of the formal technology transfer of the analytical release  
 methods for Angiozyme active ingredient, Avecia LSM will take responsibility  
 for the release of this product for further processing for human use. RPI  
 will conduct some repeat verification testing, this will be pre-agreed with  
 Avecia.  
  
 QA release will involve the QC release testing of the active ingredient,  
 together with a complete review of all batch documentation by Avecia  
 Grangemouth Works QA.  
  
 RPI will review the Avecia test procedures, to ensure that there are no  
 errors in the translation from RPI documentation.  
  
 RPI will be responsible for the validation of all the release test methods  
 and will ensure any repeat validation considered appropriate on transfer to  
 Avecia's analytical sites is prescribed as part of the Analytical Technology  
 Transfer protocol.  
  
 RPI will initially provide any necessary analytical reference standards,  
 together with their characterisation data. This may be reviewed at a future  
 date, as it becomes necessary to qualify further reference standards.  
  
 RPI will audit Avecia's laboratories to assess their suitability for use.  
 Audit observations will be communicated in writing to Avecia LSM and  
 corrective actions mutually agreed.  
  
 RPI will be responsible for specifying packaging and shipping conditions  
 which have been demonstrated to preserve the product's quality and integrity  
 during transport.  
  
  
11. Control and Supply of Samples  
  
 Avecia will take and retain samples of Angiozyme in accordance with sampling  
 plans pre-agreed between RPI and Avecia QA representatives. As a minimum,  
 Avecia LSM will retain sufficient material from each batch to allow full  
 repeat testing at least twice.  
  
 Retention samples will be retained for at least one year after the  
 expiration date of the batch, or, if Angiozyme has a defined retest period,  
 for 3 years after the batch is distributed. Retention samples will be  
 packaged and stored under conditions prescribed by RPI.  
  
 S-17  
  
  
 RPI will provide details of any sample requirements for shipment to their  
 premises, prior to manufacture of the batch concerned. This is to ensure  
 material is manufactured at the appropriate scale to cover sample  
 requirements and that arrangements for sampling can be made in a timely  
 manner.  
  
 Responsibility for analytical reference standards is covered in section 10  
 above.  
  
12. Transport and Distribution  
  
 RPI will provide Avecia LSM with formal specifications for packaging and  
 shipping of Angiozyme.  
  
 Avecia LSM will be responsible for ensuring the requirements of these  
 specifications are met.  
  
 On departure from Avecia's Grangemouth site, responsibility for the API  
 passes to RPI.  
  
  
13. Complaints and Recall  
  
 Any complaints from RPI to Avecia LSM should be directed to the Avecia LSM  
 commercial representative, who will then be responsible for informing the  
 Avecia LSM QA representative. The Avecia LSM QA representative will assemble  
 a team to address the complaint and, if appropriate, carry out an  
 investigation. The complaint will be handled in accordance with the Avecia's  
 quality procedures.  
  
 Avecia shall be responsible for advising RPI immediately of any systematic  
 failure discovered which may cast doubt on reliability of previous  
 manufacture or analysis. Communication in such situations will be involve  
 the Commercial and QA representatives from Avecia LSM and the QA  
 representative at RPI. RPI will be responsible for the implementation of any  
 decision they might take to recall the product as a result.  
  
  
14. Safety, Health and Environment  
  
 Avecia will take responsibility for ensuring that the facilities, procedures  
 and equipment used for manufacture are designed and operated in accordance  
 with relevant legislation.  
  
 RPI will be responsible for all toxicological and Eco-tox data required for  
 the product to gain appropriate registration for manufacture, shipment and  
 use within the USA and Europe.  
  
 Avecia and RPI shall advise each other of any events that give raise to  
 concerns about the safety profile of the process.  
  
 S-18  
  
  
 Avecia shall take responsibility for all on site incidents and will advise  
 RPI of all significant events that may have an impact on product  
 manufacturing rate, economics, safety profile or product quality.  
  
 RPI is responsible for the API on its departure from Avecia's Grangemouth  
 site.  
  
  
15. Stability  
  
 RPI will take responsibility for all stability studies relating to Angiozyme  
 active pharmaceutical ingredient and will provide Avecia LSM with the  
 details of appropriate storage conditions to maintain its quality and  
 integrity.  
  
 RPI will provide Avecia LSM with information to allow Avecia LSM to assign  
 an expiry or retest date to material manufactured at Avecia LSM.  
  
  
16. Validation  
  
 Avecia LSM will take responsibility for the qualification of the facilities  
 and equipment used in the manufacture of Angiozyme at Avecia Grangemouth  
 Works. RPI will audit this qualification activity.  
  
 RPI is responsible for the validation of all analytical test methods used  
 for the release of raw materials and in in-process testing and release of  
 the final active pharmaceutical ingredient.  
  
 Angiozyme is currently in Phase 1 clinical trials. As the drug moves to  
 later stage clinical trials RPI and Avecia LSM will discuss and agree  
 responsibilities for further process or analytical development and process  
 validation activities.  
  
  
17. Subcontracting  
  
 Avecia LSM will not subcontract any activity associated with the  
 manufacture of Angiozyme without prior notification and approval from RPI.  
  
 Avecia LSM will take responsibility for the certification of all  
 subcontractors to the required regulatory standards.  
  
 Avecia LSM will make any appropriate audit reports available to RPI on  
 request.  
  
  
18. Deviations and Change Control  
  
 S-19  
  
  
 QA representatives from RPI, Avecia Grangemouth Works and Avecia LSM shall  
 meet and agree a shared understanding of the definitions of changes and  
 deviations. Discussion will cover what changes are considered significant  
 and would require prior approval by RPI and similarly for deviations, what  
 would be considered significant and require notification of RPI.  
  
 Any significant change proposed by either RPI or Avecia shall be  
 communicated in writing via the QA representatives in each organisation. The  
 change will then be considered by a team of representatives from the  
 appropriate departments, in accordance with local change control procedures.  
 If appropriate a formal programme of work will be proposed and formally  
 agreed by representatives from each company.  
  
 Deviations will be handled through Avecia Grangemouth Works Deviation and  
 non-conformance procedure.  
  
19. Documentation and Archiving  
  
 Avecia LSM will be responsible for the retention and storage of all batch  
 documentation in a secure QA archive. Documentation will be stored for a  
 minimum of ( whichever of those listed below is the longest):-  
 a) The term of the commercial agreement.  
 b) Five years after the expiry date of the batch manufactured.  
  
  
 RPI personnel may audit the batch documentation on request, given reasonable  
 notice.  
  
 Copies of the master batch records will be made available to RPI on request.  
  
  
  
20. Regulatory  
  
 Avecia LSM will provide RPI with appropriate CMC information in support of  
 regulatory submissions.  
  
 The format and content of this information will be pre-agreed by  
 representatives from Avecia LSM and RPI's QA/Regulatory functions.  
 RPI will be responsible for submitting this information to the regulators as  
 part of their regulatory submission, but will allow Avecia LSM QA function  
 to review the information concerning Avecia prior to submission, to ensure  
 there are no errors in transcription which may result in Avecia being  
 misrepresented.  
  
 RPI will be responsible for requesting information from Avecia LSM  
 QA/Regulatory function as appropriate e.g. for annual updates.  
  
 S-20  
  
  
 Avecia LSM QA representative will be responsible for informing RPI of  
 proposed changes to any activity associated with the manufacture of  
 Angiozyme, prior to implementation, to ensure that its regulatory impact can  
 be assessed and any necessary action agreed.  
  
 Avecia LSM will inform RPI of any corrective actions from a regulatory  
 inspection that may have an impact on the continued supply of Angiozyme.  
  
 S-21  
  
  
 SCHEDULE 4  
 ----------  
  
  
 Avecia LifeScience Molecules  
 DNA Medicines  
  
  
  
 Technology Transfer Plan  
 Manufacture of Angiozyme  
 at  
 Grangemouth Works  
  
 December 1999  
  
  
  
\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
Issued By:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
(Business Operations Manager)  
\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
Approved By:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
(Quality Assurance)  
\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
 S-22  
  
  
 CONTENTS  
  
  
  
SECTION PAGE NO.  
   
1 Introduction..................................................... 3  
  
2 Aims............................................................. 3  
  
3 Initiation....................................................... 4  
  
4 Project Nominees................................................. 5  
  
5 Communication.................................................... 6  
  
 5.1 Documentation............................................... 6  
 5.2 Reviews.....................................................  
  
6 Information Transfer............................................. 6  
  
7 Initial manufacture.............................................. 7  
  
 7.1 Commissioning support....................................... 7  
 7.2 Initial manufacture......................................... 7  
 7.3 Change control.............................................. 7  
  
8.1 Technology transfer completion................................... 8  
  
 8.1 Criteria for successful technology transfer.................  
 8.2 Technology transfer review and sign-off.....................  
 8.3 Post technology transfer....................................  
  
9 Appendices 9  
  
 Appendix I: Flow chart for technical transfer  
  
 Appendix II: Timetable for RPI Technology Transfer Plan  
  
 Appendix III Information required from RPI  
  
 Appendix IV: Information required form Avecia  
  
 Appendix V : Information required to complete technology transfer  
  
 Appendix VI: Technology transfer acceptance document  
  
  
 S-23  
  
  
1 INTRODUCTION  
  
  
 This plan details the mechanism by which the RPI Angiozyme process will be  
 technology transferred between RPI and LifeScience Molecules Grangemouth  
 Works and sets out the activities, information required and timetable in  
 order to successfully complete the technology transfer exercise.  
  
 A well managed technology transfer is key to the establishment of a  
 manufacturing process which is consistent in operation and generates  
 Angiozyme of equivalent quality to that manufactured by RPI.  
  
 Material provided by LSM in Grangemouth will be used in a process  
 registered in the United States and the rest of the world. As such:  
 technology transfer, commissioning, validation and change control must be  
 undertaken to ensure that material produced in the Campaign is equivalent  
 to material produced by RPI for submissions to the FDA.  
  
 The material produced by this manufacture will be used for: Phase ()  
 Clinical Trials  
  
 Technology transfer will be conducted in three phases:  
  
  
 Initiation: Identification of responsible personnel  
 agreement on information to be transferred (protocol)  
 transfer of information  
  
  
 Commissioning: Pre manufacture Technical Transfer review  
 Initial manufacture  
  
  
 Note: The pre manufacturing technical transfer review must include  
 agreement of and actions to minimise the risks that may result from the  
 differences between the facilities at RPI and that at Grangemouth  
  
 Completion: Post manufacturing review of success of technology  
 transfer Sign -off of Technology transfer protocol  
  
 A flow chart outlining the process is attached as Appendix I  
  
 It is intended that sign-off will take place following the initial  
 campaign, subject to successfully meeting the required standards and  
 criteria.  
  
  
2 AIMS  
  
  
 The purpose of technology transfer is to supply technical expertise and  
 associated information to enable Avecia Life Science Molecules, Grangemouth  
 facility, to successfully undertake manufacture of RPI Angiozyme in light  
 of the fact that the LSM and RPI facilities are not identical.  
  
  
 The agreed timetable is detailed in Appendix II.  
  
  
 The critical success factors for successful transfer are as follows:  
  
 . Avecia Life Science Molecules, Grangemouth Works will manufacture an  
 initial quantity of Angiozyme by the end of [ \*. ] Future  
 manufacture may be carried out following the initial Campaign.  
  
  
 . The Grangemouth Works manufacturing process will be specified by the  
 current RPI process. Processing will be carried out within the scope  
 of the pre-determined parameters.  
  
  
 . An established change control mechanism should be used for any changes.  
  
  
 S-24  
  
  
 . The quality of the Angiozyme supplied by Avecia Life Science Molecules  
 Grangemouth Works must be within specification and typical of  
 manufacture from RPI.  
  
 . Technology transfer, plant operation, processing and cleaning will be  
 carried out to Grangemouth Works Quality standards.  
  
3 INITIATION  
  
 Technology transfer of RPI Angiozyme will be formally initiated in [ \*. ]  
 Functional nominees are identified below and a checklist of relevant  
 documents is given in Appendices III and IV.  
  
4 PROJECT NOMINEES  
  
  
  
-------------------------------------------------------------------------------  
FUNCTION RPI CONTACT No LSM CONTACT No  
-------------------------------------------------------------------------------  
   
Technology Transfer Leader [ \* ] [ \* ] [ \* ] [ \* ]  
  
-------------------------------------------------------------------------------  
Chemistry [ \* ] [ \* ] [ \* ] [ \*-]  
  
-------------------------------------------------------------------------------  
Process Engineering [ \* ] [ \* ] [ \* ] [ \* ]  
  
-------------------------------------------------------------------------------  
Quality Assurance [ \* ] [ \* ] [ \* ] [ \* ]  
  
-------------------------------------------------------------------------------  
Engineering [ \* ] [ \* ] [ \* ] [ \* ]  
  
-------------------------------------------------------------------------------  
Analytical Methods and [ \* ] [ \* ] [ \* ] [ \* ]  
Specifications  
  
-------------------------------------------------------------------------------  
Safety, Health and Environment [ \* ] [ \* ] [ \* ] [ \* ]  
  
-------------------------------------------------------------------------------  
Manufacture and waste disposal [ \* ] [ \* ] [ \* ] [ \* ]  
  
-------------------------------------------------------------------------------  
Raw Materials and purchasing [ \* ] [ \* ] [ \* ] [ \* ]  
  
-------------------------------------------------------------------------------  
  
  
5 COMMUNICATION  
  
  
 5.1 DOCUMENTATION  
  
  
 The Technology transfer managers on each site will be formally responsible  
 for ensuring document issue and control.  
  
 All documents must be numbered and where appropriate version controlled  
  
 The transfer of all documents will must be done within a change control  
 system  
  
 S-25  
  
  
 A copy of all documents outlined in Appendices III and IV (information  
 required before commissioning) and Appendix V (information required before  
 technology transfer completion) must be supplied via the QA  
 representatives. This data will form the basis of the respective sites  
 technology transfer documentation.  
  
 5.2 REVIEWS  
  
 Meetings should be held between functional nominees as appropriate to  
 ensure complete transfer of information and progress on actions.  
  
 A formal pre-commissioning review will take place to ensure information  
 transfer is complete and that all relevant information has been  
 incorporated into Grangemouth Works systems.  
  
 Performance of the initial manufacture should be reviewed and documented as  
 early as possible after the campaign.  
  
 Following completion of the Campaign a technology transfer review will be  
 held prior to sign-off to ensure documentation is complete and  
 satisfactory.  
  
6 INFORMATION TRANSFER  
  
 Information requirements from RPI and LifeScience Molecules are specified  
 in Appendices III and IV.  
 This data must be in place prior to the start of manufacture.  
  
 Key Elements:  
  
 Process guide and reporting ranges.  
  
 Quality Assurance.  
  
 Plant cleaning  
 Control of change  
  
 Analytical methods, standards and specifications  
  
 Raw material sources and specifications  
  
 Safety, Health and Environmental data  
  
 Hazard data sheets  
 Process Waste Streams  
  
 Pre commissioning review: Approval to manufacture  
  
7 INITIAL MANUFACTURE  
  
 7.1 COMMISSIONING SUPPORT  
  
 Prior to commissioning, the arrangement for technical support between RPI  
 and LifeScience Molecules will be agreed.  
  
 Visits to each site of relevant staff of each discipline in preparation for  
 manufacture will be encouraged. This will include the requirements for  
 technical and analytical support from RPI  
  
 S-26  
  
  
 Throughout the technical transfer process progress will be monitored via a  
 steering committee which will include  
  
 [ \* ]  
  
 7.2 Initial Manufacture  
  
 A project Plan should be prepared for the plant before commissioning. The  
 following issues should be addressed:  
  
 . Engineering Validation including Installation and Operational  
 Qualifications carried out by LifeScience Molecules.  
  
 . Cleaning - Demonstration of appropriate levels of cleaning, between  
 different materials manufactured in the facilities and the manufacture  
 of RPI Angiozyme will be carried out to current Grangemouth Works  
 systems.  
  
 . Analytical technical transfer plan  
  
 . Training of Avecia personnel by RPI including recording of any training  
 received  
  
 7.3 CHANGE CONTROL  
  
 An agreed procedure will be issued defining requirements for change  
 control.  
  
 During Technology Transfer the starting point for Change Control will be  
 defined as the information supplied by RPI to define the technology.  
  
 Amendments to the RPI technology should be covered by the Grangemouth Works  
 change control procedure and should not be adopted without prior  
 authorisation from RPI.  
  
8 TECHNOLOGY TRANSFER COMPLETION  
  
 On completion of Technology Transfer responsibility will pass to  
 Grangemouth Works to control change independently.  
  
 Elements that cannot be changed without prior authorisation should be  
 identified as part of the technology transfer completion review.  
  
 8.1 CRITERIA FOR SUCCESSFUL TECHNOLOGY TRANSFER  
  
 A number of criteria are outlined below which must be met before technology  
 transfer can be formally completed.  
  
 8.1.1 Process  
  
 S-27  
  
  
 . Demonstrate that specified processing parameters can be operated to and  
 that product, which meets specification, typical of material produced  
 in RPI, can be manufactured.  
  
 . Demonstrate operation of an effective mechanism for control of change  
 opposite process technology.  
  
 . Demonstrate the ability to operate the process at the required capacity  
 and operational quality.  
  
8.1.2 Raw Materials  
  
 . Demonstrate that a secure supply of raw materials and starting material  
 from agreed suppliers has been established.  
  
 . Demonstrate control of change procedure for raw material supplies.  
  
8.1.3 Waste Streams  
  
 . Demonstrate that a secure suitable waste disposal routes has been  
 established.  
  
8.1.4 Analytical and Specifications  
  
 . Demonstrate a complete implementation of technology.  
  
 . Demonstrate satisfactory operation of the transferred methods before  
 data is used for batch release.  
  
 . Operate an effective mechanism for control of change of analytical  
 technology.  
  
8.1.5 Safety, Health & Environment  
  
 . Demonstrate that adequate hygiene procedures and practices are in place  
 to ensure that manufacture of Angiozyme does not result in adverse  
 occupational health effects.  
  
 . Demonstrate that adequate precautions are built into plant design and  
 layout and procedures to ensure the safe operation of the process.  
  
 . Demonstrate adequate environmental protection measures and secure  
 authorisation from relevant pollution inspectorate.  
  
8.1.6 Regulatory Compliance  
  
 . Demonstrate that the process can be operated satisfactorily to cGMP.  
  
 . Demonstrate compliance with the agreed manufacturing process,  
 analytical methods and specifications.  
  
8.1.7 Engineering  
  
 . Demonstrate that the plant has been built and validated to the  
 appropriate regulatory standard.  
  
 S-28  
  
  
8.2 TECHNOLOGY TRANSFER REVIEW AND SIGN-OFF  
  
 Following the initial manufacturing campaign there will be a review to  
 define whether the critical success factors listed in 8.1 have been met.  
  
 The review will comprise the preparation and approval of documents  
 (appendix V) and a meeting to agree a list of any outstanding actions.  
  
 In the event of Grangemouth Works conducting a second or subsequent  
 campaign of Angiozyme prior to sign-off of technology transfer a written  
 plan will be agreed between RPI and Grangemouth Works covering outstanding  
 issues.  
  
 After a final review to confirm that technology transfer has been  
 successfully concluded then the Technology Transfer Completion Document  
 will be issued for authorisation.  
  
 Completion is targeted for end of November 2000.  
  
8.3 POST TECHNOLOGY TRANSFER  
  
 As part of technology transfer sign off a plan will be agreed in the event  
 of any future manufacturing campaigns. Routes of communications between  
 the two sites will be clearly identified emphasising the need for  
 continuity. A technical manager will be nominated from each site to act as  
 first line contacts for transfer of information.  
  
 S-29  
  
  
 APPENDIX I  
  
 [FLOOR PLAN APPEARS HERE]  
  
 S-30  
  
  
APPENDIX II  
  
  
Timetable for Angiozyme Technology Transfer Plan: Target Dates  
  
Initiation of Technology Transfer [ \* ]  
  
Technology Transfer Plan Preparation [ \* ]  
  
Information Transfer [ \* ]  
  
Pre-commissioning Review  
  
Commissioning/ Initial Manufacture  
  
Equivalence Testing  
  
Completion Review and Audit  
  
  
 S-31  
  
  
APPENDIX III  
  
Information Required From RPI  
  
  
  
 1 PROCESS  
  
---------------------------------------------------------------------------------------------------------------------------  
 Information RPI Avecia Target Completion  
 Responsible Responsible Date Date  
 person Person  
---------------------------------------------------------------------------------------------------------------------------  
   
 1.1 Process Guide for Angiozyme in [ \* ] [ \* ]o  
 controlled format  
---------------------------------------------------------------------------------------------------------------------------  
 1.2 RPI approval that Avecia materials of [ \* ] [ \* ]  
 construction are suitable for  
 manufacture of Angiozyme  
---------------------------------------------------------------------------------------------------------------------------  
 1.3 Report of any know critical parameters [ \* ] [ \* ]  
 associated with the process (synthesis,  
 cleavage/deprotection, purification ,UF,  
 Lyophilisation) which may impacts on  
 the quality of final product  
  
---------------------------------------------------------------------------------------------------------------------------  
 1.4 Environmental Control standards: [ \* ] [ \* ]  
 Confirmation that LSM standards for  
 control of the manufacturing  
 environment are adequate for the  
 manufacture of Angiozyme  
---------------------------------------------------------------------------------------------------------------------------  
 1.5 RPI to define acceptable hold points [ \* ] [ \* ]  
 and conditions for storage of  
 in-process material and intermediates  
---------------------------------------------------------------------------------------------------------------------------  
 1.6 Schedule of technical support during [ \* ] [ \* ]  
 manufacture  
---------------------------------------------------------------------------------------------------------------------------  
 1.8 Report on development of manufacture [ \* ] [ \* ]  
 of Angiozyme  
---------------------------------------------------------------------------------------------------------------------------  
 1.9 Requirements for Clearance of Final [ \* ] [ \* ]  
 Product  
---------------------------------------------------------------------------------------------------------------------------  
1.10 Ultra-filtration development reports [ \* ] [ \* ]  
 including summary of optimised  
 conditions and [ \* ]  
---------------------------------------------------------------------------------------------------------------------------  
1.11 Freeze drying development report [ \* ] [ \* ]  
 including agreement on any further  
 characterisation of technologies  
---------------------------------------------------------------------------------------------------------------------------  
1.12 Report on assessment of risk arising [ \* ] [ \* ]  
 from differences between RPI and Avecia  
 facilities Scale/MOC/ Operating methods/  
 Process control  
---------------------------------------------------------------------------------------------------------------------------  
  
  
 S-32  
  
  
  
  
PROCESS  
  
------------------------------------------------------------------------------------------------------------------------------  
 Information RPI Avecia Target Completion  
 Responsible Responsible Date Date  
 person Person  
------------------------------------------------------------------------------------------------------------------------------  
   
 1.13 Controlled copy of all documents [ \* ]  
 associated with purification including  
 efficiency test and results, sample  
 strength (OD, %FLP), solvent  
 gradients, solvent temperatures,  
 fraction times and any associated  
 stability data.  
------------------------------------------------------------------------------------------------------------------------------  
 1.14 Controlled copies of all document [ ]  
 associated with recycle of product  
------------------------------------------------------------------------------------------------------------------------------  
 1.15 Details of lagging material used for [ \* ]  
 insulation HPLC column.  
------------------------------------------------------------------------------------------------------------------------------  
 1.16 Detailed report of any known critical [ \* ]  
 parameters associated with the  
 purification of product including all  
 available stability data.  
------------------------------------------------------------------------------------------------------------------------------  
 1.17 Synthesis method for manufacture of [ \* ]  
 Angiozyme on APB Oligo Pilot  
------------------------------------------------------------------------------------------------------------------------------  
 1.18 Details of all stability trials on raw [ \* ]  
 materials, in-process samples and  
 final product for assignment of shelf  
 life.  
------------------------------------------------------------------------------------------------------------------------------  
 1.19 Compositions of waste streams [ \* ]  
------------------------------------------------------------------------------------------------------------------------------  
 1.20 Details of serious deviations from [ \* ]  
 normal operations outlining causes,  
 impact and preventative measures adopted.  
  
------------------------------------------------------------------------------------------------------------------------------  
  
  
SCHEDULE 5 RAW MATERIALS  
----------  
  
------------------------------------------------------------------------------------------------------------------------------  
 Information RPI Avecia Target Completion  
 Responsible Responsible Date Date  
 person Person  
------------------------------------------------------------------------------------------------------------------------------  
   
 2.1 Raw Material Master List indicating [ \* ] [ \* ]  
 critical raw materials to be purchased  
 from RPI named suppliers  
------------------------------------------------------------------------------------------------------------------------------  
 2.2 Reports on any audits of Raw Material [ \* ] [ \* ]  
 Vendors which Avecia will use.  
------------------------------------------------------------------------------------------------------------------------------  
 2.3 Raw Material Specifications including [ \* ] [ \* ]  
 packaging materials  
------------------------------------------------------------------------------------------------------------------------------  
 2.4 Details of any special storage or [ \* ]  
 handling procedures for raw materials  
------------------------------------------------------------------------------------------------------------------------------  
  
  
SCHEDULES 5 ANALYTICAL AND SPECIFICATIONS  
-----------  
  
 S-33  
  
  
  
  
-------------------------------------------------------------------------------------------------------------------------------  
 Information RPI Avecia Target Completion  
 Responsible Responsible Date Date  
 person Person  
-------------------------------------------------------------------------------------------------------------------------------  
   
 3.1 Analytical Technology Transfer Plan [ \* ] [ \* ]  
-------------------------------------------------------------------------------------------------------------------------------  
 3.2 Methods of analysis and Specification [ \* ] [ \* ]  
 for Angiozyme.  
-------------------------------------------------------------------------------------------------------------------------------  
 3.3 Specification and methods for analysis [ \* ] [ \* ]  
 of Raw Materials including  
 packaging materials.  
-------------------------------------------------------------------------------------------------------------------------------  
 3.4 Methods and specifications for [ \* ] [ \* ]  
 in-process and intermediate tests  
-------------------------------------------------------------------------------------------------------------------------------  
 3.5 Methods and specifications for [ \* ] [ \* ]  
 cleaning verification tests  
-------------------------------------------------------------------------------------------------------------------------------  
 3.6 Analytical reference standards [ \* ] [ \* ]  
-------------------------------------------------------------------------------------------------------------------------------  
 3.7 Sampling requirements [ \* ] [ \* ]  
-------------------------------------------------------------------------------------------------------------------------------  
 3.8 Analytical Technical transfer report [ \* ] [ \* ]  
-------------------------------------------------------------------------------------------------------------------------------  
 3.9 Transfer protocol for individual methods [ \* ] [ \* ]  
-------------------------------------------------------------------------------------------------------------------------------  
 3.10 Validation reports of method developed at RPI [ \* ] [ \* ]  
-------------------------------------------------------------------------------------------------------------------------------  
  
  
SCHEDULE 5 REGULATORY  
----------  
  
-------------------------------------------------------------------------------------------------------------------------------  
 Information RPI Avecia Target Completion  
 Responsible Responsible Date Date  
 person Person  
-------------------------------------------------------------------------------------------------------------------------------  
   
 4.1 QA agreement which outlines [ \* ] [ \* ]  
 responsibilities for validation.  
-------------------------------------------------------------------------------------------------------------------------------  
 4.2 Format and content guidance for CMC [ \* ]  
 information required for regulatory  
 submission  
 (This is Product Dependent)  
  
 Angiozyme [ \* ]  
  
 Heptazyme  
-------------------------------------------------------------------------------------------------------------------------------  
  
  
 S-34  
  
  
  
  
SCHEDULE 5 HEALTH AND SAFETY  
----------  
  
------------------------------------------------------------------------------------------------------------------------------  
 Information RPI Avecia Target Completion  
 Responsible Responsible Date Date  
 person Person  
------------------------------------------------------------------------------------------------------------------------------  
   
 5.1 Substance Information sheets (HDS) and [ \* ] [ \* ]  
 information on RPI Operating methods  
 used when handling Angiozyme  
------------------------------------------------------------------------------------------------------------------------------  
 5.2 Substance information sheets on raw [ \* ] [ \* ]  
 materials (MSDS)  
------------------------------------------------------------------------------------------------------------------------------  
 5.3 Available analytical methods for [ \* ] [ \* ]  
 Angiozyme for any occupational  
 hygiene monitoring undertaken by RPI  
------------------------------------------------------------------------------------------------------------------------------  
  
  
SCHEDULE 5 CONTROL OF CHANGE  
----------  
  
------------------------------------------------------------------------------------------------------------------------------  
 Information Responsible Avecia Target Completion  
 person Responsible Date Date  
 Person  
------------------------------------------------------------------------------------------------------------------------------  
   
 6.1 Procedure for obtaining RPI [ \* ] [ \* ]  
 authorisation for proposed  
 amendments  
------------------------------------------------------------------------------------------------------------------------------  
  
  
SCHEDULE 5 TRAINING  
----------  
  
------------------------------------------------------------------------------------------------------------------------------  
 Information Responsible Avecia Target Completion  
 person Responsible Date Date  
 Person  
------------------------------------------------------------------------------------------------------------------------------  
   
 7.1 A plan for training personnel involved [ \* ] [ \* ]  
 in the manufacture of RPI products  
 including method of recording any  
 training received  
------------------------------------------------------------------------------------------------------------------------------  
  
  
 S-35  
  
  
APPENDIX IV  
  
  
Information Required From LSM  
  
  
  
  
SCHEDULE 5 PROCESS  
----------  
  
-------------------------------------------------------------------------------------------------------------------------------  
 Information Avecia RPI Target Completion  
 Responsible Responsible Date Date  
 person Person  
-------------------------------------------------------------------------------------------------------------------------------  
   
 1.1 A commissioning plan for Angiozyme [ \* ]  
 including engineering and equipment  
 qualification reports  
-------------------------------------------------------------------------------------------------------------------------------  
 1.2 Justified assurance that the plant has [ \* ]  
 been cleaned prior to start of  
 manufacture of Angiozyme  
-------------------------------------------------------------------------------------------------------------------------------  
 1.3 Process record sheet for Angiozyme for [ \* ]  
 RPI comments and approval  
-------------------------------------------------------------------------------------------------------------------------------  
 1.4 Latest "for construction" line diagrams. [ \* ]  
  
 An "as-built" plant diagram will be  
 provided as soon as practicable For  
 use as reference documents for control  
 of change  
-------------------------------------------------------------------------------------------------------------------------------  
 1.5 Materials of construction for plant: [ \* ] [ \* ]  
 Avecia to generate MOC document for  
 RPI approval  
-------------------------------------------------------------------------------------------------------------------------------  
 1.6 A batch timetable for the initial Campaign [ \* ]  
-------------------------------------------------------------------------------------------------------------------------------  
 1.7 A schedule for technical cover during [ \* ]  
 commissioning  
-------------------------------------------------------------------------------------------------------------------------------  
  
  
SCHEDULE 5 RAW MATERIALS  
----------  
  
-------------------------------------------------------------------------------------------------------------------------------  
 Information Avecia RPI Target Completion  
 Responsible Responsible Date Date  
 person person  
-------------------------------------------------------------------------------------------------------------------------------  
   
 2.1 Evidence that suppliers of raw [ \* ]  
 materials to be used in the  
 Grangemouth campaign have been approved  
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 S-36  
  
  
  
  
SCHEDULE 5 ANALYTICAL AND SPECIFICATIONS  
----------  
  
-------------------------------------------------------------------------------------------------------------------------------  
 Information Avecia RPI Target Completion  
 Responsible Responsible Date Date  
 person Person  
-------------------------------------------------------------------------------------------------------------------------------  
   
 3.1 Grangemouth Works methods of analysis [ \* ]  
 and specifications to be used for Raw  
 Materials, intermediates and API for  
 RPI to check and approve.  
-------------------------------------------------------------------------------------------------------------------------------  
 3.2 Analytical results from cross [ \* ]  
 correlation studies.  
 . Raw materials  
 . Intermediates  
 . API  
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SCHEDULE 5 HEALTH AND SAFETY  
----------  
  
-------------------------------------------------------------------------------------------------------------------------------  
 Information Avecia RPI Target Completion  
 Responsible Responsible Date Date  
 person Person  
-------------------------------------------------------------------------------------------------------------------------------  
   
 2.1 Assurance that all appropriate risk [ \* ]  
 assessments have been completed prior  
 to start of manufacture.  
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SCHEDULE 5 ENVIRONMENTAL  
----------  
  
-------------------------------------------------------------------------------------------------------------------------------  
 Information Avecia RPI Target Completion  
 Responsible Responsible Date Date  
 person person  
-------------------------------------------------------------------------------------------------------------------------------  
   
 7.1 Evidence of approval for manufacture from [ \* ]  
 the appropriate authorities.  
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SCHEDULE 5 CONTROL OF CHANGE  
----------  
  
-------------------------------------------------------------------------------------------------------------------------------  
 Information Avecia RPI Target Completion  
 Responsible Responsible Date Date  
 person person  
-------------------------------------------------------------------------------------------------------------------------------  
   
 7.1 Guidelines for Grangemouth [ \* ]  
 Works, system of pre-approval of change  
 control to be agreed with RPI.  
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 S-37  
  
  
APPENDIX V  
  
Information And Reports Required Before Technology Transfer Can Be Concluded  
  
  
   
1 PROCESS SOURCE  
  
1.1 Pre Manufacturing technology transfer review LSM  
  
1.2 Manufacturing Report LSM  
  
SCHEDULE 5 Control of change procedure for routine manufacture  
----------  
  
1.4 Summary report on suitability of Angiozyme produced at Grangemouth RPI  
  
1.5 Summary report on the suitability of the process RPI  
 for future manufacture  
  
SCHEDULE 5 RAW MATERIALS  
----------  
  
2.1 Report on raw material sources LSM  
  
  
SCHEDULE 5 ANALYTICAL  
----------  
  
3.1 Summary of all results, and review of operation LSM  
 of methods  
  
3.2 Cross validation reports LSM  
  
4 HEALTH, SAFETY & ENVIRONMENT  
  
4.1 Report on health and hygiene monitoring LSM  
  
4.2 Confirmation of acceptable occupational health LSM  
 position  
  
4.3 Waste disposal routes used LSM  
  
5 TECHNOLOGY TRANSFER  
  
5.1 Technology Transfer Closure Report RPI/LSM  
  
5.2 Definition of responsibilities and routes of RPI/LSM  
 communication post technology transfer  
  
  
 S-38  
  
  
APPENDIX VI :  
  
TECHNOLOGY TRANSFER ACCEPTANCE DOCUMENT  
  
The RPI Angiozyme process has been transferred from RPI to LifeScience  
Molecules Grangemouth Works and the reports required by the Technology Transfer  
Plan completed.  
  
--------------------------------------------------------------------------------  
The Product Name: Number of Stages:  
--------------------------------------------------------------------------------  
CAS nomenclature Stage Name:  
  
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The attached completion report provides a summary of technology transfer and any  
actions outstanding.  
  
--------------------------------------------------------------------------------  
For RPI:  
  
Quality Assurance Manager:  
  
  
\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
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For RPI:  
  
Technology Transfer Manager:  
  
  
\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
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For Avecia:  
  
Quality Assurance Manager:  
  
  
\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
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For Avecia:  
  
Technology Transfer Manager:  
  
  
\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
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 S-39  
  
  
 SCHEDULE 5  
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 Yield and Price Matrix  
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 Order size (Kg)  
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--------------------------------------------------------------------------------------------------------------  
 Raw material cost ($/g of 1 3 5  
 product)  
--------------------------------------------------------------------------------------------------------------  
   
[ \* ] [ \* ] [ \* ] [ \* ]  
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[ \* ] [ \* ] [ \* ] [ \* ]  
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[ \* ] [ \* ] [ \* ] [ \* ]  
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 S-40