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Rick Doblin, Ph. D.
MAPS
3 Francis Street
Belmont, MA 02478

Dear Rick:

As discussed, Chemic Laboratories has received a response letter from Mr. Joel Egertson of the Department of Health and Human Services (copy Attached). In short Mr. Egertson and the reviewing body have rejected the protocol and have recommended NIDA not provide research grade marijuana to Chemic Laboratories to complete the vaporizer studies.

The reviewers indicated HHS's focus is the support of "clinically" meaningful research. Chemic has been quite clear that the study was not a clinical investigation but a GLP study to support the assessment of the vaporizer device. Secondly the comparison of NIDA versus Dutch Medicinal marijuana is commented to be of little scientific value. Chemic's objective was to evaluate the differing vaporization efficiencies of CBD and CBN. Chemic's current understanding is that the only source of marijuana of varying concentrations is that of the Dutch Medical Office. It is unclear to me how this is "of little scientific value".

Mr. Egertson does indicate the aims of the project appear to be works necessary to be conducted as part of a GLP clinical study, but appear that some of the work had been previously completed. As you are aware Chemic did complete several pilot investigations with the volcano. All these previous studies were proof of concept studies supporting the development of a protocolled cGMP study. It appears this point has not been recognized by the reviewers.

Lastly there is some confusion over the analytical techniques. It was intended that the cannabinoids would be assayed by HPLC-DAD-MS. That diode array detection would be used for quantitation and the MS would be used for qualitative identification. Also The GC-MS analysis was to be used for the analysis of pyrolysis products not cannabinoids as referenced by the reviewers.

Although, Chemic Laboratories will provide Mr. Egertson a response letter, it appears that approval of the study is not forthcoming. Please do not hesitate to contact me with additional questions or comments you may have surrounding this study.

Sincerely,
CHEMIC LABORATORIES, INC.
Joseph St. Laurent
President/ CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

RECEIVED 8/1/05

JUL 27 2005

Joseph P. St. Laurent
President, CSO
Chemic Laboratories Inc.
480 Neponset Street-Bldg. 7C
Canton MA 02021

Dear Mr. St. Laurent:

This is to advise you that a committee of scientists from the U.S. Public Health Service has reviewed the study protocol (submitted on January 29, 2004) titled, "Evaluation of Volcano Vaporizer for the efficient emission of THC, CBD, and CBN and the significant reduction and/or elimination of total particulate matter (TPM) and tar components (various organic compounds in TPM that absorb UV radiation)." The study protocol was not approved by the review committee for the provision of research-grade marijuana from the National Institute on Drug Abuse (NIDA).

The review was conducted pursuant to the provisions of the "Guidance on Procedures for the Provision of Marijuana for Medical Research" dated May 21, 1999, employing criteria set forth in the guidance. We remind you that our review was only for the purpose of determining whether to provide research-grade marijuana for this specific protocol under the HHS guidance. Any practitioner wishing to conduct research on a Schedule I substance must also submit their protocol for review by the Drug Enforcement Administration (DEA) (see section 303 (f) of the Controlled Substance Act (CSA) and 21 CFR Part 1301). The DEA refers all Schedule I protocols to the Food and Drug Administration (FDA) for review of the qualifications and competency of the practitioners and the merits of the research protocol before making a registration determination. Whether or not FDA concludes that the practitioners are qualified and competent and the research protocol has merit, the practitioners must also separately satisfy the criteria set out in the HHS guidance before research-grade marijuana will be provided. Section III of the guidance states in part, "The focus of HHS's program is the support of quality research for the development of clinically meaningful research. HHS intends to make available a sufficient amount of research-grade marijuana to support those studies that are most likely to yield usable essential data."

In general, the review process takes into consideration a number of factors, including the scientific quality of the proposed study, the quality of the organizations' peer-review process, and the objectives of the research. For example:

U.S. Public Health Service

1) The extent to which the protocol incorporates the elements of good clinical and laboratory research;
2) The extent to which the protocol describes an adequate and well-controlled clinical study to evaluate the safety and effectiveness of marijuana and its constituent cannabinoids in the treatment of a serious or life threatening condition;
3) The extent to which the protocol describes an adequate and well-controlled clinical study to evaluate the safety and effectiveness of marijuana and its constituent cannabinoids for a use for which there are no alternative therapies;
4) The extent to which the protocol describes a biopharmaceutical study designed to support the development of a dosage form alternative to smoking; and
5) The extent to which the protocol describes high-quality research designed to address basic, unanswered scientific questions about the effects of marijuana and its constituent cannabinoids or about the safety or toxicity of smoked marijuana.

This proposal, as described in the review comments below, was found by the committee to be lacking in areas primarily related to criteria relating to the quality of the research and the adequacy of protocol design.

Summary of Application:

This protocol is a revision of an earlier proposal from Chemic Laboratories. In a letter dated October 12, 2003, the investigator was advised that after preliminary review it was determined that the application contained insufficient information to judge the merits of the proposal. The applicant was advised further on the application procedure and review criteria, and was invited to revise and resubmit. This protocol was subsequently received early in 2004.

The current application states in part: "This protocol is intended to provide guidance for the conduct of several analytical investigations associated with the assessment of a vaporizer device labeled Volcano®. It has been demonstrated in previous experiments that the act of vaporization…significantly reduces the production of tar, total particulate matter (TMP) and polynuclear aromatics (PNAs) while delivering a comparable concentration of cannabinoid components."

The protocol proposes to use medical grade marijuana (MJ) to test the efficiency of a vaporization device (Volcano®). It describes in detail the procedures used to vaporize MJ by heating materials from two different sources to 3 temperature levels (140 – 160, 160 - 180, and 180 – 200 degrees) below the combustion temperature of 240°C. The protocol will collect 5 samples and test 3 aliquots from each sample (n=15), measuring MJ components delta-9-Tetrahydrocannabinol (THC), Tetrahydrocannabinol-acid (THCA), Cannabidiol (CBD), and Cannabinol (CBN).

Additionally, the protocol proposes "to determine the cannabinoid baseline concentration, ruggedness of the device used for multiple product sources, and compare the quality and relative percentage of available cannabinoids (e.g., THC, THCA, CBD, CBN) in material

provided by the NIDA and material provided by the Dutch medical marijuana production program, solvent/Soxlett extraction, of extracted analytes of the two products compared in triplicate (e.g., n=6) will be compared. Final solvent extracts will be assayed using High Performance Liquid Chromatograph-Diode Array-Mass Spectrometry (HPLC-DAD-MS), and product potency will be determined using methods of external and internal standardization."

Review Comments:

There appear to be three general aims of this project. The first one does not appear to be a hypothesis driven research project. Rather it is structured like a Good Laboratory Practices (GLP) or Good Manufacturing Practices (GMP) internal protocol. It merely presents the methods by which the applicant will determine the "precision, accuracy, robustness and efficacy" of the vaporizing device. This is analogous to a process that is used to "validate" an analytical method. As such, it looks like a laboratory Standard Operating Procedure (SOP). It would be the requisite analytical steps required if, for example, someone wanted to do an efficacy study of THC. These GLP validated methods would ensure that the THC and other analyses performed were accurate, reliable and compliant.

The second aim of the proposed research is to compare marijuana obtained from NIDA to marijuana obtained from the Dutch medicinal marijuana program. There is no rationale provided for this comparison. Marijuana varies in THC content and simply demonstrating that this device can measure those differences is of little scientific value.

Finally, the third aim is to conduct a reliability study of the device by analyzing multiple vapor collections. It is not clear how this aim differs from the first aim.

Thus, overall the aims of the project appear to be descriptions of work that would need to be conducted as part of good standard laboratory procedures prior to a clinical study. This in and of itself is not research but might be worth conducting, except that it appears that some of this work has previously been conducted. A report entitled "Evaluation of Volcano® Vaporizer for the efficient emission of THC, CBD, CBN and the significant reduction and/or elimination of polynuclear-aromatic (PNA) analytes resultant of pyrolysis" from Chemic Laboratories was submitted in support of a project at the Center for Medicinal Cannabis Research (CMCR). The approved trial is underway and is examining the pharmacodynamics and pharmacokinetics of several different potencies of marijuana in human volunteers using the Volcano® device. It is difficult to see what additional scientific knowledge will be provided by the current protocol, considering the prior work done by the applicant, as described in the above report, and the ongoing clinical trial at CMCR.

Some of the technical aspects of this proposal are also unclear. For example, the protocol describes using High Performance Liquid Chromatograph-Diode Array-Mass Spectrometry (HPLC-DAD-MS). This is really an HPLC with 2 different detectors. So one would use HPLC with Diode Array Detection (DAD) for the analysis of some

compounds and HPLC-MS for others. However, the protocol is not specific regarding which detector is being used and for which analysis. There is also some concern regarding use of terms. For example, the protocol refers to "acceptable dose precision, dose accuracy and device robustness," but doesn't explain what "acceptable" means.

Furthermore, the study proposes to analyze some cannabinoids by Gas Chromatography-Mass Spectrometry (GC-MS). This would require derivatization of the cannabinoids, which is not in the protocol. HPLC-MS may be a better option, as this method is applicable to both types of samples. Using full scan Liquid Chromatography-Mass Spectrometry (LC-MS) is questionable as well. The use of SIM would probably produce better quantitative data. Plus, scanning down to 50 daltons on an LC-MS may lead to interference problems.

Other technical concerns include using caffeine as an internal standard. Caffeine would be a poor internal standard because its chemical structure is very different from the cannabinoids. Therefore, its solubility, extraction characteristics, ionization, chromatographic and mass spectral characteristics are quite different. An internal standard should be as chemically similar to the analyzed drug as possible.

Summary and Conclusion:

In summary, while the ultimate goal of research to develop alternate (and presumably less harmful) dosage forms and delivery systems for cannabinoids and perhaps other constituents of marijuana is laudable, the review committee concluded that this project does not add to the scientific knowledge base in a significant way. The rationale for each aim of the proposal is not clearly defined in the protocol, and the significance of the study to furthering the field of knowledge and the clinical potential of the study are not presented. In addition a number of technical concerns were noted.

Therefore, pursuant to the "Guidance on Procedures for the Provision of Marijuana for Medical Research" dated May 21, 1999, the review committee has recommended that the National Institute on Drug Abuse not provide research-grade marijuana to Chemic Laboratories for the purposes of conducting this study.

Sincerely,

Joel A. Egertson