[redacted] & Associates, P.C.

1800 Alexander Bell Drive, Suite 200
Reston, VA 20191
1050 Seventeenth Street, N.W., Suite 600
Washington, DC 20036
202.466.6937 • Fax 202.466.6938
www.emord.com

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VIA OVERNIGHT MAIL
Patricia Holobaugh
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1488
Telephone: (301) 827-6221

Re: Warning Letter, February 1, 2007, Patient Advocacy Council

Dear Dr. Holobaugh,

On behalf of our client Patient Advocacy Council ("PAC") and its parent corporation Compass Point Research, we hereby respond in detail to the agency's February 1, 2007 warning letter concerning the [redacted] Also in this letter we provide the additional information requested by FDA. PAC is committed to maintain the highest quality and accountability in its oversight of clinical trials and seeks a more direct, open and thorough exchange with FDA regarding all concerns expressed by the agency in its warning letter. In particular, please inform us of a time and place convenient for us to meet in person with FDA CBER staff to permit an open dialogue. As explained in detail herein, certain representations in the warning letter are false; others are out-dated, referring to matters unilaterally corrected by PAC before the last FDA inspection; and a few remaining items are ones for which corrective actions have already been implemented.

It is essential to note that the warning letter arises from PAC's role in [redacted] 2004 studies. It does not reflect PAC's current system. FDA reviewed PAC's current system in January, 2006 and had no critical observations or suggested changes, except requiring PAC to have an oncologist on PAC's board. In fact, the FDA inspector then commented that it was clear to her that the quality program in place at PAC was effective. In 2004, Compass Point Research designed an independent quality assurance and improvement program for PAC. By January 2005, the program was fully implemented, including audit procedures, audit tools, and a dedicated full-time Quality Coordinator who is a Compass Point Research employee, not a PAC employee. Thus, the February 2007 Warning Letter

should not serve as the basis for any regulatory action regarding PAC's current system. Instead, any regulatory action should be made based on the January 2006 inspection of PAC's current system.

After reviewing the warning letter, PAC's records, and interviewing key PAC personnel we have determined that the warning letter is based in part on certain false representations. Correction of those false representations removes the essential foundation for issuance of the warning letter. The false representations appear to be the product of on-site FDA agents not reporting to FDA headquarters complete and accurate facts, thus compromising the integrity of FDA's regulatory oversight.

The proposition that PAC staff failed to supply complete records at the FDA agents' requests is completely false. No documentation was withheld in response to any FDA request during the inspection. Attached to this letter are the sworn statements of the PAC staff that worked with the on-site investigators confirming that no documents were withheld. Complete records of the [redacted] FDA requested were provided along with the PAC minutes for those studies.

The proposition that the inspection took place for four days, as though the inspection lasted all day for each of those four days, is misleading. FDA investigators Patricia Smith and Jason Abel were present each day from September 18 through 21, 2006 as indicated in the letter, but spent no more than approximately 8 hours on site prior to the exit meeting.

The corporate history and structure of PAC is in error in the warning letter. The letter from the FDA refers to PAC's parent institution as "Compass Point Research, Inc. (formerly known as Discovery Alliance)." That is incorrect. Discovery Alliance is not and has never been PAC's parent company. Both PAC and Discovery Alliance are subsidiaries of the same parent company. That company was known as "Discovery Alliance International." "Discovery Alliance" and "Discovery Alliance International" were never the same corporate entities. In 2006, the name of the parent company "Discovery Alliance International" was changed to the d/b/a "Compass Point Research."

We address additional factual inaccuracies below.

Response to Specific Points

1. **FDA**: The IRB failed to assure that the selection of subjects is equitable while being particularly cognizant of the special problems of research involving vulnerable populations, and failed to require additional safeguards to protect the rights and welfare of economically or educationally disadvantaged persons included as subjects in research. (21 CFR 56.111(a)(3) and (b)). The IRB did not record any consideration of the status of these additional subjects as economically and educationally disadvantaged subjects.

The IRB's meeting minutes of 3/2/04 show that the IRB approved the changes to the informed consent form....The IRB did not record any consideration of the status of these additional subjects as economically and educationally disadvantaged subjects. Despite the IRB's duty to be particularly cognizant of the special problems of research involving vulnerable populations, the IRB did not request further information about the source of the vulnerable population.

PAC'S RESPONSE: That representation is false. In point of fact the IRB did evaluate the selection of subjects cognizant of the special problems of research involving vulnerable populations. The February 24, 2004 research site submission to PAC requesting permission to consent and enroll economically or educationally disadvantaged people in the study stated:

> I understand that those who are economically or educationally disadvantaged are considered to be a 'vulnerable population' by federal regulation (both FDA and OHRP) in that they may be more likely to feel pressured and/or influenced to participate in a study. I also understand that the Belmont Report emphasizes the importance of ensuring that both the benefits and burdens of research be fairly distributed across the population and that we, as researchers, neither overprotect nor underprotect vulnerable groups. In an effort to provide additional safeguards to this vulnerable patient population, I will ensure that an impartial witness (a person not affiliated with the research center) is present for the entire consent discussion for potential participants who are economically or educationally disadvantaged. In addition, we are requesting your approval of a revision of the informed consent form to add a signature line for the impartial witness and to include the following statement to explain the impartial witness' signature: 'my signature attests that I was present during the entire consent discussion and that the information in the consent form was accurately explained to, and apparently understood by the subject and that informed consent was freely given by the subject.'

PAC's 3/2/04 minutes regarding this submission state:

> The requested revisions to the informed consent form involved the addition of an impartial witness line and statement, due to the fact that these sites wish to include economically or educationally disadvantaged people as potential study participants.

The minutes reflect that PAC did in fact consider the status of the additional subjects as economically and educationally disadvantaged subjects. The minute reflect that PAC voted on and approved use of those subjects in this study.

PAC considered the site's proposed additional safeguards to be appropriate. The minutes state:

After further review of the above referenced document, the Board recommended that requested revisions be incorporated into the informed consent form.

That conclusion was appropriate based on the information submitted by the investigator. The investigator suggested a procedural safeguard to guard against coercion in signing the informed consent in the presence of an impartial witness. PAC's deliberations and conclusions met the regulatory requirement of 21 C.F,R, § 111(b). FDA's enumerated points in the warning letter are not regulatory requirements but do include valuable observations that are reflected in the specific PAC procedures below.

CURRENT PROCEDURES: The following applicable changes have been implemented in 2007:

a. PAC's SOP #220 has been revised to state (revised SOP attached): "the following are considered when determining whether additional safeguards are appropriate:
   - why members of the vulnerable population are considered appropriate candidates for the study;
   - any special accommodations that will be used to ensure members of the vulnerable population are enrolled safely (such as special equipment, facilities, staff, etc.);
   - criteria the PI will use to determine which subjects are considered vulnerable;
   - whether members of the population would be vulnerable to coercion or undue influence (e.g., due to compensation for study participation, potential study benefits, diminished autonomy, status relative to the investigator/research site, etc.);
   - whether members of the population would be able to fully understand the requirements of the study including potential risks to self and others;
   - whether members of the population would be in settings where study participation could be detrimental to the subject or others;
   - whether the consent form is appropriate for the population and whether consent form revisions would meaningfully add to the protection of the rights and welfare of subjects from this population."

b. PAC member checklists have been revised to reflect the specific considerations in the revised SOP.

c. The Application for Initial Review has been modified to require the site to provide more specific information referenced in the revised SOP for each vulnerable population proposed to be potential research participants

d. PAC minutes regarding studies proposing to enroll members of a vulnerable population will document the discussion of whether to approve

each of the proposed vulnerable populations for enrollment and the results of the vote.

e. The Certificates of Approval will indicate which vulnerable populations, if any, have been approved by PAC for enrollment.
f. Finally, the Quality Coordinator will add to her audit of the minutes and Certificates of Approval a check to ensure that the above documentation has been included.

2. **FDA:** The IRB failed to follow written procedures for conducting continuing review of research, 21 CFR 56.108(a). The IRB failed to follow SOP 221 'Conducting Continuing Review' which states that 'Particular attention is paid to new information, changes to the protocol, or if unanticipated risks were discovered during the research.' In reference to [redacted] studies, the IRB received reports of serious and unanticipated events, and reports of a total of 131 protocol deviations. Nevertheless, the IRB allowed the studies to continue without paying 'particular attention' to this new information.

PAC'S RESPONSE: PAC received no reports of "serious and unanticipated events" occurring at the research sites conducting this study. In fact, PAC received reports of three, anticipated serious adverse events (SAE's) at the sites. All of those SAE's were either anticipated risks of the study and/or anticipated risks of a pre-existing condition and its treatment. These SAE's are as follows:

a. SAE reported on 3/15/04: hospitalization due to acute myocarditis;
b. SAE reported on 4/20/04: mild cardiac enzyme abnormalities;
c. SAE reported on 6/18/04: hospitalization due to somatic transformation; (patient "lost feeling in her legs" two hours after receiving an epidural injection to treat chronic lower back pain; this event occurred approximately one month after receiving the study [redacted]).

The informed consent form clearly identifies "cardiac complications," including myocarditis, as a known risk of the [redacted]. Thus, while serious, those adverse events were not unanticipated.

Regarding the total number of deviations cited, PAC does not require sites to submit all deviations, only those that are significant. PAC's definition of a significant protocol deviation is any deviation that considerably affects the safety of the participants or the scientific quality of the study and any deviation implemented to eliminate immediate hazards to the subject. Sometimes sites submit all deviations, including those minor deviations that are not required to be reported to PAC. This appears to be the case here as many of the deviations submitted for the study referenced in FDA's 2/1/07 warning letter were not significant and, thus, recitation of the total number of deviations rather than just the 3 SAEs creates a misleading impression. It is also important to note that those deviations were not submitted at one time, but over a four-month period. FDA's recitation of a violation of SOP 221 ignores the nature of the deviations report, the site's acknowledgement of changes to ensure future compliance and corrections and PAC's meeting minutes' content.

The deviations received and reviewed for protocol [redacted] were as follows:

a. 3/17/04: 30 deviations were reported along with the site's corrective actions. The site referred to the deviations as "informed consent errors" and review of the errors reveals that they consist of missing initials from particular pages or no witness signatures. The site's notice states:

> Whenever possible, patients will initial missing pages upon their next study visit. In future a witness will be made available to assist with the consenting process. The study staff responsible for the consenting of patients have [sic] received additional training regarding the use of the witness line on this consent.

Thus, the site's notice contained detailed acknowledgment of the mistakes and corrective actions already implemented. The minutes from this meeting list all of the deviations submitted by patient identification and the site's summary. The minutes state, "After review of the above referenced deviations, the Board recommended that the principal investigator provide an explanation of these occurrences and what processes have been put in place to keep them from re-occurring," and, "the Board voted (7-0-0) to send the principal investigator a letter requesting an explanation for these protocol deviations and what processes have been put in place to keep these incidences from re-occurring." We address the issue of this letter in further detail below.

b. 4/22/04: 27 deviations were reported. The letter from the site states "the following is a list of visits that took place out of window due to patient no shows and rescheduling." The minutes from this meeting identify the number of deviations and state that the site's letter was reviewed. The minutes state further, "The Board discussed the 'missed windows' and although the number was high, the Board concluded that this type of study could not control patients showing up for appointments" and "The Board reviewed the protocol deviations. It was noted that no further action is required at this time" (emphasis added).

c. 5/12/04: 16 deviations were reported. Out of the sixteen, nine were scheduling related (either visits were not scheduled on the appropriate day or patient did not show when visits were scheduled). The remaining seven deviations were failures of medical personnel to follow the clinical protocol. The minutes from this meeting listed all sixteen deviations by patient identification and the site's summary of the deviation. The minutes state "The Board reviewed and noted the protocol deviations. No further action was required"

d. 7/27/04: 59 deviations were reported for 32 of the study subjects. A review of the deviations show that while some are from staff noncompliance with the clinical protocol, more than half of the deviations are from patient noncompliance such as with scheduling visits and

completing diary cards. PAC's meeting minutes recites all 59 deviations by patient identifier and closes with the statement: "The Board reviewed and noted the protocol deviations. No further action was required."

Thus, PAC paid attention to each and addressed each deviation reported in its meetings. FDA's criticism that PAC failed to pay particular attention in accordance with SOP 221 is unjustified. While the meeting minutes are not extensive, PAC conducted an appropriate review and paid attention to the deviations, according to their seriousness.

CURRENT PROCEDURES: PAC has identified a need to improve the minutes taken for each meeting to more accurately reflect the content of the board's review of matters submitted to it. PAC will implement the following by March 31, 2007: 1) the minutes will record PAC members determination whether any submitted deviations are significant; 2) if a deviation is determined to be significant, the minutes will record if they "considerably affect the safety of participants" and/or "considerably affects the scientific quality of the study" or if they were deviations implemented by the site "to eliminate immediate hazards to the subject;" 3) if deviations are considered significant, the minutes will record PAC's discussion of whether the deviations require particular attention in that they are "new information, changes to the protocol, or unanticipated risks;" and 4) the minutes will record any PAC actions taken regarding significant deviations. PAC has evaluated whether identification of significant deviations should mandate any action by PAC and determined that requiring action eliminates PAC's need to determine appropriate response on a case-by-case basis. Mandated responses undermine the independent review function of an institutional review board.

3. **FDA:** The IRB also failed to follow SOP 232 which states 'When PAC learns of an instance of noncompliance, the investigator will be sent a 'notification of noncompliance' that includes a description of the noncompliance and a deadline by which the investigator must submit a response.'

PAC's RESPONSE: The quoted passage that is the basis of the charge of noncompliance was not a part of SOP 232 in effect at the March 30, 2004 meeting. A copy of SOP 232 in effect at that time (with an effective date of April 25, 2003) is attached to this letter. A notification of noncompliance was not required for PAC under that SOP. At that time, the SOP concerned only serious and/or continuing noncompliance and did not define those terms. As part of PAC's continuing efforts to improve its quality, PAC has revised that SOP three times from that version to its present day form. In those revisions PAC has defined "noncompliance," "serious noncompliance," and "continuing noncompliance" and has offered guidance for PAC responses in each circumstance. At the time of the March 30, 2004 meeting, failure to send a letter was not a violation of SOP 232. Thus, FDA's charge in its warning letter is

unfounded, a retroactive application of a SOP non-existent at the time of the event in question.

FDA states that PAC "acknowledged this violation" in its letter. That is incorrect. In its October 16, 2006 letter PAC acknowledged that it had no record of the letter being sent. PAC did not acknowledge a "violation," as none occurred.

CURRENT PROCEDURES: Since 2005 PAC's Quality Coordinator (a Compass Point Research employee not supervised by any PAC employee) audits PAC's minutes against the correspondence to make sure all notices have been sent accordingly. She also audits to make sure that, if the investigator does not respond by the requested date, the administrative staff places that item on the next agenda so that the IRB can consider appropriate follow up action. Under current procedures it would thus be near impossible for PAC to fail to send a letter or document that the letter was sent.

4. **FDA**: Many of the protocol deviations were directly related to the economically and educationally disadvantaged subjects that the IRB had allowed to be enrolled into the vaccine studies.

PAC'S RESPONSE: That representation is false, entirely unsupported by any evidence. The deviation reports from the site identified patients only by numerical code. It is impossible to tell whether any of the patients at issue were economically and/or educationally disadvantaged subjects. Moreover, the FDA agents do not identify which subjects, if any, they presume were economically and/or educationally disadvantaged. The records that identify those subjects, if any, are stored with the investigator.

If FDA is making the assumption that the protocol deviations concerning lack of a witness signature to the informed consents were "directly related to the economically and educationally disadvantaged subjects," there are additional facts that contradict that assumption, making FDA's statement false. None of the deviations reporting lack of a witness signature on the informed consent state that there was a lack of an impartial witness. All PAC informed consent forms include a signature line for a witness. The impartial witness consent forms approved on March 2, 2004 had a separate line labeled "impartial witness" that was in addition to the general witness signature line. Thus a deviation notation "no witness signature" cannot reasonably be presumed to apply to economically and educationally disadvantaged subjects without evidence to support that conclusion.

As stated in the study's final report, subjects were consented for the [redacted] protocol starting January 19, 2004. The Principal Investigator requested permission to enroll vulnerable subjects on February 28, 2004 and the PAC voted to allow it on March 3, 2004. The last consent on the site was taken on March 30, 2004. The deviation report that included the "witness signature" deviations was

dated March 17, 2004. Thus, subjects were consented before permission for vulnerable populations was given. FDA's assumptions about lack of consents by vulnerable populations is thus to the contrary and without foundation.

Finally, FDA's characterization using the term "many" is misleading. Of the 131 deviations reported for the [redacted] protocol only 19 were identified as "no witness signature." The Final Report submitted to PAC states that the [redacted] protocol had 172 patient consents. Of those consented patients 109 did not meet the enrollment criteria. Characterizing those 19 without a witness as "many" in light of the total number of consented subjects (172), the total number of consented subjects that did not meet the enrollment criteria (109), and the total number of reported deviations (131) is misleading.

5. **FDA**: The IRB failed to make all records required by regulation to be fully accessible for inspection and copying by authorized representatives of the Food and Drug Administration. The administrative director of the IRB denied the FDA investigators full access to all study records and meeting minutes that related to studies reviewed by the IRB. Study binders were never provided for full review; instead, only limited, incomplete and redacted photocopies of minutes related to the [redacted] studies were provided to FDA investigators".

   PAC's RESPONSE: As stated above, this representation is patently false. Both the PAC IRB administrator and the Compass Point Research Quality Coordinator assigned to PAC have signed affidavits attesting to the fact that the FDA inspectors were given full access to all study records they requested. The studies had been archived, so there were no "study binders" to give the inspectors. The study records were removed from the archive boxes and given in total to the FDA inspectors. Concerning the meeting minutes, the FDA inspectors requested the meeting minutes pertaining to the studies. They did not ask for original, signed copies of the complete meetings minutes at which these studies were discussed. The PAC administrator removed the sections of the minutes pertaining to other studies before giving the agents the minutes concerning the [redacted] The PAC administrator informed the agents that she had performed that redaction upon the agent's inquiry. The FDA inspectors neither objected to the redacted minutes nor requested the full set of minutes.

IRB Member Rosters

Finally, concerning IRB member rosters, we accept your recommendation to maintain a single roster that lists both the regular and alternate members to avoid any confusion about the IRB membership. We implemented this change immediately upon receiving your recommendation.

Bias

FDA agent Patty Smith informed Compass Point Research employees that she did not trust "for profit" clinical research organizations. She apparently believes the "desire for profit" supersedes all other bases for decision-making in for-profit clinical research organizations. That bias combined with the presence of mischaracterizations and omissions of material facts in the warning letter call into question the integrity of the agency review upon which the warning letter is based. Compass Point Research hereby requests that Agent Smith no longer be assigned to inspect Compass Point Research including, but not limited to, any of its subsidiaries (Discovery Alliance and PAC) or clinical trial sites. Bias negates the "reasonable manner" requirement imposed on agency investigation to ensure professionalism, accuracy, and fairness.

Request for a Meeting

Due to the seriousness of the issues raised in the February 1, 2007 warning letter, as well as the false statements of fact identified herein, we respectfully request a meeting with CBER representatives to discuss these matters. We also will file a formal complaint against the FDA inspectors in question with their regional office and request that they be formally reprimanded and required to receive retraining to avoid recurrence of bias and false reporting.

Conclusion

We respectfully request that FDA withdraw its warning letter in light of its lack of factual foundation. The numerous mischaracterizations and erroneous conclusions based on incomplete or false facts irreparably harm PAC and Compass Point Research's professional reputations. PAC and Compass Point Research request that the warning letter and this response not be posted on FDA's website and be considered exempt from disclosure under the Freedom of Information Act (FOIA). Should FDA disagree and post the February 1, 2007 warning letter on its website and otherwise provide it pursuant to

FOIA, this letter must be provided with the warning letter to reduce the risk that the warning letter will be considered an accurate statement of facts by the public and the regulated class.

Sincerely,

Jonathan W. Emord
Andrea G. Ferrenz

CC: Compliance Oversight Branch
Office for Human Research Protections
U.S. Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

H. Tyler Thornburg, District Director
New Orleans District
Food and Drug Administration
04 BNA Drive, Building 200, Suite 500
Nashville, Tennessee 37217

Enclosures