INDEPENDENT ASSESSMENT OF A UNIVERSITY OF MINNESOTA INSTITUTIONAL REVIEW BOARD NON-COMPLIANCE DETERMINATION
March 11, 2015

Dr. Brian Herman
Vice President, Research
University of Minnesota
Office of the Vice President for Research
420 Johnston Hall
101 Pleasant St. SE
Minneapolis, MN 55455

Re: Independent Assessment of a University of Minnesota Institutional Review Board (IRB) Non-compliance Determination

Dear Dr. Herman:

Attached please find FTI Consulting’s (“FTI”) Report which summarizes our independent assessment of the University of Minnesota Institutional Review Boards (“IRB”) non-compliance determination concerning Dr. Stephen Olson’s research studies involving the investigational drug Bifeprunox (more specifically, the University of Minnesota IRB Protocols #0309M52653, #0610M95446 and #0710M19084).

Thank you for the opportunity for FTI to weigh in on this critically important matter. Please feel free to contact us should you have any questions regarding this report.

Sincerely,

Scott Lipkin, DPM, CIP
Managing Director
# TABLE of CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Summary</td>
<td>3</td>
</tr>
<tr>
<td>Background</td>
<td>5</td>
</tr>
<tr>
<td><strong>FTI Assessment</strong></td>
<td></td>
</tr>
<tr>
<td>Charge 1a</td>
<td>7</td>
</tr>
<tr>
<td>Charge 1b</td>
<td>8</td>
</tr>
<tr>
<td>Charge 2a</td>
<td>10</td>
</tr>
<tr>
<td>Charge 2b</td>
<td>13</td>
</tr>
<tr>
<td>Charge 2c</td>
<td>15</td>
</tr>
<tr>
<td>Charge 2d</td>
<td>16</td>
</tr>
<tr>
<td>Charge 3</td>
<td>16</td>
</tr>
<tr>
<td>Charge 4a</td>
<td>17</td>
</tr>
<tr>
<td>Charge 4b</td>
<td>17</td>
</tr>
<tr>
<td>Charge 4c</td>
<td>18</td>
</tr>
<tr>
<td>Appendix A: Bio-sketches</td>
<td>20</td>
</tr>
<tr>
<td>Appendix B: Documents and Interviews</td>
<td>22</td>
</tr>
</tbody>
</table>
Executive Summary

Early in 2014, the Chair of the University of Minnesota Executive Institutional Review Board ("IRB") Committee received a written request from one of its faculty members to investigate complaints related to certain psychiatric research projects at the University of Minnesota ("the University"). Shortly thereafter, the University received a complaint filed by an individual ("the "Complainant") who in 2007 participated in Protocol #0309M52653, an open label, non-randomized clinical trial to assess the safety and effectiveness of Bifeprunox, an investigational anti-psychotic drug.

Subsequently, the University's IRB Executive Committee (the "Committee") voted to convene a formal inquiry in response to the allegations identified by the faculty member and the complainant. In accordance with University policy, the IRB Executive Committee assembled an investigation sub-group (the "Investigation Sub-group"). The Investigation Sub-group was charged with investigating specific allegations involving three studies involving the drug Bifeprunox and reporting its findings to the Committee.

After review and discussion of the Investigation Sub-group report, the Committee voted on each of the charges and issued a final report. The Committee’s final report was forwarded on to the University of Minnesota Institutional Official and Vice President of Research, Dr. Brian Herman. Dr. Herman, in his capacity as Institutional Official, sought an independent assessment of the Committee’s final report.

Dr. Herman engaged FTI Consulting ("FTI") to conduct the independent assessment of the Committee’s determinations. To complete the work, FTI reviewed records and conducted on-site interviews (Appendix B). FTI’s findings are summarized below:

1. Were adequate mechanisms in place to evaluate whether the complainant had capacity to provide informed consent?
   - Yes (Charge 2a)

2. Did the Complainant lack capacity to provide legally effective informed consent?
   - No (Charge 2a)

3. Did the misdated signature by the subject advocate constitute non-compliance?
   - No (Charge 2a)

4. Was the Complainant pressured or coerced by the Principal Investigator ("PI") into participating in the study?
   - No (Charge 2b)
5. Did the writing of a NPO research order by the PI prior to obtaining legally effective informed consent from the Complainant constitute non-compliance?
   - FTI agrees with the IRB that non-compliance occurred; however, FTI finds that the non-compliance rose to the level of serious non-compliance.

6. Did the PI follow requirements for handling and reporting adverse events to the study sponsor and the IRB?
   - Yes (Charge 2c)

7. Were provisions in place to allow participants to freely withdraw from the study?
   - Yes (Charge 2d)

8. Did informed consent documents disclose that a research participant died in 2004 from complications related to the study drug?
   - Yes (Charge 4a)

9. Was the FDA decision not to approve the investigational drug a significant new finding that should have been reported to research participants?
   - Yes (Charge 4b)

10. Was the FDA decision not to approve the investigational drug reported to research participants?
    - No (Charge 4b)

11. Were participant injuries and complaints appropriately reported to the IRB?
    - Yes (Charge 4c)
Independent Assessment of a University of Minnesota Institutional Review Board Non-compliance Determination

University of Minnesota Principal Investigator: Stephen Olson, MD

Affected University of Minnesota IRB Protocols:

- 0610M95446, A Multi-Center, Open-Label, Parallel-Group, Randomized, Flexible Dose Study to Evaluate the Safety and Tolerability of Switching From Existing Atypical Antipsychotics to Bifeprunox in Subjects with Schizophrenia or Schizoaffective Disorder, Protocol SI543020
- 0710M19084, A Randomized, Multicenter, Double-Blind, Parallel Group Study to Compare the Effects of Bifeprunox and Quetiapine on Weight Changes in Stable Schizophrenic Patients, Protocol SI54.3.021

Background

On January 2, 2014, the Chair of the University of Minnesota Executive Institutional Review Board ("IRB") Committee received a written request from one of its faculty members, to investigate complaints related to certain psychiatric research projects at the University of Minnesota. Shortly thereafter, on February 6, 2014, the University received a complaint filed by an individual ("the "Complainant") who in 2007 participated in a clinical trial sponsored by Solvay Pharmaceuticals at the Fairview Hospital. The specific clinical trial (University of Minnesota IRB #0309M52653) was an open label, non-randomized trial to assess the safety and effectiveness of Bifeprunox, an investigational anti-psychotic drug. The University of Minnesota Principal Investigator for the affected studies was Stephen Olson, MD (hereinafter referred to as "Stephen Olson, MD"; or the "PI").

Responding to the Complainant’s and to request, the University of Minnesota’s IRB Executive Committee (the “Committee”) voted to convene a formal inquiry at its February 10, 2014 meeting. In accordance with University IRB policy No. 408/408A, the IRB Executive Committee assembled an investigation sub-group (the "Investigation Sub-group"), comprised of three IRB members with relevant expertise, to obtain pertinent facts and then report back to the Committee. The Investigation Sub-group was tasked with the following:

Charge 1a: Conduct an investigation into three studies involving the drug Bifeprunox (IRB Protocols #0309M52653, #0610M95446 and #0710M19084), led by Stephen Olson, MD, to determine whether serious or continuing non-compliance was found with regard to the rights and welfare of the Complainant in 2007 under Protocol #0309M52653.
Charge 1b: Conduct an investigation into three studies involving the drug Bifeprunox (IRB Protocols #0309M52653, #0610M95446 and #0710M19084), led by Stephen Olson, MD to determine whether serious or continuing non-compliance related to investigator obligations occurred in any of the three studies. The investigation must follow the procedures outlined under IRB Policy 408A: Investigation Process.

Charge 2a: Examine any and all aspects of the Complainant’s participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to, whether there were adequate mechanisms in place to evaluate whether the Complainant had the capacity to consent to participation? Is there evidence that suggests that the Complainant lacked capacity to consent?

Charge 2b: Examine any and all aspects of the Complainant’s participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to, whether proper recruitment strategies were followed. Is there evidence that the Complainant was pressured to participate in the study?

Charge 2c: Examine any and all aspects of the Complainant’s participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to, whether proper procedures were followed regarding the handling and reporting of adverse events. Is there evidence that the PI failed to address serious adverse events experienced by the Complainant or failed to report the Complainant’s concerns or adverse events to the IRB?

Charge 2d: Examine any and all aspects of the Complainant’s participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to, whether participants were freely allowed to withdraw from participation. Is there evidence that the Complainant’s right to withdraw from the study was not respected?

Charge 3: If you find serious non-compliance regarding the rights and welfare of the Complainant, examine whether there was serious non-compliance with respect to the rights and welfare of other participants under the three protocols.

Charge 4a: Examine whether there was serious or continuing non-compliance by Stephen Olson, MD with respect to investigator obligations under the three protocols, including but not limited to, whether the risks of taking Bifeprunox were adequately disclosed to the research participants. Should the research consent forms have disclosed that a subject died in 2004 or disclosed a risk of hepatorenal failure? Should the PI have informed participants of the subject’s death once the sponsor suspended the studies in December 2007?

Charge 4b: Was the FDA decision not to approve Bifeprunox in August 2007 a significant new finding that should have been reported to the research participants?

Charge 4c: Did the PI fail to report participant injuries or complaints to the IRB?

After completion of the review and subsequent discussions regarding the Investigation Sub-group report, the IRB Executive Committee, functioning as a convened IRB at its October 13,
2014 meeting, determined that two instances of non-compliance not rising to the level of serious or continuing, occurred by Stephen Olson, MD as related to the Complainant’s activity in trial #0309M52653. Specifically, the non-compliance determinations were related to:

1. The PI’s 2007 written order of “” prior to obtaining the Complainant’s informed consent.
2. The subject advocate’s signature on the informed consent form which was dated one day after the Complainant signed and dated the consent document.

As part of its determination, the IRB Executive Committee required the following corrective actions of the PI:

1. Establish procedures to ensure that research consent forms will be signed before any study activity has begun, including initiating a medication “washout” period or keeping a subject NPO.
2. Establish procedures to ensure that the research advocate’s signature and date correspond with the consent date, and that will require in the future, the research advocate to document her/his research consent process involvement in writing, with a line or two in the subject’s research records and/or the medical record.

The final report was forwarded to Brian Herman, Vice President for Research, who in his capacity as Institutional Official retains authority to provide a final determination. As such, Dr. Herman sought to obtain an independent, external assessment of the IRB’s review and determinations prior to making his final determination related to the complaints from and the Complainant.

FTI Assessment of IRB Noncompliance Findings
Listed in Order By Charge

Charge 1a: Conduct an investigation into three studies involving the drug Bifeprunox (IRB Protocols #0309M52653, #0610M95446 and #0710M19084), led by Stephen Olson, MD, to determine whether serious or continuing non-compliance was found with regard to the rights and welfare of the Complainant in 2007 under Protocol #0309M52653.

University of Minnesota IRB Findings Regarding Charge 1a:

The University of Minnesota IRB concluded that non-compliance occurred regarding the rights and welfare of the Complainant in 2007, but that the non-compliance did not rise to the level of serious or continuing non-compliance. In particular, the IRB investigation sub-group identified the following two issues of non-compliance related to the participation of the Complainant in IRB #0309M52653:

1. The subject advocate’s signature on the consent form was dated one day after the participant signed; and
2. Prior to documenting consent by signing the study consent form, the Complainant was held NPO the (Sunday) night before he enrolled in the study in anticipation of the protocol screening laboratory tests (Monday).

FTI Assessment Regarding Charge 1a:

FTI disagrees with both of the University of Minnesota IRB Executive Committee findings for the reasons stated under sections 2a and 2b of this report.

Charge 1b: Conduct an investigation into three studies involving the drug Bifeprunox (IRB Protocols #0309M52653, #0610M95446 and #0710M19084), led by Stephen Olson, MD to determine whether serious or continuing non-compliance related to investigator obligations occurred in any of the three studies. The investigation must follow the procedures outlined under IRB Policy 408A: Investigation Process.

University of Minnesota IRB Findings Regarding Charge 1b:

The University of Minnesota IRB concluded that there were no serious or continuing non-compliance issues with regard to investigator obligations for reporting to the IRB for Protocol #0309M52653 and Protocol #0610M95446. The IRB noted that Protocol #0710M19084 was terminated by sponsor prior to IRB final approval, therefore no research activity occurred.

FTI Assessment Regarding Charge 1b:

FTI disagrees with this IRB finding. For the reasons stated below, FTI believes that: (a) the investigator failed to promptly report to the IRB an unanticipated problem involving risks to subjects or others (i.e., an August 10, 2007 FDA non-approval determination regarding the study drug Bifeprunox) and (b) the failure to promptly report constituted serious noncompliance. (See Charge 4b for additional FTI findings relative to other investigator obligations.) In support of this conclusion, we offer the following:

Governing Authorities:

FDA regulations at 21 CFR 56.108(b) provide that each IRB shall follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) any unanticipated problems involving risks to subjects or others; (2) any instance of serious or continuing non-compliance with governing FDA regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

FDA regulations do not define “prompt reporting” “unanticipated problems” or “serious or continuing non-compliance with governing FDA regulations or the requirements or determinations of the IRB.” As a result, in order for an IRB to satisfy regulatory requirements regarding written IRB procedures, an IRB must define these terms for itself.
**Prompt Reporting of Unanticipated Problems:**

In accordance with FDA regulations at 21 CFR 56.108(b), the University IRB developed IRB Policy 411 to address prompt reporting to the IRB, appropriate institutional officials, and the FDA of unanticipated problems involving risks to subjects or others.

According to IRB Policy 411 (version date 9/29/06), any unanticipated problem involving risks to subjects or others (UPIRTSO) must be reported promptly (within 10 working days of knowledge of the event) to the IRB. Per the policy, an unanticipated problem is defined as any problem or event which in the opinion of the local investigator was unanticipated, serious and at least possibly related to the research procedures. This policy states that the “following events meet the IRB’s definition of UPIRTSO and should be reported [to the IRB] within the 10 day time frame: ... Any publication in the literature, safety monitoring reports (including Data and Safety Monitoring Reports), interim results or other finding that indicates an unexpected change to the risk/benefit ratio of the research; ... “

Thus, in accordance with University IRB Policy 411, any publication in the literature, safety monitoring reports (including Data and Safety Monitoring Reports), interim results or other finding that indicates an unexpected change to the risk/benefit ratio of the research is an unanticipated problem that must be reported to the IRB within 10 working days of knowledge of the event.

**Serious and Continuing Non-Compliance:**

In accordance with FDA regulations at 21 CFR 56.108(b), the University of Minnesota IRB developed IRB Policy 408; a policy addressing prompt reporting to the IRB, appropriate institutional officials, and the FDA of, among other items, any instance of serious or continuing non-compliance with the regulations or the requirements or determinations of the IRB. According to IRB Policy 408, an activity is considered to be non-compliant if it varies from: (a) the approved IRB protocol; (b) IRB policies and procedures; or (c) relevant state or federal laws. This policy further defines serious and continuing non-compliance as follows:

Serious Non-Compliance: Non-compliance that jeopardizes the rights and welfare of the human subject research participants. Examples may include enrolling research participants who do not meet inclusion/exclusion criteria in an experimental protocol with possible serious health-related consequences for participants or failure to use the current IRB-approved consent form with all potential risks and alternatives to participation outlined.

Continuing Non-Compliance: Non-compliance that evidences a pattern of deviating from IRB requirements or engaging in study practices that might jeopardize the rights and welfare of participants. This may be illustrated by a researcher’s repeated lack of attention to or knowledge or understanding of regulations or ethics or failure to consistently respond to requests for reports, such as Continuing Review reports.

Thus, in accordance with University IRB Policy 408, an activity is deemed to constitute serious non-compliance if the activity (a) varies from the approved IRB protocol, IRB policies and procedures or relevant state or federal laws; and (b) jeopardizes the rights and welfare of human subject research participants.
Applicat ion of IRB Policies 411 and 408 to IRB Protocol #0309M52653 and Protocol #0610M95446.

In a letter dated August 10, 2007, the FDA notified the study sponsor, via a non-approval letter, that the study drug Bifeprunox was not as effective as other approved antipsychotics. This FDA non-approval letter was reported on by a number of news organizations shortly after the letter was issued.

FTI concludes that this "not-as-effective as other approved antipsychotics" determination constituted an unanticipated problem under University IRB Policy 411 because it is a finding that indicates an unexpected change to the risk/benefit ratio of clinical trials involving Bifeprunox. As a result, the investigator should have reported this information to the IRB within 10 working days of knowledge of the event, not approximately one and a half months after the August 10, 2007 FDA letter was issued, as was done in this instance. While FTI acknowledges that the record is inconclusive regarding when Dr. Olson first received notice of this August 10, 2007 FDA non-approval letter, FTI believes that Dr. Olson should have become aware of the FDA non-approval letter shortly after its issuance given the press coverage surrounding the FDA non-approval announcement.

Furthermore, FTI concludes that the investigator's failure to promptly report the unanticipated problem to the IRB constituted serious non-compliance under University IRB Policy 408. As described under Charge 4b, research participants should have been informed of the FDA "not-as-effective" determination as this would have had immediate impact on their decision to continue participation in Bifeprunox trials.

Charge 2a: Examine any and all aspects of the Complainant's participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to, whether there were adequate mechanisms in place to evaluate whether the Complainant had the capacity to consent to participation? Is there evidence that suggests that the Complainant lacked capacity to consent?

University of Minnesota IRB Findings Regarding Charge 2a:

The University of Minnesota IRB concluded that: (a) mechanisms were adequate to evaluate whether the Complainant had the capacity to consent to participate; and (b) evidence showed that the Complainant had the capacity to consent.

FTI Assessment Regarding Charge 2a:

FTI concurs with this University of Minnesota IRB finding. Specifically, FTI agrees that adequate measures were in place to reasonably assure that potential participants had capacity

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1 FTI did not review Protocol #0710M19098 because it was terminated by the sponsor prior to IRB final approval.
to provide legally effective informed consent. Based upon available evidence, FTI: (a) agrees that the Complainant had capacity to provide informed consent in accordance with regulatory requirements, University of Minnesota IRB policies and procedures, and the determinations of the University of Minnesota IRB; but (b) disagrees with the University of Minnesota IRB non-compliance determination as related to the subject advocate’s signature on the Complainant’s informed consent document.

**Assessing Capacity and Obtaining Legally Effective Informed Consent:**

To assure that potential participants for Protocol #0309M52653 had capacity to understand all aspects of study participation and that they were capable of providing legally effective informed consent in an environment free from coercion and undue influence, the IRB and the PI provided the following additional protections:

- The IRB required utilization of a Subject Advocate.
- The IRB required completion of the “Evaluation to Sign Consent Form” for each enrolled participant.
- The IRB reviewed and approved the PI’s informed consent process.

**Subject Advocate:**

- The role of the subject advocate was defined in the IRB approved informed consent document as:
  
  o Subject Advocate: A person designated by you, or someone recommended by the researchers, but not otherwise involved in this research, will go through this consent form with you. This person (your "subject advocate") will assist you to make a decision about whether or not to participate in this study. If while in the study your ability to make decisions becomes impaired to the point that you cannot protect your own interests, then your subject advocate will determine if it is still consistent with your interests and your original choice to continue in the study. If this person determines that it is not in your interest to continue, you will be removed from the study. Once you leave the hospital, you will need to return to the Ambulatory Research Center for your study visits. At the end of this form is a schedule that lists all of the visits and study procedures. You will also be given a copy of this.

- A subject advocate was required for each participant in the trial. Although there was a mistake related to signing and dating of the Complainant’s informed consent by the subject advocate, the Complainant informed the IRB Investigation Sub-group that he recalled the subject advocate being present during the informed consent process.

**Evaluation to Sign Consent Form:**

- The IRB required completion of the “Evaluation to Sign Consent Form” for each enrolled participant. This form was utilized by the research coordinator who was involved in the informed consent process to assess a participants understanding of the study. The questions were read to the participant and transcribed on the Evaluation Form. The questions were:
• Is the subject alert and able to communicate with the examiner?
  • Ask the subject to describe the purpose of the study.
  • Ask the subject to describe one or two potential risks incurred as a result of participating in the study.
  • Ask the subject to describe any benefits that may result in participating in the study, including the acknowledgement that there may not be any.
  • Ask the subject to describe what is expected of he or she as a participant in the study.
  • Ask the subject what would happen if he or she no longer wants to participate in the study.
  • The research coordinator documented the Complainant’s response to all questions listed above. The responses provided by the Complainant indicated that

Informed Consent Process:

• The IRB approved a comprehensive informed consent process as part of initial protocol approval.
• The PI’s account of the informed consent process for the Complainant was as follows:

In summary, FTI concludes that “best practice” measures were in place to reasonably assure that potential participants had capacity to provide legally effective informed consent. Based upon available evidence, FTI concludes that the Complainant did not lack capacity to provide informed consent in accordance with regulatory requirements, University of Minnesota IRB policies and procedures, and the determinations of the University of Minnesota IRB.

Non-compliance related to the Subject Advocate’s Signature:

Governing Authorities:

As previously stated, the University of Minnesota IRB developed IRB Policy 408; a policy addressing prompt reporting to the IRB, appropriate institutional officials, and the FDA of, among other items, any instance of serious or continuing non-compliance with the regulations or
the requirements or determinations of the IRB. According to IRB Policy 408, an activity is considered to be non-compliant if it varies from: (a) the approved IRB protocol; (b) IRB policies and procedures; or (c) relevant state or federal laws.

FTI applied the above referenced regulatory and policy guidance to the University of Minnesota IRB findings and concluded that the failure of the Subject Advocate to sign and date her portion of the consent form on the same day as the Complainant did not constitute non-compliance as defined by University of Minnesota policy because this activity did not vary from: (a) the IRB approved protocol; (b) University of Minnesota IRB policies and procedures; or (c) any state or federal laws that were in effect in 2007 regarding subject advocate signatures on consent forms. It was clear from responses provided by the Complainant and from the work of the Investigation Sub-group that the subject advocate was in fact present during the informed consent process.

It is important to note that the University of Minnesota IRB Investigation Sub-group did not reference any governing IRB policies or procedures or state or federal laws/regulations mandating that subject advocates sign and date informed consent forms on the same day that the participant signs and dates informed consent forms. Moreover, FTI could not locate any requirement in the IRB approved protocol, University of Minnesota IRB policies and procedures or any state or federal laws mandating the same. In fact, one of the corrective actions required of the PI was to establish a procedure that will ensure that subject advocates sign and date the informed consent form on the same day that research participant signs and dates the informed consent form. FTI assumes that this corrective action was required of the PI because there are no University of Minnesota IRB procedures addressing this scenario.

**Charge 2b:** Examine any and all aspects of the Complainant's participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to, whether proper recruitment strategies were followed. Is there evidence that the Complainant was pressured to participate in the study?

**University of Minnesota IRB Findings Regarding Charge 2b:**

The University of Minnesota IRB concluded that recruitment appears to have been conducted in accord with the process detailed in Protocol application #0309M52653.

**FTI Assessment Regarding Charge 2b:**

FTI concurs with this University of Minnesota IRB finding relating to the recruitment process but disagrees with the non-compliance determination related to holding the Complainant NPO prior to obtaining legally effective informed consent. In particular, FTI concludes that the participant was recruited into Protocol #0309M52653 in accordance with the IRB approved protocol. (See description under charge 2a.) However, FTI concludes that holding the Complainant NPO - for the sole purpose of obtaining protocol screening labs - before obtaining the Complainant's informed consent constituted serious non-compliance because this activity varied from the IRB approved protocol; University of Minnesota Policy 701; and federal regulations at 21 CFR 50.20. Specifically,
Section 11.1.2 of Amendment 3 of the protocol (dated March 7, 2005) - the version of the protocol in effect at the time that the Complainant was enrolled into the study - provided the following:

Subjects will not be screened or treated until the subject has signed an approved informed consent written in a language that is understandable to the subject.

University of Minnesota Policy 701 – Documentation and General Requirements of Consent - provides that "researchers must obtain documentation of consent from individual subjects or their legally authorized representative prior to implementing research procedures on them, unless a request for waiver or alteration of said documentation has been requested, reviewed and approved by the IRB."

FDA regulations at 21 CFR 50.20 provides that except as provided in sections 50.23 (exception from general informed consent requirements) and 50.24 (exception from informed consent requirements for emergency research), no investigator may involve a human being as a subject in research covered by these regulations (21 CFR 50) unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

Moreover, the activity of holding the Complainant NPO - for the sole purpose of obtaining protocol screening labs - before obtaining the Complainant's informed consent varied from the FDA guidance titled “Screening Tests Prior to Study Enrollment” This guidance document states that “informed consent must be obtained prior to initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient subjects why certain tests are being conducted.”

Lastly, the Department of Health and Human Service Office for Human Research Protections ("OHRP") has provided guidance on what constitutes serious non-compliance. OHRP has consistently opined, through both informal communications with regulated industry, as well as via OHRP determination letters, that it considers the following scenarios to constitute serious non-compliance:

1. Implementing more than minor protocol changes without IRB approval, except when necessary to prevent immediate hazard(s) to subjects;
2. Conducting non-exempt human subjects research without IRB review and approval; and
3. Failing to obtain the legally effective informed consent of subjects, when required by the IRB, prior to involvement of subjects in non-exempt human subjects research activities.

3 http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm
While FTI acknowledges that OHRP did not have jurisdiction over this particular study, FTI finds that the serious non-compliance examples noted above – in particular Example #3 - fall squarely within the University of Minnesota IRB Policy 408 definition of serious non-compliance; a written IRB procedure that is mandated by both OHRP and FDA and applies equally to FDA regulated research and OHRP regulated research.

Given the above, FTI finds that the action of holding the Complainant’s (see ) did constitute non-compliance because: (a) holding an individual NPO in preparation of conducting a research blood draw/fasting screening procedure for a research study constitutes a research procedure that violated (b) University of Minnesota IRB Policy 701 and (c) section 11.1.2 of the IRB approved protocol which provided “Subjects will not be screened or treated until the subject has signed an approved informed consent written in a language that is understandable to the subject.”

Moreover, FTI concludes that this non-compliance constitutes serious non-compliance under University of Minnesota IRB Policy 408 and federal regulations. Of note, IRB Policy 408 defines serious non-compliance as “non-compliance that jeopardizes the rights and welfare of human subject research participants”. FTI concludes that conducting a research intervention prior to obtaining legally effective informed consent, in this case, holding the participant NPO in preparation of conducting a research blood draw/fasting screening procedure, jeopardized the rights of the participant.

**Charge 2c:** Examine any and all aspects of the Complainant’s participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to, whether proper procedures were followed regarding the handling and reporting of adverse events. Is there evidence that the PI failed to address serious adverse events experienced by the Complainant or failed to report the Complainant’s concerns or adverse events to the IRB?

***University of Minnesota IRB Findings Regarding Charge 2c:**

The University of Minnesota IRB found that: (i) proper procedures were followed with regard to handling and reporting adverse events; and (ii) there was no evidence that the PI failed to address the Complainant’s complaints expressed at the time of admission or during participation in the study.

***FTI Assessment Regarding Charge 2c:**

FTI concurs with this University of Minnesota IRB finding. Research records show that the PI reviewed and reported adverse events in a manner consistent with ICH and FDA Good Clinical

5 See University of Minnesota IRB Policy 408 which references both FDA and OHRP regulations.

6 FTI’s serious non-compliance finding is limited to the NPO order only. The evidence was inconclusive regarding whether informed consent was obtained prior to research screening labs having been drawn. See document titled: Bifeprunox Investigation Documents Supplemental Search Based on IRB Executive Members’ Questions(email 6/11/14) which provides the following for See also enrolled in Solvay 3002A Bifeprunox Study.
Practice guidelines and University of Minnesota IRB policy. Sponsor monitoring reports also confirm the PI’s compliance with reporting requirements.

**Charge 2d:** Examine any and all aspects of the Complainant’s participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to, whether participants were freely allowed to withdraw from participation. Is there evidence that the Complainant’s right to withdraw from the study was not respected?

*University of Minnesota IRB Findings Regarding Charge 2d:*

The University of Minnesota IRB concluded that there was evidence that the Complainant was allowed to withdraw freely and without pressure.

*FTI Assessment Regarding Charge 2d:*

FTI concurs with this University of Minnesota IRB finding. In support of FTI’s conclusion, we offer the following:

Question #6 of the “Evaluation to Sign Consent Form” specifically addressed the issue of voluntary departure from the study. The questions read, “Ask the subject what would happen if he or she no longer wants to participate in the study.” The Complainant answered the question by stating: [redacted].

In addition, [redacted]. Lastly, there was no documented evidence indicating that the Complainant was coerced to remain in the study.

**Charge 3:** If you find serious non-compliance regarding the rights and welfare of the Complainant, examine whether there was serious non-compliance with respect to the rights and welfare of other participants under the three protocols.

*University of Minnesota IRB Findings Regarding Charge 3:*

The University of Minnesota IRB did not find any serious or continuing non-compliance with regard to the rights and welfare of the Complainant under Protocol #0309M52653. As a result, the Investigation Sub-group did not review individual subject files for other subjects under Protocol #0309M52653 or Protocol #0610M95446.

*FTI Assessment Regarding Charge 3:*

FTI disagrees with this University of Minnesota IRB finding for the reasons stated above under Charge 2b. FTI concluded that there was serious non-compliance under Protocol #0309M52653.
**Charge 4a:** Examine whether there was serious or continuing non-compliance by Stephen Olson, MD with respect to investigator obligations under the three protocols, including but not limited to whether the risks of taking Bifeprunox were adequately disclosed to the research participants. Should the research consent forms have disclosed that a subject died in 2004 or disclosed a risk of hepatorenal failure? Should the investigator have informed participants of the subject's death once the sponsor suspended the studies in Dec 2007?

**University of Minnesota IRB Findings Regarding Charge 4a:**

The University of Minnesota IRB concluded that: (a) the risks of taking Bifeprunox were adequately disclosed to research participants; (b) including the risk of death related to a liver abnormality; and (c) that there was no need to inform subjects who discontinued Bifeprunox of the one death associated with a liver abnormality given the low frequency of the risk (single subject world-wide).

**FTI Assessment Regarding Charge 4a:**

FTI agrees with the University of Minnesota IRB findings regarding item (b) and (c) above, but disagrees with the University of Minnesota IRB finding relating to whether the risks of taking Bifeprunox were adequately disclosed to research participants. In particular, FTI concludes that the University of Minnesota IRB approved and the investigator used, an informed consent document for Protocol #0309M52653 that did not disclose the risks of medication washout. Please note that the IRB approved ICFs for the other two Bifeprunox studies *did* in fact include risks of washout.

**Charge 4b:** Was the FDA decision not to approve Bifeprunox in Aug 2007 a significant new finding that should have been reported to the research participants?

**University of Minnesota IRB Finding Regarding Charge 4b:**

The University of Minnesota IRB concluded that the FDA decision not to approve Bifeprunox did not need to be reported to research participants.

**FTI Assessment Regarding Charge 4b:**

FTI disagrees with the University of Minnesota IRB determination and believes that participants in all Bifeprunox trials should have been informed of this new information that may have affected their willingness to continue participating in Bifeprunox trials. In support of this conclusion, we offer the following:

FDA regulation 21 CFR 50.25 (b) provides that in seeking informed consent, the following additional information, when appropriate, shall be provided to each subject: .... “(5) A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.”

FTI notes that in accordance with 21 CFR 50.25(b), the University of Minnesota IRB- approved informed consent form for study #0309M52653 stated as follows: “During the course of the study, you will be told by the study doctor of any new significant findings that may affect your
willingness to continue to participate.” Elsewhere in the IRB approved consent document it provided “If your disease worsens, if the side effects become intolerable, or, if scientific developments occur that indicate that the study drug is no longer in your best interest, your participation will be stopped and other alternatives will be discussed with you.”

Notwithstanding the above, in a letter dated August 10, 2007, the FDA notified the study sponsor, via a non-approval letter, that the study drug Bifeprunox was not as effective as other approved antipsychotics. FTI believes that this “not-as-effective as other approved antipsychotics” determination constituted a significant new finding because this information would have a bearing on whether enrolled subjects would be willing to continue participating in Protocol #0309M52653, a 52-week long protocol studying three flexible doses of Bifeprunox.

Moreover, the PI had the responsibility to promptly inform enrolled subjects, as well as the reviewing IRB, of this significant new finding. The IRB record reveals that the PI never informed enrolled subjects of this significant new information. Moreover, while the IRB record reflects that the PI informed the IRB of the August 10, 2007 FDA non-approval letter via a continuing review form, the PI failed to notify the IRB promptly. Based on the IRB record, it appears that the investigator notified the IRB of this FDA decision somewhere between one and a half to two months after the decision was rendered.

Lastly, while the PI notified the IRB of the non-approval letter approximately one and a half months after Solvay received the August 10, 2007 FDA letter, the IRB did not take any action on the letter. Specifically, the documents show that the PI notified the University of Minnesota IRB that the FDA issued a Bifeprunox non-approval letter to the sponsor on the grounds that there was inconsistent efficacy relative to other FDA approved antipsychotics. Subsequently, in a Full IRB Committee Review – Continuing Review Form for Protocol #0309M52653 (signed 10/30/07) an IRB reviewer noted that the “FDA issued a non-approvable letter” regarding the investigational drug. Although the IRB reviewer acknowledged the letter, there is no evidence showing that the IRB investigated or discussed what effect, if any, the non-approval letter would have on open studies involving Bifeprunox. The FDA Bifeprunox non-approval and the fact that it was reported in a number of publications between August 10, 2007 and October 30, 2007, should have triggered a discussion among the IRB members to determine whether the study should have continued and if so, what modifications to the informed consent form should have been made and whether the research participants should have been re-consented.

Charge 4c: Did the PI fail to report participant injuries or complaints to the IRB?

University of Minnesota IRB Findings:

The University of Minnesota IRB found that that the PI did not fail to report participant injuries or complaints to the IRB.

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7 See undated Full Committee Review – Continuing Review Form that was submitted to the IRB prior to October 22, 2007
FTI Assessment:

FTI agrees with the University of Minnesota IRB finding regarding Charge 4c. Evidence shows that the PI fulfilled his reporting obligations as we have described in our conclusions under Charge 2c.

Conclusion:

Thank you for choosing FTI to assist the University of Minnesota with this important and interesting matter. Please do not hesitate to contact us should you have any questions regarding our assessment or if you require additional assistance with this matter.
Appendix A

FTI Research & Compliance Practice and Select Bio-Sketches

FTI Consulting Health Solutions' Clinical Research and Compliance Practice assists research organizations in navigating and/or avoiding issues with research, enforcement and regulatory agencies. The Clinical Research and Compliance Practice provides a comprehensive array of healthcare related research and compliance support services including the following:

- Research Billing and Medicare Coverage Analysis
- Human Subject Protections
- Conflicts of Interest and Physician Sunshine Act
- Research Compliance Services
- Research Administration and Performance Improvement
- Grants Management and Compliance
- Research Misconduct
- Good Clinical Practice Standards
- Compliance Program Effectiveness
- International Research Support Services

Scott Lipkin, DPM is a Managing Director with more than 27 years of clinical and administrative research experience. He focuses his practice on clinical research and compliance matters including human research protections, conflicts of interest, research misconduct investigations, grants management, and research compliance services. Dr. Lipkin previously served as the Executive Director of the Lehigh Valley Health Network’s Office for Research and Innovation and prior to that, he served as Director of the Human Research Protection Program and the IRB Chair. He was a practicing surgical podiatrist and served as Chief of Lehigh Valley Hospital’s Division of Foot and Ankle Surgery for ten years. Dr. Lipkin served on the AAHRPP Council of Accreditation (and was previously the Vice-Chair) for four years and conducted site visits for AAHRPP in the capacity of team leader for six years. Dr. Lipkin serves on the Planning Committee for PRIM&R’s AER and is a frequent speaker on human research protections and other research compliance matters.

Lisa Rooney, JD advises clients on Human Research Protection Program (HRPP) matters. As part of her practice, Lisa assists clients in improving their Human Research Protection Programs by conducting effectiveness reviews of their HRPPs, helping clients respond to inquiries from OHRP and the FDA, and educating clients about HRPP regulations and policies. Prior to joining
FTI Consulting, Lisa spent 6 years working for OHRP as a compliance oversight coordinator. In this capacity, Lisa conducted over 30 compliance oversight evaluations of Federalwide Assurance (FWA) holding institutions’ HRPPs; evaluated hundreds of unanticipated problems, serious and continuing noncompliance, and suspensions or terminations of IRB approval reports submitted to OHRP; educated research community members on HRPP regulations and policies; and conducted quality assurance/quality improvement assessments of institutions’ HRPPs. Before joining OHRP, Lisa spent four years working at an academic medical center as a Research Compliance Specialist and, for a short time, as the Director of the IRB. Before joining the academic medical center, Lisa spent nearly 7 years working at the FDA in a variety of positions and offices, all of which focused on medical device law and regulation.
Appendix B
Documents and Interviews

FTI reviewed the following documents as part of this work:

- University of Minnesota IRB policies and procedures
- IRB Executive Committee minutes
- Investigation Panel records, reports, correspondences
- Complainant's medical and research records
- 0309M52653 protocol and IRB records
- 0309M52651 protocol and IRB records
- 0610M95446 protocol and IRB records
- 0710M19084 protocol and IRB records

On-Site interviews:

- Session 1: VP of Research and Director, Human Research Protection Program
- Session 2: Investigation Panel Members and IRB Executive Committee Member
- Session 3: PI
- Session 4: IRB Executive Committee Members
- Session 5: Investigation Panel Members and IRB Executive Committee Member
- Session 6: Chair and Vice-Chair of IRB Executive Committee
- Session 7: VP of Research