PUBLIC HEALTH SERVICE

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

This Cooperative Research and Development Agreement, hereinafter referred to as the "CRADA," consists of this Cover Page, an attached Agreement, and various Appendices referenced in the Agreement. This Cover Page serves to identify the Parties to this CRADA:

(1) the following Bureau(s), Institute(s), Center(s) or Division(s) of the National Institutes of Health ("NIH"), the Food and Drug Administration ("FDA"), and the Centers for Disease Control and Prevention ("CDC"):

Food and Drug Administration , hereinafter singly or collectively referred to as the Public Health Service ("PHS"); and

(2) Conformia, 1001 Marshall Street, Suite 550, Redwood City, CA 94063-2000, hereinafter referred to as the "Collaborator."

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

Article 1. Introduction

This Cooperative Research and Development Agreement (CRADA) between PHS and the Collaborator will be effective when signed by all Parties. The research and development activities which will be undertaken by each of the Parties in the course of this CRADA are detailed in the Research Plan (RP) which is attached as Appendix A. The funding and staffing commitments of the Parties are set forth in Appendix B. Any exceptions or changes to the CRADA are set forth in Appendix C. This CRADA is made under the authority of the Federal Technology Transfer Act, 15 U.S.C. '3710a and is governed by its terms.

Article 2. Definitions

As used in this CRADA, the following terms shall have the indicated meanings:

2.1 "Affiliate" means any corporation or other business entity controlled by, controlling, or under common control with Collaborator. For this purpose, "control" means direct or indirect beneficial ownership of at least fifty (50) percent of the voting stock or at least fifty (50) percent interest in the income of such corporation or other business.

2.2 "Cooperative Research and Development Agreement" or "CRADA" means this Agreement, entered into by PHS pursuant to the Federal Technology Transfer Act of 1986, as amended, 15 U.S.C. 3710a et seq. and Executive Order 12591 of October 10, 1987.

2.3 "Government" means the Government of the United States as represented through the PHS agency that is a Party to this agreement.

2.4 "IP" means intellectual property.

2.5 "Invention" means any invention or discovery which is or may be patentable or otherwise protected under title 35, United States Code, or any novel variety or plant which is or may be protectable under the Plant Variety Protection Act (7 U.S.C. 2321 et seq.).

2.6 "Principal Investigator(s)" or "PIs" means the persons designated respectively by the Parties to this CRADA who will be responsible for the scientific and technical conduct of the RP.

2.7 "Proprietary/Confidential Information" means confidential scientific, business, or financial information provided that such information does not include:

2.7.1 information that is publicly known or available from other sources who are not under a confidentiality obligation to the source of the information;

2.7.2 information which has been made available by its owners to others without a confidentiality obligation;

2.7.3 information which is already known by or available to the receiving Party without a confidentiality obligation; or

2.7.5 information which relates to potential hazards or cautionary warnings associated with the production, handling or use of the subject matter of the Research Plan of this CRADA.

2.8 "Research Materials" means all tangible materials other than Subject Data first produced in the performance of this CRADA.

2.9 "Research Plan" or "RP" means the statement in Appendix A of the respective research and development commitments of the Parties to this CRADA.

2.10 "Subject Invention" means any Invention of the Parties, conceived or first actually reduced to practice in the performance of the Research Plan of this CRADA.

2.11 "Subject Data" means all recorded information first produced in the performance of this CRADA by the Parties.

Article 3. Cooperative Research

3.1 Principal Investigators. PHS research work under this CRADA will be performed by the PHS laboratory identified in the RP, and the PHS Principal Investigator (PI) designated in the RP will be responsible for the scientific and technical conduct of this project on behalf of PHS. Also designated in the RP is the Collaborator PI who will be responsible for the scientific and technical conduct of this project on behalf of the Collaborator.

3.2 Research Plan Change. The RP may be modified by mutual written consent of the Principal Investigators. Substantial changes in the scope of the RP will be treated as amendments under Article 13.6.

Article 4. Reports

4.1 Interim Reports. The Parties shall exchange formal written interim progress reports on a schedule agreed to by the PIs, but at least within twelve (12) months after this CRADA becomes effective and at least within every twelve (12) months thereafter.

Such reports shall set forth the technical progress made, identifying such problems as may have been encountered and establishing goals and objectives requiring further effort, any modifications to the Research Plan pursuant to Article 3.2, and identify Subject Inventions pursuant to Article 6.1.

4.2 Final Reports. The Parties shall exchange final reports of their results within four (4) months after completing the projects described in the RP or after the expiration or termination of this CRADA.

Article 5. Financial and Staffing Obligations

5.1 PHS and Collaborator Contributions. The contributions of the Parties, including payment schedules, if applicable, are set forth in Appendix B. PHS shall not be obligated to perform any of the research specified herein or to take any other action required by this CRADA if the funding is not provided as set forth in Appendix B. PHS shall return excess funds to the Collaborator when it sends its final fiscal report pursuant to Article 5.2, except for staffing support pursuant to Article 10.3. Collaborator acknowledges that the U.S. Government will have the authority to retain and expend any excess funds for up to one (1) year subsequent to the expiration or termination of the CRADA to cover any costs incurred during the term of the CRADA in undertaking the work set forth in the RP.

5.2 Accounting Records. PHS shall maintain separate and distinct current accounts, records, and other evidence supporting all its obligations under this CRADA, and shall provide the Collaborator a final fiscal report pursuant to Article 4.2.

5.3 Capital Equipment. Equipment purchased by PHS with funds provided by the Collaborator shall be the property of PHS. All capital equipment provided under this CRADA by one party for the use of another Party remains the property of the providing Party unless other disposition is mutually agreed upon by in writing by the Parties. If title to this equipment remains with the providing Party, that Party is responsible for maintenance of the equipment and the costs of its transportation to and from the site where it will be used.

Article 6. Patent Applications

6.1 Reporting. The Parties shall promptly report to each other in writing each Subject Invention and any patent applications filed thereon resulting from the research conducted under this CRADA that is reported to them by their respective employees. Each Party shall report all Subject Inventions to the other Party in sufficient detail to determine inventorship. Such reports shall be treated as Proprietary/Confidential Information in accordance with Article 8.4.

6.2 Filing of Patent Applications. Each party shall be responsible for filing patent or other IP applications in a timely manner and at its own expense and after consultation with the other Party. The Parties will consult and mutually determine a filing strategy for jointly-owned subject inventions.

6.3 Patent Expenses. The expenses attendant to the filing of patent or other IP applications generally shall be paid by the Party filing such application. If an exclusive license to any Subject Invention is granted to the Collaborator, the Collaborator shall be responsible for all past and future out-of-pocket expenses in connection with the preparation, filing, prosecution and maintenance of any applications claiming such exclusively-licensed inventions and any patents or other IP grants that may issue on such applications. The Collaborator may waive its exclusive license rights on any application, patent or other IP grant at any time, and incur no subsequent compensation obligation for that application, patent or IP grant.

6.4 Prosecution of Intellectual Property Applications. Within one month of receipt or filing, each Party shall provide the other Party with copies of the applications and all documents received from or filed with the relevant patent or other IP office in connection with the prosecution of such applications. Each Party shall also provide the other Party with the power to inspect and make copies of all documents retained in the patent or other IP application files by the applicable patent or other IP office. Where licensing is contemplated by Collaborator, the Parties agree to consult with each other with respect to the prosecution of applications for PHS Subject Inventions and joint Subject Inventions. If the Parties agree that Collaborator shall file and prosecute IP applications on joint Subject Inventions, then Collaborator agrees to grant PHS an associate power of attorney (or its equivalent) on such IP applications.

Article 7. Licensing

7.1 Option for Commercialization License. With respect to Government IP rights to any Subject Invention not made solely by the Collaborator's employees for which a patent or other IP application is filed, PHS hereby grants to the Collaborator an exclusive option to elect an exclusive or nonexclusive commercialization license, which is substantially in the form of the appropriate model PHS license agreement. This option does not apply to Subject Inventions conceived prior to the effective date of this CRADA that are reduced to practice under this CRADA, if prior to that reduction to practice, PHS has filed a patent application on the invention and has licensed it or offered to license it to a third party. The terms of the license will fairly reflect the nature of the invention, the relative contributions of the Parties to the invention and the CRADA, the risks incurred by the Collaborator and the costs of subsequent research and development needed to bring the invention to the marketplace. The field of use of the license will be commensurate with the scope of the RP.

7.2 Exercise of License Option. The option of Article 7.1 must be exercised by written notice mailed within three (3) months after either (I) Collaborator receives written notice from PHS that the patent or other IP application has been filed; or (ii) the date Collaborator files such IP application. Exercise of this option by the Collaborator initiates a negotiation period that expires nine (9) months after the exercise of the option. If the last proposal by the Collaborator has not been responded to in writing by PHS within this nine (9) month period, the negotiation period shall be extended to expire one (1) month after PHS so responds, during which month the Collaborator may accept in writing the final license proposal of PHS. In the absence of such acceptance, or an extension of the time limits by PHS, PHS will be free to license such IP rights to others. In the event that the Collaborator elects the option for an exclusive license, but no such license is executed during the negotiation period, PHS agrees not to make an offer for an exclusive license on more favorable terms to a third party for a period of six (6) months without first offering Collaborator those more favorable terms. These times may be extended at the sole discretion of PHS upon good cause shown in writing by the Collaborator.

7.3 License for PHS Employee Inventions and Joint Inventions. Pursuant to 15 U.S.C. ' 3710a(b)(1)(A), for Subject Inventions made under this CRADA by a PHS employee(s) or jointly by such employee(s) and employees of the Collaborator and licensed pursuant to the option of Article 7.1, the Collaborator grants to the Government a nonexclusive, nontransferable, irrevocable, paid-up license to practice the invention or have the invention practiced throughout the world by or on behalf of the Government. In the exercise of such license, the Government shall not publicly disclose trade secrets or commercial or financial information that is privileged or confidential within the meaning of 5 U.S.C. 552(b)(4) or which would be considered as such if it had been obtained from a non-Federal party.

7.4 License in Collaborator Inventions. Pursuant to 15 U.S.C. ' 3710a(b)(2), for inventions made solely by Collaborator employees under this CRADA, the Collaborator grants to the Government a nonexclusive, nontransferable, irrevocable, paid-up license to practice the invention or have the invention practiced throughout the world by or on behalf of the Government for research or other Government purposes.

7.5 Third Party License. Pursuant to 15 U.S.C. ' 3710a(b)(1)(B), if PHS grants an exclusive license to a Subject Invention made wholly by PHS employees or jointly with a Collaborator under this CRADA, the Government shall retain the right to require the Collaborator to grant to a responsible applicant a nonexclusive, partially exclusive, or exclusive sublicense to use the invention in Collaborator’s licensed field of use on terms that are reasonable under the circumstances; or if the Collaborator fails to grant such a license, to grant the license itself. The exercise of such rights by the Government shall only be in exceptional circumstances and only if the Government determines (I) the action is necessary to meet health or safety needs that

are not reasonably satisfied by Collaborator, (ii) the action is necessary to meet requirements for public use specified by Federal regulations, and such requirements are not reasonably satisfied by the Collaborator; or (iii) the Collaborator has failed to comply with an agreement containing provisions described in 15 U.S.C. 3710a(c)(4)(B). The determination made by the Government under this Article is subject to administrative appeal and judicial review under 35 U.S.C. 203(2).

7.6 Joint Inventions Not Exclusively Licensed. In the event that the Collaborator does not acquire an exclusive commercialization license to IP rights in all fields in joint Subject Inventions then each Party shall have the right to use the joint Subject Invention and to license its use to others in all fields not exclusively licensed to Collaborator. The Parties may agree to a joint licensing approach for such IP rights.

Article 8. Proprietary Rights and Publication

8.1 Right of Access. PHS and the Collaborator agree to exchange all Subject Data produced in the course of research under this CRADA. Research Materials will be shared equally by the Parties to the CRADA unless other disposition is agreed to by the Parties. All Parties to this CRADA will be free to utilize Subject Data and Research Materials for their own purposes, consistent with their obligations under this CRADA.

8.2 Ownership of Subject Data and Research Materials. Subject to the sharing requirements of Paragraph 8.1 and the regulatory filing requirements of Paragraph 8.3, the producing Party will retain ownership of and title to all Subject Inventions, all Subject Data and all Research Materials produced solely by their investigators. Jointly developed Subject Inventions, Subject Data and Research Materials will be jointly owned.

8.3 Dissemination of Subject Data and Research Materials. To the extent permitted by law, the Collaborator and PHS agree to use reasonable efforts to keep Subject Data and Research Materials confidential until published or until corresponding patent applications are filed. Any information that would identify human subjects of research or patients will always be maintained confidentially. To the extent permitted by law, the Collaborator shall have the exclusive right to use any and all CRADA Subject Data in and for any regulatory filing by or on behalf of Collaborator, except that PHS shall have the exclusive right to use Subject Data for that purpose, and authorize others to do so, if the CRADA is terminated or if Collaborator abandons its commercialization efforts. Collaborator acknowledges the basic research mission of the PHS, and agrees that after publication, PHS may make unpatented research materials arising out of this CRADA available to third parties for further research.

8.4 Proprietary/Confidential Information. Each Party agrees to limit its disclosure of Proprietary/Confidential Information to the amount necessary to carry out the

Research Plan of this CRADA, and shall place a confidentiality notice on all such information. Confidential oral communications shall be reduced to writing within 30 days by the disclosing Party. Each Party receiving Proprietary/Confidential Information agrees that any information so designated shall be used by it only for the purposes described in the attached Research Plan. Any Party may object to the designation of information as Proprietary/Confidential Information by another Party. Subject Data and Research Materials developed solely by the Collaborator may be designated as Proprietary/Confidential Information when they are wholly separable from the Subject Data and Research Materials developed jointly with PHS investigators, and advance designation of such data and material categories is set forth in the RP. The exchange of other confidential information, e.g., patient-identifying data, should be similarly limited and treated. Jointly developed Subject Data and Research Material derived from the Research Plan may be disclosed by Collaborator to a third party under a confidentiality agreement for the purpose of possible sublicensing pursuant to the Licensing Agreement and subject to Article 8.7.

8.5 Protection of Proprietary/Confidential Information. Proprietary/Confidential Information shall not be disclosed, copied, reproduced or otherwise made available to any other person or entity without the consent of the owning Party except as required under court order or the Freedom of Information Act (5 U.S.C. ' 552). Each Party agrees to use its best efforts to maintain the confidentiality of Proprietary/Confidential Information. Each Party agrees that the other Party is not liable for the disclosure of Proprietary/Confidential Information which, after notice to and consultation with the concerned Party, the other Party in possession of the Proprietary/Confidential Information determines may not be lawfully withheld, provided the concerned Party has been given an opportunity to seek a court order to enjoin disclosure.

8.6 Duration of Confidentiality Obligation. The obligation to maintain the confidentiality of Proprietary/Confidential Information shall expire at the earlier of the date when the information is no longer Proprietary Information as defined in Article 2.7 or three (3) years after the expiration or termination date of this CRADA. The Collaborator may request an extension to this term when necessary to protect Proprietary/Confidential Information relating to products not yet commercialized.

8.7 Publication. The Parties are encouraged to make publicly available the results of their research. Before either Party submits a paper or abstract for publication or otherwise intends to publicly disclose information about a Subject Invention, Subject Data or Research Materials, the other Party shall be provided thirty (30) days to review the proposed publication or disclosure to assure that Proprietary/Confidential Information is protected. The publication or other disclosure shall be delayed for up to thirty (30) additional days upon written request by any Party as necessary to preserve U.S. or foreign patent or other IP rights.

Article 9. Representations and Warranties

9.1 Representations and Warranties of PHS. PHS hereby represents and warrants to the Collaborator that the official signing this CRADA has authority to do so.

9.2 Representations and Warranties of the Collaborator.

(a) The Collaborator hereby represents and warrants to PHS that the Collaborator has the requisite power and authority to enter into this CRADA and to perform according to its terms, and that the Collaborator's official signing this CRADA has authority to do so. The Collaborator further represents that it is financially able to satisfy any funding commitments made in Appendix B.

(b) The Collaborator certifies that the statements herein are true, complete, and accurate to the best of its knowledge. The Collaborator is aware that any false, fictitious, or fraudulent statements or claims may subject it to criminal, civil, or administrative penalties.

Article 10. Termination

10.1 Termination By Mutual Consent. PHS and the Collaborator may terminate this CRADA, or portions thereof, at any time by mutual written consent. In such event the Parties shall specify the disposition of all property, inventions, patent or other IP applications and other results of work accomplished or in progress, arising from or performed under this CRADA, all in accordance with the rights granted to the Parties under the terms of this Agreement.

10.2 Unilateral Termination. Either PHS or the Collaborator may unilaterally terminate this entire CRADA at any time by giving written notice at least thirty (30) days prior to the desired termination date, and any rights accrued in property, patents or other IP rights shall be disposed of as provided in paragraph 10.1, except that PHS may, at its option, retain funds transferred to PHS prior to unilateral termination by Collaborator for use in completing the Research Plan solely or with another partner.

10.3 Staffing. If this CRADA is mutually or unilaterally terminated prior to its expiration, funds will nevertheless remain available to PHS for continuing any staffing commitment made by the Collaborator pursuant to Article 5.1 above and Appendix B, if applicable, for a period of six (6) months after such termination. If there are insufficient funds to cover this expense, the Collaborator agrees to pay the difference.

10.4 New Commitments. No Party shall make new commitments related to this CRADA after a mutual termination or notice of a unilateral termination and shall, to the extent feasible, cancel all outstanding commitments and contracts by the termination date.

10.5 Termination Costs. Concurrently with the exchange of final reports pursuant to Articles 4.2 and 5.2, PHS shall submit to the Collaborator for payment a statement of all costs incurred prior to the date of termination and for all reasonable termination costs including the cost of returning Collaborator property or removal of abandoned property, for which Collaborator shall be responsible.

Article 11. Disputes

11.1 Settlement. Any dispute arising under this CRADA which is not disposed of by agreement of the Principal Investigators shall be submitted jointly to the signatories of this CRADA. If the signatories are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the Assistant Secretary for Health (or his/her designee or successor) shall propose a resolution. Nothing in this Article shall prevent any Party from pursuing any additional administrative remedies that may be available and, after exhaustion of such administrative remedies, pursuing all available judicial remedies.

11.2 Continuation of Work. Pending the resolution of any dispute or claim pursuant to this Article, the Parties agree that performance of all obligations shall be pursued diligently in accordance with the direction of the PHS signatory.

Article 12. Liability

12.1 Property. The U.S. Government shall not be responsible for damages to any Collaborator property provided to PHS, where Collaborator retains title to the property, or any property acquired by Collaborator for its own use pursuant to this CRADA.

12.2 NO WARRANTIES. EXCEPT AS SPECIFICALLY STATED IN ARTICLE 9, THE PARTIES MAKE NO EXPRESS OR IMPLIED WARRANTY AS TO ANY MATTER WHATSOEVER, INCLUDING THE CONDITIONS OF THE RESEARCH OR ANY INVENTION OR PRODUCT, WHETHER TANGIBLE OR INTANGIBLE, MADE, OR DEVELOPED UNDER THIS CRADA, OR THE OWNERSHIP, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE OF THE RESEARCH OR ANY INVENTION OR PRODUCT.

12.3 Indemnification. The Collaborator agrees to hold the U.S. Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of the use by the Collaborator for any purpose of the Subject Data, Research Materials and/or Subject Inventions produced in whole or part by PHS employees under this CRADA, unless due to the negligence or willful misconduct of PHS, its employees, or agents. The Collaborator shall be liable for any claims or damages it incurs in connection with this CRADA. PHS has no authority to indemnify the Collaborator.

12.4 Force Majeure. Neither Party shall be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this CRADA, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform shall promptly notify the other Party. It shall further use its best efforts to resume performance as quickly as possible and shall suspend performance only for such period of time as is necessary as a result of the force majeure event.

Article 13. Miscellaneous

13.1 Governing Law. The construction, validity, performance and effect of this CRADA shall be governed by Federal law, as applied by the Federal Courts in the District of Columbia. Federal law and regulations will preempt any conflicting or inconsistent provisions in this CRADA.

13.2 Entire Agreement. This CRADA constitutes the entire agreement between the Parties concerning the subject matter of this CRADA and supersedes any prior understanding or written or oral agreement.

13.3 Headings. Titles and headings of the articles and subarticles of this CRADA are for convenient reference only, do not form a part of this CRADA, and shall in no way affect its interpretation. The PHS component that is the Party for all purposes of this CRADA is the Bureau(s), Institute(s), Center(s) or Division(s) listed on the Cover Page herein.

13.4 Waivers. None of the provisions of this CRADA shall be considered waived by any Party unless such waiver is given in writing to the other Party. The failure of a Party to insist upon strict performance of any of the terms and conditions hereof, or failure or delay to exercise any rights provided herein or by law, shall not be deemed a waiver of any rights of any Party.

13.5 Severability. The illegality or invalidity of any provisions of this CRADA shall not impair, affect, or invalidate the other provisions of this CRADA.

13.6 Amendments. If either Party desires a modification to this CRADA, the Parties shall, upon reasonable notice of the proposed modification or extension by the Party desiring the change, confer in good faith to determine the desirability of such modification or extension. Such modification shall not be effective until a written amendment is signed by the signatories to this CRADA or by their representatives duly authorized to execute such amendment.

13.7 Assignment. Neither this CRADA nor any rights or obligations of any Party hereunder shall be assigned or otherwise transferred by either Party without the prior written consent of the other Party.

13.8 Notices. All notices pertaining to or required by this CRADA shall be in writing and shall be signed by an authorized representative and shall be delivered by hand or sent by certified mail, return receipt requested, with postage prepaid, to the addresses indicated on the signature page for each Party. Notices regarding the exercise of license options shall be made pursuant to Article 7.2. Any Party may change such address by notice given to the other Party in the manner set forth above.

13.9 Independent Contractors. The relationship of the Parties to this CRADA is that of independent contractors and not agents of each other or joint venturers or partners. Each Party shall maintain sole and exclusive control over its personnel and operations. Collaborator employees who will be working at PHS facilities may be asked to sign a Guest Researcher or Special Volunteer Agreement appropriately modified in view of the terms of this CRADA.

13.10 Use of Name or Endorsements. By entering into this CRADA, PHS does not directly or indirectly endorse any product or service provided, or to be provided, whether directly or indirectly related to either this CRADA or to any patent or other IP license or agreement which implements this CRADA by its successors, assignees, or licensees. The Collaborator shall not in any way state or imply that this CRADA is an endorsement of any such product or service by the U.S. Government or any of its organizational units or employees. Collaborator issued press releases that reference or rely upon the work of PHS under this CRADA shall be made available to PHS at least 7 days prior to publication for review and comment.

13.11 Exceptions to this CRADA. Any exceptions or modifications to this CRADA that are agreed to by the Parties prior to their execution of this CRADA are set forth in Appendix C.

13.12 Reasonable Consent. Whenever a Party's consent or permission is required under this CRADA, such consent or permission shall not be unreasonably withheld.

Article 14. Duration of Agreement

14.1 Duration. It is mutually recognized that the duration of this project cannot be rigidly defined in advance, and that the contemplated time periods for various phases of the RP are only good faith guidelines subject to adjustment by mutual agreement to fit circumstances as the RP proceeds. In no case will the term of this CRADA extend beyond the term indicated in the RP unless it is revised in accordance with Article 13.6.

14.2 Survivability. The provisions of Articles 4.2, 5-8, 10.3-10.5, 11.1, 12.2-12.4, 13.1, 13.10 and 14.2 shall survive the termination of this CRADA.

SIGNATURES BEGIN ON THE NEXT PAGE

FOR PHS:

_____ _____

Date

Date

_____

Mailing Address for Notices:

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FOR THE COLLABORATOR:

_____ _____

Date

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Mailing Address for Notices:

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APPENDIX A

RESEARCH PLAN

Survey of Pharmaceutical Development Needs

FDA Investigators:	Jonathan Cook and Jon Clark
FDA Co-Investigators:	Rajendra Uppoor, Ph.D. Guiragos Poochikian, Ph.D. Vilayat Sayeed, Ph.D.
Conformia Investigator:	Anjali Kataria, Vice President, Business Development, Conformia
Term of CRADA:	Three(3) years.

Goals/ CRADA Research Objectives

1. Survey pharmaceutical and related companies on difficulties they have encountered in their pharmaceutical development processes.

2. Concurrently review guidances and regulatory requirements that impact the pharmaceutical development process.

3. While maintaining the confidentiality of individual responses to the survey, evaluate the potential impact of changes in guidance documents and regulatory requirements that may have an effect on the time and resources required by firms to complete pharmaceutical development.

4. Communicate research findings to the U.S. pharmaceutical industry through publications and workshops with the aim of enhancing understanding of factors that may impact on pharmaceutical development and regulatory or other changes that might be helpful.

Background

Current market literature, conferences and roundtable discussions from American Association of Pharmaceutical Scientists (AAPS), Product Quality Research Institute (PQRI), Arden House, Drug Information Association (DIA), and other industry forums point to a number of "increasing pressures" facing the pharmaceutical industry, including but not limited to: rising costs in development, high costs of healthcare, increasing competition, extensive Merger & Acquisition activity in the industry, increasing use of Contract Research Organizations, Contract Manufacturing Organizations, collaborations, and overall pressures on the development organization to produce drugs more efficiently. These pressures, at a macro level, are intensifying the challenges pharmaceutical companies face in bringing innovative science to market as fast and as safely as possible.

Conformia's own market research (January 2003-December 2003) suggests that a major component of this problem is "how information is managed across the development process of a new drug." When a pharmaceutical company is not able to provide an accurate, reliable, and replicable history of the development process, subsequent understanding can be very difficult, at best, and nearly impossible at worst. Conformia's research to date also indicates that there is a significant opportunity to gain greater

operational efficiency in the drug submission processes by understanding the root causes of these information bottlenecks in the drug development process.

Through this project, extra attention will be paid to why drugs that could help the public are not coming to market as fast and as efficiently as possible. Through the findings, presentations, future state case study, and discussion with FDA, more clarity will emerge as to why it is taking the time it is taking now to bring high quality products to market, i.e., whether companies are misinterpreting guidelines, whether FDA is /isn't getting the data they need, and improving understanding around "what " the root causes are that could be addressed to enable the public to receive better quality drugs in a more efficient manner.

FDA will have the opportunity to learn where the regulatory process can be improved and what the implications are of the current state of affairs for companies in trying to meet submissions requirements. Also, more effective means of gathering relevant data (as opposed to volumes of data) will be explored. Through the CRADA, FDA will also help shape and refine the existing survey research study topics such that those areas that are also of concern to FDA will be prioritized in Conformia's research.

Research Plan

This CRADA is being developed to follow along with FDA's Pharmaceutical cGMPs for the 21st Century initiative, also referred to as the Drug Quality Program for the 21st Century. At the completion of the study Conformia will disseminate the research agenda, findings, and FDA comments to all participants and make the findings available to the public through publication(s) of findings. Conformia will summarize the findings in a manner that is consistent with the protection of all participating company identities. By disseminating this research to pharmaceutical and related companies, the limited resources used to complete this research on both FDA and Conformia's side can be leveraged to provide benefit to pharmaceutical companies, and ultimately the public. The intended use of these findings is to improve the understanding of the factors contributing to problems drug companies face in efficiently bringing to market better therapeutics, particularly with respect to product development, process development, analytical testing and commercial manufacturing.

Conformia will conduct a survey research study with 25 companies, blinded to the FDA, ranging in size and type of products produced (proprietary small and large molecule based products, generics, and biotechnology products). The research will provide insights into:

1) the existing root causes of bottlenecks in the drug development process resulting from inadequate information capture;
2) the types of infrastructure and processes which will be necessary in order for companies to implement closed loop, continuous improvement, quality by design and risk based approach to new drug development;
3) expectations of future guidance from the agency that might better assist companies in successfully gaining approval for new drugs as fast and effectively as possible.

The proposed study will occur over a 3 year period and the output will be a series of reports that will be made available to the public.

Conformia believes that, during the "Candidate to Commercial" phases of development, there may be systemic issues brought about by historical processes and historical infrastructure, which, if left unaddressed, may reduce a company's ability to compete with market forces and their ability to comply with new guidance. If left unexamined, these bottlenecks could place fundamental limits on achieving product and process quality by design, or continuous improvement.

This CRADA will extend Conformia's preliminary research to uncover the challenges companies face in managing information associated with bringing new drugs to market. The research will shed light on the current state and explore what a future state could look like.

Conformia plans to share research findings at various stages of the 3 year study and gain feedback from FDA subject matter experts on "blind company" specific areas of question. Conformia will be able to receive clarity on areas of guidance that are unclear, as well as on the research that is emerging: Are these findings specific to a company, or are they "trends" that are occurring across the industry?

Through collaboration with FDA, Conformia will gain feedback from a cross section of subject matter experts as needed, who have knowledge of science and risk based, systematic approaches to drug development, leading to IND, BLA, NDA submissions. Conformia will also gain feedback from FDA on relevant data and guidance involved in producing high quality drug products. Working with the FDA, Conformia has the best chance of getting correct interpretations and industry feedback and correctly understanding the guidance set forth by FDA.

Through the research, FDA hopes to gain important insights in meeting the goals for its Pharmaceutical cGMPs for the 21st Century and critical path initiatives. A major component of the critical path to market of new pharmaceuticals is the time taken in pharmaceutical development. Of particular interest to FDA are what kinds of steps it can take to help companies reduce time spent in pharmaceutical development and speed the adoption of new technologies (like Process Analytic Technologies) which are aimed at producing higher quality products as well as reducing product cost. For example, the CRADA research will help FDA to determine modifications to current guidances and what new guidances may be needed to meet these objectives.

Conformia plans to utilize this research to evaluate the potential application of its Enterprise Conformance Management software to problems facing the pharmaceutical industry during the pharmaceutical developmental process. At the heart of the software is the concept of an Electronic Development History Record (eDHR) covering the "Candidate to Commercial Phase" of drug development. Conformia has successfully applied the eDHR concept to other industries.

The draft research agenda will address the following areas of investigation:

1. Process and Product Understanding Information Challenges
2. Pilot Plant Information Management (Scale-Up Processes)
3. Manufacturing Science
4. Information Retrieval
5. Quality Systems
6. Pre-Clinical Development Challenges: Collecting, managing and using toxicology information in an effective manner

For a complete list of proposed research questions, see the Attachment to Appendix A.

The plans for the research are as follows:

PHASE I: AGENDA SETTING AND COMPLETION OF SURVEY

1) Agenda setting meeting (to be scheduled as soon as possible) and survey conduct.
   i) FDA to comment on proposed research agenda and make suggestions regarding direction, focus, and scope of topics. Through the CRADA, FDA will have opportunity to add topics to research agenda as song as they are mutually agree on.
   ii) The survey will then follow.

2) Mid point Review
   i) Conformia to present preliminary findings on topics agreed on in Agenda Setting meeting.
   ii) FDA to provide feedback on these findings, including areas that need further investigation.

3) Final Research Review
   i) Conformia to modify research agenda and complete survey.
   ii) Conformia to present final findings on topics agreed to in Agenda Setting meeting.

PHASE II. DISCUSSION OF FINDINGS

1) Formal Presentation of Findings.
2) Collaborative Review and Analysis of Findings.
3) Discussion of next steps.

PHASE III. PUBLIC PRESENTATION/DISCOURSE

1) Publication/Dissemination
2) Workshop(s)

Confidentiality

Conformia plans to maintain confidentiality of all participating companies at all times and will protect this confidentiality through signed Non-Disclosure Agreements (NDAs) with each company. The NDA's will maintain the confidentiality of each company's identity, and their respective intellectual property.

Contributions of CRADA Partners

The study and publication are to be completed over a 3+ year period, commencing upon execution of this CRADA

FDA's Contributions: FDA resources needed for this CRADA include human resources in the form of technical expertise and project management/coordination; office and related facilities; and computer processing:

1. Human Resources: The FDA will provide resources in the form of technical expertise to:
   - review the research agenda for relevance;
   - identify guidances and regulatory requirements related to pharmaceutical development;
   - identify informational resources available to Conformia employee and provide access to these, subject to appropriate security requirements;
   - provide technical expertise on regulatory aspects of pharmaceutical development;
   - review firms selected for survey for representativeness;
   - review findings to determine potential impact of regulatory guidances;
   - participate in presentations and/or panel discussions at workshops;

- collaborate in identifying possible solutions to problems identified during survey;
- review research findings in context of contemplated future regulatory approaches.

FDA's estimated personnel resources are given in the table below:

Phase	Project Management	Technical Experts
I	50 hours	80 hours
II	100 hours	240 hours
III	50 hours	100 hours

2. Office and related facilities: FDA will provide an office and computer system with internet access at its headquarters office to facilitate the work of the Conformia employee identified below (see Conformia Contributions). FDA will provide appropriate access to systems and guidances necessary to conduct research while stationed at FDA. FDA will provide for necessary security measures to assure that the confidentiality of its files is maintained.

Conformia's Contributions:

1. Conduct of research. Conformia will provide resources necessary for the conduct of the research including: development of final research agenda, conduct of survey, summarization of findings in interim and final reports/Powerpoint presentations, and hosting relevant public workshops with FDA. Conformia will also provide access to its scientific advisory board and technical experts. The overall effort for the CRADA is estimated at 2 Full Time People, Scientific Technical Advisory input as needed and $450,000 over the CRADA period.

A break down of Conformia's estimated 2 FTE resources are given in the table below:

Phase	Project Management	Business Analyst	Support	Technical
I	270 hours	1700 hours	270	80 hours
II	270 hours	1500 hours	270	240 hours
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2. Shared personnel. One of the FTE's will be a shared resource. Conformia will hire a full time individual with appropriate pharmaceutical training to work on this project. This person will be a Conformia employee, and Conformia will be responsible for assuring that this person commits to necessary confidentiality agreements to preserve blinding of participating companies. Conformia will pay the salary and all costs of travel and lodging expenses related to the CRADA.

3. Financial Resources: Conformia has budgeted approximately $150,000 per year for CRADA related marketing, research, and travel costs, which totals $450,000 over the 3 year period. Up to 10% of this budget may be used by FDA for joint travel or shared marketing/research expenses directly related to the CRADA work per year in accordance with Conformia and FDA expense policies and with prior approval from Conformia.

4. Summary of Total Contributions over the CRADA Period

Resource	Estimated Amount
2 FTE Salary	$600,000
Technical Experts	$80,000
Travel Marketing/ Research	$450,000

Outcomes

Publication and Workshops

Conformia will summarize both the relevant research findings as well as the relevant FDA comments in a publication (or publications). Publication will be distributed to pharmaceutical companies interested in the report. Workshops or seminars will also be conducted by Conformia in conjunction with appropriate FDA involvement based on the outcome of the research.

Timeline

The study, publication(s), and workshop(s) are to be completed over a 3+ year period, upon execution of this CRADA. The parties will then assess any necessary next steps.

Attachment to Appendix A. Proposed Research Questions

I. Process and Product Understanding Information Challenges

1. What are they and what is the impact on new drug?
2. How many companies would say they have a development information bottleneck and what kinds of bottlenecks exist?
3. What are causes of these Bottlenecks and why?
    a. Lack of regulatory clarity (Guidance not clear?)
    b. Data volume vs. relevance to the proposed manufacturing process(es)
        i. Data may be necessary for development, but irrelevant to the proposed manufacturing process and decision making.
        ii. Although irrelevant to proposed manufacturing process, data may be necessary to accumulate and document in order to justify future changes in the manufacturing process(es).
        iii. Should data that do not justify the proposed manufacturing process need to be submitted?
    c. Ability of infrastructure to adequately address tech transfer?
    d. Does a company's infrastructure allow for the ability to develop processes, transfer, and apply information from company to third party [Contract Manufacturing Organization (CMO), Contract Research Organization (CRO), Collaboration Partner (CP) etc.]
    e. How are these information challenges different between development of a product and its manufacturing process?

4. What does this mean for the Public ?
    a. Timeliness
    b. Efficacy
    c. Safety
    d. Quality

5. Possible solutions ?

II. Pilot Plant Information Management (Scale-Up Process)

1. How effectively do companies manage the pilot plant information?
    - Commercial Systems—challenges of inputting into electronic systems
    - Proprietary Systems
    - Pen/Paper
2. What challenges are companies facing in managing pilot plants? (Grouped into categories, i.e., safety, quality, controls, etc)
    - Is the background information provided adequate to provide a basis for scale up?
    - Are the appropriate personnel designated as information resources for additional information needed?
    - Are the nature and reasons for the changes made at scale up adequately captured?
    - Are processes being controlled and documented to company and regulatory requirements?
        - Impact of not fully controlling and documenting processes may include the following:
            - Not documenting the appropriate critical parameters and controls for the processes

- Loss of API? (Unable to use due to inadequate documentation of changes or unusable impurity profile)
- Loss of continuity of manufacturing
    - Changes in impurity profiles
    - Changes in yields
- Reliability, consistency, making expected yield inadequate (purity+impurity) – change in impurity profile
- Mass balance (weight/weight balance) material accountability – where did your starting materials end up (product, process impurities, waste stream)?
- Demonstration of adherence to GMPs.
- To what extent are companies spending time/money for investigation of parameters to ensure process is robust? Is there a "pressure" to produce adequate material in a timely manner?
- Other?

o Are companies being too strict in trying to comply with their understanding of GMPs?
    - Too Rigorous
    - Incorrect interpretations
    - Other?

o Are there any trends FDA is seeing in managing Pilot Plant data submitted as registration batches? What about Tox studies?

3. Where are companies most challenged in managing information needed for submissions from first pivotal lot to manufacturing plant (first year)?
    o Tech transfers from:
        - Early to late stage within chemical, biological and pharmaceutical groups
        - Chemical, biological, and pharmaceutical group(s) to clinical trial/supply production
        - Chemical, biological, pharmaceutical, and clinical supplies development to manufacturing

- Biological, pharmaceutical, and chemical to clinical trial/supply production
- Clinical, chemical, biological, pharmaceutical development to manufacturing

- Are there differences between chemical process development (CPD), pharmaceutical process development (PPD), and biologic development (BD) in terms of information management or information needs?

4. Why is there a data volume problem for companies and how does this affect submissions?
   - How does the problem manifest itself?
     - Paper vs. electronic
     - Reports vs. structured data
   - Is anything required by FDA that is not relevant from Companies perspectives?
   - What's the balance between good data (quality) vs. delays in getting an efficacious drug to market?
5. How are companies addressing these challenges now ("Current State")?
6. What do these companies/FDA desire in the future ("Future State")
7. Are there any areas that are unique challenges to Pilot Plants that haven't been covered yet?
   - Transition from non-GMP to cGMP environment within pilot plant (pre-IND to IND, and IND to NDA)
   - How are companies managing the need for flexibility and predictability?
   - Where companies are using general purpose equipment in Pilot Plants, are there any special informational gaps that occur when they transition to manufacturing and use specific equipment?

III. Manufacturing Science

1. What are most significant "top of mind" issues in producing registration batches? Why are these issues challenging the appropriate production of registration batches ?
2. What data is FDA looking for but not finding in submitted registration batches
   a. NDA
      i. In both full scale and pilot scale lots
      ii. Adequate process understanding , identification of sources of variability, and process controls
   b. Material analysis, toxicology results
   c. Drug Product Formulation

3. What are the biggest reasons for discrepancies in quality and yield when transferring from Development group to Manufacturing? Not knowing the critical controls that are necessary for a manufacturing process?
4. How are companies addressing these challenges now ("Current State")?
5. What would a future state look like?
    a. FDA perspective
    b. Industry perspective

IV. Information Retrieval

1. Once information is generated when does a company need to go back and look at that information?
2. How easily and reliably is this done today?
3. What are the inherent problems of the status quo in terms of traceability and reusability?
    a. Without naming company specifics and with full protection of identity, we will explore actual real life examples.
4. Are there any case studies on failures/successes that we can highlight as to how/why they are able to overcome these challenges?
5. What would a future state of information retrieval look like?
    a. FDA perspective
    b. Industry perspective

V. Quality Systems

1. What are the biggest "Gaps in Quality Systems" which companies believe they are facing now and will face in the future?
2. What steps to introduce quality in development are being taken by companies?
3. How can we develop and address processes to routinely ensure high quality of product?
4. How many errors are occurring that can the be categorized as follows:
    - Human, Waste, Rework
6. What are the biggest challenges in generating and reporting information that affects quality of product such as reporting on polymorphs, impurities, contamination issues etc.
7. Do these problems have any impact on product and data integrity?
8. Other?

VI. Pre-Clinical Development Challenges: Collecting, managing and using toxicology information in an effective manner

1. Are companies challenged in managing toxicology information? What are the biggest areas (Categories) and why is this occurring?
2. Bottlenecks from:
    a. Discover to Lab Scale
    b. Lab scale to Pilot
    c. Pilot to Commercial Production
3. How does Toxicology information get processed as compared to information relating to the route selection/synthesis of the API? As compared to the Formulation development?
4. From the discovery handoff to the commercial manufacturing handoff, where along the development timeline are companies collecting and reporting toxicology information?
5. What are the best practices in toxicology information management, and its use in a drug product development and manufacturing?

ABSTRACT

The U.S. Food and Drug Administration and Conformia are working together under a Cooperative Research and Development Agreement (CRADA) to conduct a research study on the challenges that drug product companies face in managing relevant development history information which is critical to the success of bringing best/first in-class, products of quality, to market as efficiently as possible.

Through this CRADA, Conformia will utilize a survey based research approach including interviews, review of existing material, and questionnaires to examine the current state of development history information capture from candidate selection to commercial manufacturing. Specific attention will be paid to "Process Critical Control Points" (PCCPs); process understanding (PAT) in the context of development history information; traceability of information; retrievability; risk based reduction versus mitigation; challenges in adoption of new information infrastructure; as well as organization and communication strategies.

Twenty-five companies will be selected to voluntarily participate in the study which will span a combination of large and small pharmaceutical, biotechnology, and generic companies. Conformia will summarize research findings periodically for review with the FDA and for FDA comment. At the conclusion of the CRADA study, the findings will be publicly distributed to Life Sciences Companies having an interest in these research findings. Workshops or seminars will also be conducted at FDA and other places to disseminate the information gathered during the study.

APPENDIX B

FINANCIAL AND STAFFING CONTRIBUTIONS OF THE PARTIES

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APPENDIX C

EXCEPTIONS OR MODIFICATION TO THIS CRADA

None.