DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Frank A.Wingrove, D.D.S.
Ames Periodontal Specialists
515 Grand Avenue, Suite 202
Ames Iowa 50010

Ref: 07-HFD-45-0601

Dear Dr. Wingrove:

Between May 24 and June 8, 2005, Ms. Barbara Breithaupt, representing the Food and Drug Administration (FDA), met with you to review your conduct of the following clinical study of the investigational drug, [ ] for which you served as the sponsor and clinical investigator:

Protocol entitled "Evaluation of the Use of Topical [ ] as a Method to Regenerate Periodontal Tissues into Defects Resulting From Chronic Periodontal Disease in Humans."

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Breithaupt presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to permit an authorized officer of FDA to have access to, copy, or verify records or reports related to the conduct of the study noted above [21 CFR 312.68].**

Pursuant to 21 CFR 312.58 and 21 CFR 312.68, "[a]n investigator shall upon request from any properly authorized officer or employee of the [FDA], at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under [an IND]." Ms. Breithaupt made multiple attempts over a two week period from May 24, 2005 to June 7, 2005, to obtain access to your study records for the above-referenced study, for purposes of copying and verifying those records. Despite Ms. Breithaupt's repeated and persistent efforts to obtain access to your study records, you failed to provide access to any of the records that would have been responsive to the inspection request. Your failure to provide such access constitutes a refusal to permit inspection of records to which FDA is entitled to access pursuant to 21 CFR 312.68. The inspection was concluded on June 8, 2005, with the issuance of a Form FDA 483, Inspectional Observations.

Absent access to source records, FDA is unable to verify any aspect of your study, including, but not limited to, whether adequate informed consent was obtained, whether protocol-required pregnancy testing was performed prior to administration of study drug to female subjects with child-bearing potential, protocol-required assessments of the extent of periodontal disease, the number of subjects enrolled, the formulation of the study drug, the amount of study drug administered to subjects, and the occurrence and reporting of adverse events. Absent access to source records, FDA also cannot confirm that you conducted your study in compliance with the regulatory responsibilities for investigators set forth in 21 CFR Part 312, in particular, the general responsibility to protect the rights, safety, and welfare of study subjects.

2. **You failed to maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)].**

We note that, instead of providing the FDA investigator with direct access to your study records, you decided that all interactions with FDA would be handled through your attorneys. More than two weeks after the inspection was closed because of your refusal to permit access to study records, your attorneys provided the FDA District Office with redacted, primarily illegible, photocopies purportedly derived from microfiche copies of clinical records. However, the documents you provided are not adequate and accurate case histories for purposes of verifying data in studies conducted under an IND [21 CFR 312.62(b)]. Upon delivery of these records, your attorneys acknowledged that the records provided were incomplete, and in many cases, copies of copies (including hardcopies of microfiche records). Therefore, these incomplete records cannot be linked reliably to original study records.

As detailed above, FDA has no assurance that records were submitted in their entirety, and many of those records that were submitted, were illegible. Without the availability of source records for review, we cannot confirm that you conducted your study in compliance with the commitments to which you agreed when you signed the Form FDA 1572, Statement of Investigator.

3. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

The records submitted are inadequate to reconcile the amount of drug formulated with the amount administered or dispensed to subjects and any subsequent disposition of the drug.

4. You failed to retain records for the requisite time period [21 CFR 312.62(c)].

Per regulation, investigators shall retain records that are required to be maintained under this part for two years following the date a marketing application is approved for the drug being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. The documents submitted to FDA were copies of existing records and microfiched documents. It is our understanding that your lawyers informed officials of the Kansas City FDA district office that source documents were destroyed after being microfiched.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you must notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at (240) 276-8829; FAX (240) 276-8844. Your written response and any pertinent documentation should be addressed to:

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Gary Della'Zanna, D.O., M.Sc.
Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gary DellaZanna
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