Exhibit 10.41  
  
 Confidential Materials omitted and filed separately with the  
 Securities and Exchange Commission. Askterisks denote omissions.  
  
 AGREEMENT  
  
 FOR  
  
 MANUFACTURING AND SUPPLY OF ZILEUTON  
  
 Made as of February 8, 2005 (the "Effective Date")  
  
 by and between  
  
CRITICAL THERAPEUTICS, INC., (hereinafter referred to as "CTI"), a corporation  
duly organized and validly existing under the laws of the State of Delaware with  
its principal offices at 00 Xxxxxxxx Xxxxxx, Xxxxxxxxx, XX 00000 XXX  
  
 and  
  
RHODIA PHARMA SOLUTIONS LTD., (hereinafter referred to as "RPS"), a corporation  
duly organized and validly existing under the laws of England, with its  
principal offices at Dudley, Xxxxxxxxxxx, Xxxxxxxxxxxxxx, XX00 0XX, Xxxxxxx  
  
 WHEREAS, CTI and RPS and RPS' affiliate, Rhodia Pharma Solutions Inc. are  
parties to a certain Confidential Proposal Agreement ANNSEN22032004A dated March  
23, 2004, under which RPS and Rhodia Pharma Solutions Inc. provided CTI with  
certain research and development services concerning the manufacturing of the  
Compound (as defined below); and  
  
 WHEREAS, CTI and RPS desire to enter into a contract for the supply of  
commercial scale Compound batches manufactured by RPS at its Manufacturing Site  
(as defined below), subject to the terms and conditions contained herein.  
  
 NOW, THEREFORE, CTI and RPS hereby agree as follows:  
  
1.0 DEFINITIONS  
  
 Unless otherwise specifically set forth herein, the following terms shall  
have the meanings set forth below:  
  
1.1 Affiliate  
  
 Shall mean in relation to a party, any other entity controlled, directly  
 or indirectly, by a Party at the time in question or controlling that  
 Party or controlled directly or indirectly by an entity controlling the  
 Party, and where the term "control" means the holding of more than 50% of  
 the equity of an entity or having the right to appoint and/or remove more  
 than 50% of its board of directors or like penultimate governing body.  
  
1.2 Agreement  
  
 Shall mean this Agreement for the Manufacturing and Supply of ZILEUTON and  
 all annexes hereto.  
  
1.3 Annual Contract Volume  
  
 Shall mean for any Calendar Year, the lesser of (i) [\*\*] percent ([\*\*]%)  
 of the commercial scale volume of Compound required by CTI and its  
 Affiliates in that  
  
  
  
 Calendar Year for the manufacture of Drug Products plus any Excess  
 Compound Demand that RPS is entitled to produce in accordance with Section  
 2.1(b)(iii) below, and (ii) the [\*\*] at the Manufacturing Site at Annan  
 during such Calendar Year.  
  
1.4 cGMP  
  
 Shall mean the current good manufacturing practices promulgated by  
 Governmental Authorities and the International Conference on Harmonisation  
 ("ICH"), including ICH guideline Q7A.  
  
1.5 Compound  
  
 Shall mean the compound (+)-1-(1-benzo[b]thien-2-ylethyl)-1-hydroxyurea,  
 also known as zileuton.  
  
1.6 Confidential Information  
  
 Shall mean all information, whether technical or non-technical, trade  
 secrets, discoveries, data, drawings, techniques, documents, models,  
 samples and know-how, whether or not patented or patentable, owned or  
 possessed by a Party on the date of this Agreement or later developed by  
 them that is not in the public domain. CTI's Confidential Information  
 shall include Intellectual Work Product (as defined in Section 8.1 (a).  
  
1.7 Contract Year  
  
 Shall mean each calendar year during the Term hereof beginning upon  
 January 1st and ending upon December 31st of such year.  
  
1.8 Drug Product  
  
 Shall mean any and all pharmaceutical preparations suitable for human use  
 manufactured by or for CTI that contain the Compound.  
  
1.9 EMEA Territories  
  
 Shall mean the European countries of Austria, Belgium, Cyprus, Czech  
 Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary,  
 Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands,  
 Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United  
 Kingdom, and such other countries as may from time to time become member  
 states of the European Union.  
  
1.10 European Union  
  
 Shall mean the European countries of Austria, Belgium, Cyprus, Czech  
 Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary,  
 Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the  
 Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the  
 United Kingdom, and such other countries as may from time to time become  
 member states of the European Union.  
  
1.11 Excess Compound Demand  
  
 As defined in Section 2.1(b)(iv) below.  
  
1.12 FDA  
  
 Shall mean the United States Food and Drug Administration, or any  
 successor entity.  
  
1.13 Governmental Approval  
  
 Shall mean all authorizations by the appropriate Governmental Authorities  
 that are required for the manufacture (other than manufacturing facility  
 licenses, approvals, or authorizations), marketing, promotion, and sale of  
 the Compound in the United States and the European Union.  
  
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1.14 Governmental Authority  
  
 Shall mean any national, supra-national, regional, state, or local  
 regulatory agency, department, bureau, commission, council, or other  
 governmental entity in the United States or the European Union involved in  
 the granting of Governmental Approval for the Compound, including, without  
 limitation, the FDA and the EMEA.  
  
1.15 Initial Delivery Period  
  
 Shall mean the period commencing with the Effective Date and ending upon  
 December 31, 2006.  
  
1.16 Manufacturing Site  
  
 Shall mean one or both of RPS' manufacturing facilities located at Dudley,  
 Xxxxxxxxxxx, Xxxxxxxxxxxxxx, XX00 0XX, Xxxxxxx and Xxxxx Xxxxx Xxxx,  
 Xxxxxx, Xxxxx, Xxxxxxxxxxxxx, XX00 0XXX, Xxxxxxxx  
  
1.17 Manufacturing Site Capital Project  
  
 Shall mean the capital build-out projects at the Manufacturing Site at  
 Annan, Scotland required to increase RPS' Compound manufacturing capacity  
 at the Manufacturing Site at Annan from [\*\*] to [\*\*] of Compound per  
 Calendar Year sites, together with the estimated costs and expenses of  
 such project and the estimated project timeline shown on Annex 12 attached  
 hereto.  
  
1.18 Party  
  
 Shall mean CTI or RPS, and when used in the plural form both CTI and RPS.  
  
1.19 Proposal Agreement  
  
 Shall mean the Confidential Proposal Agreement described in the preamble  
 of this Agreement together with any amendments and change orders agreed to  
 in writing between the Parties, a copy of which is attached hereto at  
 Annex 11.  
  
1.20 Quality Agreement  
  
 Shall mean the written quality agreement for the manufacturing of the  
 Compound agreed between the Parties and attached hereto as Annex 9, as  
 such agreement shall be amended from time to time in writing by the  
 Parties.  
  
1.21 Raw Materials  
  
 Shall mean all materials, chemicals and solvents used in the production of  
 the Compound by RPS hereunder.  
  
1.22 Recall  
  
 Shall mean any action by CTI and its Affiliates or RPS and its Affiliates,  
 to recover title or possession or halt distribution, prescription, or  
 consumption of the Compound or any Drug Product sold or shipped to Third  
 Parties. The term "Recall" also applies to Compound or Drug Products that  
 would have been subject to recall if the Compound or Drug Products, as the  
 case may be, had been shipped.  
  
1.23 Seizure  
  
 Shall mean any action by the FDA or other governmental authority to detain  
 or destroy the Compound or the Drug Products or prevent the distribution,  
 prescription, consumption, or release of the Compound or Drug Products.  
  
1.24 Specifications  
  
 Shall mean the specifications for the Compound attached hereto in Annex 1.  
  
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1.25 Supply Chain Introduction Date  
  
 Shall mean the date, for a given drum of Compound that is shipped by RPS  
 hereunder, upon which CTI or CTI's designated agent first breaks the seal  
 of such drum.  
  
1.26 Term  
  
 Shall mean the duration of this Agreement as provided in Section 10.1  
 hereof.  
  
1.27 Third Party  
  
 Shall mean any party other than CTI and its Affiliates and RPS and its  
 Affiliates.  
  
1.28 Validations  
  
 Shall mean process validation, test method validation, milling validation  
 and cleaning validation, contemplated by the Parties to be undertaken for  
 preparation of the Process Validation Report.  
  
1.29 Process Validation Report  
  
 Shall mean a written report prepared by RPS in consultation with CTI  
 evidencing the repeatability of Compound quality and stability over the  
 production of [\*\*] Compound batches, as required for commercial release of  
 the Compound under applicable Government Approvals, and all Validations  
 and the achievement of any other production validation criteria so  
 required and as the Parties shall mutually agree, and which report shall,  
 subject to Section 10.6, be attached hereto at Annex 10 upon completion  
 and sign off, in writing, by both Parties.  
  
1.30 Validation Schedule and Timeline  
  
 Shall mean the schedule of work and timelines for the Validations and the  
 manufacture by RPS of Phase 1 validation batches of Compound, described at  
 Annex 3 hereto.  
  
1.31 Validation Success Criteria  
  
 Shall mean the criteria agreed between the parties for the Validations and  
 the successful completion of the manufacture by RPS of validation batches  
 of Compound, as set forth in the Validation Schedule and Timeline.  
  
1.32 Vendors  
  
 Shall mean any and all Third Party suppliers of materials, processing  
 services and/or testing services engaged by RPS in connection with this  
 Agreement.  
  
2.0 AGREEMENT SCOPE AND MANUFACTURE AND SUPPLY OF COMPOUND  
  
2.1 (a) Phase 1 - Validation Batches of Compound.  
  
 During the Term, RPS will manufacture at the Manufacturing Site under cGMP  
 [\*\*] validation batches of the Compound from the Manufacturing Site at  
 Xxxxxx and [\*\*] validation batches of the Compound from the Manufacturing  
 Site at Annan in accordance with the Proposal Agreement, the Validation  
 Schedule and Timeline and the Validation Success Criteria. Should any such  
 validation batch be prepared under conditions determined not to meet the  
 Validation Success Criteria to the mutual satisfaction of the Parties, RPS  
 shall manufacture a new validation batch or batches. The price for these  
 Phase 1 validation batches of Compound is set forth in the Proposal  
 Agreement; provided, however, that CTI shall only be responsible for  
 paying for the [\*\*] validation batches from the Manufacturing Site at  
 Xxxxxx and the [\*\*] validation batches from the Manufacturing Site at  
 Annan as outlined in the  
  
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 Proposal Agreement regardless of how many validation batches are needed to  
 be produced to achieve [\*\*] validation batches that meet the Validation  
 Success Criteria. Further, the foregoing price shall be inclusive of the  
 cost of the Process Validation Report and all validation batches,  
 excluding the cost of the milling part of the Validations to the extent  
 any milling is done by a Third Party, in which case, the cost of such  
 milling by a Third Party shall be the sole responsibility of CTI. For the  
 milling validation part of the Validations, the extent of the milling  
 required of Compound from the foregoing validation batches, including, but  
 not limited to, how much Compound to be milled and the timing thereof,  
 shall be determined by CTI, in its reasonable discretion, in consultation  
 with RPS.  
  
 (b) Phase 2 - Commercial Batches of Compound.  
  
 (i) Price: The price for commercial scale batches of Compound shall be  
 US$[\*\*] per kilo, [\*\*] (per INCOTERMS 2000), during the Initial Delivery  
 Period. The foregoing price is inclusive of CTI's obligation to [\*\*], but  
 not more than $[\*\*], of (i) any costs and expenses incurred by RPS in  
 connection with the work described in the Manufacturing Site Capital  
 Project Project and (ii) the reasonable out-of-pocket cost of [\*\*] any  
 such capital improvements that RPS must undertake, provided that CTI  
 performs its [\*\*] per Section 2.1(b)(ii) below. The price for commercial  
 scale batches during any Calendar Year thereafter shall vary as provided  
 in Schedule 13 attached hereto depending upon the volume of Compound  
 ordered by CTI for such Calendar Year. The Parties shall meet no less than  
 once a Calendar Year to review Compound pricing under Schedule 13 of this  
 Agreement with a goal of achieving a Compound price of US$[\*\*] per kilo  
 for Calendar Year volumes of Compound equal to or greater than [\*\*] metric  
 tons, provided that no adjustments or changes to Schedule 13 pricing will  
 be binding upon the Partiers absent an amendment to Schedule 13 signed by  
 both of the Parties.  
  
 (ii) Compound Delivery Volumes: Subject to the terms of this Agreement,  
 during the Initial Delivery Period, RPS will manufacture at the  
 Manufacturing Site under cGMP, and CTI will purchase, [\*\*] metric tons of  
 commercial scale batches of Compound Subject to the terms of this  
 Agreement, during each Calendar Year after the Initial Delivery Period,  
 RPS will manufacture at the Manufacturing Site under cGMP, and CTI will  
 purchase, the Annual Contract Volume.  
  
 (iii) Orders: If CTI has not already done so as of the Effective Date, CTI  
 will provide RPS with a written, rolling, twenty-four month forecast of  
 its Compound requirements no later than [\*\*] months prior to the first  
 date proposed for delivery by RPS of commercial scale Compound batches  
 hereunder and shall provide an update of such forecast on or before the  
 first [\*\*] thereafter during the Term of this Agreement (e.g., [\*\*]). Such  
 forecasts shall constitute [\*\*] months of firm orders from CTI for the  
 requested volume of Compound and shall then include [\*\*] months of pro  
 forma volumes of Compound and [\*\*] months of Compound delivery planning  
 horizon. The latter [\*\*] months of each such forecast shall be  
 non-binding, subject always to CTI's minimum Compound volume purchase  
 obligations hereunder. RPS shall advise CTI if it cannot meet any of the  
 proposed delivery dates for Compound contained in CTI's newly forecasted  
 [\*\*] within fifteen (15) business days of receiving each [\*\*] updated  
 forecast, and the Parties shall negotiate mutually agreeable alternative  
 delivery dates. For the avoidance of doubt, once RPS has agreed that it  
 can accommodate the delivery dates for the first [\*\*] months of CTI's  
 forecasts delivered as above, RPS shall only be able to object to the  
 delivery dates proposed in the updated forecast next due from CTI for the  
 [\*\*] months immediately following the [\*\*] months of firm orders then  
 pending under CTI's forecast. CTI's forecasts will also forecast the total  
 Compound requirements for CTI and its Affiliates over the forecast period  
 to the extent not reflected in CTI's firm orders. It is understood and  
 agreed between the  
  
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 Parties that, for any Compound needed by CTI for commercial production of  
 Drug Product, RPS shall be the sole and exclusive supplier of Compound to  
 CTI and its Affiliates until the end of the Initial Delivery Period.  
  
 (iv) Right of First Refusal: Beginning with the Calendar Year 2007, CTI  
 hereby grants to RPS the right of first refusal to supply CTI and its  
 Affiliates with an additional [\*\*] percent ([\*\*]%) of their total annual  
 Compound requirements above [\*\*] percent ([\*\*]%) of such volume under this  
 Agreement ("Excess Compound Demand"), which right shall be exercisable by  
 RPS for all or any part of such Excess Compound Demand that RPS is capable  
 of producing subject to the capacity limitations at the Manufacturing Site  
 for any such Calendar Year by written notice issued to CTI within fifteen  
 (15) days after the date that RPS first receives from CTI firm orders for  
 Compound for that Calendar Year under Section 2.1(b)(iii) above (i.e.,  
 forecast due date from CTI of April 1st of each Calendar Year covering the  
 twenty-four (24) month period commencing with July 1st of that year) (the  
 "Exercise Period"). If RPS has received written notice from CTI on or  
 prior to an Exercise Period, containing reasonably detailed information  
 and supporting documents for RPS' evaluation (subject always to any  
 confidentiality obligations to Third Parties to which CTI or its  
 Affiliates may be bound), that CTI and/or one or more of its Affiliates  
 have received a written offer, binding upon a Third Party supplier(s) of  
 Compound, to supply CTI and/or its Affiliates with between [\*\*] percent  
 ([\*\*]%) and [\*\*] percent ([\*\*]%) of its Compound requirements for the  
 succeeding Calendar Year and such offer, or offers on average if there are  
 more than one, evidence a lower price delivered to the final destination  
 designated by CTI than that which will be payable hereunder during such  
 succeeding Calendar Year, taking into account [\*\*], then RPS' right of  
 first refusal for the Excess Compound Demand represented by such offer(s)  
 shall be subject to RPS' agreement to supply such Excess Compound Demand  
 hereunder at a price that is more favorable to CTI than such offered  
 price. If RPS does not exercise its right of first refusal with an  
 agreement by RPS to supply all or any part of such Excess Compound Demand  
 at a price that is more favorable to CTI than the offered price, then CTI  
 shall be free to purchase any Excess Compound Demand so declined by RPS  
 for the relevant succeeding Calendar Year from the Third Party supplier(s)  
 who has made the competitive offer.  
  
 (c) Compound Deliveries  
  
 All deliveries of Compound shall be made by RPS to CTI, either [\*\*].  
 facility of RPS' Affiliate, Rhodia Pharma Solutions Inc. [\*\*] to the  
 carrier nominated by CTI or its designated agent or [\*\*] (per INCOTERMS  
 2000) as the Parties shall agree based upon CTI's firm Compound orders,  
 and title and risk of loss to the Compound shall pass from RPS to CTI upon  
 completion of delivery as aforesaid. CTI shall be the importer of record  
 and shall be responsible for paying all customs duties and any other  
 importation charges and fees on any Compound brought into the United  
 States, including without limitation any [\*\*] that RPS must maintain at  
 [\*\*] per Section 2.1(d) below, but CTI shall not take title to the  
 Compound until delivered to the carrier selected by CTI and/or its  
 designated agent at [\*\*].  
  
 It is expressly understood by the Parties that [\*\*] in the [\*\*] hereunder  
 or [\*\*] agreed between the Parties.  
  
 (d) [\*\*]  
  
 During the Term of this Agreement, RPS agrees to [\*\*], as requested by  
 CTI, an [\*\*] RPS' then-current monthly production capacity of Compound at  
 the Manufacturing  
  
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 Site, or [\*\*] agreed between the Parties ("[\*\*]") to support RPS' [\*\*]  
 hereunder; provided, however, that after the milling portion of the  
 Validations is complete, a [\*\*] of the [\*\*] in [\*\*] Compound to be  
 processed by CTI or its designated agents into Drug Product in the United  
 States, as advised by CTI to RPS with appropriate advance notice, shall  
 [\*\*] unless otherwise agreed in writing by the Parties (e.g. if [\*\*] of  
 CTI's [\*\*] are for the processing of Drug Products in the United States,  
 then [\*\*] of the [\*\*] will be [\*\*]). Notwithstanding the foregoing, CTI  
 agrees that RPS will not be obligated to have such [\*\*] until [\*\*], and  
 that [\*\*], RPS shall only be required to [\*\*] a [\*\*] of [\*\*] as a [\*\*].  
  
 CTI further agrees that RPS may supply Compound to CTI [\*\*], including for  
 milling validation as described in section 2.1(a), but shall [\*\*] to the  
 extent necessary to have the [\*\*]; provided, however, the [\*\*] by RPS [\*\*]  
 will, if reasonably required by CTI, be [\*\*] by RPS, at RPS' sole expense,  
 [\*\*] to CTI to [\*\*] that the [\*\*]. Title and risk of loss to Compound [\*\*]  
 shall at all times remain with RPS prior to the delivery to CTI of such  
 Compound by RPS. CTI shall purchase [\*\*] from RPS at the termination of  
 this Agreement for any reason whatsoever, at RPS's cost of [\*\*] unless  
 [\*\*] from CTI to be filled by RPS during the termination periods set forth  
 in Sections 10.2, 10.5 and 10.6 below or as otherwise agreed between the  
 Parties in which case [\*\*] by CTI at the price for [\*\*] hereunder.  
  
 CTI shall be provided with all batch records related to the [\*\*] and shall  
 be agreed between the Parties as contemplated in Section 2.2(b) below.  
  
 (e) Price Adjustments [\*\*]  
  
 After the Initial Delivery Period, RPS shall be allowed to [\*\*] the  
 Compound price each Calendar Year by [\*\*]. By way of example only, if  
 [\*\*], RPS will be entitled to [\*\*] the Compound price [\*\*]. RPS will  
 advise CTI in writing of any such [\*\*] during the term of this Agreement,  
 and will adjust any invoices already submitted to CTI for Compound  
 produced during the new Calendar Year that do not reflect such [\*\*] and  
 shall submit a [\*\*] to the next succeeding Compound invoice following such  
 written notice to CTI. [\*\*]  
  
 (f) Price Adjustment for [\*\*]  
  
 In the event that RPS [\*\*] the cost of the [\*\*] Compound hereunder to a  
 price, delivered to the Manufacturing Site, to [\*\*], whether through the  
 [\*\*] or otherwise, then [\*\*] percent ([\*\*]%) of such [\*\*] shall be [\*\*]  
 through [\*\*] the purchase price per kilogram for the Compound.  
  
2.2 (a) All Compound shall be manufactured to meet the Specifications  
 indicated in Annex 1. Any reasonable changes in Annexes 1, 2, 4, 5, 6, 9  
 and/or 10 provided by CTI, or required due to new or changed governmental  
 laws rules or regulations that come into force during the term hereof,  
 shall be adopted and the relevant Annex shall be amended by a signed  
 written amendment to this Agreement to reflect the change, provided that  
 CTI shall reimburse RPS, on terms designated by RPS, for any and all  
 increased costs and expenses that RPS incurs to produce Compound in  
 compliance with such changes. In the event that RPS wishes, in its  
 reasonable discretion, to amend Annexes 1, 2, 4, 5, 6, 9 and/or 10, RPS  
 shall provide such proposed amendment to CTI and the terms of such changes  
 will be evidenced in a signed, written amendment to this Agreement  
 negotiated between CTI and RPS and the costs and expenses of producing  
 Compound in compliance with such changes shall be for RPS account. All Raw  
 Materials and intermediates necessary for the manufacturing by RPS of the  
 Compound at the Manufacturing Site will be supplied by  
  
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 RPS without additional charge to CTI. A list of critical Raw Materials  
 necessary for the manufacture of the Compound by RPS is set forth at Annex  
 2 hereto.  
  
 (b) Batch records, specifications for Raw Materials and intermediates to  
 be used in the manufacture by RPS of the Compound and the analytical test  
 methods for same will be developed by RPS in consultation with CTI during  
 the Phase 1 stage of this Agreement, and shall be reduced to writing and  
 attached hereto at Annex 4. [\*\*]. All batch record forms, specifications  
 for Raw Materials and intermediates to be used in the manufacture by RPS  
 of the Compound and the analytical test methods for same must be approved  
 in writing by CTI prior to use by RPS, which approval will not be  
 unreasonably withheld or delayed. Any material changes in the batch  
 records, specifications for Raw Materials and intermediates to be used in  
 the manufacture by RPS of the Compound and the analytical test methods for  
 same or equipment specifically used for the Compound by RPS at the  
 Manufacturing Site will require prior written approval by CTI as per the  
 Quality Agreement attached hereto at Annex 9. RPS will provide a  
 Certificate of Analysis and a Certificate of Compliance with cGMP in the  
 forms shown at Annex 5 attached hereto and executed batch record(s) in the  
 then agreed form with each shipment of the Compound hereunder.  
  
 (c) RPS shall follow the Procedures for Release of Compound attached at  
 Annex 6 hereto prior to delivery of any Compound to CTI. The procedures to  
 be followed upon the occurrence of an Out of Specification ("OOS") event  
 are contained in the standard operating procedures ("SOPs") for the  
 Manufacturing Site. Current copies of such SOPs will be provided by RPS to  
 CTI and shall be reviewed by CTI and shall be subject to CTI's approval  
 before implementation in relation to this Agreement, which approval will  
 not be unreasonably withheld or delayed. No new SOP shall be adopted by  
 RPS in relation to this Agreement without the express written approval of  
 CTI, which approval will not be unreasonably withheld or delayed. RPS will  
 promptly provide CTI with any changes to such SOPs that RPS desires to  
 make in relation to this Agreement. Such changes shall be reviewed by CTI  
 and shall be subject to CTI's approval before implementation with respect  
 to this Agreement, which approval will not be unreasonably withheld or  
 delayed. These procedures contain specific timelines for investigation of  
 OOS events. Procedures to be followed for a batch failure due to  
 circumstances other than OOS events shall also be contained in the SOPs  
 for the Manufacturing Site. As outlined in the Quality Agreement, RPS will  
 retain samples of each batch of Compound and samples of all Raw Materials  
 and intermediates used in the manufacturing thereof hereunder for a period  
 of at least five (5) years following the expiry of the last Drug Product  
 incorporating such Compound. Prior to the destruction or disposal of any  
 such retained samples, RPS shall notify CTI and CTI shall have the option  
 to take possession of such retained samples at CTI's expense.  
  
 (d) RPS shall be responsible for conducting an approval program for  
 Vendors utilized by RPS in connection with manufacturing of the Compound  
 as required to comply with cGMP. CTI shall also have the right, but not  
 the obligation, to independently audit the Vendors; provided, however,  
 that, in the case of Vendors of materials used by RPS in the manufacture  
 of the Compound, CTI shall only have such audit right with respect to the  
 Vendors of critical Raw Materials as listed in Annex 2; further provided  
 that RPS will not have any liability to CTI in the event that any such  
 Vendor refuses to permit CTI to conduct such an audit. Where RPS conducts  
 an audit of a vendor, RPS will provide CTI with a copy of RPS' audit  
 procedures and analytical approval process, and any updates or amendments  
 to such procedures and process. CTI shall have the right, during audits of  
 the Manufacturing Site conducted by CTI as permitted hereunder, to review  
 the records for all Vendor audits conducted by RPS. In addition, CTI shall  
 also have the right to  
  
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 review the qualification records (as required by cGMP) of the Vendors for  
 the Raw Materials for the Compound, provided the Raw Materials are  
 produced under cGMP. RPS shall promptly inform CTI in the event of a  
 concern with the quality or manufacturing compliance with respect to a Raw  
 Material used in the manufacture of the Compound and RPS will coordinate  
 with CTI to assure a prompt resolution of any such concern. RPS shall  
 provide CTI with copies of the results of all Vendor audits conducted by  
 RPS upon CTI's request.  
  
 (e) Under no circumstances, shall RPS change a Vendor of critical Raw  
 Materials identified on Annex 2 hereto, or process or testing Vendor  
 without the prior written consent of CTI, which consent shall not be  
 unreasonably withheld or delayed.  
  
2.3 Payment for all Compound purchased from RPS by CTI in accordance with this  
 Agreement, and any other sums that may be payable by CTI to RPS hereunder,  
 shall be made within thirty (30) days after the date of RPS' invoice, by  
 wire transfer in immediately available funds to RPS' bank account set  
 forth in Annex 7 hereto, or as RPS shall otherwise direct payment to be  
 made in writing. RPS will be entitled to charge interest on late payments  
 at the rate of two percent (2%) per annum above the base lending rate  
 charged by HSBC Bank plc prevailing from time to time, both before and  
 after judgment, from the date due until the date cleared funds are  
 received by RPS. RPS shall not invoice CTI for any batch of Compound prior  
 to the issuance of the batch records and the Certificates of Analysis and  
 Compliance for such batch.  
  
2.4 During the term of this Agreement and for a period of at least five (5)  
 years thereafter, RPS shall maintain records of inspection and testing,  
 lab notebooks and procedures made in connection with the Compound  
 manufacturing work conducted under this Agreement. Prior to the  
 destruction or disposal of any such records, RPS shall notify CTI and CTI  
 shall have the option to take possession of such records at CTI's expense.  
 RPS shall provide CTI with the necessary information that would be  
 included in a Drug Manufacturing File ("DMF") or in support of a Chemistry  
 and Master Controls ("CMC") portion of an NDA or equivalent filing so that  
 such information can be included by CTI in its NDA or equivalent filing in  
 the United States, the European Union, or such other location designated  
 by CTI. [\*\*]  
  
2.5 RPS shall keep CTI regularly informed of the status and progress of all  
 stages of Phases 1 and 2 through regular telephone or e-mail updates,  
 [\*\*], and through written summaries. During all periods that RPS is  
 conducting any manufacturing for CTI, RPS shall perform an annual product  
 review, including a review of production history, deviations (if any), OOS  
 events, investigation programs adopted and the outcome of any  
 investigations, any reprocessing conducted, and ongoing stability results,  
 if generated at an RPS site. This review shall comply with section 2.50 of  
 ICH Q7a and a copy shall be provided to CTI one month prior to the  
 regulatory annual report due date. This review shall list all of the  
 changes made during the year that impact on regulatory submissions and  
 also summarize the stability data generated during the year in question.  
 Additional review(s) will be undertaken if necessary to comply with cGMP.  
  
3.0 INSPECTIONS AND CONTROLS  
  
3.1 Subject to confidentiality obligations contained in Section 7, RPS agrees,  
 without additional charge to CTI, to allow inspections of the  
 Manufacturing Site by representatives of CTI or its agents during normal  
 working hours upon prior written notice to RPS, which notice will occur at  
 least three (3) days in advance of the inspection, unless not possible due  
 to an inspection on the same date by a  
  
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 Governmental Authority. RPS shall grant access to such premises and to the  
 documentation necessary for or appropriate to the manufacturing and  
 quality control of the Compound including, but not limited to, full copies  
 of all batch records. During such visits, RPS shall make sure that at  
 least one technical person from its quality assurance/control department  
 and, if reasonably possible, that appropriate RPS product management  
 personnel are present to answer questions or discuss matters of concern  
 with the CTI personnel conducting such audit or inspection.  
  
3.2 RPS shall ensure all relevant and/or critical Compound manufacturing, test  
 and inspection equipment at the Manufacturing Site is maintained under a  
 documented calibration and maintenance program. This includes providing  
 equipment calibration certifications as required.  
  
3.3 RPS will maintain environmental controls, including particulate and  
 bioburden monitoring, pest controls and housekeeping procedures in  
 accordance with cGMP. The use of supplies of process water, air and  
 particulate handling, etc., for manufacture of the Compound, shall be  
 consistent with relevant cGMP specifications and guidelines.  
  
3.4 RPS shall maintain a quality assurance/control department, which is a  
 distinct department separate from manufacturing. RPS quality  
 assurance/control personnel will perform incoming, in-process and finished  
 product inspections, review records, perform line clearance inspections,  
 maintain batch history records, provide batch history records for review  
 and accuracy and completeness and provide product release services, all in  
 accordance with the Quality Agreement and the Procedures for Release of  
 Compound. RPS quality assurance/control personnel will also manage the  
 storage and handling of all Raw Materials and intermediates used in the  
 manufacture of the Compound, as well as any finished batches of Compound,  
 in accordance with the Quality Agreement.  
  
3.5 RPS will promptly notify CTI of any FDA or other material Governmental  
 Authority inspection of the Manufacturing Site related, directly or  
 indirectly, to the Compound, and will promptly provide CTI with a copy of  
 any non-privileged documentation relating to such inspection. CTI shall  
 have the right to communicate at any time with the FDA or any Governmental  
 Authority regarding such matters, provided any such communication is done  
 after consultation with RPS and is coordinated with RPS. CTI will provide  
 appropriate support for any such inspection, including data and  
 information relating to critical parameters and other information relevant  
 to the Compound.  
  
3.6 At all times during the term of this Agreement, each of the Parties shall  
 carry and keep in force a general liability insurance policy, in support  
 of their liability obligations to one another hereunder. The policy  
 maintained by the Parties shall afford limits of not less than five (5)  
 million dollars (US $5,000,000) in the case of CTI, and five million Euros  
 ((euro)5,000,000) in the case of RPS, for each occurrence and not less  
 than seven and a half (7.5) million dollars (US $7.5,000,000) in the case  
 of CTI, and seven and a half (7.5) million Euros ((euro)7,500,000) in the  
 case of RPS, in the annual aggregate in respect of products and completed  
 operations liability. In the event that such policy is written on a  
 claims-made basis, such policy shall provide no less than twelve (12)  
 months extended reporting period from the date of termination of this  
 Agreement. A Certificate of Insurance evidencing RPS' coverage and a  
 Certificate of Insurance evidencing CTI's coverage are attached hereto as  
 Annex 8 hereto.  
  
4.0 WARRANTIES/LIMITATIONS  
  
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4.1 (a) Product Warranty  
  
 RPS warrants and represents that the Compound manufactured by RPS and  
 delivered to CTI shall conform to the Specifications when delivered and be  
 manufactured in accordance with cGMP and all other applicable Governmental  
 Approvals, and was not and will not be adulterated or misbranded while in  
 the possession of RPS (as the terms "adulterated" and "misbranded" are  
 used and interpreted under the U.S. Food, Drug and Cosmetic Act). RPS will  
 maintain at least 25 to 50 grams of the Compound from each batch produced  
 as a retained sample. Such retained sample will be maintained at the  
 Manufacturing Site or other RPS facility and RPS will store such retained  
 sample under storage conditions set forth in the Quality Agreement.  
  
 EXCEPT FOR THE FOREGOING AND RPS' WARRANTY IN SECTION 4.3 BELOW, RPS MAKES  
 NO WARRANTY OR REPRESENTATION OF ANY KIND, EITHER EXPRESS OR IMPLIED,  
 INCLUDING, BUT NOT LIMITED TO, THE WARRANTIES OF MERCHANTABILITY AND  
 FITNESS FOR A PARTICULAR PURPOSE AND ANY REPRESENTATION OR ANY WARRANTY  
 THAT USE OF THE PROCESS FOR MANUFACTURE OF THE COMPOUND OR USE OR SALE OF  
 THE COMPOUND, WHETHER OR NOT SUCH COMPOUND IS MADE BY THE PROCESS FOR  
 MANUFACTURE OF THE COMPOUND, WILL NOT INFRINGE THE CLAIMS UNDER ANY PATENT  
 OR OTHER INTELLECTUAL PROPERTY RIGHT OF ANY THIRD PARTY.  
  
 (b) Limitations  
  
 RPS'S SOLE LIABILITY AND CTI'S EXCLUSIVE REMEDY IN THE CASE OF COMPOUND  
 DELIVERED HEREUNDER TO CTI THAT DOES NOT MEET THE SPECIFICATIONS SHALL BE,  
 AT CTI'S OPTION, FOR RPS TO USE COMMERCIALLY REASONABLE EFFORTS TO REPLACE  
 THE DEFECTIVE COMPOUND WITH COMPOUND THAT CONFORMS WITH THE SPECIFICATIONS  
 OR FOR RPS TO REFUND THE PURCHASE PRICE PAID TO RPS FOR SUCH  
 NON-CONFORMING COMPOUND. ALL CLAIMS CONCERNING COMPOUND DELIVERED TO CTI  
 HEREUNDER MUST BE MADE IN WRITING RECEIVED BY RPS WITHIN THE EARLIER OF  
 (A) NINETY (90) DAYS AFTER THE SUPPLY CHAIN INTRODUCTION DATE AND (B)  
 TWELVE (12) MONTHS AFTER THE DATE OF DELIVERY TO CTI OR ITS DESIGNATED  
 AGENT, FAILING WHICH CLAIM NOTICE SUCH COMPOUND SHALL BE DEEMED ACCEPTED  
 BY CTI "AS IS" AND ALL CLAIMS BY CTI IN RELATION TO SUCH DELIVERED  
 COMPOUND SHALL BE DEEMED WAIVED, EXCEPT IN RESPECT TO DEFECTS IN COMPOUND  
 QUALITY THAT COULD NOT HAVE BEEN DISCOVERED BY CTI PRIOR TO THE EXPIRATION  
 OF THE EARLIER TO OCCUR OF SUCH NINETY (90) DAY AND TWELVE (12) MONTH  
 PERIODS THROUGH THE EXERCISE OF COMMERCIAL DILIGENCE REQUIRED OF  
 MANUFACTURERS OF DRUG END PRODUCTS FOR HUMAN CONSUMPTION FOR SALE IN THE  
 UNITED STATES AND THE EUROPEAN UNION.  
  
 IN NO EVENT SHALL EITHER RPS OR CTI BE LIABLE TO THE OTHER FOR INDIRECT,  
 SPECIAL, CONSEQUENTIAL (INCLUDING WITHOUT LIMITATION LOST PROFITS UNDER  
 SEC. 2-715 OF THE UNIFORM COMMERCIAL CODE), PUNITIVE OR INCIDENTAL DAMAGES  
 IN ANY WAY ASSOCIATED WITH THIS AGREEMENT, REGARDLESS OF THE FORM OR BASIS  
 OF ANY CLAIM OR ACTION.  
  
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 NOTWITHSTANDING ANYTHING TO THE CONTRARY HEREIN CONTAINED, THE FOREGOING  
 LIMITATIONS IN THIS SECTION 4.1(B) (I) DO NOT APPLY TO THE OBLIGATIONS OF  
 THE PARTIES CONTAINED IN SECTION 9 (INDEMNIFICATION) OF THIS AGREEMENT,  
 EXCEPT THAT RPS SHALL HAVE NO LIABILITY WHATSOEVER UNDER SECTION 9  
 RELATING TO ANY COMPOUND CONCERNING WHICH CTI HAS WAIVED ITS CLAIMS IN  
 THIS SECTION 4.1(B), AND (II) RELIEVE RPS OF ANY LIABILITY UNDER SECTION 5  
 RELATING TO ANY COMPOUND CONCERNING WHICH CTI HAS WAIVED ITS CLAIMS IN  
 THIS SECTION 4.1(B).  
  
4.2 CTI Use and Non-Infringement Warranty and Covenant  
  
 CTI represents and warrants that it is entering into this Agreement solely  
 to obtain Compound for use by CTI in the manufacturing of Drug Products,  
 and it shall at all times comply with all applicable laws and regulations  
 relating to its activities under this Agreement, and its transportation,  
 export, handling, storage, marketing, sale, and distribution, or any other  
 use of the Compound or any Drug Products. Without limiting the foregoing,  
 in no event will CTI sell any Compound or Drug Product to any Third Party  
 for human consumption prior to the completion of the Validation Report, as  
 contemplated herein. In addition, CTI acknowledges that it has disclosed  
 the CTI Technology to RPS for use in making the Compound and in otherwise  
 performing RPS' obligations hereunder and that RPS will use the CTI  
 Technology for such purpose and CTI further represents and warrants that:  
 (i) CTI owns the CTI Technology and/or has the unencumbered right to  
 disclose the CTI Technology to RPS and to authorize use of the CTI  
 Technology by RPS for such purpose, and (ii) to the best knowledge of CTI  
 as of the Effective Date use of any CTI Technology by RPS in the  
 performance of its obligations hereunder, including without limitation  
 RPS' obligations to manufacture (including manufacture of any required  
 intermediate compounds) and sell the Compound, will not infringe the  
 patent rights or any other intellectual property rights of any Third  
 Party, except the rights of Xxxxxx Laboratories in the Abbott Technology,  
 as defined below, under which CTI has secured certain licenses from Xxxxxx  
 Laboratories and has secured the agreement of Xxxxxx Laboratories not to  
 assert such rights against CTI or third parties acting on behalf of CTI,  
 as set forth in the letter of January 28, 2005, from Xxxxxx Laboratories  
 to CTI (the "Abbott Letter"), a copy of which is attached hereto as Annex  
 14.  
  
 EXCEPT FOR THE FOREGOING, CTI MAKES NO WARRANTY OR REPRESENTATION OF ANY  
 KIND, EITHER EXPRESS OR IMPLIED, AND ALL SUCH WARRANTIES ARE EXPRESSLY  
 DISCLAIMED.  
  
4.3 Debarment Warranty  
  
 RPS warrants that it will not knowingly use in connection with the  
 services rendered under this Agreement in any capacity the services of any  
 person debarred under the U.S. Food, Drug & Cosmetic Act or any other  
 similar law or regulation governing drug manufacturing.  
  
4.4 Supply Chain Introduction Date Records  
  
 CTI will maintain, and will cause any of its designated agents to whom  
 Compound manufactured hereunder is delivered to maintain, accurate written  
 records evidencing  
  
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 the Supply Chain Manufacturing Date for all Compound delivered by RPS  
 hereunder, and CTI will provide RPS with copies of such records promptly  
 upon RPS' request.  
  
5.0 RECALLS AND SEIZURES  
  
 (a) Information to CTI and RPS  
  
 The Parties shall keep each other fully informed of any notification or  
 other information, whether received directly or indirectly, which might  
 affect the marketability, safety or effectiveness of the Compound or which  
 might result in Recall or Seizure of the Compound or Drug Products. CTI  
 will notify RPS of any Recall or Seizure that is likely to affect the  
 manufacture of the Compound as contemplated hereunder as soon CTI learns  
 of any such information. In the event of any Compound or Drug Product  
 Recall or Seizure, RPS will co-operate as reasonably required by CTI,  
 having regard to all applicable laws and regulations  
  
 (b) Recall/Seizure  
  
 In the event of any Compound or Drug Product Recall or Seizure arising  
 solely out of RPS' breach of this Agreement, or the negligence or willful  
 misconduct of RPS or its Affiliates, then RPS shall, at the election of  
 CTI, either (i) supply Compound, without charge to CTI, in an amount  
 sufficient to replace (x) the amount of the Compound recalled or seized  
 and (y) the amount of Compound contained in any recalled or seized Drug  
 Product, or (ii) refund to CTI, and/or give credit to CTI against  
 outstanding receivables due from CTI hereunder or receivables to become  
 due from CTI hereunder for purchases of Compound, in amounts equal to the  
 price paid by CTI for the volume of Compound affected by such Recall or  
 Seizure, plus all transportation costs and export and import duties not  
 recovered by CTI in respect of such recalled or seized Compound or Drug  
 Product; provided that RPS will have no liability under this Section 5(b)  
 in the case of any Recall or Seizure relating to Compound concerning which  
 CTI has waived its claims per Section 4.1(b) above.  
  
 (c) Recall/Seizure Costs and Expenses  
  
 In the event of any Recall or Seizure arising solely from RPS breach of  
 this Agreement or the negligence or willful misconduct of RPS or its  
 Affiliates, then, in addition to its obligations in Section 5(b) above,  
 RPS shall pay CTI's reasonable out-of-pocket expenses incurred in  
 connection with such Recall or Seizure. In the event of any Recall or  
 Seizure where there is comparative fault of the Parties, the cost and  
 expenses resulting from such Recall or Seizure shall be apportioned  
 between the Parties by mutual agreement based upon the percentage of  
 relative fault they bear to one another in respect thereof. All other  
 Recalls and Seizures involving the Compound and/or Drug Products and,  
 notwithstanding anything to the contrary contained in this Article 5, any  
 Recall or Seizure relating to Compound concerning which CTI has waived its  
 claims per Section 4.1(b) above, shall be the sole responsibility and  
 liability of CTI, including without limitation any Recalls or Seizures  
 caused by the fault of Third Parties, and CTI shall pay to RPS any  
 reasonable out-of-pocket expenses incurred by RPS in connection with such  
 Recall or Seizure. It is understood and agreed between the Parties that  
 the costs and expenses concerning which they must reimburse one another  
 under this Section 5 are deemed to be direct damages of the Party entitled  
 to such reimbursement.  
  
6.0 INDEPENDENT CONTRACTOR STATUS  
  
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6.1 Each of the Parties in performing this Agreement shall be and be deemed to  
 be acting as an independent contractor and not as the agent or employee of  
 the other. Neither RPS nor CTI shall have any authority whatsoever to act  
 as agent or representative of the other party nor any authority or power  
 to contract or create any obligation or liability on behalf of the other  
 party or otherwise bind any other party in any way for any purpose.  
  
7.0 CONFIDENTIALITY  
  
7.1 Each Party shall hold all Confidential Information received from the other  
 Party in strictest confidence and shall use the same level of care to  
 prevent any unauthorized use or disclosure of such Confidential  
 Information as it exercises in protecting its own information of similar  
 nature. A Party shall not disclose any Confidential Information received  
 from the other Party to any third party without the prior written consent  
 of the other Party and shall not use such Confidential Information for any  
 purposes other than the purposes of this Agreement.  
  
7.2 The Confidential Information shall be supplied to the Parties in written  
 form and shall be identified as being confidential and disclosed under the  
 provisions of this Agreement.  
  
7.3 Each Party shall have the right to disclose the Confidential Information  
 of the other Party only to those officers and employees of such receiving  
 Party who need to know it for the purposes of this Agreement. Such  
 disclosure is allowed only on condition that the persons to whom the  
 Confidential Information will be disclosed shall be, by law, contract or  
 other binding undertaking, under confidentiality obligations at least as  
 restrictive as those set out in this Agreement.  
  
7.4 The disclosing Party retains all rights to its Confidential Information.  
  
7.5 The confidentiality obligations of this Agreement shall not apply to:  
  
 a) Confidential Information which at the time of the disclosure is in  
 the public domain; or  
  
 b) Confidential Information which, after disclosure, becomes part of  
 the public domain otherwise than by breach of this Agreement; or  
  
 c) Confidential Information which can be established by reasonable and  
 competent proof to have already been in the receiving Party's  
 possession prior to disclosure and was not acquired, directly or  
 indirectly, from the disclosing Party; or  
  
 d) Confidential Information which a receiving Party shall receive from  
 a third party who has the legal right to disclose it and who would  
 by disclosure not breach, directly or indirectly, any  
 confidentiality obligation to either Party; or  
  
 e) Confidential Information which is released for disclosure by prior  
 written consent of the disclosing Party; or  
  
 f) Confidential Information which has been independently developed by a  
 Party hereto without the use or benefit of Confidential Information  
 received from the other Party; or  
  
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 g) Confidential Information which is required to be disclosed by law or  
 by order of court of competent jurisdiction, provided that due  
 advance notice is given to the other Party of such a requirement and  
 also such disclosure is then made only to the minimum extent so  
 required.  
  
7.6 The burden of proving that any of the above exceptions is applicable to a  
 Party to relieve it of its liability or obligations hereunder shall be  
 upon the Party claiming such exception(s).  
  
7.7 Notwithstanding anything to the contrary in this Agreement, each Party  
 acknowledges and agrees that the other Party may disclose the terms of  
 this Agreement, and may provide a copy of this Agreement or to include a  
 copy of this Agreement in its public filings with the U.S. Securities and  
 Exchange Commission, NASDAQ or any other party, if the disclosing Party,  
 in its sole discretion, believes such disclosure or filing is required by  
 applicable law or by any rule, requirement or regulation of any  
 governmental entity or regulatory authority, any stock exchange or NASDAQ.  
  
8.0 INTELLECTUAL PROPERTY RIGHTS  
  
8.1 (a) As used herein "Intellectual Work Product" means all inventions,  
 modifications, discoveries, improvements (including, without limitation,  
 process improvements and improvements in analytical methods), processes,  
 techniques, analytical methods, documentation, scientific and technical  
 data, drawings and other information) that is generated as a result of any  
 of the performance by RPS of its obligations hereunder. RPS reserves all  
 rights in and to all present and future documentation, scientific and  
 technical data, processes, test procedures and other information and  
 techniques that are owned, developed or licensed by RPS other than in the  
 performance of its obligations hereunder (the "RPS Technology"). Without  
 limiting the foregoing definition of "RPS Technology", it is expressly  
 understood and agreed that such term shall include any and all  
 intellectual property rights owned, developed or licensed by RPS relating  
 to the [\*\*]. CTI shall not have any rights in any of the RPS Technology,  
 except to the extent that RPS is required to license such RPS Technology  
 to CTI in accordance with the terms of Section 10.7 below.  
  
 (b) The Parties hereto understand and agree that no rights are being  
 conveyed to RPS (or any of its Affiliates) to use any CTI Technology (as  
 hereafter defined) for any purpose other than the sole purpose of  
 manufacturing the Compound for CTI in accordance with the terms of this  
 Agreement. As used herein, "CTI Technology" means all present and future  
 documentation, scientific and technical data, processes, test procedures,  
 information, techniques, technology, patents, patent rights, inventions  
 and other intellectual property rights that are owned, developed, or  
 licensed by CTI, including, without limitation, certain patents and  
 technology of Xxxxxx Laboratories for manufacturing the Compound and/or  
 manufacturing any starting or intermediate materials for use in making the  
 Compound (the "Abbott Technology") licensed by CTI.  
  
8.2 (a) RPS acknowledges that CTI shall be the sole and exclusive owner of all  
 Intellectual Work Product. In consideration of the covenants contained  
 herein, and for other good and valuable consideration set forth herewith,  
 RPS hereby assigns and transfers to CTI and its successors and assigns all  
 right, title and interest that RPS has or may later acquire in and to such  
 Intellectual Work Product under copyright, patent, trade secret and  
 trademark law. Such assignment includes the assignment of the entire  
 right, title and interest in and to all applications for letters patent  
 and any and all letters patent or patents in the United States of America  
 and  
  
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 all foreign countries which may be granted on and in connection with such  
 Intellectual Work Product.  
  
 (b) RPS agrees to cooperate with CTI so that CTI may enjoy to the fullest  
 extent the entire right, title and interest in and to the Intellectual  
 Work Product. In connection therewith, RPS agrees to execute, if  
 necessary, additional papers and documents and to take all actions  
 requested by CTI in order to (a) further evidence ownership of  
 Intellectual Work Product by CTI and its successors and assigns and (b)  
 allow CTI to procure, maintain and enforce all letters patent and  
 intellectual property rights to the Intellectual Work Product. CTI agrees  
 to reimburse RPS all reasonable costs in relation to the production of  
 such additional papers and documents.  
  
8.3 CTI hereby grants to RPS a non-exclusive, royalty-free, license to use any  
 and all CTI Technology provided by CTI to RPS in connection with this  
 Agreement and the Proposal Agreement for use by RPS in the performance of  
 its obligations under this Agreement. Except as specifically described in  
 this Agreement, no right, title, interest, or license in or to any  
 trademark, patent, copyright or service xxxx or symbol or any other  
 intellectual property right of a party is granted to the other party under  
 this Agreement. CTI hereby covenants and agrees to maintain at its sole  
 cost and expense the validity of the licenses referred to in the Abbott  
 Letter (the "Licenses") to the extent necessary for RPS to have valid and  
 enforceable rights at all times under the license granted by CTI under  
 this Section 8.3 to use the CTI Technology, including the Abbott  
 Technology, to manufacture, sell, and deliver Compound to CTI as  
 contemplated hereunder. In addition, CTI agrees to provide RPS with  
 written notification as soon as possible of any actual or prospective  
 termination of the Licenses for any reason.  
  
9.0 INDEMNIFICATION PROVISIONS; FORCE MAJEURE; ARBITRATION  
  
9.1 CTI will indemnify and hold harmless RPS, its affiliates, any present or  
 future parent or subsidiary of them, and their respective officers,  
 directors, employees, counsel, agents and affiliates (the "Indemnified RPS  
 Parties") against any and all losses, liabilities, damages, costs and  
 expenses incurred in defending against any litigation, commenced or  
 threatened, or any claim (including, but not limited to, reasonable  
 attorney fees and any and all reasonable expenses), and all amounts  
 reasonably paid (with RPS' prior written consent) in settlement of any  
 claim or litigation, commenced or threatened ("Losses"), to the extent  
 such Losses arise out of (i) the breach of any of CTI's representations,  
 warranties, or covenants contained in this Agreement, (ii) any negligent  
 act or omission or willful misconduct of CTI in relation to this  
 Agreement, (iii) the storage, handling, transportation of the Compound by  
 CTI or the use by CTI of the Compound in the manufacture of Drug Products,  
 (iv) Recalls or Seizures for which CTI is responsible under Article 5  
 hereof, (v) the promotion, marketing, distribution and sale, whether  
 directly or through distributors, of the Compound purchased hereunder or  
 any Drug Product, or (vi) any claim that (a) making, using, importing,  
 offering for sale, or selling the Compound, or (b) making or using any  
 starting or intermediate material that is required to be made and/or used  
 in order to make the Compound in accordance with the CTI Technology, or  
 (c) using the CTI Technology to make the Compound infringes the  
 intellectual property rights of any Third Party; PROVIDED, HOWEVER, THAT  
 IN NO EVENT SHALL CTI HAVE ANY OBLIGATION TO INDEMNIFY OR HOLD HARMLESS  
 ANY OF THE INDEMNIFIED RPS PARTIES TO THE EXTENT THAT RPS OR ANY  
 INDEMNIFIED RPS PARTY, IS IN ANY WAY RESPONSIBLE BY NEGLIGENT OR WILLFUL  
 ACT FOR SUCH LOSSES (EXCLUDING, FOR THE AVOIDANCE OF DOUBT,  
  
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 COMPOUND CONCERNING WHICH CTI HAS WAIVED ITS CLAIMS PER SECTION 4.1(B)  
 ABOVE).  
  
9.2 RPS will indemnify and hold harmless CTI, its affiliates, any present or  
 future parent or subsidiary of any of them, and their respective officers,  
 directors, employees, counsel, agents and affiliates (the "Indemnified CTI  
 Parties") against any and all losses liabilities, damages, costs and  
 expenses incurred in defending against any litigation, commenced or  
 threatened, or any claim (including, but not limited to, reasonable  
 attorney fees and any and all reasonable expenses), and all amounts  
 reasonably paid (with CTI' prior written consent) in settlement of any  
 claim or litigation, commenced or threatened ("Losses"), to the extent  
 such Losses arise out of (i) the breach of any of RPS' representations,  
 warranties, or covenants contained in this Agreement, (ii) any negligent  
 act or omission or willful misconduct of RPS in relation to this  
 Agreement, (iii) the storage, handling or use of any Raw Materials or  
 intermediates used in the manufacture of the Compound hereunder or any  
 storage or handling of the Compound, (iv) Recalls or Seizures for which  
 RPS is responsible under Article 5 hereof; PROVIDED, HOWEVER, THAT, IN  
 ADDITION TO THE EXCLUSION OF LIABILITY FOR RPS IN INDEMNITY CONCERNING  
 COMPOUND FOR WHICH CTI HAS WAIVED ITS CLAIMS PER SECTION 4.1(B) ABOVE, IN  
 NO EVENT SHALL RPS HAVE ANY OBLIGATION TO INDEMNIFY OR HOLD HARMLESS ANY  
 OF THE INDEMNIFIED CTI PARTIES TO THE EXTENT THAT CTI OR ANY INDEMNIFIED  
 CTI PARTY, IS IN ANY WAY RESPONSIBLE BY NEGLIGENT OR WILLFUL ACT FOR SUCH  
 LOSSES.  
  
9.3 Conditions of Indemnification  
  
 With respect to any indemnification obligations of either Party to the  
 other Party under this Agreement, the following conditions must be met for  
 such indemnification obligations to become applicable:  
  
 a) The indemnified Party shall notify the indemnifying Party promptly in  
 writing of any claim which may give rise to an obligation on the part of  
 the indemnifying Party hereunder;  
  
 b) The indemnifying party shall be allowed to timely undertake the sole  
 control of the defense of any such action and claim, including all  
 negotiations for the settlement, or compromise of such claim or action at  
 its sole expense; provided that in no event will the indemnifying Party  
 enter into any settlement or compromise of an indemnified claim without  
 the indemnified Party's prior written consent;  
  
 c) The indemnified Party shall at its sole expense render reasonable  
 assistance, information, cooperation and authority to permit the  
 indemnifying Party to defend such action.  
  
9.4 Force Majeure  
  
 Neither party shall be liable to the other for damages of any sort arising  
 from any delay or default in such party's performance hereunder caused by  
 events or conditions beyond such party's reasonable control and which such  
 party is unable through the exercise of due diligence to prevent,  
 including, but not limited to, acts of nature, government action, war,  
 civil commotion, destruction of public utilities or synthesis or  
 production facilities or materials by earthquake, explosion, fire, flood  
 or storm ("Force Majeure"). Each party agrees promptly to notify the other  
 party of any event of Force Majeure and to employ all reasonable efforts  
 toward prompt resumption of its performance when possible. If Force  
 Majeure prevents performance by one party of its obligations hereunder in  
 whole or in part for more than thirty (30) days, the other party shall  
 have the right to terminate any remaining  
  
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 Phase or Phases of the Project or the remainder of this Agreement upon  
 written notice to the non-performing party. In no event shall Force  
 Majeure affecting RPS obligate RPS to procure supplies of Product for CTI  
 from alternate suppliers, or to allocate its available manufacturing  
 resources and product supplies in other than a fair and reasonable manner  
 giving equal consideration to the internal manufacturing needs of RPS and  
 its Affiliates and to the needs of CTI and RPS' other regular customers  
 whether or not they are then under contract. However, if an event of Force  
 Majeure prevents RPS from providing Compound to CTI, RPS shall provide any  
 reasonable assistance required by CTI in establishing a new supplier of  
 the Compound, at CTI's sole cost and expense.  
  
 Notwithstanding anything to the contrary in the immediately preceding  
 paragraph of this Section 9.4, it is understood and agreed that any action  
 by the British Health and Safety Executive, or other governmental body  
 having jurisdiction, not brought about due to the negligence or willful  
 misconduct of RPS and that requires RPS, in its reasonable judgment, to  
 curtail, delay, suspend or cease the manufacturing of the Compound due to  
 health, safety or environmental issues associated with the use of CTI  
 Technology to manufacture Compound at the Manufacturing Site will be  
 deemed to be an event of Force Majeure within the terms of such preceding  
 paragraph.  
  
9.5 Arbitration  
  
 Any controversy or claim arising under this Agreement, or the breach  
 thereof which cannot be settled amicably within a period of two (2) months  
 after the date of notification, by registered mail, of the controversy or  
 claim by one Party to another shall be settled exclusively by arbitration  
 in Boston, Massachusetts, in accordance with the Rules of Conciliation and  
 Arbitration of the International Chamber of Commerce ("ICC") then in  
 effect, such arbitration to occur before a single arbitrator mutually  
 agreeable to both parties; provided however that, in urgent situations in  
 which time is of the essence to obtain proper remedies, the rights of the  
 Parties to bring claims or actions in Courts of law shall remain  
 unimpaired. The arbitrator shall render his/her decision within thirty  
 (30) days of the completion of the hearing, and may, in his/her  
 discretion, award costs and expenses (including attorneys' fees) to the  
 winning Party. The judgment and award of the arbitrator shall be final and  
 binding and may be entered in any court having jurisdiction thereof, or  
 application may be made to such court for judicial acceptance of any award  
 or an order of enforcement, as the case may be. Under no circumstances  
 shall the arbitrator be authorized to award punitive or multiple damages,  
 including but not limited to federal or state statutes permitting multiple  
 or punitive damage awards, except to the extent that a party entitled to  
 indemnification under Section 9 above is finally determined to be liable  
 to a Third Party for such damages and the arbitrator awards recovery of  
 such damages to the indemnified party under the terms of Section 9. Any  
 purported award of punitive or multiple damages or of other damages not  
 permitted under this Agreement shall be beyond the arbitrator's authority,  
 void, and unenforceable. RPS and CTI shall share equally the fees and  
 expenses of the arbitrator. It is further understood between the parties  
 that both the arbitration proceeding and the arbitration award will be  
 confidential and kept confidential by the arbitrator, the ICC and the  
 Parties, except for such disclosure as may be required to comply with  
 legally required corporate disclosure and disclosure to shareholders,  
 investors, alliance partners, accountants, attorneys and financial  
 advisors of the disclosing party.  
  
10.0 TERM AND TERMINATION  
  
10.1 This Agreement shall enter into force as of the Effective Date of the  
 Agreement and, unless earlier terminated, shall continue in full force and  
 effect through December 31, 2009, and this Agreement shall automatically  
 renew for successive Contract Years  
  
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 thereafter (collectively the "Term") at the Compound price last in effect  
 in the immediately preceding Contract Year, unless RPS provides CTI with  
 not less than eighteen (18) months prior written notice of cancellation of  
 this Agreement.  
  
10.2 CTI shall have the right to terminate this Agreement for any reason upon  
 twelve (12) months advance written notice to RPS, provided that CTI may  
 not terminate this Agreement prior to January 1, 2008 through the exercise  
 of its termination right under this Section 10.2 for the purpose of  
 replacing RPS as the exclusive supplier of Compound to CTI and its  
 Affiliates during the Initial Delivery Period and/or as the supplier of  
 the Annual Contract Volume to CTI and its Affiliates through December 31,  
 2007.  
  
10.3 Sections 4, 5, 8, 9, and 13 shall survive any termination of this  
 Agreement. The obligations under Section 7 of this Agreement shall  
 terminate five (5) years after the termination of this Agreement.  
  
10.4 Either Party shall have the right, without prejudice to any other rights  
 or remedies available to it, to terminate this Agreement for cause with  
 immediate effect by written notice to the other Party in any of the  
 following events:  
  
 a) The other Party defaults in the performance of any of its material  
 obligations under this Agreement and such default continues  
 unremedied for thirty (30) days from the date that written notice of  
 such default is delivered to the defaulting Party, except that such  
 cure period shall (i) be limited to ten (10) business days from the  
 date of delivery of such notice in the case of a payment default and  
 (ii) not be available to CTI in the case of a breach by CTI of any  
 of its covenant to maintain the Licenses contained in Section 8.3  
 here above;  
  
 b) The other Party intentionally makes (or is discovered to have  
 intentionally made) any material false representations in connection  
 with this Agreement;  
  
 c) Any of the representatives of the Parties engages in (or is  
 discovered to have engaged in) fraudulent, criminal or negligent  
 conduct in connection with this Agreement;  
  
 d) The other Party files a petition in bankruptcy, has a petition in  
 bankruptcy involuntarily filed against it, is adjudicated a  
 bankrupt, files for reorganization, is placed in liquidation, makes  
 a general assignment for the benefit of its creditors (other than a  
 solvent financial reorganization), becomes insolvent or is otherwise  
 unable to fulfill its payment obligations generally as they become  
 due.  
  
10.5 CTI may also terminate this Agreement at any time upon six (6) months  
 prior written notice to RPS in the event that CTI terminates its plans to  
 commercialize the Compound for all therapeutic indications, whether human  
 or veterinary.  
  
10.6 Notwithstanding anything to the contrary herein contained, the Parties may  
 terminate this Agreement if the Parties, together, determine that one or  
 more of the Validations concerning the Compound as required under  
 applicable Governmental Approvals, including without limitation the  
 repeatability of the manufacturing process and other requirements under  
 applicable cGMP, is not feasible.  
  
10.7 Consequences of Termination  
  
 19  
  
  
 (a) Promptly after notice of termination from either Party under any  
 provision of Section 10.5 and 10.6, CTI and RPS shall meet to  
 discuss and agree in writing upon a manufacturing wind down plan for  
 this Agreement ("Wind Down Plan"). Such Wind Down Plan shall  
 include, among other things, a mutually agreeable quantity of  
 Compound that RPS will continue to manufacture during the  
 termination period, if any; provided however,that  
 in the event of a termination by CTI under Section 10.5, at a  
 minimum, RPS shall be entitled to complete the manufacturing of all  
 Compound work-in-progress at the time CTI's notice of termination is  
 received by RPS. In the case of termination by CTI under Section  
 10.2 or by RPS under Section 10.1 the Parties shall also meet to  
 agree on a Wind Down Plan, provided, however, that each of the  
 Parties shall be expected to carry out their  
 respective Compound manufacturing, sale, and purchase obligations  
 hereunder through the applicable termination date without any  
 reduction in the volume of Compound required to be so manufactured,  
 sold and purchased.  
  
 (b) In the event of a termination by CTI under Section 10.5, CTI will  
 pay to RPS the price applicable hereunder for all Compound  
 manufactured by RPS hereunder prior to receipt of CTI's termination  
 notice (including without limitation all validation batches and  
 [\*\*]), for all additional Compound that has been agreed by the  
 Parties in the Wind Down Plan to be made during the termination  
 period, if any, and, if none, then CTI will purchase all Compound  
 manufactured from work-in-progress at the time CTI's termination  
 notice is received by RPS at RPS's cost; provided, however, that CTI  
 shall not be obliged to purchase any minimum additional volume of  
 Compound to be produced during such termination period as might be  
 required under the terms of Section 2.1(b) unless CTI wishes to do  
 so in its sole discretion;  
  
 (c) In the event of a termination by CTI under Sections 10.2 or 10.5,  
 CTI will reimburse RPS for its cost of unused Raw Materials and  
 intermediates to the extent that RPS is not able to cancel an order  
 for or resell any of such Raw Materials and intermediates to Third  
 Parties. Upon the request of CTI, RPS shall deliver all such Raw  
 Materials and intermediates to a location indicated by CTI, at CTI's  
 sole cost and expense;  
  
 (d) In the event of a termination by CTI under Sections 10.2 or 10.5,  
 CTI will reimburse RPS for all other out-of-pocket costs and  
 expenses reasonably incurred by RPS due to the early termination of  
 this Agreement by CTI, including without limitation any cost  
 associated with the cancellation of contracts for supplies,  
 materials and services purchased by RPS in reliance upon this  
 Agreement running for its full Term and will reimburse RPS for  
 [\*\*]-percent ([\*\*]%), or such lesser percentage as mutually agreed  
 at the time (taking into account, among other things, the amount of  
 Compound purchased by CTI as of the date of the notice of  
 termination and the extent of the capital work already completed),  
 of (i) any costs and expenses incurred by RPS in connection with the  
 work described in the Manufacturing Site Capital Project and (ii)  
 the reasonable out-of-pocket cost of [\*\*] any such capital  
 improvements that RPS must undertake; provided, however, that the  
 combined total of (i) and (ii) shall not exceed US$ [\*\*], and that  
 CTI will have no liability to RPS for such costs in (i) or (ii) if  
 CTI purchases no less than [\*\*] metric tons of Compound hereunder at  
 a price of no less than the Initial Delivery Period price of  
 US$[\*\*] per kilo;  
  
 (e) At CTI's request, RPS shall provide to CTI all Intellectual Work  
 Product documentation and information that is in RPS' possession,  
 including, but not limited to, identification of suppliers of Raw  
 Materials and instructions for the synthesis, processing and  
 analysis of the Compound and shall provide such reasonable  
 assistance needed by CTI to transfer the production of the Compound  
 or any Raw Material to a Third Party ("Technology Transfer");  
  
 20  
  
  
 (f) In the event that CTI terminates this Agreement under Sections 10.2  
 or the Parties terminate this Agreement under Section 10.6, CTI  
 shall reimburse RPS for any reasonable out-of-pocket costs and  
 expenses RPS incurs for the Technology Transfer, including without  
 limitation FTE expenses at RPS at the rates then charged by RPS;  
  
 (g) In the event that RPS terminates this agreement under Section 10.1,  
 CTI shall not be obligated to reimburse RPS for any costs or  
 expenses, including FTE costs, that RPS expends for any Technology  
 Transfer;  
  
 (h) RPS shall grant a fully paid-up, royalty-free, worldwide, perpetual  
 non-exclusive license (with the right to sub-license) to any RPS  
 Technology concerning the manufacturing of the raw material 2ABT;  
 and  
  
 (i) In the event of the termination of this Agreement under Section  
 10.6, CTI's sole liability shall be for the payment to RPS of (i)  
 the purchase price for the validation batches of Compound produced  
 by RPS per Section 2.1(a) above and (ii) the purchase price for any  
 commercial scale Compound then produced by RPS under Section 2.1(b)  
 above (including without limitation all validation batches and  
 [\*\*]).  
  
 (j) It is understood and agreed between the Parties that the types of  
 costs and expenses that CTI must reimburse to RPS as described in  
 this Section 10.7 are deemed to be direct damages of RPS, and  
 nothing in this Section 10.7 shall limit RPS' right to recover such  
 costs and expenses as direct damages from CTI in the event of a  
 breach of this Agreement by CTI, including without limitation (i)  
 any costs and expenses incurred by RPS in connection with the work  
 described in the Manufacturing Site Capital Project and (ii) the  
 reasonable out-of-pocket cost of [\*\*] any such capital improvements  
 that RPS must undertake; provided, however, that the combined total  
 of (i) and (ii) shall not exceed the lesser of [\*\*]-percent ([\*\*]%)  
 of such costs and expenses or US$ [\*\*], and that CTI will have no  
 liability to RPS for such costs in (i) or (ii) if CTI purchases no  
 less than [\*\*] metric tons of Compound hereunder at a price of no  
 less than the Initial Delivery Period price of US$[\*\*] per kilo.  
  
11.0 CRITICAL INTERFACES AND NOTICES  
  
11.1 All notices referred to herein shall be sent by prepaid registered mail,  
 by recognized courier service (such as Federal Express), or by facsimile  
 and shall be deemed delivered if sent to the addresses of the respective  
 Parties hereinbelow indicated, or such other address as is furnished by  
 such notice to the other Party.  
  
 Notices to RPS shall be made to:  
  
 RHODIA PHARMA SOLUTIONS LTD.  
 Dudley, Xxxxxxxxxxx  
 Xxxxxxxxxxxxxx XX00 0XX  
 Xxxxxxx  
 Attn: Xxxxxxxx Xxxx  
 Fax: 000 00 000 000 0000  
 Phone: 000 00 000 000 0000  
 e-mail: xxxxxxxx.xxxx@xx.xxxxxx.xxx  
  
 with a copy to:  
  
 RHODIA PHARMA SOLUTIONS INC.  
 000 Xxxxxxxx Xxxxxx Xxxx  
 Xxxxxxxx, XX 00000-0000  
  
 21  
  
  
 Attn: Xxxx Xxxxxxx  
 Fax: 919/000-0000  
 Phone: 919/000-0000  
 e-mail: xxxx.xxxxxx@xx.xxxxxx.xxx  
  
 Notices and invoices to CTI shall be made to:  
  
 CRITICAL THERAPEUTICS, INC.  
 00 Xxxxxxxx Xxxxxx  
 Xxxxxxxxx, XX 00000  
 XXX  
 Attn: Chief Financial Officer  
 Fax: 000-000-0000  
 Phone: 000-000-0000  
  
11.2 Status Updates  
  
 RPS shall keep CTI regularly informed of the status and progress of all  
 Phase 1 and 2 work through regular telephone or e-mail updates, [\*\*] and  
 through written summaries.  
  
11.3 Contact Procedures  
  
 The following individuals shall serve as initial points of contact at RPS  
 and CTI with respect to any questions or occurrences that may arise with  
 respect to the Agreement and the work conducted hereunder:  
  
 RPS CONTACTS:  
  
 Technical Matters: Xxx Xxxxxxx  
  
 Payment or Financial Matters: Xxxxx Xxxxxx  
  
 Business Matters: Xxxx Xxxxxxx/Xxxxxxxx Xxxx  
  
 Contract Matters: Xxxxxxx Xxxxxxx, Esq.  
  
 CTI CONTACTS:  
  
 Technical Matters: Xxxxxx Xxxxxxxxx  
  
 Payment or Financial Matters: Xxxxx Xxxxxx  
  
 Business Matters: Xxxxx Xxxxxxxxx  
  
 Contract Matters: Xxxxxxx X. Xxxxxxxx, Esq.  
  
11.4 Change Management  
  
 RPS will promptly notify CTI whenever there is a change in management or  
 key personnel connected with the work to be conducted by RPS hereunder.  
  
11.5 Complaint Procedures  
  
 Procedures to address any complaint related to the manufacturing of the  
 Compound are contained in the standard operating procedures (SOPs) for the  
 Manufacturing Site.  
  
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11.6 Responsibility for Regulatory Communications  
  
 (a) CTI will have responsibility for initial regulatory communication with  
 the FDA and other Governmental Authorities regarding the manufacture of  
 the Compound.  
  
 (b) RPS will have responsibility for providing back-up assistance and  
 support as requested by CTI in connection with communications with the FDA  
 and other Governmental Authorities regarding the manufacture of the  
 Compound.  
  
12.0 ASSIGNMENT  
  
12.1 This Agreement is deemed personal to CTI and RPS. Neither Party shall,  
 without prior written consent of the other Party, assign this Agreement or  
 any of its rights nor delegate any of its duties or obligations herein;  
 provided, however, that either party shall be entitled to assign its  
 rights under this Agreement to an Affiliate or in connection with the sale  
 of all or substantially all of its business and assets to which the  
 subject matter of this Agreement pertains without the prior consent of the  
 other party so long as the permitted assignee assumes in writing, in form  
 and substance reasonably satisfactory to the non-assigning party, all  
 obligations of the assigning party under this Agreement or the obligations  
 under the specific terms of this Agreement that are the subject of such an  
 assignment.  
  
13.0 MISCELLANEOUS  
  
13.1 Waivers  
  
 Failure of either Party at any time to require strict performance by the  
 other Party of any of the provisions of the Agreement shall in no way  
 affect the right thereafter to enforce the same, nor shall the waiver of  
 any term, provision, covenant or condition hereof be taken or held to be a  
 waiver of any subsequent breach hereof or as nullifying the effectiveness  
 of such term, provision, covenant or condition.  
  
13.2 Counterparts  
  
 This Agreement may be executed in two or more counterparts, which all  
 together shall constitute one instrument.  
  
13.3 Entire Agreement  
  
 This Agreement embodies the entire understanding of the Parties concerning  
 the manufacturing of the Compound from and after the Effective Date and  
 shall supersede all previous communications, representations, or  
 understandings, either oral or written, between the Parties relating to  
 that subject matter hereof; provided that it is expressly understood that  
 this Agreement shall not supersede the Proposal Agreement, and, in respect  
 of such Proposal Agreement: (a) this Agreement supplements the terms  
 thereof and, in particular, shall govern the rights and obligations of the  
 parties to the extent that any validation batches of Compound that are the  
 subject of such Proposal Agreement become commercial batches of Compound  
 after the completion of the requisite Validations hereunder, and (b) in  
 the event of any conflict between the terms of this Agreement and the  
 terms of such Proposal Agreement, the terms of this Agreement shall  
 control.  
  
13.4 Amendments  
  
 No amendments or modifications of this Agreement will be deemed legally  
 binding unless made in writing and signed by both Parties hereto.  
  
13.5 Severability  
  
 In case one or more of the provisions contained in this Agreement shall,  
 for any reason, be held invalid, illegal, or unenforceable in any respect,  
 such invalidity,  
  
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 illegality or unenforceability shall not affect any other provision of  
 this Agreement, but this Agreement shall be construed by amending or  
 limiting such invalid, illegal, or unenforceable provision so as to  
 conform as closely as possible to the intent of the Parties or, if such is  
 not possible, by deleting such provision from this Agreement.  
  
13.6 Annexes  
  
 Should any internal discrepancies or variances occur between this  
 Agreement and its annexes, this Agreement shall take precedence except to  
 the extent that any provision in such annexes specifically cites the  
 provision in this Agreement over which it takes precedence.  
  
13.7 Governing Law  
  
 This Agreement is made under and shall be construed in accordance with the  
 laws of the State of Delaware, without regard to the conflicts of law  
 principles thereof. The Parties agree that the United Nations Convention  
 on Contracts for the International Sale of Goods (1980) shall not apply to  
 this Agreement.  
  
13.8 Headings  
  
 The headings in this Agreement may not be used in the interpretation of  
 any provisions hereof.  
  
13.9 Use of Names & Publicity  
  
 Except as expressly required pursuant to law, neither Party or its  
 Affiliates will without prior written consent of the other:  
  
 (a) Use in advertising, publicity, promotional premiums or otherwise,  
 any trade name, trademark, trade device, service xxxx, symbol, or  
 any abbreviation, contraction or simulation thereof owned by the  
 other Party,  
  
 (b) Represent, either directly or indirectly, that any product or  
 service of one Party is a product or service of the other, or  
  
 (c) In addition to any public announcements allowed under Section 7.7  
 above, issue or cause to be issued any press release or other  
 announcement or public communication with respect to this Agreement  
 or the transactions contemplated hereby and, in addition to  
 obtaining the other Party's prior consent, the other Party will be  
 consulted concerning the timing and content of such press release,  
 announcement or communication before the same is issued or  
 published.  
  
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 IN WITNESS WHEREOF, the Parties hereto through their authorized  
representatives have executed this Agreement as of the Effective Date.  
  
RHODIA PHARMA SOLUTIONS LTD.  
  
By: /s/ Xxxx Xxxxx  
 ----------------------------------  
  
Title: President  
  
Date: 2/8/05  
  
  
CRITICAL THERAPEUTICS, INC.  
  
By: /s/ Xxxxxx Xxxxxxxx  
 ----------------------------------  
  
Title: Chief Operating Officer  
  
Date: 2/8/05  
  
  
 25  
  
  
 ANNEX 1  
  
Rhodia Pharma Solutions Authorized: /s/ X. Xxxxxxxx  
 13-10-2004  
  
[\*\*] (micronised IR) Page 1 of 4  
  
METHOD OF ANALYSIS No: 6000721/S/2  
  
 First Issued: GB/SW  
 Revised & Re-issued LW/TMS  
  
 CHANGES SINCE PREVIOUS ISSUE  
  
 1. Updated following customer review.  
  
Written by: Checked by: Authorised by: Date of Issue: Review Date:  
/s/Xxx Xxxxxxx /s/Xxxx Xxxxx /s/X. Xxxxxxxx 12-10-2004 October 2006  
  
  
  
[LOGO] Authorised:  
  
QUALITY DEPARTMENT  
  
[\*\*] MICRONISED (IR) Page: 2 of 4  
  
SPECIFICATION No: [\*\*]  
  
1. Appearance  
  
 [\*\*]  
  
2. Identity by Infra Red Spectrum  
  
 The sample spectrum should compare to that of an authentic reference  
 standard.  
  
3. Specific Rotation  
  
[\*\*]  
  
4. Residue on Ignition  
  
[\*\*]  
  
5. Foreign matter 2% solution in methanol  
  
[\*\*]  
  
6. Clarity 2% Methanol  
  
[\*\*]  
  
7. Heavy Metals  
  
[\*\*]  
  
8. Colour 2% in Methanol  
  
[\*\*]  
  
9. Particle Size  
  
[\*\*]  
  
  
10. Tapped Density  
  
  
  
[LOGO] Authorised:  
  
QUALITY DEPARTMENT  
  
[\*\*] MICRONISED (IR) Page: 3 of 4  
  
SPECIFICATION No: [\*\*]  
  
[\*\*]  
  
11. Water Content  
  
[\*\*]  
  
12. Assay and Impurity (Identity)  
  
[\*\*]  
  
 Impurities: [\*\*]  
[\*\*]  
  
13. [\*\*]  
  
 [\*\*].  
  
14. Residual Solvents  
  
[\*\*]  
  
15. Crystal Form by XRD  
  
[\*\*]  
  
16. Salmonella  
  
[\*\*]  
  
17. E. Coli  
  
[\*\*]  
  
18. Aerobic Microbial Count  
  
[\*\*]  
  
19. Surface Area  
  
  
  
[LOGO] Authorised:  
  
QUALITY DEPARTMENT  
  
[\*\*] MICRONISED (IR) Page: 4 of 4  
  
SPECIFICATION No: [\*\*]  
  
[\*\*]  
  
20. Particle Size by laser diffraction  
  
[\*\*]  
  
  
  
Rhodia Pharma Solutions Authorized: /s/ X. Xxxxxxxx  
 13-10-2004  
  
[\*\*] (micronised IR) Page 1 of 25  
  
METHOD OF ANALYSIS No: [\*\*]  
 Version 3  
  
 First Issued: GB/SW  
 Revised & Re-issued GB/TMS  
 Revised & Re-issued LW/TMS  
  
 CHANGES SINCE PREVIOUS ISSUE  
  
 1. Updated following customer review.  
  
Written by: Checked by: Authorised by: Date of Issue: Review Date:  
/s/Xxx Xxxxxxx /s/Xxxx Xxxxx /s/X. Xxxxxxxx 12-10-2004 October 2006  
  
  
  
[LOGO] Authorized:  
  
[\*\*] (MICRONISED IR) Page 2 of 19  
  
METHOD OF ANALYSIS No: [\*\*]Version 3  
  
NOTE THE REFERENCES TO SOP'S CONTAINED WITHIN THE TEXT IN THIS METHOD OF  
ANALYSIS, ARE SPECIFIC TO THE QC LABORATORY RHODIA PHARMA SOLUTIONS XXXXX. OTHER  
LABORATORIES USING THIS METHOD SHOULD REFER TO THEIR OWN RELEVANT PROCEDURES  
  
1. APPEARANCE  
  
 See relevant SOP "use of the G210 colour matching cabinet"  
  
 View the appearance of the sample against a white background noting the  
 presence of any visible impurities.  
  
2. IDENTITY BY IR  
  
 See relevant SOP " use of the XXXXXX-XXXXX RX II spectrum FTIR" and "Use  
 of KBr disks"  
  
 Prepare a KBr disc of the sample as per the SOP. Scan the spectrum between  
 4000 cm(-1) and 400 cm(-1). Alternatively scan a neat sample between  
 4000cm(-1) and 400cm(-1) using a diamond ATR accessory. Compare the  
 spectrum to that of an authentic reference standard.  
  
3. SPECIFIC ROTATION  
  
 See relevant SOP "Use of the Polaar 2001 polarimeter".  
  
3.1 Procedure  
  
 NOTE: Procedure must be performed at 25 degrees C.  
  
 Weigh 100mg of sample into a 10ml volumetric flask, dissolve and dilute to  
 volume with methanol, transfer this solution into a 1dm micropolarimeter  
 tube and determine the angular rotation of the solution. Carry out a blank  
 determination using methanol and correct the sample readings accordingly.  
  
3.2 Calculation  
  
  
   
Specific rotation = (sample rotation degrees - blank rotation degrees) x 100  
 ------------------------------------------------------- x 100  
 1(dm) x (100 - moisture) x (sample weight g/100ml)  
  
  
  
  
[LOGO] Authorized:  
  
[\*\*] (MICRONISED IR) Page 3 of 19  
  
METHOD OF ANALYSIS No: [\*\*]Version 3  
  
4. RESIDUE ON IGNITION  
  
 See relevant SOP "Use of the muffle furnace".  
  
4.1 Procedure  
  
 Pre-treat a clean porcelain crucible with sulphuric acid at 600 degrees C  
 + or - 25 degrees C overnight, allow to cool and record the weight.  
 Accurately weigh 1-2g of sample into the crucible. Heat gently until  
 thoroughly charred, do not allow the sample to ignite into flames. Moisten  
 the residue with 1ml of sulphuric acid and heat gently until no white  
 fumes are produced. Ignite at 600 degrees C + or - 25 degrees C in a  
 muffle furnace until all of the carbon is consumed. Allow the crucible to  
 cool for 3 minutes then place into a dessicator and allow to cool to room  
 temperature, reweigh and record the weight.  
  
 Note: the time taken to cool to room temperature should approximate that  
 of the cooling time prior to analysis (approximately 45 minutes) although  
 this will increase if more than one crucible has to be cooled at the same  
 time. Report the result to 1 decimal place.  
  
4.2 Calculation  
  
 % residue on ignition = weight of residue (g) x 100  
 ----------------------------  
 Weight of sample (g)  
  
5. FOREIGN MATTER 2% SOLUTION IN METHANOL  
  
 Dissolve 0.2g of sample in 10ml of methanol and observe the solution for  
 foreign matter.  
  
6. CLARITY 2% METHANOL  
  
6.1 Solution Preparations  
  
6.1.1 Hydrazine Sulphate  
  
  
  
[LOGO] Authorized:  
  
[\*\*] (MICRONISED IR) Page 4 of 19  
  
METHOD OF ANALYSIS No: [\*\*]Version 3  
  
 Dissolve 1.0g of hydrazine sulphate R in 100ml of water, allow to stand  
 for 4 to 6 hours.  
  
6.1.2 Hexamethylenetetramine Solution  
  
 Dissolve 2.5g of hexamethylenetetramine R in 25.0ml of water in a 100ml  
 glass stoppered flask.  
  
6.1.3 Primary Opalescent Suspension  
  
 To the hexamethylenetetramine solution prepared as per 6.1.2 add 25ml of  
 the hydrazine sulphate solution prepared as per 6.1.1. Mix and allow to  
 stand for 24 hours. This has an expiry of 2 months if kept in a glass  
 container free from surface defects. The suspension must not adhere to the  
 glass and must be mixed well before use.  
  
6.1.4 Opalescence Standards  
  
 Dilute 15ml of primary opalescent suspension prepared as per 6.1.3 to  
 1000ml with water. This has an expiry of 24 hours. Pipette 5ml and 10ml of  
 the opalescence standard suspension into two separate 100ml volumetric  
 flasks and dilute to volume with water. Fill two 50ml colour comparison  
 tubes with each of the standards. These are reference suspensions 1 and 2  
 respectively.  
  
6.2 Sample Preparation  
  
 Weigh 2g of sample into a 100ml volumetric flask, dissolve and dilute to  
 volume with methanol. Retain this sample for colour test.  
  
6.3 Blank Preparation  
  
 Fill a 50ml colour comparison tube to the xxxx with methanol.  
  
6.4 Procedure  
  
 View the tubes in diffused daylight 5 mins after preparation. View  
 vertically against a black background such that the blank, reference  
 suspension 1 and reference suspension 2 can be easily distinguished from  
 one another.  
  
  
  
[LOGO] Authorized:  
  
[\*\*] (MICRONISED IR) Page 5 of 19  
  
METHOD OF ANALYSIS No: [\*\*]Version 3  
  
 A liquid is considered clear if its clarity is the same as the solvent  
 used, or if its opalescence is not more pronounced than that of  
 opalescence reference suspension 1 when examined under the conditions  
 explained above.  
  
7. HEAVY METALS  
  
7.1 Reagent Preparation  
  
7.1. Lead Nitrate Solution  
  
 To 100ml of water add 1ml of nitric acid and 159.8mg of lead nitrate.  
 Dissolve and dilute with water to 1000ml (prepare and store in glass  
 containers).  
  
7.1.2 Standard Lead Solution  
  
 Dilute 10.0ml of lead nitrate stock solution to 100.0ml with water.  
  
7.1.3 pH 3.5 acetate buffer  
  
 Dissolve 25.0g of ammonium acetate in 25ml of water, add 38.0ml of 6M  
 hydrochloric acid, adjust the pH to 3.5 using 6M hydrochloric acid or 6M  
 ammonium hydroxide. Dilute with water to 100ml and dissolve.  
  
7.1.4 Thioacetamide TS  
  
 Dissolve 4g of thioacetamide in 100ml of deionised water.  
  
7.1.5 1.0M Sodium Hydroxide  
  
 Prepare from "convols" or other material Available from chemical  
suppliers.  
  
7.1.6 Glycerin base TS  
  
 To 200g of glycerol (glycerin) add deionised water and bring the weight to  
 235g. Add 140ml of 1.0M sodium hydroxide and 50ml of deionised water.  
  
7.1.7 Thioacetamide Glycerin Base TS  
  
  
  
[LOGO] Authorized:  
  
[\*\*] (MICRONISED IR) Page 6 of 19  
  
METHOD OF ANALYSIS No: [\*\*]Version 3  
  
 Mix 0.2ml of thioacetamide TS and 1ml of glycerin base TS and heat in a  
 boiling water bath for 20 seconds. Use the mixture immediately.  
  
7.1.8 1N (1M) acetic acid  
  
 Available preprepared from chemical suppliers  
  
7.1.9 6N (6M) Hydrochloric Acid  
  
 Dilute 51mls of conc hydrochloric acid to 100mls with deionised water.  
  
7.1.10 6N (6M) ammonium hydroxide  
  
 Dilute 33.6mls of "880" (Sp gr 0.88) ammonia to 100ml with deionised  
 water".  
  
7.2 Standard Preparation  
  
 Pipette 2ml of standard lead solution into a 50ml colour comparator tube  
 and dilute to 25ml with water. Adjust to between pH 3.0 and 4.0 with 1M  
 acetic acid or 6M ammonium hydroxide and, dilute to 40ml with water and  
 mix.  
  
7.3 Sample Preparation  
  
 Transfer 1g of sample into a crucible, wet sample with sulphuric acid and  
 ignite at low temperature until thoroughly charred.  
  
 Add 2ml of nitric acid and 5 drops of sulphuric acid to the crucible, heat  
 cautiously until white fumes are no longer produced. Ignite in a muffle  
 furnace at 600 degrees C +/- 25 degrees C until all the carbon is burned  
 off.  
  
 Cool in a dessicator, add 4ml of 6M hydrochloric acid, cover and digest on  
 a steam bath for 15 minutes, uncover and evaporate to dryness on a steam  
 bath.  
  
 Moisten with 1 drop of hydrochloric acid and add 10ml of hot water and  
 digest for 2 minutes.  
  
 Add 6M ammonium hydroxide dropwise, until the solution is just alkaline.  
 Dilute contents to 25ml with water, adjust the pH to between 3.0 and 4.0  
 with 1M acetic acid.  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
 If necessary, filter the solution, wash the crucible and the residue  
 with 10ml of water, pour the filtrate into a graduated 50ml colour  
 comparator tube, dilute to 40ml and mix well.  
  
7.4 Procedure  
  
 To each tube add 2ml of pH 3.5 acetate buffer and 1.2ml of  
 thioacetamide-glycerin base TS. Dilute each tube to 50mls mix and stand  
 for 2 minutes. View downwards over a white surface. The colour of the  
 sample solution should not be darker than that of the standard.  
  
8. COLOUR 2% IN METHANOL  
  
8.1 Solution Preparation  
  
 NOTE The reference colour standards B6 and BY6 can be purchased from  
 chemical suppliers and should be accompanied with certification, or  
 alternatively they can be made by the method shown below  
  
8.1.1 Yellow Solution  
  
 Dissolve 46g of ferric chloride R in about 900ml of a mixture of 25ml of  
 hydrochloric acid R and 975ml of water (0.3N hydrochloric acid) and dilute  
 to 1000ml with this mixture.  
  
 Place 10ml of solution, 15ml of water, 5ml hydrochloric acid R and 4g of  
 potassium iodide into a 250ml stoppered conical flask. Allow to stand in  
 the dark for 15 minutes and add 100ml of water.  
  
 Titrate the liberated iodine with standardised 0.1N sodium thiosulphate.  
 Towards the end of the titration when the solution is a light yellow  
 colour (about 16ml) add 0.5ml of starch indicator, continue the titration  
 until the blue colour has gone.  
  
 Calculate the concentration of the solution using the following equation:  
  
 FeCl(3)6H(2)0(mg/ml) = mls of Na(2)S(2)0(3) x N of Na(2)S(2)0(3) x 27.03mg  
  
 Adjust the concentration to within 10% of 45mg/ml by diluting with  
 0.3N hydrochloric acid using the calculation below.  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
 ml of 0.3N HCl per 100ml of yellow solution = 100 - 4500  
 --------------------  
 FeCl(3)6H(2)0 mg/ml  
  
8.1.2 Red Solution  
  
 Dissolve 60g of cobalt chloride R in about 900ml of a mixture of 25ml of  
 hydrochloric acid R and 975ml of water, dilute to a 1000ml with the same  
 mixture.  
  
 Place 5ml of the solution, 5ml of dilute hydrogen peroxide and 10ml of 30%  
 w/v sodium hydroxide into a 250ml ground glass stoppered flask.  
  
 Boil gently for 10 minutes, allow to cool and add 60ml of dilute sulphuric  
 acid and 2g of potassium iodide.  
  
 Close the flask and dissolve the precipitate by shaking gently.  
  
 Titrate the liberated iodine with standardised 0.1N sodium  
 thiosulphate. Towards the end of the titration (about 12ml) add 0.5ml of  
 starch indicator, continue the titration until the solution turns pink and  
 an end point has been reached.  
  
 Calculate the concentration of the solution using the following equation.  
  
 mg/ml Co(11)Cl(2) = ml of Na(2)S(2)0(3) x N of Na(2)S(2)0(3) x 23.79mg/0.5ml  
  
 Adjust the concentration to within 10% of 59.5mg of C0Cl(2)6H(2)0 per ml  
 by diluting with 0.3N hydrochloric acid using the calculation below:  
  
 ml of 0.3N hydrochloric acid per 100ml red solution = 100 - 5950  
 -----------------  
 mg/ml Co(11)Cl(2)  
  
8.1.3 Blue Solution  
  
 Dissolve 63g of copper sulphate R in about 900ml of a mixture of 25ml  
 hydrochloric acid and 975ml water, dilute to 1000ml with the mixture.  
  
  
  
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 Place 10ml of solution, 50ml of water, 12ml of dilute acetic acid R and 3g  
 of potassium iodide into a 250ml ground glass stoppered conical flask.  
  
 Titrate the liberated iodine with standardised 0.1N sodium thiosulphate.  
 Towards the end point (about 24ml) add 0.5ml of starch indicator, continue  
 titrating until the end point (disappearance of blue to a slight pale  
 xxxxx).  
  
 Calculate the concentration of the solution using the  
 calculation shown below:  
  
 mg/ml CuS0(4)5H(2)0 = mlNa(2)S(2)0(3) x N of Na(2)S(2)O(3) x 24.97mg  
  
 Adjust the solution to within 10% of 62.4mg/ml by diluting with 0.3N  
 hydrochloric acid using the calculation below:  
  
 ml/HCl = 100 - 6240  
 --------------------  
 mg/ml CuS0(4).5H(2)0  
  
8.1.4 0.3N Hydrochloric Acid  
  
 Thoroughly mix together 25ml of hydrochloric acid and 975ml of water.  
  
8.1.5 (0.1M) 0.1N Sodium Thiosulphate  
  
 Prepare from convols or other material available from chemical suppliers.  
  
8.1.6 Starch Indicator  
  
 0.5% prepared from 1% solution obtainable from chemical suppliers.  
  
8.1.7 Dilute Acetic Acid  
  
 Dilute 11.7ml of glacial acetic acid to 100ml with deionised water.  
  
8.1.8 Dilute Hydrogen Peroxide  
  
 Dilute 10.0ml of 30% hydrogen peroxide to 100ml with deionised water.  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
8.1.9 Dilute Sulphuric Acid  
  
 Dilute 5.5ml of sulphuric acid to 100mls with deionised water.  
  
8.1.10 30% w/v Sodium Hydroxide Solution  
  
 Dissolve 30g of sodium hydroxide in 100ml of deionised water.  
  
8.1.11 1% w/v Hydrochloric Acid  
  
 Dilute 1g of hydrochloric acid to 100ml with deionised water.  
  
8.2 Standard Solution B  
  
 Into a 200ml volumetric flask pipette 30ml of yellow primary solution,  
 30ml of red primary solution, 24ml of blue primary solution and 16ml of 1%  
 w/v hydrochloric acid.  
  
8.2.2 Standard Solution BY  
  
 Into a 200ml volumetric flask pipette 24ml of yellow primary solution,  
 10ml of red primary solution, 4ml of blue primary solution and 62ml of 1%  
 w/v hydrochloric acid.  
  
8.3 Reference Standard Solution Preparation  
  
 Note: Prepare reference standards immediately before use.  
  
8.3.1 Reference Standard B6  
  
 Into a 200ml volumetric flask pipette 5ml of standard solution B and 95ml  
 of 1% w/v hydrochloric acid.  
  
8.3.2 Reference Standard BY6  
  
 Into a 200ml volumetric flask pipette 5.0ml of standard solution BY and  
 mix with 95ml of 1% w/v hydrochloric acid.  
  
8.4 Sample Preparation  
  
 See sample preparation for colour test section 6.  
  
8.5 Procedure  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
 Transfer the B6, BY6 reference solutions and the sample solution to  
 identical xxxxxxx cylinders. The depth of the layer should be 40mm,  
 compare the solutions in diffused daylight, viewing vertically against a  
 white background.  
  
 The sample solution should not be more intensely coloured than the  
 reference solutions B6 or BY6.  
  
9. PARTICLE SIZE  
  
 See appropriate SOP "Use of Micron Air-jet sieve".  
  
9.1 Operating Conditions  
  
 Vacuum: not less than 12 inches of water.  
 Time: 120 seconds  
 Sieve: [\*\*]  
  
9.2 Procedure  
  
 Weigh 3 x 20g of sample.  
  
 Inspect the sieve for defects and cleanliness.  
  
 Assemble the sieve rubber gasket and cover and weigh.  
  
 Place assembled sieve on top of the vacuum unit and test the vacuum top  
 ensure it is within the specified limits.  
  
 Distribute the sample evenly onto the sieve and sieve for 120 seconds,  
 record the initial vacuum to the nearest 0.1 inch of water.  
  
 After the sieve stops, reweigh.  
  
 Using at least one additional sieve repeat the above procedure for the two  
 remaining samples. Report result to 1 decimal place.  
  
9.3 Calculation  
  
 % retained = final weight (g) - tare weight (g)  
 ---------------------------------- x 100%  
 Sample weight (g)  
  
 Where: final weight = weight of sieve assembly after sieving  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
 Tare weight = weight of sieve assembly before adding sample  
  
 Sample weight = weight of sample placed on sieve  
  
  
10. TAPPED DENSITY  
  
 See appropriate SOP "Use of bulk density equipment".  
  
10.1 Procedure  
  
 Place the empty cylinder on the balance and tare. Add approximately  
 40g of sample to the cylinder while holding the cylinder at a 30 degrees C  
 angle. Gradually bring the cylinder upright and level the powder, record  
 the weight of sample used. Place the cylinder into the bulk density  
 apparatus and tap 1000 times, record the volume of the sample after  
 tapping is complete and calculate the density. Report result to 2 decimal  
 places.  
  
10.2 Calculation  
  
 Tapped density = weight of sample (g)  
 -----------------------  
 volume of sample (ml)  
  
11. WATER CONTENT  
  
 See appropriate SOP "Use of the Xxxxxxx XX00 Xxxx Xxxxxxx titrator"  
  
11.1 Procedure  
  
 Following the SOP, use a sample weight of 0.90 - 1.10g and methanol as the  
 carrier solvent. Determine the water content % w/w in duplicate. Report  
 the mean result to 1 decimal place  
  
12. ASSAY AND IMPURITY (IDENTITY)  
  
 See relevant SOP "Use of HP1100 series HPLC system".  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
12.1 Conditions  
  
[\*\*]  
  
12.2 Mobile Phase and Diluent Preparation  
  
[\*\*]  
  
12.3 Gradient Program  
  
[\*\*]  
  
12.4 Impurities Reference Solution (stable for [\*\*])  
  
[\*\*]  
  
[LINE GRAPH]  
  
 [\*\*]  
[LINE GRAPH]  
  
  
  
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 [\*\*]  
  
[LINE GRAPH]  
  
12.10 Integration  
  
 ONLY INTEGRATE UP TO 90 MINS. Integrate all impurities greater than 0.01%  
 of the main [\*\*] peak area. For any impurities that are not weighed out in  
 the impurity standard calculate the impurity content as per the assay  
 calculation using the [\*\*] peak area and weight and the relevant RF for  
 the imp from section 12.9.  
  
12.11 Manual Calculations  
  
 %recovery = Area std 2 x weight imp in Std 1 x 100  
 Mean area std 1 weight imp in Std 2  
  
 Assay (%w/w) = Area(sample) x Weight of std (mg) x reference purity x RF  
 Mean area (std1) weight of sample (mg)  
  
 Assay anhydrous = Assay x 100  
 -----------------------  
 100 - % water content  
  
  
   
Weighed Impurity content (%w/w) = Area(sample) x weight of impurity (mg) x 1 x Reference purity  
 -------------------------------------------------------------  
 Mean area (std1) weight of sample (mg) 100  
  
  
 [\*\*]  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
 The identity shall be positive if the retention time of the [\*\*] resembles  
 that of an authentic reference standard within +/- 0.5 mins.  
  
13. [\*\*] DETERMINATION  
  
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[LINE GRAPH]  
  
[\*\*]  
  
[LINE GRAPH]  
  
[\*\*]  
  
  
  
[LOGO] Authorized:  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
[LINE GRAPH]  
  
13.11 Manual Calculations  
  
 % Recovery of STD 2 = area std 2 x weight std 1 x 100  
 --------------------------------------  
 Mean area std 1 weight std 2  
  
 [\*\*](ppm) = area (sample) x std weight (mg) x 5 x reference purity  
 -------------------------------------------------------  
 Mean area (std1) sample weight (mg)  
  
14. RESIDUAL SOLVENTS  
  
 See relevant SOP "Use of HP5890 and HP6890 series gas chromatographs".  
  
14.1 GC Conditions  
  
[\*\*]  
  
14.2 Headspace Conditions  
  
[\*\*]  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
[LINE GRAPH]  
  
[\*\*]  
  
[LINE GRAPH]  
  
14.9 Manual Calculations  
  
 % recovery std 2 = R std 2  
 ------------  
 Mean R std 1  
  
 Response ratio (R ) analyte = area analyte  
 -------------  
 area ISTD  
  
 Solvent content (% w/w) = R sample x weight of std (g) x 1 x 2 x purity  
 ------------------------------------------------  
 R std weight of sample (g) 100 100  
  
 Weight of standard (g) = vlme taken (ml) x specific gravity  
  
  
  
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 [\*\*]  
  
15 XRD  
  
 This analysis shall be performed by the Analytical Development Group,  
 Rhodia Pharma Solutions, Xxxxxx.  
  
 See appropriate SOP "Philips X'pert X-Ray Diffractometer  
  
 [\*\*]  
  
16. SALMONELLA  
  
 Analysis will be performed by an external laboratory.  
  
17. E COLI  
  
 Analysis will be performed by an external laboratory.  
  
18. AEROBIC MICROBIAL COUNT  
  
 Analysis will be performed by an external laboratory.  
  
19. SURFACE AREA  
  
 This will be carried out by an external laboratory.  
  
20. PARTICLE SIZE (BY LASER DIFFRACTION)  
  
 When required this analysis will be carried out by an external laboratory  
  
  
  
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METHOD OF ANALYSIS No: [\*\*]Version 3  
  
21. HANDLING INFORMATION  
  
  
  
 CHEMICAL RISK CATEGORY HANDLING CATEGORY  
---------------------- ------------- -----------------  
   
Zileuton ([\*\*]) 12 C  
Methanol 1,2,12 B  
Sulphuric acid 2,12 D1  
Hydrazine sulphate 2,5,6,12 D1  
Hexamethylenetetramine 2,4,5,12 D1  
Nitric acid 1,2,12,13 D1  
Lead nitrate 1,2,6,9,12 C  
Ammonium acetate 2,12 B  
Hydrochloric acid 1,2,1,2,13 D1  
Acetic acid 1,2,12,13 D1  
Thioacetamide 2,4,11,12 D1  
1.0M sodium hydroxide 1,2,12,13 C  
Glycerol 2,12 B  
Ammonia 2,12,13 D2  
Ferric chloride 2,12,13 C  
Potassium iodide 2,6,12 C  
Sodium thiosulphate 1,2 D1  
Starch indicator 3 B  
Cobalt chloride 2,3,4,5,6,12 D1  
Hydrogen peroxide 2,12,13 B  
Copper sulphate  
 Hydranal composite 5 2,12 D1  
Triethylamine 2,12,13 D1  
THF 2,11,12 C  
Acetonitrile 1,5,6,12 D1  
Acetohydroxamic acid  
 IPA 1,2,12 B  
Ethanol 2,12 B  
 Ethyl acetate 2,12 B  
 DMA 2,12 C  
 Toluene 2,6,9,11,12 D1  
  
  
  
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[RHODIA LOGO]  
  
PHARMA SOLUTIONS  
  
 PROCESS PERFORMANCE QUALIFICATION PROTOCOL  
  
PROJECT NAME: [\*\*] PROJECT NO. N/A  
  
PPQP NO. PPQ.04.23 PPQP.04.23 ISSUE NO. 1  
  
PREPARED BY: /s/ X. Xxxxxxxx DATE: 7TH OCTOBER 2004  
  
REVIEWED BY:  
  
Validation: /s/ Xxxxx Xxxxx DATE: 07 Oct 2004  
  
APPROVED BY:  
  
R & D Chemist (if applicable): /s/ X. Xxxx DATE: 7-10-04  
  
Quality Services /s/ X. Xxxxxx DATE: 8th October 2004  
  
Manufacturing /s/ X. Xxxxxxx DATE:7.10.04  
  
OQ Manager: /s/ Xxxxx Xxxxxxx DATE: ................  
  
  
  
 ADDENDUM  
UPDATE DATE ATTACHED REASON FOR UPDATE  
------ --------- -------- -----------------  
   
  
  
  
  
  
REVISION DATE REASON FOR REVISION  
-------- -------- -------------------  
   
  
  
  
DISTRIBUTION LIST  
ORIGINAL- VALIDATION FILE D SOWERBY S TREVENEN A XXXXXX CTI  
S XXXXXXX K THOMSON R XXXXXX  
  
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3. OBJECTIVES  
  
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PPQP NO.04.23  
  
1. SUMMARY  
  
 The process for the manufacture of [\*\*] is to undergo validation in the  
 Pilot Plant production building, Rhodia Pharma Solutions (RPS) (Dudley),  
 Cramlington, Northumberland.  
  
 This protocol has been written in accordance with D.SOP014A/018 and  
 D.SOP014A/008.  
  
 In accordance with D.SOP014A/008, the customer has requested that the  
 validation batches be released on a batch-by-batch basis prior to the  
 completion of the validation study.  
  
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2. INTRODUCTION  
  
 [\*\*] is an API manufactured for CTI and is used in the treatment of  
 asthma.  
  
 [\*\*] is manufactured in the Xxxxxx Pilot Plant production building. The  
 material is then sent to [\*\*] for milling, then returned to RPS for for  
 full analytical testing and release.  
  
 The purpose of this protocol is to demonstrate how the PPQ exercise  
 relating to the manufacture at Xxxxxx will be conducted, controlled and  
 documented.  
  
 The milling exercise at [\*\*] will be validated separately.  
  
 The PPQ will be carried out in accordance with this protocol.  
  
 D.SOP014A/008 states that:  
  
 `a pre-validation review is conducted following the manufacture of the  
 commissioning / demonstration batches.'  
  
 This review shall not occur during the current campaign prior to the  
 validation exercise and after the commissioning batches, as the validation  
 campaign is proposed to commence with the first batch of the campaign. The  
 pre-validation review will therefore be conducted by reviewing the second  
 campaign report as per D.SOP014A/008.  
  
 The review will be conducted in this fashion as a [\*\*] batch  
 pre-validation manufacturing campaign using the identical process and  
 equipment during July 2004. No changes have been made to the process or  
 the equipment since this campaign. Therefore, the material produced during  
 July 2004 will be considered as the commissioning batches and on this  
 basis, the validation campaign will commence with the first batch of the  
 current manufacturing campaign.  
  
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3. OBJECTIVES  
  
 - [\*\*] API (excluding milling) process will operate consistently  
 according to the approved PRS.  
  
 - [\*\*] API (excluding milling) process will consistently produce  
 material that meets the current analytical specification.  
  
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4. VALIDATION METHODOLOGY  
  
 4.1 OVERALL PHILOSOPHY  
  
 4.1.1 The process to be validated will be that specified in the Rhodia  
 Pharma Solutions.  
  
 4.1.2 [\*\*] pre-nominated consecutive batches must meet validation  
 criteria.  
  
 4.1.3 Validation of the [\*\*] manufacture will be considered complete upon  
 compliance with this protocol.  
  
 4.1.4 Once the PPQ has been completed, a PPQ Report will be issued  
 summarising the validation activity and the achievement against the  
 requirements of the protocol.  
  
 4.1.5 Data will be compiled in a copy of the table in Section 8 as part of  
 the PPQ Report.  
  
 4.1.6 Raw materials must comply with the applicable specifications and be  
 released by QC prior to use.  
  
 4.2 PREREQUISITES  
  
 Before commencement of the Process Performance Qualification (PPQ)  
 exercise the following conditions must be satisfied:  
  
 4.2.1 All instruments or equipment used to monitor process parameters must  
 be calibrated and calibration must cover the range of use and be  
 within the current calibration period.  
  
 4.2.2 Satisfactory completion of process [\*\*]. [Ref. No. 04.23]  
  
 4.2.3 Satisfactory completion of any relevant analytical methodology  
 validation.  
  
 4.2.4 Satisfactory completion of any relevant software validation.  
  
 4.2.5 Completion of the pre-validation review of any commissioning /  
 demonstration batches.  
  
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 4.2.6 Pre-nomination of the validation batches by the production  
 representative. The pre-nominated batches are recorded in the table  
 in Section 7.  
  
 4.2.7 The table in Section 7 will be completed prior to commencement of  
 the PPQ to document that all the pre-requisites are in place prior  
 to start up.  
  
 4.3 PROCESS SUMMARY  
  
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THERE ARE [\*\*] REACTIONS INVOLVED IN THE SYNTHESIS OF [\*\*].  
  
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 4.4 CRITICAL PROCESSING PARAMETERS  
  
 Critical processing parameters have been identified for the [\*\*]  
 process, illustrated below and are included in Section 8. These  
 parameters have been established by Xxxxxx Laboratories and are  
 listed and justified in a report provided by Abbott.  
  
  
  
 CRITICAL TARGET CONSEQUENCE OF  
OPERATION RANGE RANGE DEVIATION  
--------- -------- ------ --------------  
   
 [\*\*]  
[\*\*] [\*\*] [\*\*] [\*\*]  
  
[\*\*] [\*\*] [\*\*] [\*\*]  
  
[\*\*] [\*\*] [\*\*] [\*\*]  
  
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 [\*\*]  
   
[\*\*] [\*\*] [\*\*] [\*\*]  
  
[\*\*] [\*\*] [\*\*] [\*\*]  
  
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[\*\*] [\*\*] [\*\*] [\*\*]  
  
[\*\*] [\*\*] [\*\*] [\*\*]  
  
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 [\*\*]  
   
[\*\*] [\*\*] [\*\*] [\*\*]  
  
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 [\*\*]  
   
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[\*\*] [\*\*] [\*\*]  
[\*\*] [\*\*] [\*\*]  
[\*\*] [\*\*] [\*\*]  
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[\*\*] [\*\*] [\*\*]  
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[\*\*] [\*\*] [\*\*] [\*\*]  
  
  
(1.) With respect to the [\*\*]  
  
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 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
  
  
  
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PPQP NO.04.23  
  
2. With respect to the [\*\*]  
  
All L/KG refer to litres per kilogram of [\*\*]  
  
 4.5. YIELD  
  
Expected yield: [\*\*]  
  
Acceptable yield range: [\*\*]  
  
 [\*\*]  
  
 4.6 EQUIPMENT  
  
 The equipment used in the [\*\*] manufacturing process is located in the  
 Pilot Plant facility. The main items utilised are:  
  
[\*\*]  
  
4.7 SAMPLING & ANALYSIS  
  
 The [\*\*] pre-nominated batches will be dried and discharged. In order to  
 illustrate that a) the batch is uniform following drying, and b) the  
 composite sample taken for final batch analysis is representative of the  
 batch, the following samples will be taken.  
  
- A sample from a composite sample taken as per the normal sampling  
 procedure detailed in the PRS.  
  
- Validation samples will be sampled as specified in the following table and  
 in accordance with written and approved instructions  
  
 Analysis will comprise of that specified in the following table.  
  
  
  
 SAMPLE ANALYSIS MONOGRAPH  
--------- -------- ---------  
   
[\*\*] [\*\*] [\*\*]  
  
[\*\*] [\*\*] [\*\*]  
  
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 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
  
  
  
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PPQP NO.04.23  
  
 \* [\*\*] will be performed but are not applicable to this validation  
 exercise because compliance is controlled by the [\*\*] not the [\*\*].  
  
 4.8 ACCEPTANCE CRITERIA  
  
 4.8.1 All prerequisites will be completed prior to the start of  
manufacture.  
  
 4.8.2 The [\*\*] consecutive batches are manufactured according to the  
 approved PRS. This will be demonstrated by OQ review and approval of  
 the completed PRS.  
  
 4.8.3 The batches will be produced following the approved PRS except where  
 a deviation from the PRS has been evaluated by OQ and found to be  
 acceptable with regards to process control and quality attributes.  
  
 4.8.4 The [\*\*] batches comply with the specifications in Section 4.9.  
  
 4.8.5 Validation samples (specified in Section 4.7) meet all the criteria  
 listed in this section required to show that the process is  
 operating consistently / under control.  
  
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 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
  
  
  
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PPQP NO.04.23  
  
 4.9. SPECIFICATION  
  
 In-process analysis will be conducted in accordance with  
  
  
  
[\*\*] [\*\*] [\*\*]  
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[\*\*] [\*\*] [\*\*]  
  
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 The [\*\*] (pre milling) will be analysed according to monograph [\*\*]  
  
  
  
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PPQP NO.04.23  
  
  
  
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 The [\*\*] (post milling) will be analysed according to monograph 6000721  
  
  
  
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[\*\*] [\*\*]  
  
 [\*\*] [\*\*]Not less  
 than -0.5 degrees and  
 not more than +0.5  
 degrees calculated on  
 the anhydrous basis  
 at 25 degrees C  
  
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D.SOP014A/018 REV 3 PAGE 17 OF 33  
PPQP NO.04.23  
  
  
  
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[\*\*] The mean percent  
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 sieve is not more  
 than 7.0%  
  
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NOTE  
  
[\*\*] have been excluded.  
  
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PPQP NO.04.23  
  
5. REFERENCE DOCUMENTS  
  
 Process Record Sheet [\*\*]  
  
 Validation Master Plan ([\*\*]  
  
 [\*\*]  
  
 Process Validation Protocol Report number [\*\*] (Dated 23rd February 1998)  
  
 CONFIDENTIAL  
 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
  
  
  
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PPQP NO.04.23  
  
6. REPORTING AND ARCHIVAL  
  
 A PPQ Report will be generated upon completion of the validation batches  
 in accordance with [\*\*].  
  
 All data generated by the protocol will be stored on data record sheets,  
 which will be stored with the relevant batch record filed in OQ.  
  
 CONFIDENTIAL  
 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
  
  
  
D.SOP014A/018 REV 3 PAGE 21 OF 33  
PPQP NO.04.23  
  
7. PREREQUISITES TO PROCESS VALIDATION  
  
  
  
ITEM RESULT INITIALS DATE  
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 /\*NB: LABORATORY WORK COMPLETED. FINAL REPORT TO BE SIGNED. SP 08OCT04/  
  
PRS REFERENCE AND REVISION [\*\*]  
  
  
  
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START UP APPROVAL:  
  
Approved By: /s/ Xxxxx Xxxxxxx Date: 8.10.04  
 -----------------  
Process Manager  
/ Project Leader /s/ Xxxxx Xxxxxxx 08 Oct 04  
 -----------------  
  
Approved By: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_  
  
OQ Manager  
  
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PPQP NO. 04.23  
  
8. PROCESSING PARAMETERS  
  
The parameters listed in the following table examine the reproducibility of  
processing and subsequent batch quality. A copy of this table will be completed  
in the PPQ Report  
  
  
  
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PPQP NO. 04.23  
  
  
  
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PPQP NO. 04.23  
  
  
  
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PPQP NO. 04.23  
  
ANALYTICAL SUMMARY  
  
  
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 degrees calculated on  
 the anhydrous basis at 25  
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PPQP NO. 04.23  
  
9. RAW MATERIAL / INPUT MATERIAL SUMMARY  
  
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[\*\*] RAW MATERIAL / INPUT MATERIAL  
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 Annex 3-Validation Schedule  
  
 [\*\*]  
  
  
 ANNEX 4  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 1  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
PRS.982  
  
Date: 15th September 2004 SHEET NO: 1  
Replaces: [\*\*] PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_\_\_\_\_  
Valid until: 2 years after date of approval (unless superseded)  
  
 Plant: [\*\*]  
  
 Product: [\*\*](ZILEUTON)  
  
 Procedure: FINAL PRODUCT  
  
 Equipment: [\*\*]  
  
 Ref. No: [\*\*]  
  
  
   
Process written by: X.X.XXXXXXX....................................Date: 23.9.04.....................  
Process checked by R & D: /s/ illegible..................................Date: 23.9.04.....................  
Process authorised by Plant Manager: /s/ illegible..................................Date: 23.9.04.....................  
Process approved by Operational Quality: /s/ illegible..................................Date: 07 Oct 04...................  
  
  
 C O N F I D E N T I A L  
 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
  
  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 2  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
 HAZARDS  
  
THE PERSONAL PROTECTIVE EQUIPMENT STIPULATED IN THIS PROCESS IS THE MINIMUM  
REQUIRED AND HAS BEEN DETERMINED ON THE BASIS THAT (WHERE AVAILABLE) THE LOCAL  
EXTRACTION SYSTEM IS OPERATING SATISFACTORILY. IF THE LOCAL SYSTEM IS NOT  
OPERATING THE SUPERVISOR MUST BE CONSULTED WHO WILL ENSURE THAT CORRECTIVE  
ACTION IS TAKEN TO RESTORE THE LEV SYSTEM. OPERATIONS MUST NOT PROCEED UNTIL LEV  
SYSTEMS ARE WORKING.  
  
  
   
SODIUM HYDROXIDE: CORROSIVE SOLID. Causes severe xxxxx. Risk of serious damage to eyes.  
 NON-COMBUSTIBLE SOLID. DO NOT ALLOW SKIN/EYE CONTACT OR BREATHE DUST.  
  
HAZARD CATEGORY: R2S3  
  
50% AND 32% SODIUM HYDROXIDE SOLUTION: CORROSIVE LIQUID. CAUSES SEVERE XXXXX. RISK OF SERIOUS DAMAGE TO THE EYES.  
 NON COMBUSTIBLE LIQUID  
  
HAZARD CATEGORY: R1S3 DO NOT ALLOW ANY CONTACT OR EXPOSURE  
  
2-ACETYLBENZOTHIOPHENE: IRRITANT SOLID. Irritating to eyes. WILL BURN IN A FIRE. AVOID SKIN AND  
 EYE CONTACT. AVOID BREATHING DUST.  
  
HAZARD CATEGORY: R2S2  
  
SODIUM BOROHYDRIDE: TOXIC SOLID. Toxic by inhalation, ingestion and in contact with the skin.  
 WILL BURN IN A FIRE  
  
HAZARD CATEGORY: R3S3 DO NOT ALLOW ANY CONTACT OR EXPOSURE.  
  
ETHYL ACETATE: IRRITANT LIQUID. Irritating to the eyes. Repeated exposure may cause skin  
 dryness or cracking. Vapours may cause drowsiness and dizziness. HIGHLY  
 FLAMMABLE. AVOID SKIN AND EYE CONTACT.  
  
HAZARD CATEGORY: R2S2 AVOID BREATHING VAPOUR.  
  
  
  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 3  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
 HAZARDS  
  
THE PERSONAL PROTECTIVE EQUIPMENT STIPULATED IN THIS PROCESS IS THE MINIMUM  
REQUIRED AND HAS BEEN DETERMINED ON THE BASIS THAT (WHERE AVAILABLE) THE LOCAL  
EXTRACTION SYSTEM IS OPERATING SATISFACTORILY. IF THE LOCAL SYSTEM IS NOT  
OPERATING THE SUPERVISOR MUST BE CONSULTED WHO WILL ENSURE THAT CORRECTIVE  
ACTION IS TAKEN TO RESTORE THE LEV SYSTEM. OPERATIONS MUST NOT PROCEED UNTIL LEV  
SYSTEMS ARE WORKING.  
  
  
   
METHANOL: TOXIC LIQUID. Toxic by inhalation, ingestion and in contact with the  
 skin. Danger of very serious irreversible effects through inhalation, ingestion  
 and in contact with skin. HIGHLY FLAMMABLE LIQUID.  
  
HAZARD CATEGORY: R3S3 DO NOT ALLOW ANY CONTACT OR EXPOSURE  
  
METHYL CARBAMATE: IRRITANT SOLID. LIMITED EVIDENCE OF CARCINOGENIC EFFECT (CARC CAT 3).  
 WILL BURN IN A FIRE.  
  
HAZARD CATEGORY: R3S3 DO NOT ALLOW ANY CONTACT OR EXPOSURE  
  
50% HYDROXYLAMINE SOLUTION: HARMFUL, IRRITANT LIQUID. Harmful if swallowed. Irritating to the respiratory  
 system and skin. Limited evidence of carcinogenic effect (CARC CAT 3). Risk  
 of serious damage to eyes. May cause sensitisation by skin contact.  
 NON-COMBUSTIBLE/HEATING MAY CAUSE EXPLOSION.  
  
HAZARD CATEGORY: R3S3 DO NOT ALLOW ANY CONTACT OR EXPOSURE  
  
HYDROCHLORIC ACID 36% AR: CORROSIVE LIQUID. CAUSES XXXXX. Irritating to the respiratory system.  
 NOT CLASSIFIED AS FLAMMABLE.  
  
HAZARD CATEGORY: R3S3 DO NOT ALLOW ANY CONTACT OR EXPOSURE.  
  
TETRAHYDROFURAN: IRRITANT LIQUID. Irritating to eyes and respiratory system. HIGHLY  
 FLAMMABLE LIQUID, MAY FORM EXPLOSIVE PEROXIDES. AVOID CONTACT WITH SKIN/  
 EYES. AVOID INHALATION AND  
  
  
  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 4  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
  
   
HAZARD CATEGORY: R2S3 INGESTION  
  
  
 HAZARDS  
  
THE PERSONAL PROTECTIVE EQUIPMENT STIPULATED IN THIS PROCESS IS THE MINIMUM  
REQUIRED AND HAS BEEN DETERMINED ON THE BASIS THAT (WHERE AVAILABLE) THE LOCAL  
EXTRACTION SYSTEM IS OPERATING SATISFACTORILY. IF THE LOCAL SYSTEM IS NOT  
OPERATING THE SUPERVISOR MUST BE CONSULTED WHO WILL ENSURE THAT CORRECTIVE  
ACTION IS TAKEN TO RESTORE THE LEV SYSTEM. OPERATIONS MUST NOT PROCEED UNTIL LEV  
SYSTEMS ARE WORKING.  
  
  
   
TOLUENE: HARMFUL LIQUID. Harmful by inhalation and ingestion. Irritant to eyes  
 and skin. HIGHLY FLAMMABLE. AVOID CONTACT WITH SKIN/EYES. AVOID INHALATION  
 AND INGESTION  
  
HAZARD CATEGORY: R2S1  
  
[\*\*] (ZILEUTON): CRYSTALLINE POWDER, ACCORDING TO EXPERIENCE HARMLESS TO HEALTH. WILL BURN  
 IN A FIRE. AVOID CONTACT WITH SKIN/EYES. AVOID INHALATION AND INGESTION.  
  
HAZARD CATEGORY: R2S2  
  
  
  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 5  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
 PROCEDURES FOR THE EMERGENCY SHUTDOWN OF PROCESS PLANT EQUIPMENT  
  
In the event of evacuation from the process areas due to the sounding of Fire or  
Hazard alarms, the following action must be taken:  
  
  
   
STIRRERS: If running, do not switch off, leave running.  
  
STEAM / HOT WATER HEATING: Turn off steam or steam / water supply to jacket and allow to drift with agitation.  
  
AT REFLUX: Leave lines set for reflux with agitation. Heating set point reduced.  
  
DISTILLATION (ATMOSPHERIC): Leave lines set for distillation with agitation. Heating set point reduced.  
  
DISTILLATION (VACUUM): Leave lines set for distillation. Maintain vacuum with agitation. Heating set point reduced.  
  
GAS OR LIQUID ADDITION: Stop addition. Shut off gassing operations by cylinder valve.  
  
CIRCULATING SCRUBBERS: Leave vessels vented to circulating Scrubbers with Scrubber pumps left running.  
  
TRANSFER OPERATIONS Stop transfer operations, either venting Nitrogen from pressurised vessel and closing line valve,  
(INCLUDING VIA IN-LINE FILTERS): or circulate via pump back to charcoalation or initial reaction vessel.  
  
COOLING: Continue cooling the vessel. Maintain agitation.  
  
PRODUCT FILTRATION: Stop slurry feed to filter or centrifuge. Either maintain vacuum on filter or allow centrifuge  
 to spin dry.  
  
SOLID TRANSFERS: e.g. Charging Vessel, collecting wet cake, charging drier etc. Close all containers, chargehole  
 covers, oven doors etc and suspend operations.  
  
LIQUID TRANSFERS: Suspend operations - close valves, vent Nitrogen pressurised vessel or receiver, vent dispenser  
 or vessel under vacuum. Cap drum.  
  
  
  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 6  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
The above procedures will apply for all Steps apart from between Steps 42 to 44  
when the quench and dump operations will be carried out in the event of the  
sounding of the fire alarm. If the hazard alarm sounds during Steps 42 to 44,  
the reaction vessel will be monitored from the assembly point.  
  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 7  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
NOTES  
  
1. Throughout the process SUPERVISOR refers to Team Leader, Shift Manager,  
 Process Manager, R&D Chemist, Pilot Plant Technician, Shift Chemist or  
 Product Manager or those acting in an authorised supervisory capacity.  
  
2. At the start of manufacturing, i.e. equipment checks the  
 Technician/Supervisor must sign his full name at the top of the page, along  
 with his shift details, the time and date.  
  
3. When a new page is started the Technician is to record the date at the top  
 of the page in the space provided.  
  
4. Technician to initial and enter the time in the record columns and include  
 the date if it is different from the date at the top of the page.  
  
5. Any unusual occurrences or events that occur during the process must be  
 recorded on the observation sheet attached to the back of the PRS. If any  
 additional instructions are required as a result of an observation,  
 procedure "Control of Changes or PRSs (both planned and unplanned)" is to  
 be followed. The Development Chemist will complete the technical assessment  
 and judge whether an observation should be upgraded to a Process Deviation  
 Report (PDR).  
  
6. "Checked by: ............................." in the records column means  
 that a second person must check the operation in question as it happens  
 (typically the description and quantity of the material to be charged), and  
 initial the records entry.  
  
7. \* means delete as appropriate.  
  
8. Before commencing a step ensure all the instructions for that step have  
 been read and understood.  
  
9. Ensure a Process Control Analytical Report (PCAR) or an inspection report  
 is available for every piece of in-process analysis performed -- enclose  
 the original PCAR if analysis was performed by Plant personnel or the fax  
 copy of the inspection report if the analysis was performed by Analytical  
 Services.  
  
10. When a charge needs to be calculated and/or entered, the person who  
 calculates and/or enters the charge must sign at the relevant step  
 instructions.  
  
  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 8  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
 XXXX OF MATERIALS  
  
11. The `TIME / DATE' and `TECHNICIAN INITIALS' columns contain dotted line  
 entries (..........) for filling in against records when requested. The  
 continuous line ( \_\_\_\_\_ ) indicates the completion of a step. On many  
 occasions the last record filled in is also the end of a step, in which  
 case only the continuous line ( \_\_\_\_\_ ) is shown.  
  
12. At the shift handover the off going and on coming Technicians review the  
 documentation then the oncoming Technician completes the handover record on  
 the last sheet of this PRS.  
  
13 Xxxx of Materials for a typical batch of [\*\*]:  
  
  
  
 RAW MATERIAL MATERIAL NO. QUANTITY  
----------------------------------- ------------ --------  
   
[\*\*] 5001390 [\*\*]  
[\*\*] 1000203 [\*\*] [\*\*]  
[\*\*] 1000246 [\*\*]  
[\*\*] 1001337 [\*\*]  
[\*\*] 1000997 [\*\*]  
[\*\*] 1000082 [\*\*]  
[\*\*] 1000145 [\*\*]  
[\*\*] 1001338 [\*\*]  
[\*\*] 5005130 [\*\*]  
[\*\*] 1000817 [\*\*]  
[\*\*] 1000105 [\*\*]  
[\*\*] 1000227 [\*\*]  
[\*\*] 1000223 [\*\*]  
[\*\*] 1000226 [\*\*]  
[\*\*] 2000058 [\*\*] [\*\*]  
[\*\*] 2000024 [\*\*]  
[\*\*] 2000028 [\*\*]  
[\*\*] 2000052 [\*\*]  
  
  
  
  
 OBSERVATION SHEET  
  
PRODUCT: [\*\*](ZILEUTON) SHEET NO: 9  
REFERENCE NO: 6000550.7X1.04 PROCESS ORDER NO:\_\_\_\_\_\_\_\_\_  
  
14. CERTAIN EQUIPMENT AND OPERATIONS IN THIS PROCESS ARE CRITICAL TO THE  
 PROTECTION OF THE ENVIRONMENT. WHERE THIS IS THE CASE A PROMPT WILL BE  
 GIVEN IN THE KEY POINTS COLUMN. SATISFACTORY ABATEMENT OF RELEASES FROM THE  
 PROCESS IS ESSENTIAL FOR COMPLIANCE WITH THE ENVIRONMENT PROTECTION ACT.  
 PLEASE PLAY YOUR PART.  
  
15. CERTAIN EQUIPMENT AND OPERATIONS IN THIS PROCESS ARE CRITICAL FOR THE  
 PROTECTION OF HEALTH. ENSURE ALL PPE IS IN A SUITABLE CONDITION FOR USE.  
 WHEN LEV CHECKS ARE INDICATED WITHIN THE PRS ENSURE THAT THEY ARE CARRIED  
 OUT AND SUPERVISOR IS INFORMED OF ANY DEFECTS. OPERATIONS MUST NOT BE  
 CARRIED OUT UNTIL LEV SYSTEMS ARE RESTORED TO FULL WORKING ORDER.  
 SATISFACTORY PROTECTION FROM EXPOSURE TO CHEMICALS IS ESSENTIAL TO  
 PROTECTING HEALTH AND TO COMPLY WITH THE COSHH REGULATIONS.  
  
  
 ANNEX 5  
  
Critical Therapeutics Inc Delivery No  
00 Xxxx Xxxx Xxxxxx Customer Order No  
Lexington, MA UA 02421 Rhodia Pharma Solutions Order  
USA  
  
 CERTIFICATE OF ANALYSIS  
  
MATERIAL [\*\*] (MICRONISED IR)  
BATCH [\*\*]  
DATE OF RETEST 04/25/2005  
DATE OF MANUFACTURE 09/20/2004  
DATE OF ANALYSIS 10/26/2004  
  
  
  
 SPECIFICATION  
 -----------------  
TEST UNIT RESULT LOWER UPPER  
----------------------------------- ----- ------ ----- -----  
   
Appearance [\*\*] [\*\*]  
Identity: Infra Red Spectrum [\*\*] [\*\*]  
Specific rotation (deg mL g-1 dm-1) [\*\*] [\*\*] [\*\*]  
Residue on ignition % w/w [\*\*] [\*\*]  
Foreign matter (2% soln in methanol) [\*\*] [\*\*]  
Clarity (2% soln in methanol) [\*\*] [\*\*]  
Heavy Metals (ppm) [\*\*] [\*\*]  
Colour ("B") (2% soln in methanol) [\*\*] [\*\*]  
Colour ("BY") (2% soln in methanol) [\*\*] [\*\*]  
Percent retained on [\*\*] sieve % [\*\*] [\*\*]  
Tapped density gfml [\*\*] [\*\*]  
Identity: HPLC Retention time [\*\*] [\*\*]  
Assay on dry basis % w/w [\*\*] [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
  
  
 Page 1 of 2  
  
  
  
 CERTIFICATE OF ANALYSIS  
  
MATERIAL [\*\*] (MILLED)  
BATCH 8001362005  
  
  
  
 SPECIFICATION  
 --------------------  
TEST UNIT RESULT LOWER UPPER  
-------------------------------- ------ ------ ------ -----  
   
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] ppm [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
[\*\*] % w/w [\*\*] [\*\*]  
GLC: Total Solvents % w/w [\*\*] [\*\*]  
Crystal form [\*\*] [\*\*]  
Water Content % w/w [\*\*] [\*\*]  
Assay on wet basis (% w/w) % w/w [\*\*] [\*\*]  
Salmonella [\*\*] [\*\*]  
E.Coli [\*\*] [\*\*]  
Aerobic microbial count (target) CF(mu)/g [\*\*] [\*\*]  
Surface area M(2)/g [\*\*] [\*\*] [\*\*]  
Particle size um (laser): d90 [\*\*] [\*\*]  
Particle size um (laser): d50 [\*\*] [\*\*]  
Particle size um (laser): d10 [\*\*] [\*\*]  
  
  
Manufactured in accordance with ICH Q7A  
  
Customers name: Zileuton ([\*\*])  
Date of Manufacture of Unmilled: 7/11/2004  
  
 /s/Xxx Xxxxx  
 ------------------------------  
 Authorised Person  
 Nov. 03, 2004  
  
 Page 2 of 2  
  
  
RHODIA PHARMA SOLUTIONS  
  
Ref: [\*\*]  
  
Rhodia Pharma Solutions  
Xxxxxx  
Xxxxxxxxxxx  
Xxxxxxxxxxxxxx  
XX00 0XX  
XX  
28 October 2004  
  
LETTER OF DECLARATION OF MANUFACTURE ACCORDING TO GMP RULES  
  
We, Rhodia Pharma Solutions, hereby declare that we manufacture [\*\*] to the  
following GMP rules:  
  
GMP as defined by ICH Q7a ("Good Manufacturing Practice Guide for Active  
Pharmaceutical Ingredients").  
  
/s/ X. Xxxxxxx  
X. Xxxxxxx  
Operational Quality Manager  
  
  
  
[RHODIA LOGO] ANNEX 6  
  
 PHARMA SOLUTIONS  
  
 STANDARD OPERATING PROCEDURE  
  
 Page 1 of 6  
  
 OPERATIONAL QUALITY PROCEDURE FOR DESPATCH OF  
 FINAL PRODUCT MATERIAL FROM SITE  
  
REFERENCE NO: [\*\*] REV 1  
  
REVISED: FEBRUARY 2003  
  
REPLACES: [\*\*] VERSION 7  
  
REVIEW PERIOD: 2 YEARS (UNLESS SUPERSEDED)  
  
Prepared by: /s/ E Xxxxxx Date 10/2/03  
 -----------------------------  
Operational Quality Manager  
  
Reviewed by: /s/ G McCoull Date 11/2/03  
Warehouse -----------------------------  
  
Approved by: /s/ I B Low Date 11/2/03  
Plant Manager -----------------------------  
  
Approved by: /s/ R P G Xxxxxx Date 12 Feb 023  
Quality Manager -----------------------------  
  
 RPGH 12/2/03  
  
 CONFIDENTIAL  
 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
 VALID FOR 7 DAYS FROM DATE OF PRINTING - DATE PRINTED:  
  
  
  
[RHODIA LOGO] APPENDIX 1 TO [\*\*] REV 1  
  
 PHARMA SOLUTIONS  
  
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 VALID FOR 7 DAYS FROM DATE OF PRINTING - DATE PRINTED:  
  
  
  
[RHODIA LOGO] APPENDIX 1 TO [\*\*] REV 1  
  
 PHARMA SOLUTIONS  
  
1.0 INTRODUCTION  
  
It is the responsibility of the Operational Quality Department to ensure that  
all material to be despatched off-site has been manufactured, packaged, tested,  
examined and labelled in accordance with current Good Manufacturing Practices.  
  
This procedure covers the progress of final product from the time of its  
transfer from Manufacturing to Process Stores through to its despatch from site.  
  
2.0 DEFINITIONS  
  
None  
  
3.0 RESPONSIBILITIES  
  
Warehouse Personnel - responsible for ensuring final products for despatch are  
selected, labelled and packaged in accordance with the relevant Process Stores  
Procedure.  
  
Operational Quality - responsible for ensuring that the material to be  
despatched has been manufactured, packaged, tested, and labelled in accordance  
with the relevant Site Procedure and in compliance with cGMP.  
  
4.0 PROCEDURE  
  
4.1 RECEIPT OF FINAL PRODUCT BY S12 PROCESS STORES  
  
A batch of final product will be transferred from Manufacturing to Stores  
Department. The batch number and container details of the material being  
transferred is available on SAP.  
  
The Stores personnel will then check the conditions of the containers and the  
nett weights shown on SAP correspond to those on the containers. The Stores  
person will arrange for the material to be stored in the area of the warehouse  
designed for final product, in accordance with GMP guidelines.  
  
4.2 PRODUCT SENTENCING BY OPERATIONAL QUALITY  
  
The Operational Quality Unit will check the batch documentation and analytical  
data and sentence the material in accordance with the relevant SOP. The expiry  
date of the batch will be noted from SAP which will have generated this  
automatically.  
  
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[RHODIA LOGO] APPENDIX 1 TO [\*\*] REV 1  
  
 PHARMA SOLUTIONS  
  
4.3 RECEIPT AND ALLOCATION OF ORDERS  
  
Following receipt of an order from the customer and within the agreed lead time,  
material will be allocated by Customer Services, Xxxxxx via SAP. Batches will be  
selected in strict rotation, where possible.  
  
The OQ department will be advised by Customer Services, Xxxxxx of the order and  
sent an "Acknowledgement of Order" via fax detailing the material allocation.  
  
The OQ Department will raise a OQ Despatch Checklist (Appendix I) and ensure the  
material selected is suitable before authorising the allocation.  
  
4.4 LABELLING AND CHECKING OF CONTAINERS  
  
After OQ have authorised allocation of the order, the Stores personnel may print  
off the product labels from SAP.  
  
If labels do not print correctly then a label re-print can be made, all extra  
labels generated or destroyed should be documented on the "SAP SHIPPING LABELS  
RECONCILIATION SHEET" (Logsheet CL011, page 1).  
  
The old production labels are fixed to log sheet number CL011 against the  
corresponding SAP label number for each keg. Hence the original keg number can  
be traced to a specific keg in the order. A check will be made to ensure that  
the details on the SAP product labels, i.e. batch number, container, number,  
gross and nett weights correspond to those on Manufacturing labels. The security  
seals are checked, where applicable and any damaged seals replaced.  
  
When product labelling is complete, a check will be undertaken by a second  
person to ensure:  
  
- The containers are in good condition and free from product contamination.  
  
- The SAP product label details correspond to those on the displaced  
 Manufacturing labels and product identity is correct.  
  
- The SAP product label details correspond to those listed in the  
 "Acknowledgement of Order" and with the master Despatch label.  
  
- Security seals are secure and undamaged.  
  
- Where a numbered security seal is replaced this will be recorded in the  
 Stores seal register and OQ informed of the new seal number and the  
 batch/container to which it was affixed.  
  
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[RHODIA LOGO] APPENDIX 1 TO [\*\*] REV 1  
  
 PHARMA SOLUTIONS  
  
- All documentation will be returned to the OQ Department for checking  
 before "final release".  
  
- The OQ Department will check the order prior to signing the "final  
 release". When satisfied all details are correct, the paperwork will be  
 signed and returned to Stores for archiving. A copy of a label for each  
 batch will be retained with the OQ checklist.  
  
- The Stores person will then progress the order through SAP to the  
 appropriate status for despatch.  
  
4.5 CERTIFICATES OF ANALYSIS  
  
A Certificate of Analysis will be provided, and accompany, all material leaving  
site. This Certificate of Analysis is either generated using SAP or manually.  
  
A suitably authorised person in Quality will sign the Certificate of Analysis.  
  
Copies of Certificates of Analysis will be held in the OQ unit for at least one  
calendar year.  
  
NB - When material is to be despatched to Mexico the Certificate of Analysis  
 may only be signed by a notarised signature.  
  
5.0 DOCUMENT REVISION HISTORY  
  
  
  
 ALTERATIONS, ADDITIONS,  
 DATE SEQUENTIAL CODE OMISSIONS  
------------- --------------- ------------------------------  
   
FEBRUARY 2003 [\*\*] REV 1 FIRST ISSUE - REPLACES AGMP 18  
  
  
 CONFIDENTIAL  
 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
 VALID FOR 7 DAYS FROM DATE OF PRINTING - DATE PRINTED:  
  
  
  
[RHODIA LOGO] APPENDIX 1 TO [\*\*] REV 1  
  
 PHARMA SOLUTIONS  
  
6.0 DISTRIBUTION LOCATION  
  
 FILE LOCATIONS (XXXXXX)  
  
 A Operational Quality (Masters of all documents)  
 B Analytical Services (shift lab)  
 C Pilot Plant  
 X Xxxxxx 1 (Manufacturing/Engineering)  
 E Xxxxxx 2 (Manufacturing/Engineering)  
 F ADG  
 G R&D  
 H Main office (to hold documents for Safety/Engineering/Finance/  
 Accounts/ Human Resources/Purchasing/Planning/Commercial/Customer  
 Services  
 I Central Engineering  
 J Warehouse  
 K PPG  
 K 1. Point of Use [specify]  
 2. Point of Use [specify]  
 3. Point of Use [specify]  
  
 FILE LOCATIONS (XXXXX)  
  
 A Operational Quality File  
 B Shift Managers Office  
 C General Admin Building (Master)  
 D S12 Stores  
 E Engineering Records Office  
 F 1. Point of Use [specify]  
 2. Point of Use [specify]  
 3. Point of Use [specify]  
  
 FILE LOCATIONS (XXXXXX CHAPEL)  
  
 A Quality Assurance (copy from Xxxxxx)  
 B Engineering  
 C GPP  
 D Orion  
 E Building 44  
 F Lyra  
 G 1. Point of Use [specify]  
 2. Point of Use [specify]  
 3. Point of Use [specify]  
  
 FILE LOCATIONS (MALVERN)  
  
 A Quality Assurance (copy from Xxxxxx)  
 B 4. Point of Use [specify]  
 5. Point of Use [specify]  
 6. Point of Use [specify]  
  
 OPERATIONAL QUALITY DESPATCH CHECKLIST  
  
 CONFIDENTIAL  
 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
 VALID FOR 7 DAYS FROM DATE OF PRINTING - DATE PRINTED:  
  
  
  
[RHODIA LOGO] APPENDIX 1 TO [\*\*] REV 1  
  
 PHARMA SOLUTIONS  
  
Order No: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Reference No:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Country of Customer Material  
Destination: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ No:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Product Name:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Product Code:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Batch No's/No of Kegs  
allocated: \_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
 \_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
 \_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
 \_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Is material suitable for despatch and allocated YES/NO  
to appropriate market?  
  
Allocation Authorised Date:  
by: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Product identity/containers/labelling/security seals  
  
Checked By: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Certificates of Analysis Date:  
Produced by: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Certificates of Analysis Date:  
Checked by: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Final Check by OQ: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (Sign) Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Comments:  
  
Material Despatched: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
Operational Quality Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
  
  
 CONFIDENTIAL  
 NOT TO BE RELEASED TO UNAUTHORISED PERSONNEL  
 VALID FOR 7 DAYS FROM DATE OF PRINTING - DATE PRINTED:  
  
  
 ANNEX 7  
  
ANNEX 7 - WIRE TRANSFER INFORMATION  
  
HSBC Bank  
  
Newcastle Upon Tyne City Branch  
  
Swift Code : XXXXXX00  
IBAN : XX00 XXXX 0000 0000 0000 00  
Account : [\*\*]  
  
ANNEX 8 Client#: 1872 CRITICAL  
  
   
 DATE(mm/dd/yyy)  
XXXXX(TM) CERTIFICATE OF LIABILITY INSURANCE 11/03/04  
------------------------------------------------------------------------------------------------------------------------------------  
PRODUCER THIS CERTIFICATE IS ISSUED AS A MATTER OF INFORMATION ONLY AND  
Xxxxxxx Xxxxxxxxx Associates CONFERS NO RIGHTS UPON THE CERTIFICATE HOLDER. THIS CERTIFICATE  
Insurance Brokers, Inc. DOES NOT AMEND, EXTEND OR ALTER THE COVERAGE AFFORD BY THE  
000 Xxxxxxxx Xxxxxx POLICIES BELOW.  
Xxxxxx, XX 00000  
 --------------------------------------------------------------------  
  
 INSURERS AFFORDING COVERAGE NAIC #  
------------------------------------------------------------------------------------------------------------------------------------  
INSURED INSURER A: American Casualty Co. of Reading, PA  
 --------------------------------------------------------------------  
 Critical Therapeutics, Inc. INSURER B: Continental Casualty Company  
 00 Xxxxxxxx Xxxxxx --------------------------------------------------------------------  
 Xxxxxxxxx, XX 00000 INSURER C: Columbia Casualty  
 --------------------------------------------------------------------  
 INSURER D:  
 --------------------------------------------------------------------  
 INSURER E:  
------------------------------------------------------------------------------------------------------------------------------------  
  
  
COVERAGES  
  
THE POLICIES OF INSURANCE LISTED BELOW HAVE BEEN ISSUED TO THE INSURED NAMED  
ABOVE FOR THE POLICY PERIOD INDICATED. NOTWITHSTANDING ANY REQUIREMENT, TERM OR  
CONDITION OF ANY CONTRACT OR OTHER DOCUMENT WITH RESPECT TO WHICH THIS  
CERTIFICATE MAY BE ISSUED OR MAY PERTAIN, THE INSURANCE AFFORDED BY THE POLICIES  
DESCRIBED HEREIN IS SUBJECT TO ALL THE TERMS, EXCLUSIONS AND CONDITIONS OF SUCH  
POLICIES. AGGREGATE LIMITS SHOWN MAY HAVE BEEN REDUCED BY PAID CLAIMS.  
  
  
  
 POLICY POLICY  
1NSR ADD'L EFFECTIVE EXPIRATION  
 LTR INSRD TYPE OF INSURANCE POLICY NUMBER DATE (MM/DD/YY) DATE (MM/DD/YY) LIMITS  
------------------------------------------------------------------------------------------------------------------------------------  
   
A GENERAL LIABILITY A0000000000 10/29/04 10/29/05 EACH OCCURRENCE $1,000,000  
 ---------------------------------------  
 [X]COMMERCIAL GENERAL LIABILITY DAMAGE TO RENTED  
 [ ] [ ] CLAIMS MADE [X] OCCUR PREMISES (Ea occurrence) $ 300,000  
 [ ] ---------------------------------------  
 -------------------------- MED EXP (Any one person) $ 15,000  
 [ ] ---------------------------------------  
 -------------------------- PERSONAL & ADV INJURY $1,000,000  
 GEN'L AGGREGATE LIMIT APPLIES PER: ---------------------------------------  
 [ ] POLICY [ ] PROJECT [ ] LOC GENERAL AGGREGATE $ 2,000,00  
 ---------------------------------------  
 PRODUCTS-COMP/OP AGG $  
------------------------------------------------------------------------------------------------------------------------------------  
 AUTOMOBILE LIABILITY COMBINED SINGLE LIMIT  
 [ ] ANY AUTO (Ea Accident) $  
 [ ] ALL OWNED AUTOS ---------------------------------------  
 [ ] SCHEDULED AUTOS BODILY INJURY (Per Person) $  
 [ ] HIRED AUTOS ---------------------------------------  
 [ ] NON-OWNED AUTOS BODILY INJURY (Per accident) $  
 [ ] ---------------------------------------  
 -------------------------- PROPERTY DAMAGE  
 [ ] (Per accident) $  
------------------------------------------------------------------------------------------------------------------------------------  
 GARAGE LIABILITY AUTO ONLY-Ea Accident $  
 [ ] ANY AUTO ---------------------------------------  
 [ ] OTHER THAN EA ACC $  
 ---------------------------------------  
 AUTO ONLY: AGG $  
------------------------------------------------------------------------------------------------------------------------------------  
B EXCESS/UMBRELLA LIABILITY A2050029007 10/29/04 10/29/05 EACH OCCURRENCE $4,000,000  
 [X] OCCUR [ ] CLAIMS MADE ---------------------------------------  
 AGGREGATE $4,000,000  
 ---------------------------------------  
 $  
 ---------------------------------------  
 [ ] DEDUCTIBLE $  
 [X] RETENTION $10000 ---------------------------------------  
 $  
------------------------------------------------------------------------------------------------------------------------------------  
 WORKERS COMPENSATION AND WC STATU- OTH-  
 EMPLOYERS' LIABILITY TORY LIMITS ER  
 ---------------------------------------  
 ANY PROPRIETOR/PARTNER/EXECUTIVE E.L. EACH ACCIDENT $  
 OFFICER/MEMBER EXCLUDED? ---------------------------------------  
 E.L. DISEASE - EA  
 EMPLOYEE $  
 ---------------------------------------  
 If yes, describe under E.L. DISEASE - POLICY  
 SPECIAL PROVISIONS below LIMIT $  
------------------------------------------------------------------------------------------------------------------------------------  
C Other Products Lia ADT10643750030 10/29/04 10/29/05 7,500,000 per occ.  
 Clinical Trials 7,500,000 aggregate  
 Claims Made Retro Date: 05/20/01  
------------------------------------------------------------------------------------------------------------------------------------  
DESCRIPTION OF OPERATIONS/LOCATIONS/VEHICLES/EXCLUSIONS ADDED BY ENDORSEMENT/SPECIAL PROVISIONS  
  
------------------------------------------------------------------------------------------------------------------------------------  
  
  
CERTIFICATE HOLDER CANCELLATION  
------------------------------------------------------------------------------------------------------------------------------------  
   
 SHOULD ANY OF THE ABOVE DESCRIBED POLICIES BE CANCELLED BEFORE THE  
 EXPIRATION DATE THEREOF, THE ISSUING INSURER WILL ENDEAVOR TO MAIL 30 DAYS  
 WRITTEN NOTICE TO THE CERTIFICATE HOLDER NAMED TO THE LEFT, BUT FAILURE TO  
 DO SO SHALL IMPOSE NO OBLIGATION OR LIABILITY OF ANY KIND UPON THE INSURER,  
 Evidence of Coverage IT AGENTS OR REPRESENTATIVES.  
  
 /s/ illegible  
 ----------------------------------------------------------------------------  
 AUTHORIZED REPRESENTATIVE  
  
------------------------------------------------------------------------------------------------------------------------------------  
  
  
XXXXX 25 (2001/08) 1 of 2 #S60802/M60785 AMS ACCORD CORPORATION 1988  
  
  
 IMPORTANT  
  
If the certificate holder is an ADDITIONAL INSURED, the policy(ies) must be  
endorsed. A statement on this certificate does not confer rights to the  
certificate holder in lieu of such endorsement(s).  
  
If SUBROGATION IS WAIVED, subject to the terms and conditions of the policy,  
certain policies may require an endorsement. A statement on this certificate  
does not confer rights to the certificate holder in lieu of such endorsement(s).  
  
 DISCLAIMER  
  
The Certificate of Insurance on the reverse side of this form does not  
constitute a contract between the issuing insurer(s), authorized representative  
or producer, and the certificate holder, nor does it affirmatively or negatively  
amend, extend or alter the coverage afforded by the policies listed thereon.  
  
  
  
19th July, 2004  
  
To Whom It May Concern  
  
Dear Sirs,  
  
RHODIA U K LIMITED  
  
We act as Insurance Brokers for Rhodia U K Limited and have been asked to  
confirm details of the insurance pertaining to Public Liability and Employers  
Liability. Details are as follows:  
  
PUBLIC/PRODUCTS LIABILITY  
  
Insurer: AIG  
  
Policy No: 7 109 123  
  
Renewal Date: 1st January, 2005  
  
Cover EUR 7,500,000 any one loss, any one year  
  
EMPLOYERS LIABILITY  
  
Insurer: Zurich Commercial  
  
Policy No: 60006909  
  
Renewal Date: 31st March, 2005  
  
Cover 25,000,000 (British Sterling) per claim or  
 series of claims arising from any occurrence  
 inclusive of legal costs  
  
The policies are subject to insurers' standard terms, conditions and exceptions.  
This letter is issued for information purposes only and confers no rights to the  
holder and imposes no liability on the insurers.  
  
The insurers assume no responsibility to the holder of this letter to provide  
any notice of any material change or cancellation of the policy.  
  
Yours faithfully  
  
/s/ X. Xxxxxxxx  
  
X. XXXXXXXX (MISS)  
CLIENT SERVICE EXECUTIVE  
  
  
  
 ANNEX 9  
  
 QUALITY ASSURANCE/COMPLIANCE AGREEMENT FOR THE MANUFACTURE OF  
 ZILEUTON BY RHODIA PHARMA SOLUTIONS ON BEHALF OF CRITICAL  
 THERAPEUTICS  
  
 Version No: October 2004  
  
CIRCULATION:  
  
RPS Operational Quality, Xxxxxx (Original)  
RPS Operational Quality, Annan  
  
CTI (C Xxxxxxxxx)  
  
VALID FROM DATE:  
  
Date of last signature on page 2  
  
REVIEW DATE:  
  
Periodically but not more than 3 years from date of last signature  
  
 Page 1 of 19  
  
  
Written by: /s/ X. Xxxxxxx Date: 28th October 04  
 --------------  
 K Thomson (Product Manager, RPS)  
  
Approved by: /s/ X. Xxxxx Date: 28th October 2004  
 ------------  
 I Lisle (Head of Quality, RPS)  
  
Approved by: /s/ Xxxxxx Xxxxxxxxx Date: 29 October 2004  
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 C Xxxxxxxxx (Sr. Director QA, CTI)  
  
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1. Introduction and Scope  
  
Zileuton is an API manufactured by Rhodia Pharma Solutions Ltd (RPS) at the  
following UK sites:  
  
Rhodia Pharma Solutions, Xxxxx  
Xxxxx Xxxxx Xxxx  
Xxxxxx  
Xxxxx  
Xxxxxxxxxxxxx  
XX00 0XX  
  
Rhodia Pharma Solutions, Xxxxxx  
Xxxxxx  
Xxxxxxxxxxx  
Xxxxxxxxxxxxxx  
XX00 0XX  
  
These sites are hereinafter referred to as RPS, Annan and RPS, Dudley  
respectively.  
  
Zileuton API is made exclusively on behalf of Critical Therapeutics Inc.  
(hereinafter referred to as CTI) who are based at the following US address:  
  
00 Xxxxxxxx Xxxxxx  
Xxxxxxxxx, XX 00000  
  
Zileuton API is manufactured at RPS from [\*\*], with all downstream manufacturing  
being to full cGMP standards. The API can be milled by RPS, Annan or RPS, Xxxxxx  
or externally, by RPS's subcontractors [\*\*]  
  
[\*\*] also conduct the following activities:  
  
[\*\*]  
  
After [\*\*] packages the API, [\*\*]  
  
The material is despatched to SkyePharma (hereinafter SP) or Patheon for onward  
formulation at the following addresses:  
  
SkyePharma Production SAS  
ZA xx Xxxxxxx Ouest  
00 xxx xx Xxxxxxxxxx  
XX00  
  
 Page 4 of 19  
  
  
38291 St-Xxxxxxx-Fallavier cedex  
  
Patheon Pharmaceuticals Inc.  
0000 Xxxx Xxxxxxxxx Xxxx  
Xxxxxxxxxx  
XX 00000  
XXX  
  
[\*\*]  
  
This Quality Assurance Agreement is between Rhodia Pharma Solutions and Critical  
Therapeutics. It defines the quality assurance and quality compliance  
obligations and responsibilities of RPS and CTI that relate to the manufacture  
and supply of Zileuton API for clinical and/or commercial use. The agreement is  
structured to ensure that all pertinent quality issues are clearly identified  
and that responsibilities for the management of these issues are unequivocally  
defined. It should be noted that commercial issues (including supply, liability  
and confidentiality) are governed separately. The agreement does not apply to  
the manufacture of material for non-clinical development purposes. Specific  
quality assurance / compliance requirements relating to such material will be  
agreed separately as necessary.  
  
This agreement will come into effect on the "Valid From Date" (see pages 1 and  
2) and will be subject to review periodically or after a maximum of 3 years from  
this date. Amendments may be made at any time with the agreement of all  
signatories but, with the exception of the API specification (see Annex A),  
require the reapproval of this document.  
  
2. Definitions  
  
2.1 "cGMP" - current good manufacturing practice and standards as interpreted  
 by ICH Harmonised Tripartite Guideline, Good Manufacturing Practice Guide  
 for Active Pharmaceutical Ingredients (ICH Q7A) and relevant FDA and EMEA  
 guidance documents that relate directly to API manufacture.  
  
2.2 "API" - active pharmaceutical ingredient as defined by ICH Q7a.  
  
2.3 "CR" - controlled release  
  
2.4 "IR" - immediate release  
  
2.5 "Key raw data" - with respect to analytical data, this term means sample  
 chromatograms, spectra, x-ray diffractograms and particle size  
 distribution graphs.  
  
 Page 5 of 19  
  
  
2.6 "Reworking" - upgrading of API that does not conform to standards or  
 specifications using a process which is not part of the established  
 manufacturing process.  
  
2.7 "Reprocessing" - upgrading of API that does not conform to standards or  
 specifications using a process which is part of the established  
 manufacturing process (e.g. by repeating a crystallisation step).  
  
2.8 "USP" - the United States Pharmacopeia  
  
3. General Commitments  
  
3.1 It is the responsibility of RPS to ensure that the manufacture, analysis,  
 packaging, labelling, storage and despatch of Zileuton API that falls  
 within its scope (see Section 1 and separate commercial contract) is fully  
 in compliance with cGMP as defined in Section 2. This responsibility  
 extends to all activities at RPS Annan and Xxxxxx and also to its chosen  
 subcontractors. It should be noted that the approach to compliance for  
 clinical trial material may reflect section 19 of ICH Q7a.  
  
3.2 RPS commit to ensuring ongoing compliance with API specifications agreed  
 between CTI and RPS (including packaging, labelling and release  
 specifications). RPS will inform CTI of any significant non-compliance or  
 intended changes as per Sections 7 and 8. Note that different  
 specifications may apply to the API depending on the formulation (e.g.  
 immediate release and controlled release formulations). Current  
 specifications are set out in Annex A. Annex A may be updated (with  
 modified or additional specifications) following approval of the changes  
 by CTI and RPS, without the need for updating the main body of this  
 agreement.  
  
3.3 RPS commit to ensuring ongoing compliance with the agreed specifications  
 for critical in-process testing and for critical raw materials. RPS will  
 inform CTI of any significant non-compliance or intended changes as per  
 Sections 7 and 8.  
  
3.4 RPS will manufacture Zileuton API only at those premises agreed by RPS and  
 CTI (as specified in Section 1). RPS will not outsource / subcontract any  
 GMP activities that are related to Zileuton API (other than those already  
 specified in this document) without the prior written agreement of CTI.  
 RPS shall also ensure that its own subcontractors meet the appropriate  
 standards of cGMP. To this end RPS will periodically audit its  
 subcontractors and will implement specific formal quality  
  
 Page 6 of 19  
  
  
 agreements to define these responsibilities (as required by ICH Q7a part  
 16). RPS will provide copies of (or copies of the relevant sections of)  
 these agreements and any subcontrator audits that specifically relate to  
 Zileuton.  
  
3.5 RPS shall not use facilities to manufacture Zileuton API that have  
 previously been used for hazardous or sensitising material without the  
 prior agreement of CTI. Such materials shall include but are not limited  
 to penicillins, cephalosporins, pesticides, herbicides, rodenticides and  
 material of high pharmacological activity or toxicity such as steroids or  
 cytotoxic anti-cancer agents.  
  
3.6 RPS shall not use any person debarred, disqualified or restricted by the  
 US FDA for any activity associated with the manufacture or supply of [\*\*].  
  
3.7 CTI and RPS will all comply with the content of this quality agreement.  
  
4. Audit Programme  
  
4.1 CTI has responsibility to evaluate RPS to ensure compliance with the  
 general commitments set out in Section 3.1. RPS will support CTI in any  
 reasonable requests for such evaluation and will endeavour to implement  
 any reasonable changes to the extent that it is not in compliance with  
 such requirements. To this end, CTI shall have the right to perform a  
 formal audit of processes and procedures that relate to Zileuton API  
 (including having access to relevant personnel and facilities) on a yearly  
 frequency with an additional right to attend upon prior notice if there  
 has been a serious problem with quality. The audit may include a review of  
 regulatory compliance, GMP compliance (as defined in ICH Q7a and  
 appropriate guidelines) and compliance with this Agreement. These rights  
 are entirely separate from both parties' commitment to regular project and  
 technical meetings. In addition, CTI may, with prior agreement, attend  
 relevant RPS sites for the purpose of reviewing Zileuton-specific  
 documents.  
  
4.2 In the event of serious quality issues relating to zileuton and one (or  
 more) of RPS's subcontractors, CTI may  
  
 Page 7 of 19  
  
  
 request that RPS audit the subcontractor. RPS will support any reasonable  
 requests from CTI for such an audit and will also support CTI being  
 present during an audit of this nature.  
  
5. Analytical, Batch Release and Despatch Activities  
  
5.1 RPS is responsible for testing and release of all raw materials.  
  
5.2 RPS are responsible for in-process testing.  
  
5.3 RPS are responsible for testing and releasing the API (Zileuton) following  
 full review of the batch record (see also Section 5.5 for CTI's  
 involvement with batch release). The batch record review will cover the  
 batch production records for RPS [\*\*], review of analytical data and  
 review of any changes, deviations and out-of-specification investigations.  
 RPS shall ensure that any API that is released for onward formulation  
 conforms to the principles of cGMP and to the approved specifications.  
 However, RPS must also abide by the requirements for document provision  
 and review, change control and deviation notification as specified below  
 (see Sections 6, 7 and 8). In addition, RPS must supply CTI with the  
 following certification for each batch of API that it releases:  
  
 - A certificate of analysis (CoA) complying with ICH Q7a section 11.4  
 that provides all analytical data for which RPS are responsible.  
 This certificate will specifically reflect either the full set of  
 tests/specifications for the IR material or the full set of  
 tests/specifications for the CR material (see Annex A) (unless both  
 sets of results are required). CTI will inform RPS in advance of the  
 intended formulation (IR or CR) to ensure correct testing and Cof A  
 are provided (see Annex A).  
  
 - A certificate of conformity that confirms that the batch in question  
 was manufactured to cGMP standards and that the batch record has  
 been reviewed and the batch released by RPS quality department. In  
 addition, this certificate shall specify any deviations, changes or  
 out-of-specification investigations relating to the batch that  
 required  
  
 Page 8 of 19  
  
  
 prior notification to CTI (see Sections 7 and 8 below).  
  
 - A record of the tamper-evident seal numbers (see also section 5.7).  
  
5.4 RPS will provide a copy of the batch record to CTI for each of the NDA  
 batches made at RPS, for the first [\*\*] commercial lots and thereafter as  
 requested. These batch records will include (1) RPS's official raw  
 material release reports including, [\*\*], RPS's key raw data (2) key raw  
 data for all in-process and release testing (3) batch record from [\*\*]  
 including key analytical raw data and (4) all major and minor deviations  
 and investigations. CTI will review these executed batch records and send  
 any comments to Rhodia prior to the release of the NDA batches, the first  
 [\*\*] commercial batches from each manufacturing site and thereafter as  
 requested by CTI. In addition, Rhodia will provide CTI with an example  
 Certificate of Analysis for each raw material from each of RPS's vendors.  
 These will be from actual lots used for zileuton manufacture. New  
 certificates will be sent whenever Rhodia use a different supplier (see  
 also under 7.1).  
  
5.5 RPS are responsible for ensuring that all of the API release methods are  
 qualified / validated to an appropriate level as required by cGMP. Some of  
 the methods are compendial and hence do not require full validation. RPS  
 are also responsible for conducting a formal transfer of these methods to  
 SP and Patheon(or to their chosen subcontractor(s)). It should be noted  
 that those methods carried out by [\*\*] (i.e. particle size/surface area  
 and microbiological testing respectively) remain the responsibility of RPS  
 and, to this end, RPS will review and approve the [\*\*] validation  
 protocols and reports for these methods and will oversee the method  
 transfers to SP and Patheon. RPS will provide SP, Patheon and CTI with  
 copies of the method validation protocols and reports for review / comment  
 and will also provide CTI with the key raw data from the validation and  
 transfer programmes.  
  
5.6 RPS are responsible for characterising and providing the primary API  
 reference standard(s) for method validation purposes (except where these  
 are sourced from the USP).  
  
 Page 9 of 19  
  
  
5.7 RPS will ensure that each keg is sealed with a uniquely-numbered  
 tamper-evident seal.  
  
6. Document Provision and Review Requirements (including Process Validation)  
  
6.1 CTI and RPS are jointly responsible for approving the specifications of  
 the API (see Annex 1 for the current versions) and the packaging and  
 labelling specifications.  
  
6.2 RPS will generate detailed process documentation covering the process at  
 both Xxxxxx and Annan. These "baseline" documents will define the process,  
 plant, in-process specifications, critical parameters, the API  
 specification and methods, packaging specification, sampling requirements  
 and storage conditions. RPS shall also ensure that corresponding baseline  
 documents covering [\*\*] activities are prepared by [\*\*] respectively. RPS  
 will formally review and approve the [\*\*] documents prior to the first  
 milling of API for human use. RPS shall provide to CTI a copy of both sets  
 of baseline documents for review and approval and to faciliate compilation  
 of regulatory dossiers. This will be done prior to manufacture of any API  
 for human use so that the documents reflect the intent for ongoing  
 commerical supply (i.e. prior to the initial NDA batches). Updated copies  
 of the relevant baseline documents will be sent to CTI (as appropriate)  
 for review in the following circumstances:  
  
 - whenever a change is made to the basic synthetic route, to the site  
 of manufacture (e.g. prior to manufacture and validation on moving  
 from Xxxxxx to Annan) or to the API specification  
  
 - whenever an API analytical method is replaced Thereafter CTI will  
 review and approve changes as detailed in Section 7. RPS will  
 provide copies of other master documents relating to the manufacture  
 and testing of the API to CTI at CTI's request.  
  
6.3 RPS will provide copies of all process validation protocols and reports to  
 CTI. CTI will approve the initial protocols and reports associated with  
 each facility (Xxxxxx and Annan) and thereafter will approve any protocols  
 and reports associated with major changes.  
  
 Page 10 of 19  
  
  
7. Change Control Requirements  
  
7.1 RPS shall notify CTI of all major changes to the process, equipment,  
 facilities, analytical methods, specifications or materials that affect  
 Zileuton API. These changes will then be approved by CTI prior to  
 implementation by RPS. For the purposes of this document, a major change  
 is defined as any change that has a substantial potential to have an  
 adverse effect on the identity, strength, quality, purity or potency of  
 the product or which necessitates revalidation work or which affects any  
 regulatory submissions in such a way as to require prior notification to  
 the regulatory body (e.g. requires a minimum of a CBE in the US). The  
 following categories of change require prior notification to and  
 authorisation by CTI:  
  
 - Any change to the basic synthetic route (e.g. use of different  
 reagents)  
  
 - Any change to a critical process parameter outside the previously  
 accepted critical range  
  
 - Any change from one facility to another (even if on the same site)  
  
 - Major equipment changes affecting the API process from the final  
 solution onwards  
  
 - Major equipment changes affecting registration prior to the final  
 API solution  
  
 - Use of recycled solvents  
  
 - Changes to the specifications of the API  
  
 - Changes to the specifications associated with critical in-process  
 tests or critical raw materials  
  
 - Changes to API analytical methods that require some revalidation or  
 requalification of the method and/or which affect either  
 registrations or SP analytical methodology  
  
 - Changes to in-process and critical raw material analytical methods  
 that require some revalidation or requalification of the method and  
 which affect registrations  
  
 - Proposed use of out-of-specification raw materials.  
  
 - Changes to suppliers of critical raw materials  
  
 - Change of packaging or labelling  
  
 - Intent to outsource a GMP activity related to manufacture of  
 Zileuton API that was previously performed in-house (or vice versa)  
  
 Page 11 of 19  
  
  
 - Change of company name  
  
 - Change in the use of the Zileuton API facilities to include  
 hazardous or sensitising materials (see Section 3.6)  
  
 - Reprocessing or reworking of a batch of Zileuton API (see Section  
 8.2)  
  
 - Change to the retest date of the API (see Section 10.1)  
  
 - Change of contractors for following tests : Surface Area - Particle  
 Size Distribution -Microbio  
  
7.2 RPS shall provide CTI at the time of implementation with a copy of any  
 minor changes that impact on the regulatory submission(s). RPS shall also  
 provide CTI with a summary of all changes affecting the Zileuton  
 regulatory documentation once per annum one month prior to the annual  
 report date (see Section 12).  
  
7.3 Minor changes to the manufacturing documentation (i.e. those changes which  
 have no impact on quality or regulatory submissions) will not be notified  
 to CTI but will be available for audit.  
  
8. Deviations and Out-of-Specification Investigations  
  
8.1 RPS shall notify CTI of any major deviations that occur during the  
 manufacture, sampling, analysis, packaging, labelling, storage or despatch  
 of Zileuton API (including its registered intermediate stages) that are  
 the responsibility of RPS or any of its agreed subcontractors. This  
 notification shall occur prior to batch release. CTI will review and  
 approve the deviations and agree with RPS their impact on the release of  
 the API. Major deviations are those that could directly have a deleterious  
 impact on the quality (e.g. deviation from a critical parameter range or  
 critical in-process control) or are a significant breach of a regulatory  
 dossier commitment or represent a significant loss of control or breach of  
 GMP principles. All such deviations will also be recorded on the  
 certificate of compliance (see Section 5.3).  
  
8.2 RPS shall notify CTI within three working days of any batches of API that  
 fail to comply with the agreed specifications. Any such batches will not  
 be despatched.  
  
 Page 12 of 19  
  
  
 RPS are responsible for investigating the out-of-specification result  
 unless the investigation shows that the cause is directly related to  
 either the data provided by or requests made by CTI. CTI will approve the  
 disposition of all batches that are impacted by confirmed out-  
 of-specification results. RPS shall ensure that no reworking or  
 reprocessing is carried out without the prior agreement of CTI. Any  
 batches that have been reworked or reprocessed will be notified prior to,  
 or at the time of, despatch.  
  
9. Complaints and Recalls  
  
9.1 RPS commit to resolving all reasonable complaints made by CTI that relate  
 to the manufacture of Zileuton API. RPS shall endeavour, wherever  
 practicable, to resolve the complaint and issue a final response within 28  
 working days.  
  
9.2 RPS shall inform CTI within one working day of any quality issues that it  
 finds that have the potential to lead to a recall of any Zileuton.  
 Notification in writing shall occur within two working days. RPS shall  
 also provide reasonable and prompt assistance to investigate any recall  
 relating to Zileuton manufactured by RPS. The co-ordination and management  
 of any such recall will be the responsibility of CTI.  
  
10. Stability Programme  
  
10.1 The formal API stability programme is the responsibility of RPS. RPS will  
 provide CTI with the key raw data from this programme as it applies to the  
 NDA batches and first [\*\*] commercial/validation batches and therafter as  
 required to enable compilation of ongoing regulatory submissions (see also  
 Section 12). RPS will also provide CTI with other raw data as required and  
 requested from the stability programmes. CTI will approve the initial  
 stability protocols covering the NDA batches and [\*\*] commercial batches.  
 RPS will thereafter place [\*\*] on stability each year (unless either no  
 batches are manufactured or more are required and agreed as a result of,  
 for example, process changes). RPS will inform CTI of any proposed changes  
 to this intent and of any proposed changes to the testing regime. CTI will  
 review  
  
 Page 13 of 19  
  
  
 and approve any such changes. Any changes to the approved retest date of  
 the API that may be justified as a result of the stability programme will  
 not be implemented without the prior approval of RPS and CTI.  
  
11. Regulatory Issues  
  
11.1 RPS commit to ensuring ongoing compliance with relevant regulatory  
 submissions and to informing CTI of any significant non-compliance (see  
 also the Sections 7 and 8). CTI commit to providing up-to-date copies of  
 all sections of regulatory documents with which Rhodia must comply. CTI  
 also commits to ensuring that compliance with regulatory documents is  
 facilitated as far as is possible by, for example, ensuring that they are  
 not contradictory, that they allow for reasonable batch by batch  
 variability and that they are consistent with the baseline documentation  
 supplied by Rhodia to CTI prior to submission (see also Section 6).  
  
11.2 RPS shall inform CTI of any cGMP-based inspection (or intended inspection)  
 by a Regulatory Agency which may directly impact on the manufacture of  
 Zileuton API. Appropriate CTI employees or representatives will be able to  
 attend any inspection that is specific to Zileuton. RPS shall also provide  
 a copy of those parts of the inspection reports that directly impact  
 Zileuton.  
  
11.3 CTI is responsible for maintaining the regulatory dossiers in compliance  
 with changes handled in accordance with Section 7.  
  
12. Annual Product Quality Review  
  
12.1 RPS is responsible for conducting a product quality review on an annual  
 basis. This review shall comply with section 2.50 of ICH Q7a and a copy  
 shall be provided to CTI one month prior to the annual report due date.  
 This review shall list all of the changes made during the year that impact  
 on regulatory submissions and also summarise the stability data generated  
 during the year in question. Additional review(s) will be undertaken if  
 necessary to comply with cGMP.  
  
 Page 14 of 19  
  
  
 ANNEX A - API SPECIFICATIONS  
  
1. API specification relevant for use in the immediate release (IR)  
 formulation - version 1  
  
2. API specification relevant for use in the controlled release (CR)  
 formulation - version 1  
  
Note  
  
This page (and associated specifications) may be updated if the API  
specifications are changed and reapproved  
  
 Page 15 of 19  
  
  
1. API SPECIFICATION RELEVANT FOR USE IN THE IMMEDIATE RELEASE (IR) FORMULATION  
- VERSION 1  
  
  
  
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Approved by: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 (Rhodia Pharma Solutions)  
  
Approved by: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 (Critical Therapeutics)  
  
Specification Revision History  
  
  
  
 ALTERATIONS, ADDITIONS,  
 DATE VERSION NUMBER OMISSIONS  
--------- -------------- ----------------------  
   
JUNE 2004 VERSION 1 FIRST ISSUE  
  
  
  
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2. API SPECIFICATION RELEVANT FOR USE IN THE CONTROLLED RELEASE (CR) FORMULATION  
- VERSION 1  
  
  
  
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 Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 (Rhodia Pharma Solutions)  
  
Approved by: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 Date:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  
 (Critical Therapeutics)  
  
Specification Revision History  
  
  
  
 ALTERATIONS, ADDITIONS,  
 DATE VERSION NUMBER OMISSIONS  
--------- -------------- ----------------------  
   
JUNE 2004 VERSION 1 FIRST ISSUE  
  
  
  
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 ANNEX B - RESPONSIBLE PERSONS / CONTACTS  
  
CRITICAL THERAPEUTICS  
  
  
  
PERSON / RESPONSIBILITY TELEPHONE NUMBER FAX NUMBER  
----------------------- ---------------- ------------  
   
QA  
  
Xxxxxx Xxxxxxxxx 000-000-0000 000-000-0000  
Xxxxxx Xxxxxx 000-000-0000 000-000-0000  
QC  
Xxxxxx Xxxxxx 000-000-0000 000-000-0000  
Xxxxxx Xxxxx 000-000-0000 000-000-0000  
  
Technical  
Xxxxxx Xxxxxxxxx 000-000-0000 000-000-0000  
Xxxxxx Xxxxxx 000-000-0000 000-000-0000  
Commercial  
Xxxxx Xxxxxxxxx 000-000-0000 000-000-0000  
  
  
RHODIA PHARMA SOLUTIONS  
  
  
  
PERSON / RESPONSIBILITY TELEPHONE NUMBER FAX NUMBER  
----------------------- ---------------- ---------------  
   
QA  
Xxx Xxxxx x00 000 0000000 x00 000 0000000  
QC  
Xxx Xxxxxxx x00 0000 000000 x00 0000 000000  
Xxxx Xxxxxx x00 000 0000000 x00 000 0000000  
Technical  
Xxxxxxxxxx Xxxxxx x00 0000 000000 x00 0000 000000  
Commercial  
Xxx Xxxxxxx x00 000 0000000 x00 000 0000000  
  
  
 Page 19 of 19  
  
  
 Annex 10  
  
 Validation Report  
  
 [document to follow]  
  
 35  
  
  
 ANNEX 11  
  
[RHODIA LOGO]  
  
PHARMA SOLUTIONS  
  
 CONFIDENTIAL  
 PROPOSAL  
  
 VALIDATION OF ZILEUTON  
  
 Proposal ANNSEN22032004A  
  
 (Supercedes Proposal ANNMTH25112003)  
  
 PREPARED FOR:  
  
 XXXX X. XXXXX, M.D.  
 CHIEF EXECUTIVE OFFICER & PRESIDENT  
 CRITICAL THERAPEUTICS  
 000 XXXXXXXXXXXXX XXX. 00XX XXXXX  
 XXXXXXXXX, XX 00000  
  
 23/03/04  
  
  
  
[RHODIA LOGO] CONFIDENTIAL  
  
PHARMA SOLUTIONS  
  
 CONTENTS  
  
  
  
   
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PHARMA SOLUTIONS  
  
 1. EXECUTIVE SUMMARY  
  
Critical Therapeutics has agreed to purchase Zileuton CR and Zileuton IR from  
Xxxxxx Pharmaceuticals. Zileuton is on the market for the treatment of Asthma.  
Critical Therapeutics has asked Rhodia Pharma Solutions to review Xxxxxx'x  
process and provide a proposal through validation and commercial manufacture of  
Zileuton.  
  
Rhodia Pharma Solutions has considered the above requests and is pleased to  
offer the following proposal based on the technical data provided by both  
Critical Therapeutics and Xxxxxx Pharmaceuticals. A timeline for the activities  
described is provided for discussions between Rhodia Pharma Solutions and  
Critical Therapeutics.  
  
Based on the processing details provided, Rhodia Pharma Solutions feels we can  
reach Critical's target at the [\*\*] tonne scale of approximately $[\*\*]/kilogram.  
  
The price is estimated to be $[\*\*] to provide material for formulation  
development and to register Xxxxx as the site of manufacture and validate the  
process in A1. This price would be on a time and materials basis.  
  
  
   
PHASE 1  
  
Technical Transfer / Familiarisation Phase $ [\*\*]  
Manufacture of [\*\*] batches Dudley Pilot Plant $ [\*\*]  
Dudley Validation $ [\*\*]  
  
PHASE 2  
Cost for Analytical Validation and TT $ [\*\*]  
  
PHASE 3  
Xxxxx Validation $ [\*\*]  
Stability Studies $ [\*\*]  
 ------  
TOTAL $ [\*\*]  
 ------  
  
  
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PHARMA SOLUTIONS  
  
 2. PROPOSAL  
  
The process used to prepare Zileuton is shown below:  
  
 [\*\*]  
  
 FIG. 1 PROPOSED PILOT PLANT SYNTHESIS OF ZILEUTON  
  
Phase 1: Familiarisation Phase & Manufacture at Dudley  
  
 a) Familiarisation  
  
Abbott developed and scaled up this process in-house before licensing the  
process to Critical. As part of transferring the process, Rhodia Pharma  
Solutions would carry out laboratory and analytical familiarization.  
  
Rhodia Pharma Solutions has identified raw material suppliers. Currently, a  
Japanese supplier is holding enough 2ABT for the manufacture of [\*\*]kg of  
Zileuton. Further material is on a [\*\*] lead-time. Methyl carbamate is on a [\*\*]  
lead-time.  
  
 b) Manufacture of up to [\*\*] kg non-GMP  
  
The initial hazard evaluation work carried out by Rhodia Pharma Solutions has  
uncovered a significant safety hazard with the Abbott process. The formation of  
hydroxuyurea has been found to be unstable at the reaction temperature. In light  
of this there are some additional safety precautions required to fit the 300  
gallon stream located at Rhodia Pharma Solution's Dudley, England, facility.  
This site is not the long-term home for Zileuton but provides comparatively  
rapid entry. The hazard evaluation study has provided the basis for the  
engineering design to support both the Dudley pilot plant and the A1 commercial  
long-term home at Xxxxx.  
  
Some pilot plant refit work will be required in order to safely handle the  
hydroxylamine. (This is related to ensuring that no metal components have the  
potential to come into contact with hydroxylamine).  
  
After completion of the lab familiarisation, up to [\*\*] batches will be run to  
yield approx [\*\*]kg of Zileuton. This material will support the formulation  
development work required on either CR or IR formulation. The material will be  
milled by Micron Technologies to an agreed particle size specification.  
  
Details of the initial campaign are summarized below.  
  
 Proposal Page 4 of 24  
  
  
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TABLE 1. DETAILS FOR [\*\*]KG NON-GMP CAMPAIGN.  
  
  
  
 TOTAL  
 EQUIPMENT SIZE NUMBER OF PROCESSING  
STAGE (UK GALLONS) BATCHES DAYS  
----- ------------ -------------- ----------  
   
 1 [\*\*] [\*\*] [\*\*]  
TOTAL [\*\*]  
  
  
Skye Pharma would use the material for tabletting development work for both IR  
and CR programmes.  
  
 c) Validation  
  
In order to support the IR programme timelines, it is proposed that a validation  
campaign be carried out at Dudley. This will also provide Critical Therapeutics  
with security of supply, as Zileuton will in due course be manufactured at  
either RPS UK facility.  
  
A [\*\*]-batch campaign is planned including [\*\*] validation batches. The [\*\*]  
validation lots would be put on stability (6 months at 40 degrees C/75%RH, 24  
months at 25 degrees C/60%RH).  
  
The material would be used for sNDA stability for the IR submission and for  
tabletting by Skye Pharma for IND bioequivalence work, as well as by Skye Pharma  
for scale-up work in Lyon.  
  
TABLE 2. DETAILS FOR [\*\*]KG VALIDATION CAMPAIGN.  
  
  
  
 TOTAL  
 EQUIPMENT SIZE NUMBER OF PROCESSING  
STAGE (UK GALLONS) BATCHES DAYS  
----- ------------ -------------- ----------  
   
 1 [\*\*] [\*\*] [\*\*]  
TOTAL [\*\*]  
  
  
 Proposal Page 5 of 24  
  
  
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Phase 2: Analytical Validation  
  
In order to support the IR programme, the timeline for analytical method  
validation has been compressed. In addition full analytical method validation is  
now planned to satisfy FDA requirements. Hence the methods for raw materials,  
IPC and API will be formally validated prior to the validation campaign in A1 at  
Xxxxx and the stability programme being initiated. The API methods would be  
transferred to Skye Pharma under the same protocol.  
  
Overall, validation of the methods will require the synthesis and  
characterisation of approximately sixteen reference standards. It is assumed  
that the remaining will be purchased from USP or suppliers. The characterization  
of these impurities is also required in order to develop new analytical methods  
where necessary.  
  
Phase 3: Validation batches  
  
The Xxxxx site is especially equipped to handle API manufacture at scale. The  
process presents a good fit for the A1 plant which is suitable for the  
manufacture of up to [\*\*] Mt of Zileuton.  
  
After completion of Phase 1 & Phase 2, [\*\*] batches, including [\*\*] validation  
batches, will be run to target a yield [\*\*] kg of Zileuton. A [\*\*]kg batch size  
will be targeted. The [\*\*] validation lots would be put on stability (6 months  
at 40 degrees C/75%RH, 24 months at 25 degrees C/60%RH). The data from the Xxxxx  
validation campaign will be included in both the IR and CR submissions.  
  
Some plant refit work will be required in order to safely handle the  
hydroxylamine and the subsequent hydroxyurea reaction. This will provide a  
purpose made facility for the long-term manufacture of Zileuton.  
  
Details of the validation campaign are summarized below.  
  
TABLE 1. DETAILS FOR VALIDATION CAMPAIGN.  
  
  
  
 TOTAL  
 EQUIPMENT SIZE NUMBER OF PROCESSING  
STAGE (UK GALLONS) BATCHES DAYS  
----- ------------ -------------- ----------  
   
 1 [\*\*] [\*\*] [\*\*]  
TOTAL [\*\*]  
  
  
 Proposal Page 6 of 24  
  
  
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The material would be used for NDA stability for both the IR and CR programmes,  
as well as providing commercial IR material.  
  
 Proposal Page 7 of 24  
  
  
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PHARMA SOLUTIONS  
  
 3. ESTIMATED PRICE/KEY ASSUMPTIONS  
  
 PHASE 1: FAMILIARISATION PHASE  
  
  
  
 CALENDAR RESOURCE ESTIMATED  
 ACTIVITY TIME DAYS RESOURCE PRICE ($)  
 -------- -------- -------- -------- ----------  
   
 Lab Familiarisation [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Analytical Support [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Hazards Evaluation [\*\*] [\*\*] [\*\*] [\*\*]  
  
Materials and Columns [\*\*]  
  
 ESTIMATED TOTAL [\*\*] $[\*\*]  
  
  
 Proposal Page 8 of 24  
  
  
[RHODIA LOGO] CONFIDENTIAL  
  
PHARMA SOLUTIONS  
  
 PHASE 1: [\*\*]KG NON-GMP CAMPAIGN  
  
  
  
 CALENDAR RESOURCE ESTIMATED  
 ACTIVITY TIME DAYS RESOURCE PRICE ($)  
 -------- -------- -------- -------- ----------  
   
  
Pilot Plant Processing  
 (Including cleaning) [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Pilot Plant Safety  
 Trials [\*\*] [\*\*] [\*\*]  
  
 Safety Studies [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Chemist Support on  
 Pilot Plant [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Analytical / QA  
Support on Pilot Plant [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Documentation [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Materials and  
 Supplies [\*\*]  
  
 Hydroxylamine Refit [\*\*] [\*\*]  
  
 Milling [\*\*] Micron [\*\*]  
 Xxxxx  
 ESTIMATED TOTAL $[\*\*]  
  
  
 Proposal Page 9 of 24  
  
  
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PHARMA SOLUTIONS  
  
 PHASE 1B: [\*\*] KG VALIDATION CAMPAIGN  
  
  
  
 CALENDAR RESOURCE ESTIMATED  
 ACTIVITY TIME DAYS RESOURCE PRICE ($)  
 -------- -------- -------- -------- ----------  
   
Pilot Plant Processing  
 (Including cleaning) [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Chemist Support on  
 Pilot Plant [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Analytical/QA  
Support on Pilot Plant [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Materials and  
 Supplies [\*\*]  
  
 Milling [\*\*] Micron [\*\*]  
 Xxxxx  
 ESTIMATED TOTAL $[\*\*]  
  
  
 PHASE 2: ANALYTICAL VALIDATION  
  
  
  
 CALENDAR RESOURCE ESTIMATED  
 ACTIVITY TIME DAYS RESOURCE PRICE ($)  
 -------- -------- -------- -------- ----------  
   
 Analytical method  
 validation & tech  
 transfer [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Synthesis of 16  
 reference substances [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Analytical  
characterization of 16  
 reference substances [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Purchased of 14  
 reference substances [\*\*]  
  
 Estimated total $ [\*\*]  
  
  
 Proposal Page 10 of 24  
  
  
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PHARMA SOLUTIONS  
  
 PHASE 3: VALIDATION CAMPAIGN A1 XXXXX  
  
  
  
 CALENDER RESOURCE ESTIMATED  
 ACTIVITY TIME DAYS RESOURCE PRICE ($)  
 -------- -------- -------- -------- ----------  
   
 Processing  
 (Including cleaning) [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Chemist Support on  
 Pilot Plant [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Analytical / QA  
Support on Pilot Plant [\*\*] [\*\*] [\*\*] [\*\*]  
  
 cGMP Documentation [\*\*] [\*\*] [\*\*] [\*\*]  
  
 Materials and  
 Supplies [\*\*] [\*\*]  
  
 Plant Modifications [\*\*] [\*\*]  
  
 ESTIMATED TOTAL $[\*\*]  
  
  
 PHASE 3: STABILITY STUDIES  
  
  
  
 PROTOCOL PULLS IN MONTHS TOTAL DAYS TOTAL PRICE $  
 -------- --------------- ---------- -------------  
   
[\*\*] batches accelerated [\*\*] [\*\*] [\*\*]  
  
[\*\*] batches long term [\*\*] [\*\*] [\*\*]  
  
Program set-up [\*\*] [\*\*]  
  
ESTIMATED TOTAL [\*\*] $[\*\*]  
  
  
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PHARMA SOLUTIONS  
  
 KEY ASSUMPTIONS  
  
- Analytical methods have been supplied during the technical transfer; the  
 price includes the formal validation of the methods.  
  
 Assumed as:  
  
 6 off HPLC methods  
 3 off GC for residual solvents  
 1 off XRD ( methodology undefined at present )  
  
 Not included:  
  
 Microbiological testing, to be defined and outsourced. Surface area  
 and particle size will be subcontracted to Micron.  
  
- Stability indicating analytical methods are the same as the API release  
 methods.  
  
- Stability methods are applied to [\*\*] qualification batches out of Dudley  
 and [\*\*] validation batches out of Xxxxx. Both accelerated and real time  
 programs will be run in parallel up to [\*\*].  
  
- Milling has been included for the initial Dudley campaign and will be  
 subcontracted to Micron Technologies. Prices for milling latter campaigns  
 and validation costs are yet to be defined. The milling will be taken  
 in-house at suitable volume.  
  
- An estimate of price is given assuming suitable reference standards  
 (fourteen) can be purchased commercially. Rhodia Pharma Solutions will  
 manufacture the remaining sixteen standards.  
  
- The 2ABT is on a [\*\*] lead-time.  
  
Chemist, analyst and QA time will be billed at the rate of $[\*\*] per day.  
Chemicals, services and supplies will be billed at cost plus [\*\*]%. Pilot Plant  
time will be billed at $[\*\*] per day.  
  
The actual charges for Critical Therapeutics account will be invoiced monthly,  
with payment due net 30 days from invoice date.  
  
 Proposal Page 12 of 24  
  
  
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PHARMA SOLUTIONS  
  
 4.SCOPE OF WORK/DELIVERABLES  
  
RHODIA PHARMA SOLUTIONS WILL:  
  
- Perform tech transfer, laboratory evaluation and familiarisation  
 experiments on the process.  
  
- Synthesise and characterise sixteen reference standards targeting 1-10  
 grams of each with a minimum purity of 95%. Analyse the standards by HPLC,  
 IR, NMR and MS.  
  
- Validate the analytical methods and for the API, carry out technology  
 transfer to Skye Pharma.  
  
- Prepare approximately [\*\*] kg of Zileuton non-cGMP conditions in the Pilot  
 Plant at its Dudley, England facility.  
  
- Validate the Zileuton process during a [\*\*]kg campaign in the Pilot Plant  
 at its Dudley, England facility.  
  
- Validate the Zileuton process during the same [\*\*]kg campaign in the A1  
 Plant at its Xxxxx, Scotland facility  
  
- Provide written status reports on a monthly basis with teleconferences  
 and/or meetings to be organised as agreed appropriate.  
  
- Provide copies of master batch records used in the pilot plant.  
  
- Provide written reports summarising all phases of the work undertaken on  
 the project.  
  
- After completion of the registration campaign, carry out stability  
 programmes and provide a report.  
  
- Provide a hazard evaluation report.  
  
CRITICAL THERAPEUTICS WILL:  
  
- Agree to a final product release specification prior to scale-up  
 activities.  
  
- Provide any relevant health, safety, and environmental information.  
  
- Provide any hazard information pertaining to the process.  
  
- Provide any samples that are available to assist Rhodia Pharma Solutions  
 in polymorph determinations and analytical support.  
  
- Provide batch records / development reports for the process and arrange  
 for technical discussion / transfer with Abbott / SkyePharma.  
  
 Proposal Page 13 of 24  
  
  
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 5.TIMELINE  
  
Upon acceptance by Critical Therapeutics of this proposal, work could begin  
immediately at Rhodia Pharma Solutions. The initial Dudley non-GMP material  
would be delivered in parts, the first part delivered to Skye by [\*\*]. The  
Dudley validation campaign will be complete by [\*\*] and the Xxxxx validation  
complete by [\*\*].  
  
 6. COMMUNICATION  
  
A Rhodia Pharma Solutions technical project manager will be appointed to handle  
technology transfer and technical interface issues for the project. The Rhodia  
Pharma Solutions product manager will coordinate all timeline and financial  
aspects of the project with Critical Therapeutics and will be available for  
discussions as required.  
  
 7. TERMINATION  
  
Either party shall be entitled to terminate this agreement before the project  
has been completed by giving to the other party 90 days prior written notice of  
termination.  
  
Termination shall be effective on the expiration of the applicable notice period  
(the Effective Termination Date).  
  
All work performed by RPS prior to the Effective Termination Date of the project  
shall be paid for by Critical Therapeutics at the estimated cost provided herein  
prorated for the work performed to the Effective Termination Date. Any raw  
material/capital expenses incurred and/ or committed by RPS prior to the  
Effective Termination Date, or any expenditure required by RPS to return the  
unit to its original condition prior to commencement of the capital project  
shall be paid by Critical Therapeutics. RPS will seek to minimize all costs  
associated with the reason for termination and will provide justification of the  
expenditure to Critical Therapeutics.  
  
 Proposal Page 14 of 24  
  
  
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 0.XXXXXXX  
  
For additional information or questions, please contact:  
  
 Xxx Xxxxxxx  
 Product Manager  
 Rhodia Pharma Solutions  
 Dudley  
 Northumberland  
 England  
  
 Phone: 00-00-000-000-0000  
 Email: xxx.xxxxxxx@xx.xxxxxx.xxx  
  
 9. ACCEPTANCE  
  
Please indicate Critical Therapeutics acceptance of this proposal by returning a  
signed copy or a purchase order, referencing Proposal. This proposal is valid  
for 30 days.  
  
CRITICAL THERAPEUTICS  
  
By: /s/ Xxxx Xxxxx Date: March 23, 2004  
 -----------------------------------  
  
Name: Xxxx Xxxxx, CEO  
  
 Proposal Page 15 of 24  
  
  
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PHARMA SOLUTIONS  
  
 APPENDIX  
  
  
  
 ABBOTT NUMBER CHEMICAL NAME STRUCTURE CAS NUMBER  
 ------------- ------------- --------- ----------  
   
1. [\*\*] [\*\*] [\*\*] [\*\*]  
2. [\*\*] [\*\*] [\*\*] [\*\*]  
3. [\*\*] [\*\*] [\*\*] [\*\*]  
4. [\*\*] [\*\*] [\*\*] [\*\*]  
5. [\*\*] [\*\*] [\*\*] [\*\*]  
6. [\*\*] [\*\*] [\*\*] [\*\*]  
7. [\*\*] [\*\*] [\*\*] [\*\*]  
8. [\*\*] [\*\*] [\*\*] [\*\*]  
9. [\*\*] [\*\*] [\*\*] [\*\*]  
10. [\*\*] [\*\*] [\*\*] [\*\*]  
11. [\*\*] [\*\*] [\*\*] [\*\*]  
12. [\*\*] [\*\*] [\*\*] [\*\*]  
13. [\*\*] [\*\*] [\*\*] [\*\*]  
14. [\*\*] [\*\*] [\*\*] [\*\*]  
15. [\*\*] [\*\*] [\*\*] [\*\*]  
16. [\*\*] [\*\*] [\*\*] [\*\*]  
  
  
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[RHODIA LOGO]  
  
PHARMA SOLUTIONS  
  
 TIMELINE  
  
[\*\*]  
  
  
  
[RHODIA LOGO] CONFIDENTIAL  
  
PHARMA SOLUTIONS  
  
 SCOPE CHANGE NOTIFICATION  
  
RHODIA PHARMA SOLUTIONS, DUDLEY PROPOSAL #  
Cramlington, Northumberland, Prepared for:  
3 0XX, Xxxxxx Xxxxxxx Xxxxxx Xxxxxxx  
Tel: x00 (0)000 000 0000 CTI  
Fax: x00 (0) 000 000 0000 Tel:  
 Fax:  
PRODUCT MANAGER: XXX XXXXXXX  
  
NATURE OF CHANGE: Increased Number of Batches  
PREVIOUSLY AGREED DELIVERABLE: [\*\*] to [\*\*] batches  
IMPACT ON DELIVERY DATE Split Campaigns to [\*\*]  
REQUEST MADE BY: Xxx Xxxxxxx DATE: 24th June 04  
SCOPE CHANGE ASSESSED BY: Xxxxxx Xxxxxxxx  
  
 XXXXX SUMMARY  
  
  
  
 CALENDAR RESOURCE RESOURCE ESTIMATED  
 TIME DAYS PRICE ($)  
   
 Additional materials $ [\*\*]  
 Additional Pilot Plant Days [\*\*] $ [\*\*] $ [\*\*]  
 Additional Chemist Support [\*\*] $ [\*\*] $ [\*\*]  
Additional Analytical Support [\*\*] $ [\*\*] $ [\*\*]  
 TOTAL $ [\*\*]  
  
  
Note that price excludes milling. A separate scope change will be raised to  
cover additional milling requests.  
  
  
  
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PHARMA SOLUTIONS  
  
AGREEMENT:  
  
CUSTOMER RHODIA PHARMA SOLUTIONS  
  
Signature: /s/ Xxxxxx Xxxxxxx Signature: /s/ Xxx Xxxxxxx  
 ---------------------- ---------------  
  
Name: Xxxxxx Xxxxxxx Name: Xxx Xxxxxxx  
  
 Proposal Page 20 of 24  
  
  
[RHODIA LOGO] CONFIDENTIAL  
  
PHARMA SOLUTIONS  
  
 SCOPE CHANGE NOTIFICATION  
  
RHODIA PHARMA SOLUTIONS, DUDLEY PROPOSAL #  
Cramlington, Northumberland, Prepared for:  
XX00 0XX, Xxxxxx Xxxxxxx Xxxxxx Xxxxxxx  
Tel: x00 (0)000 000 0000 CTI  
Fax: x00 (0) 000 000 0000 Tel:  
 Fax:  
PRODUCT MANAGER: XXX XXXXXXX  
  
NATURE OF CHANGE: Additional Stability Testing  
PREVIOUSLY AGREED DELIVERABLE: [\*\*] Xxxxx batches  
NEW DELIVERABLE Now plus [\*\*] Dudley batches  
REQUEST MADE BY: Xxx Xxxxxxx DATE: 12th August 04  
SCOPE CHANGE ASSESSED BY: Xxxxxx Xxxxxxxx  
  
 XXXXX SUMMARY  
  
  
  
 ACTIVITY CALENDAR TIME ESTIMATED PRICE ($)  
 -------- ------------- -------------------  
   
Dudley validation ([\*\*]) - accelerated [\*\*] [\*\*]  
 Dudley validation ([\*\*]) - long term [\*\*] [\*\*]  
 ESTIMATED TOTAL $ [\*\*]  
  
  
AGREEMENT:  
  
CUSTOMER RHODIA PHARMA SOLUTIONS  
  
Signature: /s/ Xxxxx Xxxxxxxxx Signature: /s/ Xxx Xxxxxxx  
 -------------------------- ---------------------  
  
Name: Xxxxx Xxxxxxxxx Name: Xxx Xxxxxxx  
  
This negates Scope Change of July 21, 2004 (/s/ SB, 8/12/04)  
  
s Proposal Page 21 of 24  
  
  
[RHODIA LOGO] CONFIDENTIAL  
  
PHARMA SOLUTIONS  
  
 SCOPE CHANGE NOTIFICATION  
  
RHODIA PHARMA SOLUTIONS, XXXXXX PROPOSAL #  
Cramlington, Northumberland, Prepared for:  
XX00 0XX, Xxxxxx Xxxxxxx Xxxxx Xxxxxxxxx  
Tel: x00 (0)000 000 0000 CTI  
Fax: x00 (0)000 000 0000 Tel:  
 Fax:  
PRODUCT MANAGER: XXX XXXXXXX  
  
NATURE OF CHANGE: Additional milling requests  
PREVIOUSLY AGREED DELIVERABLE: Not applicable  
IMPACT ON DELIVERY DATE Not applicable  
REQUEST MADE BY: Xxx Xxxxxxx DATE: 28th Sept. 04  
SCOPE CHANGE ASSESSED BY: Xxxxxx Xxxxxxxx  
  
 XXXXX SUMMARY  
  
  
  
 CALENDAR RESOURCE ESTIMATED  
 TIME DAYS RESOURCE PRICE ($)  
 -------- -------- -------- ---------  
   
 Analytical Support $ [\*\*]  
Validation & Transfers $ [\*\*]  
 Milling $ [\*\*]  
 TOTAL $ [\*\*]  
  
  
AGREEMENT:  
  
CUSTOMER RHODIA PHARMA SOLUTIONS  
  
Signature: /s/ Xxxxxx Xxxxxxx Signature: /s/ Xxx Xxxxxxx  
 ------------------------- ---------------  
  
Name: Xxxxxx Xxxxxxx Name: Xxx Xxxxxxx  
  
 Proposal Page 22 of 24  
  
  
ANNEX 12 - CAPITAL DESCRIPTION  
  
In order to manufacture [\*\*]/annum on an ongoing basis RPS estimate the  
following costs  
  
[\*\*]  
  
  
  
ANNEX 13 - POST DELIVERY PERIOD PRICING  
  
Equal to or less than [\*\*]  
 $[\*\*]/kg  
  
Greater than [\*\*], up to less than [\*\*]  
 $[\*\*]/kg  
  
Equal to or greater than [\*\*], up to less than [\*\*]  
 $[\*\*]/kg  
  
Equal to or greater than [\*\*], up to less than [\*\*]  
 $[\*\*]/kg  
  
Equal to or greater than [\*\*]  
 $[\*\*]/kg  
  
Target  
 $[\*\*]/kg  
  
  
ANNEX 14  
  
ABBOTT  
  
Global Pharmaceutical Licensing and New Business Development  
Xxxxxx Laboratories  
000 Xxxxxx Xxxx Xxxx  
Xxxxxx Xxxx, Xxxxxxxx 00000-0000  
  
January 28, 2005  
  
Xxxxxxx X. Xxxxxxxx  
Chief Patent Counsel  
Critical Therapeutics, Inc.  
00 Xxxxxxxx Xxxxxx  
Xxxxxxxxx, XX 00000  
  
Dear Xx. Xxxxxxxx:  
  
Xxxxxx Laboratories, a corporation organized under the laws of the State of  
Illinois, USA, with its principal office at 000 Xxxxxx Xxxx Xxxx, Xxxxxx Xxxx,  
Xxxxxxxx 00000 ("Abbott") has granted Critical Therapeutics, Inc., a corporation  
organized under the laws of the State of Delaware, USA, with its principal  
office at 000 Xxxxxxxxxxxxx Xxxxxx, 00xx Xxxxx, Xxxxxxxxx, Xxxxxxxxxxxxx 00000  
("CTI") two licenses dated 18 December 2003 and 19 March 2004 related to the  
active pharmaceutical compound zileuton. Both of the license agreements included  
a "Covenant Not to Xxx" clause which was a promise by Abbott not to assert any  
of its patent rights against certain defined activities of CTI.  
  
CTI has now indicated a desire to contract with certain third parties for  
production of the zileuton compound and has indicated that said third parties  
have expressed a concern about being free to pursue such production free from  
liability under any Abbott patents.  
  
Abbott, in order to facilitate CTI's operation under these two licenses and  
hasten the day when CTI can reach the market with products contemplated under  
these licenses, hereby covenants not to bring any suit for patent infringement  
based upon the activities involved in manufacturing the zileuton compound by any  
such third party for CTI in support of CTI activities under these licenses. This  
promise shall run concurrently with these licenses and shall expire upon the  
expiration or termination of the later of these two license to end. It is  
intended that any such third party manufacturer be a third party beneficiary of  
this promise. CTI is free to provide a copy of this promise to any third party  
manufacturer who has expressed or expresses a concern in this regard.  
  
With kind regards,  
  
/s/ Xxxxxxx Xxxxxx  
  
Xxxxxxx X. Xxxxxx, Ph.D.  
Divisional Vice President  
Scientific Assessment and Technology Licensing  
Global Pharmaceutical Licensing  
D-R50A, AP34; 000 Xxxxxx Xxxx Xxxx  
Xxxxxx Xxxx, XX 00000-0000  
  
Cc: X. Xxxxxxxxx, X. Xxxxxx  
  
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