



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Mr. John D. Burke
Director, Human Subjects Protection Program Office
University of Louisville IRB (Kosair Children's Hospital)
Med Center One, Suite 200
510 E. Broadway
Louisville, KY 40202

MAR 30 2010

Dear Mr. Burke:

Between January 20 and January 28, 2010, Ms. Karen Cooper and Mr. Craig Rybus, representing the Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at University of Louisville. The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), parts 50 and 56. These regulations apply to clinical investigations of products regulated by FDA.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that the IRB adhered to the applicable statutory requirements and FDA regulations governing the protection of human subjects.

For helpful information on human subject protections, please visit the following FDA web page:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

We appreciate the cooperation shown to FDA Investigators Cooper and Rybus during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Kevin A. Prohaska, D.O., M.P.H.
Acting Human Subjects Protections Team Lead
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5356
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Silver Spring, MD 20993-0002



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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05 April 2010

University of Louisville IRB
ATTN: Mr. John D. Burke – Director, Human Subjects Protection Program
501 E. Broadway, Ste. 200
Louisville, KY 40202

Dear Mr. Burke:

We are enclosing a courtesy copy of the Establishment Inspection Report (EIR) for the inspection conducted at University of Louisville IRB by the U. S. Food and Drug Administration (FDA) 20-28 January 2010. We are providing this report as part of an effort to communicate better and to make FDA's regulatory process and activities more understandable to our regulated industry.

FDA has concluded that this inspection report and related enforcement documents are disclosable under 21C.F.R.20.64(d). Your copy of the narrative report may contain business or personal information, which is disclosable only to you or your firm.

Inspection and enforcement documents are available through the FOIA only after thorough review by FDA and deletion of those portions of the documents FDA deems not disclosable. You may obtain additional releasable documents through FOIA by sending a written request to:

Freedom of Information Staff (HFI-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If there are any questions about the enclosed information, feel free to contact me at (502) 425-0069 ext. 23, or write to me at 9600 Brownsboro Road, Suite 302, Louisville, KY 40241-1122.

Sincerely,

A handwritten signature in black ink, appearing to read "Troy A. Huffman", is written over the word "Sincerely,".

Troy A. Huffman
Supervisor
Cincinnati District, Louisville Resident Post

Enclosure: Establishment Inspection Report

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SUMMARY (KMC)

This was a routine surveillance inspection of the University of Louisville Institutional Review Board which oversees the biomedical Institutional Review Board (IRB) for Kosair Children's Hospital, conducted per CIN-DO FY' 10 work plan, FACTS assignment # 1108042. The assignment was requested by CDER and was performed in accordance with compliance program CP 7348.809 and written assignment memo dated October 9, 2009 (See **attachment #1**). The focus of this inspection was on pediatric studies and the IRB's compliance with 21 CFR Part 50 Subpart D (Additional safeguards for children in clinical investigations). FACTS information was reviewed and contact information, mailing address and registration was updated.

The previous inspection of the University of Louisville IRB was conducted 9/9/2009 and was listed as NAI. According to the assignment memorandum, the previous inspection date and classification

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was noted to be 9/21-28/05 and was NAI. The inspection of 2005 focused on studies involving pediatric subjects associated with Kosairs Childrens' Hospital. The U of L IRB provides review for all human subjects research conducted at Norton Healthcare, Inc. and University Medical Center Inc. including University of Louisville Hospital, the James Graham Brown Cancer Center and at Kosair Children's Hospital. The inspection of 2005 was classified as NAI and no objectionable conditions were noted.

The current inspection covered all policies and procedures conducted by the IRB including study submissions, study monitoring, followup of pending requests, continuing and expedited review, meeting minutes, correspondences, study amendments, adverse events. Three pediatric clinical trials were randomly selected and reviewed to verify compliance.

The current inspection found the IRB to be operating according to FDA regulations. No objectionable conditions were noted and an FDA 483 was not issued.

No samples were collected and no refusals were encountered.

ADMINISTRATIVE DATA (KMC)

Inspected firm: University of Louisville, Institutional Review Board
(Kosair Childrens Hospital)
Location: 510 E. Broadway
Louisville, KY 40202-1821
Phone: 502-852-5188
FAX: 502-852-2164
Mailing address: 501 E. Broadway
MedCenter One, Suite 200
Louisville, KY 40202
Dates of inspection: 1/20/2010, 1/21/2010, 1/22/2010, 1/28/2010
Days in the facility: 4
Participants: Karen M. Cooper, Investigator
Craig T. Rybus, Investigator

This inspection was preannounced to the firm prior to the Christmas holidays; however, Rebecca Higgins informed me that the University was going to be closed for two weeks due to the Christmas holidays. I informed Ms. Higgins that I would contact her after the holidays to schedule the inspection and did so on January 14, 2010. On 1/20/2010, I and CSO Rybus presented credentials and issued an FDA 482, Notice of Inspection to Mr. John D. Burke, Director for the Human Subjects Protection Program Office (HSPPO).

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Each section of the EIR is annotated with the team member who wrote it.

HISTORY (CTR)

The Human Subjects Protection Program Office (HSPPO) is the administrative office for the University of Louisville IRB with business hours from 8:00 AM-5:00 PM Monday-Friday. This office has been in existence since 2003 and at the organizational level is under the Office of the Executive Vice President of Research, please see organizational chart **ex. 1**.

There is a biomedical IRB and a behavioral IRB and both are registered with the Office of Human Research Protections. The Biomedical IRB meetings are held the first, third, fourth, and fifth Thursday of each month beginning at 12:15 PM. The Behavioral IRB meets the first Wednesday of each month at 12:15 PM.

The University of Louisville's two IRBS provide review for all human subjects research conducted at Norton Healthcare, Inc. and University Medical Center Inc. including University of Louisville Hospital, the James Graham Brown Cancer Center and at Kosair Children's Hospital. The IRBS also provide oversight for research conducted by University affiliated investigators at Jewish Hospital and the Louisville Veterans Affairs Medical Center. All paid faculty, students, and staff of the University of Louisville must use the IRBS.

All HSPPO staff members are trained to provide applicant training. This office is fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

There were no complaints in the organizational jacket needing follow up.

Please direct all correspondence to John D. Burke, Director, Human Subjects Protection Program Office, University of Louisville, Med Center One, Suite 200, 501 E. Broadway, Louisville, KY 40202.

JURISDICTION (CTR)

The IRB reviews studies involving investigational new drugs, investigational devices, food additives, and biologicals. There are currently 1450-1500 active studies being reviewed by the IRB. Approximately 336 of those studies are FDA regulated and approximately 84 of those 336 studies (~25%) involve pediatric subjects. A list of all active, FDA regulated studies is attached **ex. 2**. A list of the FDA regulated pediatric studies is identified in a separate **exhibit #3**.

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INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED (CTR)

John D. Burke, Director, Human Subjects Protection Program Office (HSPPO) was the most responsible person interviewed. The FDA 482 Notice of Inspection was issued to Mr. Burke on 1/20/2010, and he answered most questions concerning the functions of this office. He showed his authority by directing office staff to answer questions and provide requested documentation. Mr. Burke assumed this position at HSPPO on 3/31/03. Previously he was the director of Pharmacy Services at the Louisville Veterans Affairs Hospital (VA) from 1996-2003 and has worked at the VA for 33 years and is retired from the government. He has a background as a pharmacist and also has a Masters degree in management from an extension campus of Webster University, St. Louis, Mo. Mr. Burke reports to **Pamela Feldhoff, Ph.D.**, Associate Vice President for Research. Dr. Feldhoff reports to **Dr. William Pierce**, Office of Executive Vice President for Research who then reports to **Dr. James R. Ramsey** president of the University of Louisville. Mr. Burke was very knowledgeable of the day-to-day operations of the IRB, the policies and procedures, the involvement of physicians on various studies, and the BRAAN computer software system. He works very closely with the investigators with regards to inputting required information into the BRAAN system and will work with them one-on-one to help them understand and navigate through the BRAAN software. All investigational studies go through his office. As part of his responsibility for on-going review, his staff is also responsible for periodically auditing investigators. He was also familiar with the FDA regulations (21CFR50 and 21CFR56 as well as the Title 45, Public Welfare regulations part 46. He attends all IRB meetings; however, he does not have voting privileges.

Rebecca H. Higgins, Assistant Director at HSPPO was also interviewed along with Mr. Burke. She is in charge of the administrative functions and financial matters related to this office. All office staff report to her. Ms. Higgins has a Bachelor of Science (BS) degree in education from the University of Louisville. She has been working at the University since 1977 starting with a position in the Department of Medicine. She reports to John Burke. Ms. Higgins was able to answer questions concerning the administrative functions of the IRB as well as produce documentation for review. She showed her authority by ordering the office staff to assist in producing records or to answer questions from the investigators. She was very knowledgeable of the day-to-day operations of the IRB, the policies and procedures, the involvement of physicians on various studies, the FDA regulations as well as 45 CFR 46.

IRB OPERATIONS (KMC)

Since the previous inspection of 9/09-11/09, there have been no changes in operations. The Health Services Protection Office continues to be divided into two committees: the Biomedical Committee and the Behavioral Committee. See "IRB Registration" for further information, **exhibit #8**.

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IRB MEMBERSHIP_(CTR)

The “IRB Standard Operating Procedures” gives guidance on membership representation (ex. 4, pg.17-25). The IRB is to be composed of no less than five but not more than 21 members appointed for five year terms. Currently, there are 18 full committee members and 17 alternate committee members. The members are to be sufficiently qualified through experience, expertise, and diversity. A review of the roster (exhibit #5) shows that there are physicians, social scientists, community representatives, minority representatives, prison representatives, surgeons, two pediatricians, a pediatric nurse practitioner, and a pediatric otolaryngologist on the board which is consistent with 21 CFR 56.107.

The IRB SOP specifically states that no IRB member or consultant may participate in the IRB initial or continuing review of any project when a conflict of interest exists. Though an IRB member may have presented a research study, the minutes do reflect that this member did not vote on any of the deliberations involved with this project. This is consistent with 21 CFR 56.107 (e).

Alternate members are used and appointed for a specific member. The minutes reflect when an alternate member is used. The alternate is listed on the roster for whoever needs a substitute. If both the alternate and the member attend a meeting, only one of the two may vote. Alternate members are welcome to attend all committee meetings. Copies of the agenda and meeting materials will be sent to all members and alternates.

There is more than one IRB under the HSPPO; the Biomedical IRB and the Behavioral IRB. The chair for the Behavioral IRB is **Pat Leisch, Ph.D.** and the Vice Chair is **Pete Quesada, Ph.D.** The Chair for the Biomedical IRB is **Laura Clark, MD.** There are four Vice Chairpersons who can fill in for the Chairperson if that person is absent. The Vice Chairpersons are; **Serge Martinez, MD, Diller Groff, MD, Frank Walker, MD, and Julie Goldman, MD.** CSO Cooper and I did not meet with any members of the IRB.

WRITTEN PROCEDURES_(CTR)

The IRB follows an “IRB Standard Operating Procedures” (SOP) manual to conduct business ex. 4. The SOP is updated every 3 years with the last update done in 2007. There is a new approved version of the SOP but it is not in use at the time of inspection. An “Investigator Guide for Human Research” manual is distributed to the investigator with guidance on how to set up a clinical trial ex. 6. This guide can be found on the University website at <http://louisville.edu/research/humansubjects>. This is consistent with 21 CFR 56.108 and Compliance Program 7348.809. The investigator guidance mirrors what is in the SOP but is specific to the needs of the investigator. The SOP does refer to many DHHS regulations but also addresses FDA regulations and contains a section specifically addressing FDA regulated research.

CONTINUING REVIEW OF RESEARCH_(CTR)

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The IRB SOP describes the authority of the IRB ex 4, pgs. 12-13 and is consistent with 21 CFR 56.110. The IRB has authority to review, approve, and ratify all non-exempt human subject research, and approve pending receipt of specific required modifications. The IRB will request modifications to the protocol or informed consent if needed. The IRB may also defer a review pending clarification or for concerns over the safety or content of the study. They may also disapprove the initiation of new research projects if there appears to be unreasonable risks to the participants. The investigator may be asked to revise the protocol or consent form.

There are provisions for monitoring and continuing review of approved studies. The investigator must report any changes, report adverse events or unanticipated problems involving risks to subjects or others. The IRB may suspend or terminate a previously approved research project or recommend sanctions to the Office of the Executive Vice President for Research (OEVPR). The OEVPR has the authority to review decisions of the IRB and may disapprove, suspend, or terminate a project on behalf of the institution.

The University of Louisville Human Subjects Protection Program Office (HSPPO) has been established to support the IRB process. This office makes available anything needed to assist in the review process. Packets for review are sent to the reviewer at least one week in advance and include the application form, informed consent, recruitment materials, and other correspondence with subjects. The protocol and investigator's brochure is available to all members online for review. All submissions are online and are available to any member for review. Assignment of a primary reviewer is made prior to a full board meeting.

IRB REPORTING TO THE CLINICAL INVESTIGATOR AND THE INSTITUTION (CTR)

The IRB does notify the investigator and the institution of IRB actions. This is compliant with 21 CFR 56.108 (a)(3), (a)(4),(b) and 21 CFR 56.109 (d). It is noted in the SOP and the Investigator's Guide that the investigator has the responsibility to report to the IRB any changes in the research activity, and any changes made in the research must first be reviewed and approved by the IRB. If there is an IRB disapproval the researcher may make an appeal to the IRB in writing or in person. Ex 4, pg. 22.

EXPEDITED REVIEW (CTR)

The IRB SOP makes mention of the list of research that may be reviewed through an expedited review process. The list is found in the Federal Register or may be obtained by writing to the Office for Human Research Protection. Specific examples for use of expedited review are noted in the SOP ex. 4, pgs. 46-49. This is consistent with 21 CFR 56.110(a) and (b)

EMERGENCY REVIEW (CTR)

There were 3 instances of emergency use of a test article since the last inspection. Two cases reviewed during this inspection were from the same investigator. The participants were children and an informed consent could not be obtained from either, as noted in the printout from the online

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application. Both children were immuno-suppressed and were exposed to chicken pox. The available documentation from the investigator shows the reason for the urgency and the follow-up with the IRB, see **Ex. 7**. Please note, the handwritten note on the first page of exhibit 7 does not pertain to this emergency use notification.

The SOP states that “Life threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible”. This request appears to be consistent with the IRB SOP and an appropriate use of emergency use of a test article.

INFORMED CONSENT (KMC)

The informed consent forms for all three studies selected were reviewed and found to contain the eight required elements identified in 21 CFR 50.25. Additional elements of the informed consent identified in 21 CFR 50.25(b) were also covered in the consent form(s). The consent forms are initially reviewed by the IRB prior to study initiation and at any time throughout the study in which amendments are made. Since the last inspection of 9/2009, there have been no instances in which the IRB has reviewed and/or approved any protocol(s) for a waiver of informed consent.

IRB REGISTRATION (KMC)

The IRB was registered with the Office of Human Research Protections (OHRP) and a copy of their registration is included with this report as **Exhibit #8**. The registration number for the University of Louisville IRB is IORG0000147. The Biomedical IRB “A” is identified as IRB00000251 and the Behavioral IRB “B” is identified as IRB00000252. Registration expires on 12/22/2012.

Studies Reviewed for Compliance with 21 CFR 56 and 21 CFR 50 with particular emphasis on 21CFR Part 50 subpart D is as follows (KMC).

Three pediatric studies were reviewed for compliance with the above-noted regulations. Mr. Burke provided all the documents pertaining to the selected studies on individual discs for my review. The documents selected for submission with this report include meeting minutes, informed consent and pediatric assent documents, IRB meeting minutes specific to each study, protocol, continuing review documents, adverse event reports and other pertinent communication between the investigator and the IRB. The selected documents were provided to me in hard copy format by Mr. Burke.

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For each of the three pediatric studies reviewed, it was determined that there were no pediatric subjects found to be wards of the State or any other institution. Mr. Burke stated that he could not recall a time when this occurred; however, the IRB SOP does address this situation should it occur (See **Ex.4, page 139**).

According to Mr. Burke and the IRB SOP, the assent of children participating in research is always required of subjects 7-18 years of age. (See **Ex. 4, page 86**).

According to question #5 of the assignment memorandum (Attachment #1), the extent to which IRB member(s) directly review the assent process is as explained by Mr. Burke: There is a primary reviewer who is responsible for the initial review. All information including required documents, applications, consent forms, assents, study protocol, etc. are submitted by the investigator on line via the following website: <http://louisville.edu/research/humansubjects/applying-to-the-irb/download-biomedical-forms.html> and is accessible by all Board members. Board members can then go on line, add comments, questions, etc. which is then brought up for discussion at the IRB meetings. The PI or "presenter" presents the study at the IRB meeting at which time questions and/or concerns are addressed.

All studies are assigned a tracking number for identification purposes. The number begins with the last two digits of the current year followed by a consecutively assigned number. For example, the first study reviewed was assigned the tracking number of "08-0205". These numbers are computer generated by the BRAAN software system.

All information and communication between the Institutional Review Board and the Principal Investigator regarding the following studies: #08-0205, #08-0309, and #08-0424 was downloaded to a CD by Mr. Burke for easier navigation. Copies of the CD for #08-0205, 08-0309, 08-0424 and the IRB minutes for 2008 and 2009 are included as exhibits with this report (**Ex. 9 a, b, c, d**). During my review of the studies, I requested hard copies of selected documents in order to demonstrate the oversight and involvement of the Institutional Review Board and its state of compliance with 21 CFR 50 and 56.

Tracking #08-0205

[REDACTED]

The above study was presented to the IRB electronically via BRAAN software by the PI, [REDACTED] MD in April 2008. A copy of the Protocol application filled out by the investigator using the BRAAN system was included with this report as **Exhibit #10**. The study was initially reviewed by Dr. Frank Walker, a primary reviewer and submitted to the full IRB on May 1, 2008. A motion to

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approve the study was made in which 16 members voted for, 0 opposed, and 1 abstained. A quorum was present at the meeting. The study was approved pending changes to various items as noted on page 3 of the May 1, 2008 minutes (ex. 11). The IRB approved participation of children in the research as Category 2, which requires the consent of both parents (if available) and the assent of the child. Category 2 represents 21 CFR 50.52 defined as "greater than minimal risk but presenting prospect of direct benefit to individual subjects. The IRB classifies pediatric research into one of four categories based upon the categories outlined in 21CFR part 50, Subpart D and 45CFR46 and this is addressed in the IRB SOP, Ex. 4, page 138.

Documents collected pertaining to Study Protocol [REDACTED] is as follows:

IRB Reminder Letter to PI dated 5/21/08 (Ex. 12)

This letter is a reminder from the IRB to the Investigator to submit additional information to the Board so that the Board can complete their review of the application.

Expedited IRB Protocol Approval letter to PI dated 6/23/08 (Ex. 13)

Letter states that study was initially approved by the full board on 5/1/2008 contingent upon requested changes to study documents as identified to the PI. The study has been given approval through 4/30/2009.

Expedited Amendment Approval letter to PI dated 7/2/08 (Ex. 14)

Letter states that changes/modifications to several documents were reviewed and approved by board designee, Serge Martinez, M.D., using expedited review procedures and will be presented to the IRB at the next full board meeting. Two of the revised documents include the Informed Consent for Groups I-II (7-9 months), dated 6/25/2008 and the Informed Consent for Group III (12 months), dated 6/25/2008. Copies of both of these revised consent forms are included as Exhibits #15 and #16 respectively.

Expedited Amendment Approval letter to PI dated 7/10/08 (Ex. 17)

An additional co-investigator was added to the study. This amendment was reviewed and approved by board designee, Frank A. Walker, M.D., using expedited review procedures and will be presented to the IRB at the next full board meeting.

Expedited Amendment Approval letter to PI dated 9/12/08 (Ex. 18)

Letter states that changes/modifications to several documents were reviewed and approved by board designee, Laura Clark using expedited review procedures and will be presented to the IRB at the next full board meeting.

Expedited Amendment Approval letter to PI dated 9/17/08 (Ex. 19)

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Letter states that changes/modifications to several documents were reviewed and approved by board designee, Serge Martinez using expedited review procedures and will be presented to the IRB at the next full board meeting.

Expedited Amendment Approval letter to PI dated 11/24/08 (Ex. 20)

Letter states that changes/modifications to several documents were reviewed and approved by board designee, Diller Groff using expedited review procedures and will be presented to the IRB at the next full board meeting.

Expedited Amendment Approval letter to PI dated 12/23/08 (Ex. 21)

Letter states that changes/modifications to several documents were reviewed and approved by board designee, Diller Groff using expedited review procedures and will be presented to the IRB at the next full board meeting.

Expedited Amendment Approval letter to PI dated 2/10/09 (Ex. 22)

Letter acknowledges the PI's voluntary suspension request of the above-noted study. PI was instructed to report study completion or sponsor close out when appropriate by filing a Completion Report.

Full Board – Continuing Review Approval to PI dated 4/3/2009 (Ex. 23)

The following documents were submitted for continued approval: Progress Report, Research Protocol, Protocol Synopsis and Deviation Log. In addition, the IRB acknowledged that the study was on temporary hold to do an expiration date for the [REDACTED] supply used in the study. It was requested by the IRB that when the study resumes (August 2009) that revised study documents be submitted to the IRB at that time. At the IRB full board meeting of 4/2/09, the Board's approved continuation for an additional year. A motion to approve the study was made in which 12 members voted for, 0 opposed, and 1 abstained. A quorum was present at the meeting (See copy of minutes, ex. 24).

Expedited Amendment Approval letter to PI dated 4/29/09 (Ex. 25)

Letter states that revisions/modifications were reviewed and approved by board designee, Julie Goldman, M.D., using expedited review procedures and will be presented to the IRB at the next full board meeting.

Expedited Amendment Approval letter to PI dated 6/3/09 (Ex. 26)

Letter states that a modification to key personnel were reviewed and approved by board designee, Serge Martinez, M.D., using expedited review procedures and will be presented to the IRB at the next full board meeting.

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Expedited Amendment Approval letter to PI dated 7/10/09 (Ex. 27)

Letter states that changes/modifications to several documents were reviewed and approved by board designee, Julie Goldman, M.D., using expedited review procedures and will be presented to the IRB at the next full board meeting. Also noted in the letter is the fact that the enrollment status has changed from halted to closed. To date, a total of 24 subjects have been enrolled.

Adverse Events

A letter from the IRB dated 8/21/09 acknowledges receipt of an adverse event report, #AE-508 (Ex. 28). A copy of the event filed by the investigator is also included as Exhibit #29. A second adverse event (AE-638) was acknowledged by the committee in a letter to the PI dated 12/15/09 (Ex. 30).

Attachments referenced in the above noted letters are not included with this report; however, they may be retrieved from the CD that accompanies this report. (Ex. 9a, b, c, d)

Tracking #08-0309

[REDACTED]

The above study was presented to the IRB electronically via BRAAN software by the PI, [REDACTED] MD in April 2008. The study was initially reviewed by Dr. Frank Walker, a primary reviewer and submitted to the full IRB on 6/26/08. A motion to approve the study was made in which 12 members voted for, 0 opposed, and 1 abstained. A quorum was present at the meeting. The study was approved contingent upon changes to the assent as noted on in the minutes of June 26, 2008 (ex. 31). The IRB approved participation of children in the research at Category 2, which requires the consent of both parents (if available) and the assent of the child. Category 2 represents 21 CFR 50.52 defined as "greater than minimal risk but presenting prospect of direct benefit to individual subjects. The IRB classifies pediatric research into one of four categories based upon the categories outlined in 21CFR part 50, Subpart D and 5CFR46 and this is addressed in the IRB SOP, ex. 4, page 138.

Documents collected pertaining to Study Protocol [REDACTED] is as follows:

Copies of the Protocol dated [REDACTED] (Ex. 32) is submitted with the report along with the revised informed consent form (Ex. 33) and revised assent form (Ex. 34), both dated 6/30/08. As noted in the letter to the PI dated 7/10/08 (Ex. 35), these documents along with several other

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documents were reviewed and approved by the full board pending requested changes. Approval of the study was granted through 6/25/09.

Expedited Approval letter to PI dated 4/7/09 (Ex. 36)

Letter states that changes/modifications in key personnel were reviewed and approved by board designee, Julie Goldman using expedited review procedures and will be presented to the IRB at the next full board meeting.

Full Board – Continuing Review Approval letter to PI dated 7/19/2009 (Ex. 37)

The following documents were submitted for continued approval: Progress Report, Research Protocol, and Protocol Synopsis. As noted in the IRB meeting minutes of 7/18/09, the Board granted continued approval from 6/26/2009 through 6/25/2010. A motion to approve the study was made in which 12 members voted for, 0 opposed, and 1 abstained. A quorum was present at the meeting (ex. 38).

Expedited Amendment Approval letter to PI dated 6/25/09 (Ex. 39)

Letter states that changes/modifications to several documents were reviewed and approved by board designee, Diller Groff using expedited review procedures and will be presented to the IRB at the next full board meeting.

Expedited Amendment Approval letter to PI dated 7/15/09 (Ex. 40)


Letter acknowledges the receipt of a deviation/violations for DV-165. A copy of that deviation that is completed in BRAAN by the PI is included as **Exhibit #41**.

Expedited Closure Approval letter to PI dated 8/5/09 (Ex. 42)

The letter to the PI acknowledges closure of this study and informs the investigator that research activities associated with the study may not be resumed without approval from the IRB. One subject was enrolled in this study.

Attachments referenced in the above noted letters are not included with this report; however, they may be retrieved from the CD that accompanies this report. (Ex. 9a, b, c, d)

Tracking #08-0424



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Documents collected pertaining to Study Protocol [REDACTED] is as follows:

Copies of the Protocol dated [REDACTED] (ex. 48) is submitted with the report along with the Subject Assent forms for ages 12-16 (ex. 49) and ages 7-11 (ex. 50), and the informed consents (ex. 51) both upon initial approval and again at the six month continuing review. As noted in the letter to the PI dated 9/19/08 (ex. 43), these documents along with several other documents were reviewed and approved by the full board on 9/18/08 pending requested changes. As reflected in the September 18, 2008 IRB meeting minutes (ex. 52), a motion was made to approve the study in which 14 members voted for, 0 opposed and 1 abstained. The Board approved the study for a period of six months with an expiration date of March 17, 2009. The reason for the six month review is that the study is a Phase I study in children with no Data Safety Monitoring Board.

Full Board – IRB Protocol – Modifications Required letter to PI dated 9/19/2008 (Ex. 43)

The above study was reviewed at the full board meeting of 9/18/08; however, as letter states, approval was contingent upon several issues addressed by the PI, [REDACTED]

Expedited Approval letter to PI dated 12/10/08 (Ex. 44)

Letter states that the above study was reviewed and approved by Frank Walker, M.D. using expedited review procedures and was initially presented to the full board on 9/18/08 with approval contingent upon changes to the study documents. The study was approved for children under Category 3, which requires the assent of the child (over 7 years old) and both parents' signatures. Category 3 represents 21 CFR 50.53 defined as "greater than minimal risk an no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' condition or disorder." The IRB classifies pediatric research into one of four categories based upon the categories outlined in 21CFR part 50, Subpart D and 5CFR46 and this is addressed in the IRB SOP, ex. 4, page 138.

Expedited – Continuing Review Approval letter to PI dated 2/26/09 (Ex. 45)

The following documents were submitted for semi-annual continued review: Research Protocol and Synopsis, subject assent for ages 7-11 and 12-17, revised informed consent, and HIPAA information. The documents were reviewed and approved by Laura Clark, board designee, using expedited review procedures and will be presented to the IRB at the next full board meeting. The reason for the semi-annual review was based on the fact that it was a Phase I study in children. The study has continued approval through 9/18/2009.

Expedited Amendment Approval letter to PI dated 8/11/09 (Ex. 46)

Letter stated that changes/modifications to key personnel and the informed consent were reviewed and approved by board designee, Serge Martinez, M.D., using expedited review procedures and will be presented to the IRB at the next full board meeting.

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Expedited – Continuing Review Approval letter to PI dated 9/02/09 (Ex. 47)

The following documents were submitted for semi-annual continued review: Research Protocol and Synopsis, subject assent for ages 7-11 and 12-17, revised informed consent, and HIPAA information. The documents were reviewed and approved by Diller Groff, board designee, using expedited review procedures and will be presented to the IRB at the next full board meeting. The study has continued approval through 3/17/2010.

As of the date of this inspection, no subjects have yet been enrolled in this study.

Attachments referenced in the above noted letters are not included with this report; however, they may be retrieved from the CD that accompanies this report. (Ex. 9a, b, c, d)

Each letter to the PI addressing expedited approval reminds of the IRB regulations that they are required to follow. These regulations are as noted below:

1. Unanticipated or serious adverse events/side effects encountered in this research study must be reported to the IRB within five (5) days.
2. Any modifications to the study protocol or informed consent form must be reviewed and approved by the IRB prior to implementation.
3. You may not use a modified informed consent form until it has been approved and validated by the IRB.

COMPLAINTS (CTR)

There were no complaints for follow up.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

No objectionable conditions were encountered and an FDA 483 Inspectional Observations was not issued.

REFUSALS

No refusals were encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT (CTR)

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Investigator Cooper and I held the closeout meeting with John Burke and Rebecca Higgins. No inspectional observations were noted, the IRB was found to be in compliance with the FDA regulations and, therefore, an FDA 483 was not issued. CSO Rybus provided Mr. Burke with a copy of the Frequently Asked Questions of FDA regarding the protection of human subjects of research.

EXHIBITS COLLECTED

- #1 Organizational Charts (7 pages)
- #2 FDA regulated studies for 2008-2010 (18 pages)
- #3 Open FDA regulated pediatric studies, 2008-2010 (5 pages)
- #4 IRB Standard Operating Procedures (154 pages)
- #5 Membership (88 pages)
- #6 Investigator's Guide for Human Research (185 pages)
- #7 Emergency Use document (19 pages)
- #8 IRB Organization Registration Information
- #9
 - a. CD for study #08.0205
 - b. CD for study #08.0309
 - c. CD for study #08.0424
 - d. CD of IRB Minutes, 2008-2009
- #10 Protocol for [REDACTED] (study #08.0205) submitted via BRAAN software (53 pages)
- #11 Minutes, May 1, 2008 (3 pages)
- #12 IRB letter to PI, [REDACTED] dated 5/21/08
- #13 IRB letter to PI, [REDACTED] dated 6/23/08 (3 pages)
- #14 IRB letter to PI, [REDACTED] dated 7/02/08 (2 pages)
- #15 Informed Consent, Groups I & II – 7-9 months old, Protocol [REDACTED] (11 pages)
- #16 Informed Consent, Groups III – 12 months old, Protocol [REDACTED] (11 pages)
- #17 IRB letter to PI, [REDACTED] dated 7/10/08 (2 pages)
- #18 IRB letter to PI, [REDACTED] dated 9/12/08 (2 pages)
- #19 IRB letter to PI, [REDACTED] dated 9/17/08 (2 pages)
- #20 IRB letter to PI, [REDACTED] dated 11/24/08 (2 pages)
- #21 IRB letter to PI, [REDACTED] dated 12/23/08 (2 pages)
- #22 IRB letter to PI, [REDACTED] dated 2/10/09 (2 pages)
- #23 IRB letter to PI, [REDACTED] dated 4/03/09 (2 pages)
- #24 Minutes, April 2, 2009 (3 pages)
- #25 IRB letter to PI, [REDACTED] dated 4/29/09 (2 pages)

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- #26 IRB letter to PI, [REDACTED] dated 6/03/09 (2 pages)
- #27 IRB letter to PI, [REDACTED] dated 7/10/09 (2 pages)
- #28 IRB letter to PI, [REDACTED] dated 8/21/09
- #29 Serious Adverse Event (AE-08.0205), (5 pages)
- #30 IRB letter to PI, [REDACTED] dated 12/15/09
- #31 Minutes, June 26, 2008 (2 pages)
- #32 Protocol for [REDACTED] (45 pages)
- #33 Consent form for [REDACTED] (10 pages)
- #34 Assent Form for [REDACTED] (3 pages)
- #35 IRB letter to PI, [REDACTED] dated 7/10/2008 (3 pages)
- #36 IRB letter to PI, [REDACTED] dated 4/7/2009 (2 pages)
- #37 IRB letter to PI, [REDACTED] dated 6/19/2009 (2 pages)
- #38 Minutes, June 18, 2009 (2 pages)
- #39 IRB letter to PI, [REDACTED] dated 6/25/09 (2 pages)
- #40 IRB letter to PI, [REDACTED] dated 7/15/2009
- #41 Deviation/Violation Feedback form for DV-165 (2 pages)
- #42 IRB letter to PI, [REDACTED] dated 8/5/09
- #43 IRB letter to PI, [REDACTED] dated 9/19/08 (3 pages)
- #44 IRB letter to PI, [REDACTED] dated 12/10/08 (3 pages)
- #45 IRB letter to PI, [REDACTED] dated 2/26/09 (2 pages)
- #46 IRB letter to PI, [REDACTED] dated 8/11/09 (2 pages)
- #47 IRB letter to PI, [REDACTED] dated 9/02/09 (2 pages)
- #48 Protocol for [REDACTED] (50 pages)
- #49 Subject Assent form for Ages 12-16, Protocol [REDACTED] (4 pages)
- #50 Subject Assent form for Ages 7-11, Protocol [REDACTED] (2 pages)
- #51 Subject Informed Consent, Protocol [REDACTED] (14 pages)
- #52 Minutes, September 18, 2008 (3 pages)

ATTACHMENTS

FDA 482, Notice of Inspection dated 1/20/09
Assignment Memorandum dated October 9, 2009

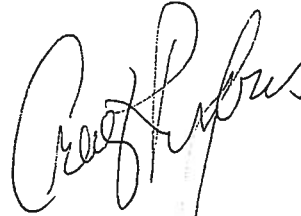
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Cincinnati District



Craig T. Rybus, Investigator
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