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February 10, 2003

Dr. James Bauer
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RE: MDMA-Assisted Psychotherapy in Subjects with Chronic Treatment-Resistant Posttraumatic Stress Disorder (PTSD)

Dear Dr. Bauer,

We are writing to inform you of our contact with a CRO that MAPS has initiated in response to your letter of February 4, 2003, and to submit some documents you requested. These documents include all written correspondence from FDA, information about the drug manufacturing and testing process, a draft informed consent form for the "partner, family member of friend" who will accompany the subject after the experimental sessions, draft release form for the exchange of medical information, and the CVs of Mark Wagner, Ph.D. and also of Amy Emerson, whose participation in the study we had not yet discussed with you. Ms. Emerson has extensive professional expertise in the management and monitoring of large Phase 1-III trials and will supervise and conduct document tracking, data management and monitoring, and FDA compliance issues.

We are also writing to share with you our responses to almost all of the issues raised in your letter. We've focused primarily on the most important issues regarding the avoidance of bias in the collection of data, namely the suggested use of a CRO and the change to a multi-site study design. We request that you consider our responses to the issue of the CRO and the multi-site design at this time, since these decisions will influence how we respond to the remaining few questions. For example, the panel requested copies of all the forms to be used in the study. Some of these forms have not

yet been written, and their exact content may be dependent upon issues of protocol design that remain unresolved.

We understand and appreciate that your review is an ongoing process with the possibility of new issues arising at any time. Once we start the study, there will be a flow of new data that will also necessitate continual reevaluation. We look forward to working with you in close collaboration with whatever data reporting schedules you request.

We would also like to offer one general comment. As we understand it, the role of the IRB is essentially to protect the rights of human subjects, and your greatest area of expertise lies with providing this protection. To that end, you have made important suggestions about safeguards in the informed consent process for those of Dr. Mithoefer's patients who may consider participating in the study, suggestions that have resulted in the creation of the role of a "veto psychiatrist." Also flowing from your review has been the addition of a third physician on the Data Safety and Monitoring Committee, and the formalization of the role of the "partner, family member of friend" who will accompany the subjects after the experimental sessions. Your suggestion about our need to take care with terminology so that we do not mislead subjects to think that they will be receiving a proven therapy has been enlightening. Your eventual critique and advice concerning the informed consent form and recruitment letters will prove invaluable. As an ancillary aspect of protecting the rights of subjects, the IRB also has a responsibility to see that the study itself is well-designed and implemented. It is regarding these later set of protocol design and implementation issues, in which every element represents a difficult trade-off between competing priorities, that we request you reconsider some suggestions made in your letter of February 4, 2003.

CONFLICT OF INTEREST

Engaging the services of a CRO or providing for a comparable system of monitoring, and conducting multi-site studies are excellent suggestions that MAPS intends to implement if and when we are able to conduct Phase III studies. However, although we have in good faith already requested a bid for data monitoring for this pilot study from one of the world's largest and most reputable CROs, we believe that these suggestions are premature and unnecessary for this initial Phase II pilot study. We believe that our fuller discussion of the steps we are taking to reduce bias in data collection will demonstrate that neither the services of a CRO nor the move to a multi-site design are needed at this stage to ensure reliable data that is scientifically tenable and able to withstand skeptical analysis.

CRO BID PROCESS

On Wednesday, February 5, Dr. Doblin spoke with Loren Miller, Ph.D., Vice President, Regulatory and Scientific Affairs, PPD Development, the clinical research (CRO) operating subsidiary of PPD (ppdi.com), a "leading global provider of discovery and development services and products for pharmaceutical and biotechnology companies…with more than 5200 employees in 24 countries." Dr. Miller works out of the PPP Development office in Research Triangle Park, Morrisville, NC., reasonably

close to Charleston, SC where Dr. Mithoefer's study will take place. Dr. Miller will offer a bid for a minimal system of data monitoring in a week or two, but has already indicated that the bid will be in excess of $20,000, perhaps substantially so.

Dr. Doblin was first introduced to Dr. Miller in the early 1990s, through his interactions with FDA's Pilot Drug Evaluation Staff (PDES), the group at FDA that regulated research with Schedule I drugs. Dr. Miller had written articles about the PDES, which FDA officials had given to Dr. Doblin. In 1999, MAPS brought Dr. Miller to Israel for its MDMA research conference, so that he would have an opportunity to learn about all the clinical research around the world being conducted with MDMA. Though MAPS benefited from his participation in the meeting, the bill for educating him about MDMA convinced Dr. Doblin that MAPS could not afford and did not need the services of a CRO unless MAPS was initiating Phase III studies. When Dr. Miller learned last week of your IRB's request for the involvement of a CRO in this pilot study, he concurred that CRO monitoring of research is much more important for Phase III trials than for Phase II pilot studies.

DR. MARK WAGNER'S EXPERTISE AND PROCEDURES

As noted in your letter, the IRB panel has not had the opportunity to review the CV (enclosed) of Mark Wagner, Ph.D., the consultant in charge of screening and outcome measures. As you can read in Dr. Wagner's letter to the IRB (enclosed), Dr. Wagner was not chosen for this position because of any prior interest in or bias concerning MDMA. He had no prior relationship with MAPS, no prior belief in the value of MDMA-assisted psychotherapy, nor was he a friend of Dr. Mithoefer's or had ever met him or Dr. Doblin in person. Rather, Dr. Mithoefer contacted Dr. Wagner because of his professional expertise in administering screening and outcome measures, as you can see in his CV. Among his other responsibilities, Dr. Wagner is Director of Neuropsychological Services, Department of Neurology, Section of Neuropsychology, Medical University of South Carolina and serves as a Peer Reviewer, Journal of Traumatic Stress, 1998–Present.

Dr. Wagner will conduct the screening and outcome measures in a manner that renders him blind to which experimental group the subjects are in. This is standard operating procedure for the conduct of FDA-approved clinical research. This approach serves as an adequate and appropriate method of resolving the issue of biased data collection for studies sponsored by pharmaceutical companies, which are at least as vulnerable to concerns about bias as MAPS. Please refer to the letter from Dr. Wagner introducing himself to the IRB panel and explaining his procedures to reduce or eliminate bias in data gathering. We believe that any CRO would be hard-pressed to find anyone more experienced and impartial in data gathering than Dr. Mark Wagner.

DATA MONITORING AND FDA COMPLIANCE BY MS. AMY EMERSON

In addition to the screening and data gathering work of Dr. Wagner, Ms Amy Emerson, Clinical Research Associate, Chiron Corporation, will supervise and conduct document

tracking, data management and monitoring and FDA compliance issues related to this protocol. Chiron is a biotechnology pharmaceutical company with one of its offices located in Emeryville, CA, where Ms. Emerson works. As Ms Emerson's resume states (enclosed), she has extensive professional expertise in the management and monitoring of large Phase 1-III trials. Ms. Emerson has offered to volunteer her services with MAPS paying only for her travel expenses related to on-site study monitoring, and thus might be considered biased by the IRB. Ms. Emerson nevertheless adds a level of expertise in FDA compliance and data monitoring that will help ensure that the study is conducted according to proper procedures. Ms. Emerson is available to meet with the IRB should a meeting be requested.

MAPS' FINANCES

A note about MAPS' finances is in order, since the panel's recommendation that MAPS turn the project over to a CRO was made in part because the panel believed that "MAPS has a significant level of funding." I have sent Ms. Erica Heath a detailed discussion of MAPS' current financial situation that demonstrates that adding the costs of a CRO to the MDMA/PTSD study budget would be a difficult burden. But the key issue is not whether or not MAPS has a significant level of funding and either could or could not afford to hire a CRO. The issue is whether the services that would be provided by a CRO add an essential element to the integrity of the data to be gathered in this study. Neither MAPS, members of the research team, nor the FDA considers this to be the case.

SUMMARY REGARDING CRO ISSUE

Since the integrity of the data gathering and analysis process does not seem to us to be fundamentally improved by CRO monitoring as compared to the services to be provided by Dr. Mark Wagner and Amy Emerson, is not required by FDA (the key evaluators for whom this study is being conducted), is not essentially a matter of subject safety, and would represent a substantial financial burden, we request that the IRB reconsider this recommendation.

SINGLE SITE V. MULTI-SITE PILOT STUDY

We understand and appreciate the goal of reducing bias that lay behind the suggestion that we add a second site to this study. However, doing so presents so many practical and theoretical problems that we request the IRB reconsider this request.

A multi-site study requires a standardized experimental intervention but at this time a standardized experimental intervention does not exist. One of the major purposes of this single-site pilot study is to gather preliminary evidence about both safety and efficacy in order to refine the experimental intervention. After we complete this initial pilot study, a subsequent single-site study will be required to standardize the intervention and operationalize a method and checklist for outside observers to evaluate whether the standardized intervention is being accurately delivered at multiple locations. Only after these two pilot studies have been completed would we be ready to move into a multi-site

study design. In addition to following FDA procedures calling for single-site studies prior to multi-site studies, scientists at the National Institute of Mental Health (NIMH) have clearly indicated to us that we need to standardize the therapy first before moving on to multi-site studies.

Data analysis with two sites is also significantly complicated as a result of the smaller number of patients at each site and potential interactions between the different experimental teams and patient safety and outcome measures. Initial analyses would first have to compare across sites, and if any effects due to site were found, subsequent analyses would have to control for site as well as to drug assignment, lowering statistical power.

Most importantly, it is doubtful that we or a CRO could find as qualified a second experimental team to conduct this initial pilot study as Dr. Michael and Annie Mithoefer, RN. I spent two years looking for a psychiatrist who had the proper qualifications to conduct this study before finding Dr. Mithoefer. The skills needed to develop and refine new experimental interventions are rarer than the skills needed to follow an already-existing standardized experimental intervention. The years of special training that both Dr. Michael and Annie Mithoefer, RN have received from Dr. Stan Grof in the use of breath to induce altered states of consciousness for therapeutic purposes are a very important part of their qualifications. Dr. Mithoefer's dual training as a psychiatrist and as an emergency room physician was another reason why he is an ideal PI for this study, with these skills highly valued by the FDA as well.

We do not know of another psychiatrist and associated co-therapist who are interested in and sufficiently qualified to conduct this pioneering pilot study. That means that any new team would have to receive substantial education in the experimental intervention. Even if we were to locate a new team that was reasonably qualified, we still lack a tested and proven way to monitor and evaluate the experimental intervention to ensure that it is standardized. Adding a second site prematurely could increase the risks to patients by exposing them to an intervention that has not yet been refined and standardized.

Finally, if we were required to find another experimental team, we would most likely end up selecting an academic research psychiatrist affiliated with an institution. This would therefore require approval from yet another IRB, which might very well be reluctant to approve the study with researchers new to this untested experimental intervention. We would also need to go back to the FDA for the revised protocol. The FDA would almost certainly be reluctant to approve such a protocol revision since it is highly unusual to conduct a multi-site study without first conducting a single-site pilot study in order to develop a standardized intervention. I can easily imagine that trying to arrange for two sites would delay the study for at least a year, if not forever, without offering any significant advantages in unbiased data collection.

SUMMARY REGARDING SINGLE V. MULTI-SITE PILOT STUDY

The primary purpose motivating the panel to propose this protocol modification was to reduce bias in data gathering. Given the tremendous complications and delays that actually implementing a second site would involve, we request that the panel reconsider this proposal. We hope that the panel will be satisfied that we have done an adequate job of ensuring reliable data after it reviews the new information about Dr. Mark Wagner's professional expertise, and criteria by which he was selected, and about Ms Amy Emerson's professional expertise and her work on data monitoring and FDA compliance issues.

PROTOCOL-STUDY DESIGN ISSUES

1. Apparently there has been a misunderstanding about the validity of CAPS. When we discussed the CAPS during our meeting, what Dr. Mithoefer meant to convey is the fact that the CAPS is well validated as a measure of PTSD diagnosis and severity and for tracking severity over time. It was used in both the Zoloft and Paxil studies that led to their FDA approval for PTSD. What is not yet validated are the cut-off scores for the different severity ranges. Nevertheless, such ranges have been proposed in the literature and are currently undergoing validation. Dr. Mithoefer chose the score of 50 because it is in the middle of the proposed “moderate severity” range. He called Kathleen Brady, MD, PhD to discuss this because she is very experienced and widely published in PTSD research and was a lead investigator in Pfizer's Zoloft/PTSD trials. It was her opinion that this score is an appropriate cut off given our desire to exclude subjects with less severe symptoms. Copies of a review article discussing the validity of the CAPS and the proposed severity ranges could be submitted upon request.

2. Regarding the drug manufacturing and testing process, two pages have been enclosed reflecting the results of the recent purity analysis required by FDA. Additional information about the specifics of the manufacturing process can be submitted upon request.

3. Dr. Mithoefer’s application for a Schedule I research license for this study was submitted to DEA in July 2002. In a recent conversation with Frank Sapienza, Ph.D., DEA Office of Diversion Control, Dr. Mithoefer was told that the application is under active review and the process is not expected to take “too much longer.” We expect that no actual progress will be made until DEA is informed that IRB approval has been obtained, subject to Dr. Mithoefer's DEA Schedule I license. Alternatively, you could consider the model adopted by FDA, which approved the study without contingency but noted that the research could not go forward until Dr. Mithoefer obtained a DEA Schedule I license.

4. Enclosed please find copies of all written correspondence from the FDA regarding this protocol. To make it easier for the panel to understand what some of FDA's documents refer to, copies of some communications from MAPS to FDA have been submitted as well. As you can tell from the documents, several issues were addressed in detail in teleconferences for which MAPS does not have a written transcript. We've found that these FDA teleconferences have been extremely helpful in discussing issues informally

before committing agreements to writing, similar to the way our January 28 personal meeting with the IRB was so valuable for all of us.

5. If we are unable to reach agreement on the issue of the bodywork, we would be willing to forego it. However, our thinking about the bodywork is that it is an element of our therapeutic method as originally developed and described by Stanislav Grof and later adapted for MDMA-assisted therapy by Ralph Metzner PhD and others. (see references in protocol). Because this is a trial of drug-assisted therapy rather than simply drug treatment, we are puzzled by your statements that it's a problem that the bodywork is "intended to be done in response to need" and that "its intent is purely therapeutic, and not related to the evaluation of MDMA-assisted psychotherapy." In therapy in general and in manualized therapy used for research, it is the norm to require or allow the option of certain interventions in response to certain situations or needs that arise.

Perhaps some confusion has arisen because we haven't explained the bodywork process well enough. Bodywork would be used when, in Dr. Mithoefer's clinical judgment, some physical pains are a symbolic reflection of emotional pains. Bodywork usually lasts less than a minute or two, and involves pressure on parts of the body, with the pressure intended to facilitate emotional release. Dr. Mithoefer would probably use bodywork on less than half the subjects. Bodywork would most likely be employed near the end of the experimental sessions, if there are residual tensions in the body that haven't resolved. Since the bodywork will be administered to subjects in case of need regardless of whether they have received the MDMA or placebo, we don't understand how this poses a potential confound. We have also described in detail how the bodywork component of our therapy is to be conducted, so that it is a standardized intervention.

On the one hand, the IRB is appropriately very concerned about subjects remaining agitated after the session ends. On the other hand, the IRB is suggesting that a technique that can reduce such agitation be forbidden because of a concern that the data will somehow be confounded. We urge the IRB to reconsider this request and suggest that the enhancement of patient safety should be prioritized over concerns about confounds, especially since we think these concerns relate more to our failure to properly explain how the bodywork is used than to actual confounds.

We think that the IRB should be reluctant to limit the therapy we propose to deliver unless it is to prevent clear and overriding compromises in scientific design that we do not see exist in this case. We propose that instead of eliminating the option to help subjects work through residual tensions and agitation through the use of bodywork, that we note every time we use bodywork in any subject and submit this data for review to Dr. Mark Wagner (at the end of study so as not to affect in any possible way his blinded status) and to the IRB whenever you request..

<u>PROTOCOL-SAFETY ISSUES</u>

1.a. We agree to report any agitation or adverse reaction by telephone to the IRB within 24 hours, with a follow-up written report to the DSMC within five business days. Two

points remain to be clarified. We presume you are referring to agitation that persists after the end of the experimental session. Depending on how "agitation" is to be defined, a subject's recall of traumatic experiences could be considered agitation but this is both to be expected and part of our therapeutic process. Similarly, by adverse reaction, we presume you mean serious adverse reactions that either persist after the experimental session or require medical attention. For example, jaw clenching is considering an adverse reaction that may occur in some subjects but is neither serious nor unexpected. Please let us know what standards you would like us to use in reporting agitation and adverse reactions.

1.b. We agree to "recruit, consent and educate" any "partner, family member of friend" who will be with (all subjects) for at least 24 hours after each experimental session. We have submitted a draft for your review.

1.c. We will elaborate on how we will "control the safety of the post-catalytic reaction" and suggest we do so after we have resolved issues of protocol design.

2. We will gladly provide CVs of the two doctors on the DSMC. However, we have not chosen the third doctor yet. We suggest we submit these CVs after we have resolved issues of protocol design.

3.We will gladly design a wallet card for subjects and will submit the prototype after we have resolved issues of protocol design.

4, We will not be employing an EMT team. Instead, we are employing a more qualified board-certified emergency room physician and a registered emergency department nurse. Dr. Mithoefer has discussed this role with several local emergency physicians who have expressed willingness to participate. Because the study has not yet been fully approved, no formal selection has been made. We will be happy to send you whatever information you require about these professionals, after they have been selected.

5. Subject confidentiality in regard to the blood sodium tests will be protected through the use of coded identification numbers instead of names. Results will be available within an hour and a half after the blood is drawn.

6. Simple fruits, nuts, crackers, soup and sandwiches will be made available to patients, along with sports drinks containing electrolytes, water, and fruit juices. We will screen all patients for food allergies.

<u>RECRUITMENT AND CONSENT ISSUES</u>

1. You suggested, "One way to reduce selection bias would be to randomize selection of potentially eligible subjects. This could be done as simply as tossing a coin." We're not sure if you mean randomizing any of Dr. Mithoefer's patients who become subjects in the study into either the MDMA or the placebo group, or if you mean randomly selecting half of Dr. Mithoefer's patients for inclusion in the study and rejecting the other half. If you

mean the former, we are already intending to randomize all subjects to either the MDMA or the placebo group. If the randomization you are requesting is in order to reject half of Dr. Mithoefer's patients who qualify as subjects for the study, we don't understand how this is necessary or achieves your stated goal of reducing selection bias. All the subjects who will be referred by other therapists will also be those whom their therapists think "might be expected to benefit from the therapeutic interventions that are part of the study." Indeed, Dr. Mithoefer needs to speak to the prescribing physician of any potential subject being administered psychoactive medications and obtain permission from that physician for their patient to be withdrawn from medication prior to participating in the study. In actual practice, these physicians will likely approve as subjects only those patients that they think might be expected to benefit from participating in the study. In any case, the random assignment of subjects to either the experimental or control group is the standard method of addressing selection bias.

Furthermore, this pilot study is not designed to generate significant results about therapeutic efficacy and FDA does not consider it inappropriate in a pilot study or even in subsequent Phase III studies to select subjects most likely to respond positively to the experimental intervention. There is even a term for this known as "subject enrichment." Once we better understand your concerns, we can develop and submit a plan for orienting the "veto psychiatrist." Incidentally, much of the research into the risks of the non-medical use of Ecstasy, including virtually all of the pilot studies, were conducted only in heavy Ecstasy users most likely to show damage. In studies into either benefits or risks, the key factor is not overgeneralizing the results.

2. Our referral letter to other therapists has already been submitted for your review. It crossed in the mail with your letter of February 4, 2003.

3. The consent form can definitely be broken up into digestible pieces. We look forward to doing so but need to wait to submit a new draft until we have resolved issues related to protocol design. We look forward to working with your staff and are indeed convinced that they will be of great assistance in this process.

DOCUMENTATION AND CONSENT

We will gladly submit all forms for your review to be used in data collection, screening, reporting of adverse events, etc. However, we have not yet created all these forms and propose to submit them to you once we have resolved issues of protocol design.

1. We have enclosed a draft of a study-specific release form for the exchange of patient information between Dr. Mithoefer, referring therapists, and other involved professionals.

2. We have heard of HIPAA but have not yet turned our attention to its requirements. We look forward to working with you to comply with its provisions.

IN CLOSING

We understand that no approval of this study has been implied or promised at this point. We have honored your request for privacy and look forward to a continued relationship that is collegial, professional and mutually respectful.

Since the issue of unbiased collection of data is of such importance to the question of the need for a CRO and a multi-site design, we'd like to offer some evidence that demonstrates MAPS and Dr. Doblin's commitment to reporting honestly whatever data is obtained, even if it refutes an experimental hypotheses. We know you already have more than enough reading, but we are also enclosing a 1 1/2 page article by Ralph Metzner, Ph.D. in which he discusses the results of Dr. Doblin's 34-year follow-up evaluation of Dr. Leary's 1961-63 Concord Prison experiment. The experiment involve the administration of psilocybin to prisoners shortly before release in order to produce a transformative, cathartic experience that would motivate behavior change in the form of reduced recidivism. Dr. Doblin undertook this follow-up in order to call attention to a classic study in the scientific literature that had long been considered by him and many others to be among the best examples of the success of psychedelic psychotherapy. Unexpectedly, Dr. Doblin discovered that the results of the study had been misleadingly presented and that the study actually produced no treatment effect. Despite this disturbing finding, Dr. Doblin published his results and debunked the experiment to the general dismay of many. Dr. Metzner's report on how he reacted to these new and disillusioning findings is eloquent.

In the case of this study of MDMA-assisted psychotherapy in the treatment of PTSD, the best safeguards against bias are methodological. They involve a qualified rater who has no vested interests in the outcome and is blind to the experimental condition of the subjects, coupled with monitoring. We feel that Mark Wagner, Ph.D. is exactly the sort of rater that should be involved in this study, and that Amy Emerson's work on document tracking, data management and monitoring, and FDA compliance issues will provide excellent procedural safeguards. While we definitely agree with the suggestion of a multi-site study design with the involvement of a CRO or similar kind of monitoring if and when we reach Phase III, we do not believe that such measures are necessary at this time. We strongly request that the committee reconsider its recommendations that we hire a CRO and move to a multi-site study design at this stage of our Clinical Plan.

Sincerely yours,

Rick Doblin, Ph.D.
MAPS President

Michael Mithoefer, MD
Principal Investigator