PRE-MARKET APPLICATION

CFS™ FOR TREATMENT OF KNEE-LIGAMENT INJURIES

PLASTAFIL, INC.

VOLUME 7

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7. PMA AMENDMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

JUN 22 1990

Andrew A. Marino, Ph.D.
President
Plastafil, Inc.
P.O. Box 268
Belcher, Louisianna 71004

RE: P900020
Plastafil CFS™ (Carbon Fiber System)
Received: March 26, 1990

Dear Dr. Marino:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We regret to inform you that your application is incomplete and cannot be filed at this time. This means that the PMA will not undergo further review by CDRH until the deficiencies listed below are corrected or adequate justification for the omission of any item is submitted.

In order for the PMA to be filed, you must respond to the following deficiencies:

1. You must provide an explanation as to why this study was not conducted in compliance with 21 CFR Part 812 as required in 21 CFR Part 814.20 (b)(6)(ii)(B). It appears from the study design reported in the PMA that several changes and deviations from the original protocol occurred in violation of 21 CFR Part 812.35. Proper compliance to the investigational plan is the responsibility of the sponsor as described in 21 CFR Part 812.46. For instance, you must provide an explanation of why you include an open phase with no control patients when there was no provision for such a trial in the original design, and why the randomization scheme was changed to result in a 3:2 ratio of device treated to controls from a 1:1 ratio. In addition, please explain why implants were used in nine patients who had injuries only to the posterior cruciate ligament which was not one of the subgroups approved for this study.

2. You must report on all complications with the device. The report on complications is not complete as required in 21 CFR Part 814.20 (b)(6)(ii) because the incidence of synovitis, extra-articular infections, intra- and extra-articular failures, graft laxity, septic arthritis, and presence of carbon particles are not reported.

3. Patient accountability is extremely poor. It is not possible to identify all patients entered in the study who remained through its completion. A flow chart showing all patient groups from the initiation of study through its termination would clarify this. All withdrawals, losses, formation of new sub-groups should be clearly indicated in the chart.

4. Patient follow-up information is incomplete and confusing as reported. The "random-sampling model" suggested is not acceptable. Information for each parameter measured should be presented in life tables to include data for each time point as specified in the study protocol (that is, 0, 3, 6, 9, 12, and 24 months) plus any length of time beyond 2 years. The intervals should be selected in such a way that each patient is represented once in each interval. The following information should be included in such a table:

   a. patients in each category;

   b. patients lost to follow-up;

   c. patients due for follow-up visit;

   d. complications;

   e. withdrawals;

   f. deaths; and

   g. missing data.

5. It is not possible to assess whether randomization of the sample population into control and treated groups was achieved. You must explain how randomization was achieved.

6. The mechanical testing data are inadequate because no bending fatigue, tensile fatigue, creep or abrasion test data have been provided. The CDRH Intra-Articular Ligament Guidance Document should be consulted in order to provide the necessary test data for this PMA submission.

7. The Manufacturing Section lacks sufficient information to validate the sterilization process for this device and to determine whether this process adversely affects the device's physical and mechanical properties. The sterilization information must include the sterility assurance level of the device for the radiation sterilization process, the radiation dose, the radiation source, and complete validation data. Also, complete information concerning device packaging, bioburden, and pyrogen testing must be submitted.

As provided by 21 CFR 814.42(d), you may resubmit the PMA with the additional information necessary to correct the above deficiencies or you may request in writing within 10 working days of your receipt of this letter an informal conference with the Director of the Office of Device Evaluation (ODE) to review the decision not to file the PMA. Any review will be based only on information within the existing PMA and will be limited to a reconsideration as to whether any of the not filing criteria in 21 CFR 814.42(e) apply. The Director of ODE will hold this informal conference within 10 working days of receipt of the request and will render a decision on filing within 5 working days after the informal conference. If, after the informal conference, FDA accepts the PMA for filing, the filing date will be the date of the decision to accept the PMA for filing. If the Director of ODE does not reverse this decision not to file the PMA, the applicant may request reconsideration of the decision from the CDRH Director.

A request for reconsideration by the Director of CDRH must be submitted in writing within 30 working days of your receipt of a denial for filing from the Director of ODE. The request must contain written descriptions of your positions on the issues critical to filing. The Director of CDRH will render a written decision within 60 days of receipt of your request. If, after the review by the Director of CDRH, FDA accepts the PMA for filing, the filing date will be the date of the decision to accept the PMA for filing. If, after his review, the Director of CDRH does not reverse this decision not to file, that denial constitutes final administrative action for the purpose of judicial review.

The following additional deficiencies were noted in this initial review. While they did not directly relate to our decision to not file your PMA, you should make every effort to address them in your next amendment.

1. Justify why the total scores for patients in the control and treated groups cannot be used to establish a success/failure criteria for this study.

2. Submit subject report forms for all patients.

3. Submit an acceptable justification for the sample size determination.

4. Provide a summary of the complication rates for each investigator.

5. Submit the baseline data for the South African studies along with a description of the selection criteria used to select these cases.

6. Provide revised chi square test analysis to compare distribution of data at time intervals that meet the conditions in Item #4.

If you need to obtain clarification regarding any of the above deficiencies and the measures required to correct them, a request for an informal conference with the Director of ODE is inappropriate. Instead, we suggest that you contact or meet informally with the reviewing ODE division.

Any resubmission of the PMA to correct the above deficiencies, any request for an informal conference with the Director of ODE to review this decision not to file the PMA, or any other correspondence pertaining to this PMA should be identified as a PMA amendment and should include the above PMA reference number to avoid unnecessary delays in its processing. Please submit 6 copies, or 3 copies in the case of a request for an informal conference. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

FDA must consider the PMA to have been voluntarily withdrawn if you do not respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to CDRH approval and must justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) respond to the above deficiencies, or (2) request an extension of time to respond and have the request approved, FDA will close this file and not accept any amendments referencing this PMA number. Under these circumstances, any resubmissions will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

This letter reflects the current progress of our review of your application. It should be noted that the time allotted for the agency to perform a filing review and the condition of your PMA may not have permitted us to identify all deficiencies that the application may contain. Please be advised that continued review of your application and/or your response to this letter may result in additional deficiencies.

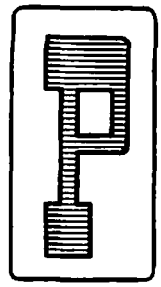
If you have any questions concerning the deficiencies listed above, please contact Michael J. Blackwell, D.V.M., M.P.H., at (301) 427-1036.

Sincerely yours,

Charles H. Kyper
Director, Premarket Approval Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

PLASTAFIL, INC.

P. O. Box 268
Belcher, Louisiana 71004



ANDREW A. MARINO, PH. D.
PRESIDENT

February 21, 1991

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

RE: P900020
Plastafil CFS™ (Carbon Fiber System)

Dear Sirs,

This letter and its appendices are in response to FDA's letter dated June 22, 1990. On December 13, 1990 I requested an extension of time within which to respond to the deficiencies listed in FDA's letter.

In what follows, "I" refers to both Plastafil, which is the sponsor of the CFS™ Carbon Fiber System, and to me personally. "PMA" refers to Plastafil's Pre-market Approval application listed above. "IDE" refers to Plastafil's investigational device exemption #G820122/S13. "Device" refers to either the portion of the CFS™ Carbon Fiber System consisting of the carbon-fiber implant itself, or to the carbon-fiber implant together with the fixation devices, whichever is appropriate in the circumstances in which the term is used. "Cases" refers to patients who received the Device; "Controls" refers to patients who received standard therapy. "Guidance Document" refers to Guidance Document for the Preparation of Investigational Device Exemptions and Pre-Market Approval Applications for Intra-Articular Prosthetic Knee Ligament Devices, Division of Surgical and Rehabilitation Devices, Center for Devices and Radiological Health, USFDA, 1987.

FDA requested responses to thirteen deficiencies, described in seven numbered paragraphs, and in six statements in one unnumbered paragraph. I have responded to each point, in the order in which it was raised. In some cases I divided FDA's comment into several parts to facilitate a reply. In each instance, FDA's comment is reproduced verbatim, followed by Plastafil's reply.

FDA: Page 1, Paragraph 1, Sentence 1: "You must provide an explanation as to why this study was not conducted in compliance with 21 CFR Part 812 as required in 21 CFR Part 814.20 (b)(6)(ii)(B)."

PLASTAFIL REPLY: The aforementioned section requires: "a statement that each study was conducted in compliance with Part 812 or Part 813 concerning sponsors of clinical investigations and clinical investigators, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance." The term "study" is not defined in Part 814, but from 21 CFR 814.20 (b)(6)(ii) it seems that the

term refers to clinical investigations involving human subjects with the Device, whether or not conducted under an IDE. Plastafil's clinical investigation under the IDE was conducted in compliance with Part 812. It was also conducted in compliance with the Institutional Review Board regulations in Part 56, and in compliance with the informed consent regulations in Part 50.

The clinical studies conducted by Drs. Mare, Demmer, Botha, and Penny reported in the PMA application were not conducted in compliance with the Institutional Review Board regulations (Part 56), the informed consent regulations (Part 50), or regulations concerning sponsors of clinical investigations and clinical investigators (Part 812). The reason for noncompliance was that the investigators had no legal or other obligation to comply with the aforementioned Parts. This information has previously been furnished (4E-1*, 2; 4E-21). In brief, the surgeons, each of whom is a citizen of a foreign country, provided the results of their clinical studies because the FDA staff felt that the information would be useful with regard to evaluating Plastafil's PMA, notwithstanding the fact that it was not generated under Plastafil's IDE.

FDA: Page 1, Paragraph 1, Sentences 2, 3, 4, and 5: "It appears from the study design reported in the PMA that several changes and deviations from the original protocol occurred in violation of 21 CFR Part 812.35. Proper compliance to the investigational plan is the responsibility of the sponsor as described in 21 CFR Part 812.46. For instance, you must provide an explanation of why you include an open phase with no control patients when there was no provision for such a trial in the original design, and why the randomization scheme was changed to result in a 3:2 ratio of device treated to controls from a 1:1 ratio. In addition, please explain why implants were used in nine patients who had injuries only to the posterior cruciate ligament which was not one of the subgroups approved for this study."

PLASTAFIL REPLY: Staff raises the issues of (1) an open phase with no control patients; (2) the use of the implant in patients who had injuries only to the posterior cruciate ligament; and (3) the use of the 3:2 ratio, not a 1:1 ratio. I will reply to the first two issues together, and the third issue separately.

Non-IDE Device Use. In mid-1983, Dr. John Albright expressed a desire to use the Device in some patients who had an injured posterior cruciate ligament or who had a totally dislocated knee (salvage patients). During the summer of 1983 I presented Dr. Albright's proposals to FDA staff during several telephone conversations. I explained Plastafil's willingness to provide the Device, and Dr. Albright's willingness to undertake the responsibility for its use. Plastafil's concern was that our actions might be construed as marketing the Device in violation of Section 301 of the Food, Drug and Cosmetic Act (FD&C) -- which was not the case. I asked: (1) Did the proposed uses amount to requests for approval of a modification of the IDE so as to include two additional study groups; (2) for the purposes of the proposed uses, was the Device a Custom Device

*Volume 4E, page 1 of the PMA. Subsequent references in this form similarly refer to the indicated volume and page numbers of the PMA.

within Section 520(b) of the FD&C Act and therefore exempt from Section 515? Initially, it was suggested that the proposal amounted to the inclusion of additional study groups, and that some formal steps were needed for the inclusion to be valid. But I pointed out: (1) The Device was not offered for commercial distribution to Dr. John Albright (or anybody else). (2) The Device was used to meet the unique needs of Dr. Albright's patients; Plastafil neither requested nor received a list of inclusion or exclusion criteria for use of the Device, nor did Plastafil make any recommendations regarding either criteria. The Device was used in particular patients whose clinical and anatomical features were, in Dr. Albright's discretion, suitable for use of the Device. (3) The Device was not commercially distributed, and no fee was charged for the Device. (4) Plastafil was not regularly engaged in providing Custom Devices, and that we would not do so for any individual other than Dr. John Albright. When Plastafil was satisfied that its actions would not be viewed as commercial distribution of an unlicensed medical device in interstate commerce, it provided the Devices to Dr. Albright to use as he thought appropriate. Plastafil never advocated the Device for use in salvage procedures because our rationale for the use of the Device did not extend to such an application; furthermore, we never advocated use of the Device for isolated PCL injuries because we had no intention of conducting a study that would directly test that hypothesis. Despite these facts, Plastafil made no attempt to impose its judgment on Dr. Albright, and made the Device available to him at his request, based on our respect for his efforts and his judgment.

21 CFR Part 812.46 describes the sponsor's responsibility in the situation in which an investigator fails to comply with the investigational plan. No investigator in Plastafil's IDE clinical study failed to comply with the investigational plan because each investigator, insofar as I am aware, substantially adhered to the investigational plan with regard to all its pertinent and substantive aspects including entry criteria, randomization, surgical procedures employed, handling and treatment of the device, and conduct of follow-up examinations.

In summary, for the abovementioned reasons, it is a mischaracterization of Plastafil's activities to assert that the issues raised were "deviations from the original protocol ... in violation of 21 CFR Part 812.35." The first issue related to a use of the Device that was thoroughly discussed with Staff at the time the use was carried out, and which was justified by considerations not pertinent to the IDE. The second issue related to an appropriate use of the Device that did not involve the hypotheses considered in the IDE study.

3:2 Allocation of Patients. In the IDE we said: "The randomization scheme used to allocate patients to treatment groups will result in approximately one experimental for each control" (emphasis added). The question posed by Staff therefore amounts to whether our use of a patient ratio of 1.5:1, and not 1:1 is a "change" within the meaning of the applicable version of Section 812.35. We concluded at the inception of the study that it was not such a change and that the use of 1.5:1 rather than 1:1 was scientifically desirable and justified. There were several bases for our conclusions.

Not a change within the meaning of Section 812.35. On January 18, 1980

the FDA promulgated a final rule regarding Section 812.35 (supplemental application), effective July 16, 1980 (45 FR 3755) that provided in pertinent part: "(a) Changes in Investigational Plan. A sponsor shall (1) submit to FDA a supplemental investigation if the sponsor or an investigator proposes a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects, and (2) obtain IRB and FDA approval of the change before implementation...."

In adopting this final rule FDA made it clear that it was intended to apply only to changes affecting the safety of subjects or the validity of the investigation: "Supplemental applications are required only for the addition of new institutions to an investigation and for changes in the investigational plan that may affect the scientific soundness of the study or the rights, safety, or welfare of subjects" (45 FR 3745).

On January 27, 1981 the FDA adopted an amendment to Section 812.35, effective July 27, 1981 which read in pertinent part: "(a) Changes in Investigational Plan. A sponsor shall: (1) Submit to FDA a supplemental investigation if the sponsor or an investigator proposes a change in the investigational plan and (2) obtain IRB approval (see Section 56.110(b)) and FDA approval of the change before implementation."

FDA again amended this Section, effective April 12, 1983 (48 FR 15621) to provide, in pertinent part: "(a) Changes in Investigational Plan. A sponsor shall: (1) Submit to FDA a supplemental investigation if the sponsor or an investigator proposes a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects and (2) obtain FDA approval of any such change and IRB (institutional review board) approval when the change involves the rights, safety, or welfare of subjects (see Sections 56.110 and 56.111), before implementation."

The Section was modified again (50 FR 25909, June 24, 1985; 50 FR 28932, July 17, 1985) and presently reads as follows: "(a) Changes in Investigational Plan. A sponsor shall: (1) Submit to FDA a supplemental investigation if the sponsor or an investigator proposes a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects and (2) obtain FDA approval under Section 812.30(a) of any such change, and IRB approval when the change involves the rights, safety, or welfare of subjects (see Sections 56.110 and 56.111), before implementation...."

Even if use of a patient ratio of 1.5:1 were to be considered a "change", the only aspect of the study to which it could reasonably be viewed as pertinent is that of the study's scientific soundness. That is, use of this ratio has no direct link with the question whether the device in any particular patient is more or less safe, or more or less efficacious. Thus, if there were a "change" within the meaning of Section 812.35, it affected "scientific soundness". But our IDE study was authorized by letter dated March 4, 1983, and the version of Section 812.35 that was in effect as of that date specifically removed "scientific soundness" as a "change" that must be submitted to FDA for prior approval. As a consequence of these considerations, I interpreted the law to mean that even if there were a "change", it was not a change that required a formal supplemental application.

Affirmative reasons for the choice of the 1.5:1 ratio. Assume that two surgical therapies are available to treat a particular disease, and that both procedures are performed routinely but that there is no scientific evidence to indicate which procedure is superior. The uncertainty could be resolved by randomizing subjects to the two procedures, and performing suitable follow-up determinations. If the investigating surgeon routinely performed both procedures, the study would contain no a priori bias regarding degree of surgical skill. However, if the patients randomized to one arm were operated on by a surgeon experienced in that procedure, and the surgeon had no experience with the second procedure, then any difference between the two patient groups might be due to either the relative merits of the procedures, or the relative skills of the surgeon. A similar difficulty in experimental design occurs whenever a new therapy is to be tested against a standard therapy; in such instances, surgeons have experience with one procedure, but not the new procedure, and consequently any measured decrement in efficacy in the new procedure might be due to relative inexperience. One acceptable strategy to overcome this difficulty is to provide, in advance, that the number of subjects receiving the new treatment will be greater than those who receive the standard treatment. The rationale is that the relative inexperience will be averaged over a larger subject population than would otherwise have been the case, thereby lessening the impact of this confounding variable on mean performance. Based on this consideration, and after reviewing other clinical studies in which a similar rationale was invoked, we chose to conduct this study at a case:control ratio of 1.5:1.

FDA: Page 1, Paragraph 2: "You must report on all complications with the device. The report on complications is not complete as required in 21 CFR Part 814.20 (b)(6)(ii) because the incidence of synovitis, extra-articular infections, intra- and extra-articular failures, graft laxity, septic arthritis, and presence of carbon particles are not reported."

PLASTAFIL REPLY: The statement suggests that Plastafil has violated the aforementioned Section because the "incidence" of the above-listed clinical states was not reported. The Section, however, is silent regarding each of the listed clinical states. Staff's assertion, therefore, is not correct.

The listed clinical states are not defined in the IDE, and I do not understand how the absence of information regarding undefined clinical states can be considered as a violation of the CFR. I cannot provide specific information unless the requests are posed using terms that have a meaning within the context of our study -- each of the listed terms have no such specific meaning because they are judgments, not dependent variables.

The phrasing of Staff's comment creates an irresolvable conflict between the meaning of a scientific term and the pattern of clinical practice. "Incidence" means frequency of occurrence of an event in a population within a particular time interval. Carbon fibers are not radio-opaque, and the presence of carbon-fiber debris (which is what I assume to be the issue raised here by Staff) cannot be determined unless the patient is arthroscoped (and even that may not be sufficient). It is not acceptable

to conduct routine arthroscopic examinations ir the absence of symptomatology, and in our IDE we expressed no intention to do so. Thus, it is impossible for me to report the incidence of carbon particles.

In alleging the deficiency, I think there has been a failure to recognize the change in the nature of decision-making within the surgical specialties which the FDA, itself, spearheaded. The public record shows that sponsors routinely presented the results of uncontrolled clinical studies in which clinical endpoints were evaluated using subjective criteria: Patients did "excellent", "good", or "poor", and they had "graft laxity", "synovitis", and they were "satisfied" or "unsatisfied." Since it is the practitioner that is the ultimate consumer of the research, the attempt to express both the design of the study and its results in clinical terms makes eminently good sense. The drawback in this approach is that it does not provide an objective basis for the degree of confidence that one may place in the conclusion of the study.

There is another procedure for conducting a clinical study. Groups representative of patients with a specific pathology are treated using alternative therapies, and the results are compared using acceptable clinical and statistical methods, stipulated in advance. These methods must be clinical, otherwise the study has no meaning; they must be statistical, otherwise the study is not superior to the alternative methodology. The basic process for implementing this procedure is to focus on a clinical state, define it in terms of a symptomatology, ascertain the grades or levels of the symptomatology, create a realistic a priori classification scheme, and finally, determine whether treatment affects distribution within the scheme (by analyzing the mean or median of the score characterizing the symptom used to define the clinical state, or the frequency distribution of patients in the various states as a function of treatment). This procedure removes (or goes a long way toward removing) the objection that the conclusion of a clinical study using the anecdotal method was too subjective. The price paid when the scientific method is used is that some clinical states, while remaining of crucial importance with regard to clinical judgment, patient management, diagnosis, and treatment, simply have no well-defined meaning within the decision-making process wherein the investigator seeks to ascertain the superior therapy. In this process, the clinical state has been replaced by the sum total of the symptoms deemed pertinent.

FDA has repeatedly made it clear that it prefers and expects well-designed clinical studies involving appropriate control groups assessed with regard to well-defined objective endpoints using appropriate statistical methodology. This is the kind of study Plastafil promised to perform when the IDE was approved in 1983, and it is the kind of study that Plastafil did, in fact, perform. Plastafil did not perform an anecdotal study, and therefore we cannot provide anecdotal evidence.

(1) With respect to "synovitis". Synovitis is a clinical condition involving inflammation of the synovial lining of the joint; its presence or absence (except in a florid condition) is a matter of clinical judgment. I am unaware of any methodology by which the presence or absence of the pathology can be uniquely determined. Moreover, the incidence of synovitis itself is not a meaningful number because, however the condition

may actually be defined, it is expected to occur in all patients to some extent. The pertinent question is whether the incidence of synovitis in the Cases (patients who received carbon fibers) differs from that in the Controls (patients who received standard therapy). The best response consists in characterizing the Cases and Controls with regard to parameters that were accepted prior to the study as being characteristic of the pathology. This was done in Volume 4E, Tables 9-14 for pain, and Tables 21-26 for swelling for all the patients in the study. The format employed in the preparation of the Tables was that specified in the Guidance Document. A pertinent response to Staff's question is also contained in the parameter SYMPTOMS defined in the IDE. The data from our study in the format SYMPTOMS is given in Enclosure 1 with this response.

(2) With respect to extra-articular infections. On page 4D-17 we reported "Mark Boolar (non-randomized study, LSU) experienced pain and tenderness in the area of the toggle, and it was removed in his physician's office under local anesthesia. Bryan Cooper (LSU) underwent removal of both medial bollards after he developed an abscess two weeks postoperatively." These were the only extra-articular infections (or possible infections) noted in our study.

(3) Intra-articular failures. I am unable to provide a definitive reply because I do not know what Staff means by "failures". If "failure" means a situation in which an initial treatment did not satisfactorily resolve an initial complaint, resulting in a second procedure for the same complaint, then the treatment failures in the Plastafil study were described on pages 4D-15 and 4D-16. There were four intra-articular treatment failures in the controls and four intra-articular treatment failures in the carbon-fiber patients in the chronic category; there were no other treatment failures.

(4) With regard to graft laxity. I am unable to provide a definitive reply because I do not know what Staff means by "graft laxity." Moreover, I do not understand the pertinence of a request for information regarding graft laxity because we have performed a controlled clinical study; consequently, no dependent variable has specific meaning except with relation to the magnitude of the corresponding variable in the control group. We provided information regarding numerous clinical tests and signs (see Tables 57-68, 103-107) that are pertinent to laxity. The tables were prepared according to the "distribution of scores for each objective item from Appendix 6 and subjective item from Appendix 5 for the entire population, at each time point of data collection according to the format of Appendix 11" as required in the Guidance Document. The data from our study in the format STABILITY is given in Enclosure 1 with this letter.

(5) Septic arthritis. We think none, but the limitations and ambiguities described in our response to the four previous clinical states applies with equal force here.

(6) Presence of carbon fibers. We were unable to report the fact or extent of presence of carbon fibers in the knee joint in any scientifically objective manner. Such a determination would have required arthroscopic surgery, tissue biopsy, and a validated quantitative procedure for

analyzing the biopsy specimens. Such a strategy was not proposed in our IDE, and would probably have been ethically unacceptable. The objective information that is available which bears on the issue, and which may be evaluated to make judgments about the existence and extent of carbon fibers in the joint consists of (1) observations regarding patient symptoms (under the hypothesis that a significant presence of carbon-fiber debris would have produced symptoms); (2) an analysis of the pertinent animal studies regarding the issue of carbon-fiber debris; and (3) the arthroscopic examinations made by Dr. Penny in a series of patients who agreed to be arthroscoped. This information has previously been presented to FDA, and we believe it supports the conclusion that trace presence of carbon fibers may be expected in the joint, but the debris does not have functional significance. I know of no countervailing evidence nor any objective method by which the question might be more adequately assessed.

FDA: paragraph 3: "Patient accountability is extremely poor. It is not possible to identify all patients entered in the study who remained through its completion. A flow chart showing all patient groups from the initiation of the study through its termination would clarify this. All withdrawals, losses, formation of new sub-groups should be clearly indicated in the chart."

PLASTAFIL REPLY: I am unable to provide a definitive reply because I do not know what Staff means by "completion", "termination", "withdrawal", "losses". None of these terms are defined in our study; consequently there is no unambiguous method to determine whether they occurred, or when.

We dealt with human beings who had their own likes, dislikes, priorities, and ambitions. When a patient chose not to return for a follow-up examination, I lacked both the legal and moral authority to require compliance. When faced with this difficulty, which occurred frequently, we accepted the patient's decision, and tried again later. No patient (with the exception discussed below) is "lost" or "terminated", and no patient "completes" the study in any absolute sense. It cannot be assumed that all subjects dutifully appear when requested to do so by their doctor, because this did not occur in the real world in which we performed our study. Indeed, any study performed on subjects who appear on command is probably worthless with regard to establishing inferences for the general population. Our study centers were chosen to provide a representative patient sample; frequently, the patients did not conform to a schedule that suited Plastafil. Banal as it may sound, patients do not respond to a physician's request like automatons, and implementation of the federal regulatory scheme for medical devices must recognize this fact. As difficult as the problem was at one year postoperative, it became increasingly more difficult as time passed.

Staff's assertion "patient accountability is extremely poor" is factually erroneous, and it is my hope that the error will be apparent when Staff evaluates our data in the format provided in this letter (Enclosure 1). The facts will show that our study is the best study involving an orthopaedic implant that has yet been performed and reported, and is probably near the theoretical limit on patient accountability for a study involving a cross-section of the population. The major difficulties I faced in reporting our data occurred because the IDE, the Guidance Document, and

the categories defined in FDA's deficiency letters frequently conflict with one another.

FDA: Page 2, Paragraph 4, Sentence 1: "Patient follow-up information is incomplete and confusing as reported."

PLASTAFIL REPLY: All follow-up information obtained during the course of this study has been summarized in the PMA; a copy of all case reports is included with this letter. Not every patient was followed at 3, 6, 9, and 12 months post-operatively for the reason that was described in the preceding Replies. The consequences of this fact are discussed below. The format of the follow-up information provided in the PMA was mandated by the Guidance Document -- it was not a format that we chose, nor a format that we proposed in the IDE. Confusion engendered by the preparation of data in the Guidance-Document format is not reasonably attributable to shortcomings on the part of Plastafil.

Plans describing (1) the format in which data would be presented for scientific evaluation, and (2) the statistical methodology that would be employed in evaluating the data were contained in the approved IDE. Below, I present: (1) the pertinent parts of the approved plan dealing with the format of the data and the decisional process to be employed in evaluating device efficacy; (2) the data obtained pursuant to this plan (Enclosures 1 and 2); (3) an analysis of pertinent changes in the implementation of this plan (compared with the plan as originally approved); and (4) the results of analysis of the data performed according to the approved methodology.

(1) The Approved Plan. The plan that Plastafil proposed for evaluating the data from the clinical study is contained in pages 13-15 in the IDE. The part of the approved plan dealing with the data format and the decisional process to be employed in evaluating device efficacy is:

Data Management

...

Efficacy: The success of the carbon-fiber treatment will be determined on the basis of statistical analysis of the results of Orthopaedic Examinations of the patients. Each patient will be evaluated with regard to the five categories listed in Table 3, using the Forms contained in APPENDIX A of this Protocol. The categories will be weighted, as shown in Table 3, to give the greatest weight to Stability (30%), equal rights to Symptoms, Function, and Patient's Evaluation (20% to each category), and the least to Deformity (10%).

Data for Symptoms and Function will be entered by the Investigator (or an appropriate assistant) at the time of the Orthopaedic Examination based on answers provided by the patient. A maximum total of 46 and 65 points respectively can be achieved in the two categories; as will be the case for all categories shown in Table 3, the actual values measured will be adjusted, using the appropriate scale factors, to obtain the desired weighting of each category.

...

Let O(t) be the orthopaedic status of the patient at time t. O(t) is defined to be the sum of the weighted scores from each of the categories as follows:

$$O(t) = Ss + Ff + Dd + Xx + Yy.$$

Where S, F, D, X, and Y, are the raw scores for each category as defined in Table 3, and the lower case symbols are the appropriate scale factors as defined in Table 3. For a patient with no knee disability, O(t) = 100.

O(t) will be measured at the time of the pre-operative visit (O(o)), and at 3-12 months post-operative. A Healing Index, HI, may be defined as the ratio of the patient's status at any particular time, compared to that found at the pre-operative visit.

$$HI = O(t)/O(o),\ t = 3, 6, 9, 12 \text{ months}.$$

Table 3. Categories to be Evaluated During Orthopaedic Examination, and Assigned Weight.

CATEGORY	CATEGORY SYMBOL	MAXIMUM RAW POINTS	FACTOR TO CONVERT TO 0-100 SCALE	RAW POINTS 0-100 SCALE	ASSIGNED WEIGHT	FACTOR TO PRODUCE ASSIGNED WEIGHT	FACTOR SYMBOL	EFFECTIVE SCALE FACTOR
Symptoms	S	46	0.42	19.2	20%	1.04	s	0.437
Function	F	65	0.42	27.2	20%	0.74	f	0.311
Deformity	D	22	0.42	9.2	10%	1.09	d	0.458
Stability	X	48	0.42	20.1	30%	1.49	x	0.626
Patient's Evaluation	Y	58	0.42	24.2	20%	0.83	y	0.349

HI(t) will be computed in the manner described above for each patient in this study, and the values from the carbon-fiber patients will be compared, using the independent t-test, at 3, 6, 9, and 12 months with those found from the corresponding control group.

(2) The Data. The data collected in this study is presented in Enclosure 1 on a patient-by-patient basis prepared according to the format described above. Enclosure 2 consists of averages obtained using the data in Enclosure 1. Enclosure 2, page 1, contains the average scores for each orthopaedic category defined in the IDE as a dependent variable, as assessed pre-operatively. Page 2 contains comparable average values obtained using all data in Enclosure 1 that was obtained more than 24 months post-operatively; also indicated on page 2 is the number of patients who contributed to the average. For example, there were 43 patients in the chronic category that received carbon fibers, and we had data regarding deformity on 41 patients that were at least 24 months post-operative; the

mean Deformity score was 20.6, compared with 19.6 in the control group (for which data was obtained on 33 of the 36 patients enrolled). The average follow-up times for each of the orthopaedic categories is listed on page 3. Page 4 of Enclosure 2 contains comparable information regarding the non-randomized group.

(3) The Changes. The decisional process itself is an essential part of the investigational plan. Wholesale or arbitrary a posteriori changes in the investigational plan would make it impossible to perform valid scientific studies, but changes in some aspects of design, conduct, or data evaluation may be necessitated by changed circumstances or unforeseen events. If so, the question whether the experimental hypotheses can still validly be assessed is raised. As discussed previously, not all patients were examined at 3, 6, 9, and 12 months post-operatively, because some patients refused to appear for scheduled clinical appointments. If a patient chose not to submit to a clinical examination at a particular time or within a particular time interval, there existed no legal nor moral force that could require compliance. There probably was not a single instance in which a patient was not requested to appear for a timed follow-up at 3, 6, 9, and 12 months post-operatively. Nevertheless, this situation constituted a change from the original plan.

What are the scientific consequences of the absence of data at the timed intervals? If a patient failed to appear at a timed interval, and also failed to appear at all subsequent times, the patient would be lost to follow-up. Every patient lost to follow-up compromises, to some extent, the confidence that one might have in decisions based on the study data, because of the possibility of bias associated with decision-making using only part of the sample. The difficulty is that the investigator could not be certain that the patients still available for follow-up reflected or characterized those that were unavailable. Thus, the existence of patients lost to follow-up inexorably injects uncertainty into the decisional process, thereby weakening any conclusion.

If no patient is lost to follow-up -- that is, if there is some data for every patient, even if the data is not obtained at the same post-operative time point for each patient, then the potential bias associated with lost patients does not exist. With only a few exceptions (discussed at length in the PMA), this situation applies to the Plastafil IDE study. That is, we have follow-up data for almost every patient (Enclosure 1). Since follow-up data beyond 24 months post-operatively was obtained for essentially every patient enrolled in the study, the question of potential bias due to lost patients becomes irrelevant and the performance of the Case and Control groups can be formally evaluated using appropriate statistical methods.

(4) Data Analysis. The healing index in the Cases in the chronic category (1.60 ± 0.57, page 2 of Enclosure 2) did not differ significantly from the Control value (1.74 ± 0.76) using the unpaired t test. The healing index in the Cases in the acute category (3.24 ± 1.50) did not differ significantly from the Control value (2.7 ± 0.79) using the unpaired t test.

FDA: Page 2, Paragraph 4, Sentence 2: "The 'random-sampling model' suggested is not acceptable."

PLASTAFIL REPLY: The basic value of a statistical approach is that, under the appropriate conditions, data obtained from a sample may be used to characterize the parent population. Indeed, in our PMA we urged that data taken on fewer than 150 patients could be used to make inferences regarding efficacy in a population (those having injured anterior cruciate ligaments) of more than 150,000/year. As established by Fisher (R.A. Fisher: J. Ministry of Agriculture of Gr. Brit. 33:503-513, 1926) and endorsed by subsequent authorities (W.J. Dixon and F.J. Massey: Introduction to Statistical Analysis, 4th Ed., McGraw-Hill: New York, 1983; B.J. Winner: Statistical Principles and Experimental Design, 2nd Ed., McGraw-Hill: New York, 1962), the validity of the inferential process depends upon establishing that the sample is representative of the population. The method of randomly choosing subjects is one process by which "representativeness" is assured. Surely if 150 subjects can characterize 150,000 subjects, then 15 subjects can (under appropriate circumstances) characterize 30 subjects. It would therefore be inconsistent to hold that, regardless of all other considerations, it is "not acceptable" to rely on a sample of a sample for the purposes of categorizing the latter; such an assertion is unscientific, and lacks both authority and a logical basis. Not only is the random-sampling model proper, it is probably the only acceptable model because it alone permits a clinical study on the true population -- all patients (not merely those whose socioeconomic, cultural, and medical backgrounds are such that they are certain to dutifully obey the orders of a physician regarding follow-up).

The pertinent que tion posed by a sample-of-a-sample methodology involves an a priori determination of the probability of occurrence of error. For our PMA, however, this consideration is not important because the sample-of-a-sample methodology is not part of the approved a priori decisional process.

FDA: Page 2, Paragraph 4, Sentences 3 and 4: "The information for each parameter should be presented in life tables to include data for each time point as specified in the study protocol (that is, 0, 3, 6, 9, 12, and 24 months) plus any length of time beyond two years. The intervals should be selected in such a way that each patient is represented once in each interval."

PLASTAFIL REPLY: I reject the notions that (1) a study exhibiting rigid chronological regularity is possible in a representative patient group, and (2) chronological regularity is a sine qua non of statistical validity. If Staff disagrees I request that FDA take whatever definitive and final steps that are necessarily entailed by its view, because it is neither necessary nor possible for us to provide data at each of the specified time points.

A life table is a table showing the proportion of a group of patients with a chronic disease that survive beyond a specific time chosen as the initial point of observation (J.A. Ingelfinger, F. Mosteller, L.A. Thibodeau and J.H. Ware: Biostatistics in Clinical Medicine, 2nd Ed., Macmillan: New York, 1987). Life tables may be used to evaluate survival as a function of differing treatments for an underlying disease (N. Eng. J.

Med. 311:1333-1339, 1984). I have been unable to find any scientific authority describing the use of life tables for evaluating the efficacy of an implant, compared with standard therapy. Death is not a useful endpoint, and it is unclear what Staff has in mind as a substitute. I can find no indication of either a format or a method of decision using "life tables" in the information disclosed by FDA under the FOI laws regarding previous ligament devices that were the subject of PMAs. I request that Staff specifically apprise me of (1) what it understands by "a life table" in the context of our study; (2) a scientific or legal authority wherein the method of computation of the life table acceptable to FDA is performed; (3) scientific or legal authority by which life tables for the Cases and Controls are to be compared for the purpose of determining any differences.

If Staff is seeking information regarding treatment failures, this information has previously been provided (4D-15).

FDA: Page 2, Paragraph 4, Sentence 5: "The following information should be included in such a table: (a) patients in each category; (b) patients lost to follow-up; (c) patients due for a follow-up visit; (d) complications; (e) withdrawals; (f) deaths; (g) missing data."

PLASTAFIL REPLY: (a) The patients in each category are listed in Table 1, Volume 4D; the Table lists the name, category, class, grade, and group of each patient. (b) I am unable to provide a definitive response to Staff's request because I do not understand what is meant by the term "lost to follow-up". If Staff means patients regarding whom Plastafil has irreversibly decided that no further follow-up can be obtained, our answer is none. If Staff means patients regarding whom follow-up information directly bearing on the decisional processes regarding safety and efficacy have received no contribution, our reply is contained in detail in Appendix 3, Volume 4D "Accounting for Patients for which the Longest Follow-up was Fewer than 24 Months"). (c) All patients are due for a follow-up visit because we are attempting to follow the group on a permanent basis. (d) I am unable to provide a definitive response because I do not understand what Staff means by "complications." If Staff means complications that clearly involved the Device, the two such instances that occurred during the study are described on page 4D-17. If the question refers to information obtained by investigators during follow-up visits ("Complications/Adverse Reactions" section of the "Follow-up Evaluation" form), all such replies received during this study are listed in Enclosure 3. The original data forms are contained in the case records which accompany this letter. (e) None. (f) William Hall was killed in an automobile accident on February 1, 1984 (4D, Appendix 3). (g) I am unable to respond because I do not understand what Staff means by "missing data." If by this term Staff means a list of follow-ups from which it may be determined when data was not obtained at 3, 6, 9, and 12 months post-operatively, this information is described in Enclosure 1.

FDA: Page 2, Paragraph 5: "It is not possible to assess whether randomization of the sample population into control and treated groups was achieved. You must explain how randomization was achieved."

PLASTAFIL REPLY: Tables of random numbers were prepared, and each number was assigned the status of "Case" or "Control", depending on a priori considerations regarding the desired frequency of each group. A probability of approximately 0.5 was chosen for the subjects at Iowa and Brooke, which was achieved by interpreting the even numbers in the table as a code for Cases, and odd numbers for Controls. A probability of approximately 0.6 for Cases at LSU was chosen by assigning even numbers plus numbers ending in the digit 1 to the Case group. At Iowa and Brooke the process was implemented by following the a priori sequence (listed in a Table) as each subject was entered in the study. At LSU the assignment sequence defined by the coding procedure was transferred to a 1-ft^2 wooden board, 3/4 inch thick, that contained a series of holes. Paper was glued to both sides of the board; when the paper on the top surface was pierced, the paper on the bottom surface could be seen. The code for the procedure to be performed was written on the bottom surface. The procedure followed was to systematically punch through the outer paper of the board, column by column, beginning with the left-most column, and proceeding from top to bottom within each column.

FDA: Page 2, Paragraph 6: "The mechanical testing data are inadequate because no bending fatigue, tensile fatigue, creep or abrasion test data have been provided. The CDHR Intra-Articular ligament guidance document should be consulted in order to provide the necessary test data for this PMA submission."

PLASTAFIL REPLY: Fatigue Testing. The Guidance Document provides (page 9) "fatigue testing must be conducted in order to determine the fatigue life of the device and the elongation due to creep." Also on page 9 the document provides "augmentation devices which are designed to degrade with time and which are not expected to retain any of their original properties in vivo may be excluded from long-term tensile fatigue testing. For these devices, the intended function must be described in detail and demonstrated with animal data. The length of time the device is expected* to carry a significant portion of the load imposed on the knee should be stated. Abbreviated tensile fatigue testing should be done as described below in which the fatigue life and elongation due to creep are determined within this time period. In addition, data concerning in-vivo device strength reduction with time must be provided."

The Guidance Document envisions either a frank prosthesis, or a device that is intended to shift load from itself to something else as a function of post-implantation time. The Device fits neither category. The theory of the Device, as was substantiated in the animal testing described in the PMA, is that the induced tissue that occurs as a response to the presence of the carbon fibers becomes oriented during its formation in the direction of the carbon fibers, and that the induced tisue joins pre-existing autologou tissue and thereby becomes capable of transmitting force across the knee. Each animal study was designed to explore an

*By "expected" in this context I understand Staff to be referring to a period of time beginning at the point of implantation during which it is anticipated that the Device will transmit a mechanical load, with the implication that if the Device does not function in such manner for such duration, the resulting situation would be viewed as a failure of the Device.

aspect of this hypothesis, including an animal therapeutic model (Carbon Fibers in Exterior Flexor Tendons of Thoroughbred Racehorses); our interpretaion of the animal data is that it supported the hypothesis. We have no specific expectation that the Device will transmit any particular mechanical load in the immediate post-operative period; we expect that, with the passage of time, the connective tissue elicited by the Device will begin to sustain mechanical loads. Clearly, fatigue and creep testing is not pertinent to a device whose rationale does not involve the transmission of force by the device.

Abrasion tests. As CDRH conceded in the Guidance Document (page 11) there exists no abrasion test procedure for the ligament devices envisioned in the Guidance Document (frank prostheses or "augmentation devices which are designed to degrade with time"). For even greater reasons, there are no objective abrasion tests regarding our Device. That is, there is no objective procedure regarding the Device that is capable of yielding a measure of a dependent variable whose value could be incorporated into objective decision-making. There is no basis upon which the meaning of any particular abrasion test could be interpreted with regard to the issues of safety or efficacy -- just as there is no basis for interpreting data from tests on surface reflectivity, temperature coefficient of expansion, or density with regard to the abovementioned endpoints. Performance of abrasion tests would serve no valid scientific purpose, consequently we performed no abrasion tests and do not intend to do so until a scientific basis or rationale for the tests is established.

FDA: Page 2, Paragraph 7: "The manufacturing section lacks sufficient information to validate the sterilization process for this device, and to determine whether this process adversely affects the device's physical and mechanical properties. The sterilization information must include the sterility assurance level of the device for the radiation sterilization process, the radiation dose, the radiation source, and complete validation data. Also, complete information concerning device packaging, bioburden, and pyrogen testing must be submitted."

PLASTAFIL REPLY: Plastafil is a small company, and we are attempting to establish our existence by following a lawful and logical pattern consistent with the fact of our limited resources. Our efforts thusfar have been concentrated on obtaining reliable scientific evidence to support our hypotheses that the Device is safe and efficacious. Our hope is that FDA will review this evidence independently from manufacturing considerations: We are not asking that these considerations be waived, but merely that their implementation be postponed until after FDA has considered the questions of safety and efficacy. If FDA agrees with us that the evidence shows that the Device is safe and efficacious, then Plastafil's task in raising capital to perform tests necessary to satisfy manufacturing criteria will be greatly eased. We sincerely expect that we will be able to propose acceptable manufacturing standards, and present evidence to indicate that these standards -- the methods for sterilization, for example -- will not alter pertinent Device properties. Even if we were unable to do so -- which is unlikely-- we have already devised a method of sterilization which resulted in not a single instance of intra-articular infection associated with the Device. Thus, even under the abovementioned dubious hypothesis, it is clear that effective manufacturing proced-

ures that result in a sterilized product do exist, and have been validated. This conclusion is in direct accord with pertinent in vitro studies involving bacterial adherence to carbon fibers, and with virtually all anecdotal evidence regarding the clinical use of the Device.

In the interest of fairness, and to help us to not fail for non-substantive reasons, I request that Staff postpone consideration of these issues until after the questions of safety and efficacy have been resolved to its satisfaction.

FDA: Page 3, Item 1: "Justify why the total scores for patients in the control and treatment group cannot be used to establish a success/failure criteria for this study."

PLASTAFIL REPLY: Because the concepts of success and failure are subjective, and are not objectively defined in science, law, or logic. In the IDE, we proposed to evaluate the Cases and Controls according to objective standards, and to determine whether the Groups differed -- this we did. The terms used by Staff were not defined in the IDE and it should therefore not be surprising that they are not employed in our conclusions.

FDA: Page 3, Item 2: "Submit subject report forms for all patients."

PLASTAFIL REPLY: One copy of the subject report forms for all patients are included with this letter.

FDA: Page 3, Item 3: "Submit an acceptable justification for the sample size determination."

PLASTAFIL REPLY: Consider the data provided on page 2, Enclosure 2. We desired to end the study when the patient sample was large enough to yield reasonable statistical power against a clinically significant hypothesis other than the null hypothesis. We chose a statistical power of 0.8 against the hypothesis that the Cases were 30% below the Controls. For the patients in the chronic category a raw effect size of 30% corresponds to a standardized effect size of 0.55 (the raw effect size divided by the root mean square standard deviation). The corresponding n (number of subjects) is 42 (Table 2.3.2, Statistical Power Analysis for the Behavioral Sciences, J. Cohen, Academic Press, New York, 1977). Since we had entered 43 Cases and 36 Controls, and had obtained 2-year follow-up on 39 Cases and 30 Controls and had obtained 72 follow-ups among the Cases and 50 follow-ups among the Controls (harmonic mean equal to 54), we concluded that a sufficient number of patients had been entered into the study.

With regard to the patients in the acute category the standardized effect size corresponding to a 30% raw effect size was .49. The corresponding n for a statistical power of 0.8 is 50. We terminated the study after entering 31 Cases and 24 Controls (page 2, Enclosure 2) for the following reason. The healing index, which was defined in the IDE as the orthopaedic status of the patient at a particular post-operative time normalized by the pre-operative orthopaedic status, was a well-defined variable for the chronic category, but not for the acute category. In many instances examinations required to provide a Deformity score could not be

performed because of the patient's condition, and numerical scores for other orthopaedic categories including Function, Symptoms, and Patient Evaluation were essentially 0. Consequently, it is more reasonable to consider the issue using post-operative orthopaedic status without normalizing with the score obtained from the pre-operative orthopaedic evaluation. From page 2, Enclosure 2 it can be seen that a raw effect size of 30% corresponds to a standardized effect size of 1.8. The number of subjects required to achieve a statistical power of 0.8 for this effect size is fewer than 20. We therefore concluded that we had entered far more than the number of subjects required to exclude the considered hypothesis.

Inclusion of the non-randomized patients (page 4, Enclosure 2) does not change the analysis. They were more seriously injured than the patients in the randomized study (average pre-operative orthopaedic status was 13.33), and the average orthopaedic status after 24 months was 72.06 (compared with 87.34 among the acute cases in the randomized study). The healing index in the non-randomized group averaged 12.75. Thus, if a judgment regarding outcome is based on the Healing Index, the contribution from the non-randomized group would tend to favor the Cases compared with the Controls. If the judgment is based on orthopaedic status, the contribution would tend to favor the Controls compared with the Cases, but the quantum of the contribution would be such that it would not affect any of the prior statistical comparisons discussed above.

FDA: Page 3, Item 4: "Provide a summary of the complications rates for each investigator."

PLASTAFIL REPLY: Enclosure 3 lists the complications/adverse reactions reported during the study. For each report, the name of the operating surgeon is listed.

FDA: Page ;3, Item 5: "Submit the baseline data for the South African studies along with a description of the selection criteria used to select these cases."

PLASTAFIL REPLY: The information I previously provided from Drs. Mare and Botha included all the pertinent documentary information that I obtained from them. I provided the information in what I believed to be a form that was convenient for review. Enclosed with this letter are photocopies of the documents themselves, as received from Drs. Botha and Mare. Dr. Demmer maintained more detailed records in such a manner that his work was suitable for publication. His results will be published in Clinical Orthopaedics in about 1-2 months; a copy of the unedited manuscript, together with copies of all documents that he provided to me are also enclosed with this letter.

Each of the surgeons who provided information did so with regard to a consecutive and inclusive series of patients operated on between the dates that I listed in the PMA. Each patient received surgery because the operating surgeon decided that the procedure was necessary and appropriate for treatment of laxity or instability. None of the three series was carried out with an eye toward publication or FDA submission, and the documentation normally expected for such data is missing. If Staff has

any specific questions about individual patients, I will do my best to obtain the desired information. Alternatively, I invite Staff to contact the surgeons directly, and pose whatever questions it considers pertinent.

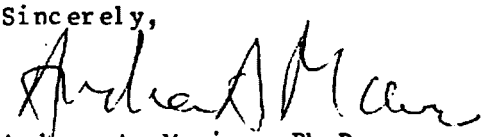
The utility of data is determined by the proposition in favor of which it is advanced. We offered the South African data in support of the limited proposition that long-term implantation of carbon fibers does not result in infection, pain, or other untoward developments. My trip to South Africa to obtain this data was not made on my own initiative, but rather at the specific request of Staff (made during our December, 1986 meeting). I did exactly what I was asked to do, and I did it as well as I could. I met each of the surgeons, and spent many hours satisfying myself regarding the accuracy and completeness of the data. The South African surgeons have no interest whatsoever in Plastafil, and yet they put up with many hours of questioning by me, and many hours of poring over their charts and records to provide information in the interest of science, with no expectation of personal benefit. Although I did what Staff asked, nevertheless a serious epistomological issue was raised because I (hence Staff) have no independent basis to evaluate the results obtained by each of the surgeons -- I must either accept their word that an infection did not occur or chronic pain was not present, or reject it. I would have made no use whatever of the South African data had not the Staff specifically requested me to furnish it.

FDA: Page 3, Item 6: "Provide chi-square test analysis to compare distribution of data at time intervals that meet the condition of item 4."

PLASTAFIL REPLY: I am unable to respond because I do not understand what Staff means by "item 4." If Staff will inform me of the hypothesis to be tested and the data to be used, and the rationale, I will supply the analyses quickly.

I have endeavored to reply directly and completely to each of Staff's concerns. I fully appreciate the responsibility that the FDA must exercise in carrying out its statutory responsibility. I hope, for its part, Staff views us as conscientious investigators who have stayed the course for many years, despite many roadblocks, and have produced a corpus of data following processes that manifested integrity. We began our work with the idea that the CFS™ was at least as good as standard treatments, and all of our subsequent areas of investigation and study ultimately supported our initial hypothesis. We have considered the published literature, performed in vitro, animal, and human studies, and considered anecdotal evidence available to us regarding the use of carbon fibers. We evolved a clear rationale for use of the Device, based on a mechanism of action that was elucidated in the animal studies. I think that we left no reasonable stone unturned in a search for evidence that might contradict our basic conclusion. I believe that it is truly appropriate for the evaluation process to go forward, and consequently I request that our PMA, as revised by this submission, be accepted for filing.

Sincerely,



Andrew A. Marino, Ph.D.

AAM:pab

CONTROL CASES
Chronic Cases

NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TREATMENT	TIME (Mos.)	SCOPE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
20	LSUMC	C-1	Woodruff, Steve	PT	Pre	22	51	38	30	38	74.58	
					22	22	45	44	38	41	81.40	1.09
					40	21	52	30	40	42	78.60	1.05
					55	20	56	21	36	42	72.95	0.98
28	LSUMC	C-1	Role, William	PT	Pre	22	17	1	40	2	41.54	
					3	18	1	7	44	7	41.60	1.00
					6	18	31	20	44	29	64.29	1.55
					32	20	55	42	44	47	88.57	2.13
					60	18	54	42	44	47	62.30	1.50
29	LSUMC	C-1	West, Paul	PT	Pre	22	23	12	24	16	43.08	
					3	22	--	--	44	--	37.62†	
					6	22	27	24	44	19	63.14	1.46
					15	22	44	23	44	31	72.17	1.68
					30	19	51	44	40	40	82.79	1.92
					48	22	65	46	44	48	94.69	2.20
31	LSUMC	C-1	Beshea, Debra	PT	Pre	18	0	0	24	8	26.06	
					3	18	25	15	44	26	59.19	2.27
					16	20	48	16	44	25	67.35	2.58
					23	20	37	28	42	26	68.27	2.62
					45	19	59	36	36	50	82.77	3.18
32	LSUMC	C-1	White, Ronald	PT	Pre	22	28	16	34	17	52.99	
					3	22	15	23	44	30	62.81	1.18
					6	18	42	36	34	36	70.89	1.34
					9	22	28	14	36	21	54.77	1.03
					12	19	29	17	32	25	53.91	1.02
					26	15	26	15	30	17	46.22	0.87
35	LSUMC	C-1	Heckford, Terry	IT Band	Pre	18	41	28	18	31	55.32	
					3	22	29	21	32	26	57.38	1.04
					9	22	60	19	32	58	77.31	1.40
					24	22	16	15	24	23	44.66	0.81
41	LSUMC	C-1	Bass, James	Biceps	Pre	21	31	15	40	22	58.53	
					9	20	62	46	36	48	87.83	1.50
					17	20	58	42	44	47	89.50	1.53
					36	20	64	44	38	55	91.28	1.56
					47	20	64	46	44	51	94.51	1.61
47	LSUMC	C-1	Sullivan, Jimmy	PT	Pre	18	30	32	30	14	55.22	
					16	22	49	43	38	33	79.41	1.44
					31	22	58	46	42	46	90.56	1.64
					45	18	56	43	36	39	80.60	1.46

CONTROL PATIENTS (Chronic Cases), continued

No.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TREATMENT	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
57	ISUMC	C-1	Houghlan, Julie	PT	Pre	22	23	14	34	20	51.61	
					6	20	--	--	44	16	42.29†	
					14	20	24	14	44	21	57.62	1.12
					26	22	34	23	42	25	65.72	1.27
					42	16	40	30	38	43	71.67	1.39
61	LSUMC	C-1	Thedford, Anthony	PT	Pre	14	13	0	26	12	30.92	
					3	15	32	47	32	31	68.21	2.21
					6	18	36	18	44	31	65.67	2.12
					9	21	60	41	44	56	93.28	3.02
					12	19	64	46	40	55	92.94	3.00
					27	19	58	46	38	51	88.43	2.86
					39	17	63	46	40	50	89.97	2.91
62	LSUMC	C-1	Staggs, James	PT	Pre	22	25	13	26	13	44.34	
					12	21	56	43	30	46	80.66	1.82
					33	20	63	36	32	52	82.66	1.86
					47	21	63	46	42	51	93.40	2.11
66	LSUMC	C-1	Hall, William	PT	Pre	22	25	13	26	16	45.39	
					7	19	27	31	38	19	61.06	1.34
	LSUMC	C-1	Jackson, Cedric	PT	Pre	17	0	0	16	2	18.50	
					10	22	63	46	44	55	96.51	5.22
					23	22	65	46	40	54	94.28	5.10
					37	18	65	46	40	56	93.14	5.03
79	LSUMC	C-1	Cooper, Roy	PT	Pre	--	13	21	22	8	29.78†	
					9	19	58	23	30	49	72.67	
					12	22	65	46	30	58	89.42	
					27	19	64	46	30	56	87.03	
80	LSUMC	C-1	Schumann, Raymond	PT	Pre	22	55	35	38	38	79.53	
					21	19	64	46	--	53	67.20†	
					38	19	64	46	28	53	84.73	1.06
85	Iowa	C-1	Scheller, Arthur	PT	Pre	20	32	18	34	19	54.89	
					3	19	18	15	40	15	51.13	0.93
					6	22	28	23	44	22	64.06	1.17
					9	22	54	44	40	44	86.49	1.58
					12	21	47	46	40	41	83.69	1.52
					24	16	57	42	38	43	82.20	1.50
					56	20	--	46	36	--	51.80†	

CONTROL PATIENTS (Chronic Cases), continued

PT. No.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TREATMENT	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
88	Iowa	C-2	Burriola, Melinda	PT	Pre	22	14	6	34	8	41.13	
					3	21	18	22	42	14	56.01	1.36
					6	21	32	22	38	32	64.14	1.56
					9	20	8	3	40	8	40.79	0.99
					12	21	9	3	20	10	29.74	0.72
					64	17	28	24	--	--	26.98†	
90	Iowa	C-1	Mullen, Christie	PT	Pre	22	44	19	24	28	56.86	
					3	18	15	17	44	14	52.77	0.93
					6	20	23	18	40	18	55.50	0.98
					9	22	41	22	38	27	65.65	1.15
					12	21	43	36	38	29	72.63	1.28
					56	20	59	46	36	46	86.20	1.52
97	Iowa	C-1	Sanderson, Joyce	PT	Pre	19	39	31	34	14	60.55	
					3	20	15	20	44	9	53.25	0.88
					6	21	37	21	42	29	66.72	1.10
					10	20	41	41	38	31	74.44	1.23
					12	16	46	44	22	27	64.06	1.06
					24	18	60	46	36	48	86.29	1.42
					40	18	59	45	36	50	86.24	1.42
					58	21	52	44	44	48	89.31	1.47
101	Iowa	C-1	Helle, Elizabeth	PT	Pre	17	21	6	24	11	35.80	
					3	20	23	10	44	15	53.46	1.49
					6	22	27	23	40	22	61.24	1.71
					9	21	40	23	40	31	67.97	1.90
					16	19	59	46	42	54	92.29	2.58
					24	20	61	46	40	55	92.47	2.58
					30	21	62	46	40	57	93.94	2.62
					58	19	61	44	36	--	69.44†	
5	Iowa	C-2	Edwards, David	Semitendinosis	Pre	18	13	9	22	15	35.23	
					3	18	29	20	34	24	55.66	1.58
					6	18	23	22	28	21	49.87	1.42
					9	18	32	22	22	31	52.40	1.49
					17	19	51	41	18	46	69.80	1.98
					23	20	52	42	32	45	79.42	2.25
					48	22	49	40	42	46	85.14	2.42
109	Iowa	C-1	Duncan, Donna	Sutured	Pre	11	0	0	--	4	6.43†	
					3	18	16	23	40	15	53.55	
					6	18	14	23	38	25	55.16	
					13	18	23	5	30	14	41.25	
3	Iowa	C-1	Molander, Jeff	PT	Pre	20	41	32	26	24	60.55	
					3	20	7	23	40	4	47.82	0.79
					10	21	28	17	40	36	63.36	1.05
					41	20	59	41	38	48	85.97	1.42

CONTROL PATIENTS (Chronic Cases), continued

NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TREATMENT	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
119	Iowa	C-1	Singletary, Angela	Semitendinosis	Pre	20	20	19	--	21	31.01†	
					3	18	13	23	38	15	51.36	
					12	19	37	20	40	15	59.22	
					18	20	59	45	38	43	85.97	
					39	22	53	30	34	29	71.07	
120	Iowa	C-1	Waterman, Kyle	PT	Pre	20	49	18	34	17	59.48	
					3	12	11	20	42	15	49.18	0.83
					6	21	35	23	40	37	68.51	1.15
					9	22	43	46	46	36	84.91	1.43
					13	20	47	21	38	46	72.80	1.22
					18	20	58	43	42	51	90.08	1.51
					51	20	60	32	40	--	66.84†	
123	Brooke	C-1	Clarke, Jeffrey	PT	Pre	19	18	14	30	7	41.64	
					3	21	28	22	44	20	62.46	1.50
					6	22	32	21	44	28	66.52	1.60
					9	20	42	44	38	37	78.15	1.88
					17	22	57	33	40	46	83.32	2.00
					24	21	49	28	42	47	79.79	1.92
					54	21	58	33	34	50	80.81	1.94
[illegible]	Brooke	C-1	Lopez, Edgar Vega	PT	Pre	21	25	21	26	22	50.52	
					3	17	12	20	44	9	50.94	1.01
					6	20	17	23	44	7	54.48	1.08
					9	21	24	21	44	13	58.34	1.15
					12	19	26	23	44	13	58.92	1.17
					24	21	40	32	38	--	59.83†	
					61	19	35	37	38	29	69.66	1.38
127	Brooke	C-1	Broyles, Keith	PT	Pre	20	31	12	24	17	45.00	
					3	22	13	15	32	14	45.59	1.01
					6	20	20	11	36	19	49.35	1.10
					9	20	26	19	30	26	53.40	1.19
					34	19	39	18	26	33	56.49	1.26
					57	21	52	43	24	47	76.01	1.69
129	Brooke	C-1	Barfield, Johnny	PT	Pre	21	33	14	26	21	49.60	
					3	18	25	21	32	28	55.00	1.11
					6	21	42	22	40	33	68.85	1.39
					9	20	46	41	38	38	78.43	1.58
					12	18	45	40	36	42	76.91	1.55
					61	18	51	43	40	32	79.10	1.59
131	Brooke	C-1	Duke, Carl	PT	Pre	22	25	17	28	13	47.34	
					3	18	4	3	--	6	12.89†	
					6	18	19	13	44	13	51.92	1.10
					40	14	24	12	34	11	44.24	0.93
					54	13	19	19	28	11	41.53	0.88

CONTROL PATIENTS (Chronic Cases), continued

NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TREATMENT	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
133	Brooke	C-1	Minehart, Mark	PT	Pre	22	37	25	20	23	53.06	
					3	22	24	20	40	11	55.16	1.04
					6	19	23	18	36	18	52.54	0.99
					9	20	37	18	32	20	55.54	1.05
					20	19	46	28	18	32	57.68	1.09
					56	16	33	31	32	20	58.15	1.10
134	Brooke	C-1	Arrington, Robert	PT	Pre	21	46	4	30	43	59.46	
					3	22	17	22	40	26	50.35	0.85
					6	20	33	21	34	35	62.10	1.04
					32	22	53	39	44	49	88.25	1.48
					44	22	59	44	44	42	89.86	1.51
					57	22	59	44	44	41	89.51	1.50
141	Brooke	C-1	Jablonski, Catherine	PT	Pre	--	0	0	--	3	1.05†	
					3	17	16	21	--	7	24.38†	
					6	20	30	23	44	37	69.00	
					9	21	46	23	44	41	75.83	
					14	19	52	46	44	52	90.67	
					32	21	56	35	44	47	86.28	
					50	21	60	44	44	48	91.80	
[illegible]	rooke	C-1	Byrd, John	PT	Pre	20	21	22	28	16	48.42	
					6	19	41	23	44	35	71.26	1.47
					9	19	40	43	44	32	78.64	1.62
					12	19	46	44	44	33	81.30	1.68
					27	22	56	46	42	41	88.20	1.82
					41	21	56	44	44	50	91.26	1.88
					56	22	60	46	42	--	75.13†	
148	Brooke	C-1	Robbins, Andrew	PT	Pre	22	41	20	24	20	53.57	
					3	21	23	16	40	23	56.83	1.06
150	Brooke	C-1	Jahn, Melanie	PT	Pre	22	33	27	--	14	37.02†	
					3	18	27	22	44	15	59.03	
					6	20	46	43	44	15	75.04	
					9	18	45	21	42	44	73.06	
					15	22	57	45	40	48	89.26	
					35	22	60	46	34	52	88.27	
					51	20	60	46	38	48	88.46	

†Incomplete score

CARBON-FIBER CASES
Chronic Cases

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
2	LSUMC	C-1	Gloer, Mark	Pre	22	34	18	14	23	45.31	
				32	21	29	42	36	22	67.20	1.48
				64	18	39	16	32	28	57.17	1.26
4	LSUMC	C-1	Rasbury, Richard	Pre	21	40	19	30	29	59.26	
				12	22	54	41	40	39	83.44	1.41
				26	21	53	41	38	44	83.16	1.40
				43	21	54	43	30	44	79.34	1.34
				58	20	43	40	34	30	71.77	1.21
12	LSUMC	C-1	Mondor, John	Pre	22	54	38	32	44	78.86	
				36	22	60	41	36	48	85.94	1.09
14	LSUMC	C-2	Cooper, Keith	Pre	22	31	28	34	24	61.61	
				6	22	36	23	44	45	74.57	1.21
				9	22	54	44	44	43	88.65	1.44
				19	19	52	23	44	43	77.48	1.26
				25	19	60	46	44	51	92.81	1.51
				41	16	46	39	34	38	73.22	1.19
				63	17	49	42	38	32	76.34	1.24
15	LSUMC	C-1	Winkler (Allen), Sharon	Pre	21	13	2	22	6	30.40	
				6	22	54	43	38	44	84.80	2.79
				23	21	50	32	26	44	70.78	2.33
				40	22	41	30	34	38	70.48	2.32
				55	19	34	24	26	33	57.56	1.89
16	LSUMC	C-1	Lux, Gregory	Pre	18	18	9	12	13	29.82	
				3	20	24	22	44	7	56.22	1.88
				6	21	52	45	44	31	83.82	2.81
				9	22	56	46	44	48	91.89	3.08
				12	21	54	43	44	48	89.50	3.00
				35	21	51	42	44	43	86.38	2.90
				56	21	55	37	44	16	76.02	2.55
17	LSUMC	C-1	Larson, Larry	Pre	21	18	9	20	4	33.06	
				3	21	22	18	40	21	56.70	1.72
				6	21	53	23	26	36	64.99	1.96
				9	21	60	39	44	51	90.66	2.74
				37	22	60	41	40	50	89.14	2.70
				55	20	51	41	40	25	76.70	2.32
18	LSUMC	C-1	Darden, Lennie	Pre	22	22	14	26	12	43.50	
				6	22	50	40	40	36	80.71	1.86
				12	22	56	34	40	41	81.70	1.88
				29	22	56	44	44	45	89.97	2.07
				53	21	57	40	44	51	90.17	2.07

CARBON-FIBER PATIENTS (Chronic Cases), continued

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Fv.	ORTHO. STATUS	HEALING INDEX
22	LSUMC	C-1	Jenkins, Larry	Pre	22	26	17	26	16	47.45	
				6	20	32	17	40	16	57.16	1.20
				20	22	13	0	40	16	44.74	0.94
				28	21	22	23	34	16	53.38	1.12
				53	17	42	12	40	30	61.60	1.30
25	LSUMC	C-1	Houston, Larry	Pre	21	25	25	28	28	55.62	
				3	22	38	17	40	29	64.48	1.16
				6	22	18	21	42	16	56.73	1.02
				25	18	50	38	32	31	71.25	1.28
				51	22	36	15	34	24	57.49	1.03
36	LSUMC	C-2	Smith, Randy	Pre	22	20	18	26	18	46.72	
				3	22	2	7	36	2	36.99	0.79
				6	22	35	23	40	25	64.78	1.39
				9	22	37	20	34	--	51.61†	
				23	22	46	35	42	33	77.49	1.66
				26	22	41	41	40	27	75.21	1.61
				36	--	--	--	--	24	8.38†	
				47	21	25	8	40	--	45.93†	
				58	19	28	7	28	36	50.56	1.08
37	LSUMC	C-1	Williams, Roberta	Pre	22	41	23	22	28	56.42	
				3	22	31	22	38	20	60.10	1.06
				6	22	54	46	44	35	77.57	1.37
				12	22	60	46	38	53	91.12	1.62
				24	22	65	46	42	56	96.23	1.70
				36	22	65	46	44	56	97.48	1.73
				49	22	65	46	44	56	97.48	1.73
40	LSUMC	C-1	Perry, David	Pre	22	43	26	26	28	60.86	
				3	22	33	12	40	22	58.30	0.96
				22	22	42	35	44	31	76.80	1.26
				53	18	44	34	40	44	77.18	1.27
42	LSUMC	C-1	Halliburton, Lloyd	Pre	22	35	29	28	27	60.58	
				3	22	40	38	40	26	73.24	1.21
				15	22	57	42	44	44	89.06	1.47
				22	22	61	42	44	48	91.70	1.51
				37	20	55	42	32	48	81.40	1.34
				49	20	64	44	32	52	86.47	1.43
55	LSUMC	C-1	McKee, Billy	Pre	20	5	3	28	8	32.35	
				15	21	14	14	40	12	49.32	1.52
				24	16	30	24	34	22	56.11	1.73
				38	15	14	6	36	7	38.82	1.20
				52	19	22	8	40	15	49.32	1.52

CARBON-FIBER PATIENTS (Chronic Cases), continued

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Fv.	ORTHO. STATUS	HEALING INDEX
58	LSUMC	C-1	Riley, Mike	Pre	22	2	6	34	5	36.35	
				6	22	55	42	44	41	87.39	2.40
				9	22	59	44	40	46	88.75	2.44
				14	22	61	44	44	48	92.57	2.55
				25	21	62	44	42	49	91.52	2.52
				51	18	49	32	40	--	62.51†	
67	LSUMC	C-1	Peart, George	Pre	22	20	7	38	14	48.03	
				9	22	57	36	44	50	88.53	1.84
				21	20	64	46	40	53	92.70	1.93
				45	21	53	28	34	36	72.18	1.50
68	LSUMC	C-1	Love, Victor	Pre	22	0	0	38	2	34.56	
				9	22	63	23	44	41	81.57	2.36
				13	22	55	43	44	44	88.87	2.57
				36	22	65	46	44	56	97.48	2.82
73	LSUMC	C-1	Banks, Leonard	Pre	22	46	26	38	40	73.49	
				21	20	55	36	40	45	82.74	1.12
				34	22	55	40	34	43	80.95	1.10
74	LSUMC	C-1	Daniel, Steven	Pre	22	15	8	36	11	44.61	
				6	21	30	21	34	19	56.04	1.26
				14	15	45	42	36	29	71.88	1.61
				27	22	38	32	24	26	59.98	1.34
				40	21	54	34	40	37	79.22	1.78
76	LSUMC	C-1	Fmanus, James	Pre	22	52	38	40	43	82.90	
				3	20	33	21	44	25	64.87	0.78
				6	22	42	46	42	41	83.84	1.01
				11	22	65	46	44	56	97.48	1.18
				30	22	65	46	44	56	97.48	1.18
81	ISUMC	C-1	Harrison, Iouis P.	Pre	22	0	0	30	2	29.55	
				12	22	59	40	34	39	80.80	2.73
				26	--	44	33	--	38	41.37†	
86	Iowa	C-1	Hill, James	Pre	19	0	0	30	2	28.18	
				3	16	16	6	42	15	46.45	1.65
				6	22	26	20	40	16	57.53	2.04
				9	21	51	43	40	39	82.92	2.94
				53	21	62	41	44	51	92.16	3.27
89	Iowa	C-1	Florey, Scott	Pre	22	42	35	32	27	67.89	
				3	18	12	17	44	9	50.09	0.74
				6	15	11	17	38	12	45.70	0.67
				9	15	22	20	38	25	54.96	0.81
				12	19	56	45	40	49	87.92	1.30
				34	21	55	44	38	47	86.14	1.27
				59	16	56	37	44	47	84.86	1.25

CARBON-FIBER PATIENTS (Chronic Cases), continued

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
92	Iowa	C-2	Grenon, George	Pre	18	15	9	26	11	36.96	
				3	12	9	15	40	5	41.64	1.13
				6	13	6	13	40	5	40.29	1.09
				9	15	4	10	44	2	40.73	1.10
				12	14	4	10	44	2	40.27	1.09
				27	20	18	23	44	12	56.54	1.53
95	Iowa	C-1	Malhotra, Kiran	Pre	22	33	32	34	13	60.14	
				3	20	10	19	38	2	45.06	0.75
				6	20	16	20	40	2	48.61	0.81
				9	21	35	23	38	22	62.02	1.03
				12	22	48	20	40	33	70.30	1.17
				24	21	56	44	38	41	84.36	1.40
				61	21	62	43	28	42	79.88	1.33
98	Iowa	C-2	Kiener, Frank	Pre	20	9	5	18	17	31.34	
				3	20	9	17	38	7	45.62	1.46
				6	21	35	44	26	26	65.08	2.08
				9	20	25	21	38	18	56.18	1.79
				12	21	33	21	36	19	58.22	1.86
				24	22	57	46	38	43	86.70	2.77
				37	20	59	46	38	45	87.10	2.78
				51	22	63	42	40	50	90.51	2.89
100	Iowa	C-1	Northrup, Daniel	Pre	18	10	11	22	14	37.62	
				24	21	18	6	2	23	27.12	0.72
103	Iowa	C-1	Haldy, Glenn	Pre	22	52	39	34	40	78.54	
				3	14	29	12	42	24	55.34	0.70
				6	22	42	46	34	24	72.90	0.93
				10	22	35	20	42	28	65.76	0.84
				13	20	54	23	38	34	71.66	0.91
				24	22	61	46	44	42	91.35	1.16
				51	18	64	45	42	49	91.21	1.16
110	Iowa	C-1	Montgomery, Lesa	Pre	22	0	0	32	15	35.34	
				3	20	5	13	38	14	45.07	1.28
				6	21	20	23	40	17	56.86	1.61
				9	20	--	--	40	--	34.20†	
				13	21	63	46	36	58	92.09	2.60
				39	19	56	39	42	49	86.55	2.45
112	Iowa	C-1	Jons, Jennifer	Pre	21	26	9	18	12	37.09	
				3	19	21	20	24	2	39.70	1.07
				9	17	10	12	18	8	30.20	0.81
				12	22	14	3	10	8	24.79	0.67
				44	20	25	7	34	--	41.28†	

CARBON-FIBER PATIENTS (Chronic Cases), continued

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
122	Brooke	C-1	Dreiling, Thomas	Pre	22	41	18	24	25	54.44	
				3	20	21	10	38	27	53.27	0.98
				6	20	40	21	24	25	54.53	1.00
				18	22	38	41	20	30	62.80	1.15
				30	22	41	44	20	31	47.91	0.88
				53	22	48	26	20	35	61.10	1.12
124	Brooke	C-1	Smetzer, John	Pre	20	22	29	26	21	46.06	
				3	20	31	23	42	21	62.47	1.36
				6	22	55	22	34	44	73.44	1.59
				9	22	54	46	24	53	80.49	1.75
				12	21	59	46	34	52	87.50	1.90
				27	22	60	44	30	51	84.54	1.84
				55	22	61	44	40	49	90.42	1.96
126	Brooke	C-1	Toney, Randy	Pre	21	37	27	34	25	62.93	
				3	21	25	22	36	13	54.08	0.86
				6	21	28	12	38	18	53.64	0.85
				9	22	41	15	38	41	67.48	1.07
				12	20	44	21	26	43	63.30	1.00
				26	21	50	42	26	41	74.11	1.18
				33	20	52	37	38	42	79.95	1.27
				57	--	47	36	--	37	43.26†	
128	Brooke	C-1	Jordan, Darryl	Pre	20	42	21	30	31	61.00	
				3	21	40	42	34	29	71.82	1.18
				6	22	42	42	24	27	65.94	1.08
				12	19	33	13	34	37	58.84	0.96
				37	21	18	13	38	25	53.41	0.88
130	Brooke	C-1	Tolley, Liza	Pre	19	30	19	20	18	45.14	
				3	20	25	23	38	26	59.85	1.32
				6	21	47	16	40	46	72.32	1.60
				9	22	48	15	30	57	70.23	1.56
				12	20	27	6	24	24	43.58	0.96
				24	21	43	30	26	48	69.13	1.53
				48	16	35	11	26	31	50.12	1.11
				60	20	40	23	34	27	62.36	1.38
132	Brooke	C-1	Landry, Andrew	Pre	21	32	6	24	19	43.85	
				3	18	21	16	40	13	51.34	1.17
				6	22	22	20	40	17	56.63	1.29
				9	19	33	17	40	19	58.06	1.32
				26	20	40	22	40	37	69.17	1.58
				45	19	35	15	40	39	64.79	1.48
				62	20	37	37	38	--	60.62†	

CARBON-FIBER PATIENTS (Chronic Cases), continued

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
138	Brooke	C-1	Bassett, Denton	Pre	22	26	16	30	24	43.15	
				3	20	23	22	30	23	52.73	1.22
				6	21	20	15	26	23	46.70	1.08
				34	20	47	26	--	36	47.70†	
				50	22	17	5	24	19	39.20	0.91
139	Brooke	C-1	Mills, Caela	Pre	--	0	0	26	4	17.67†	
				3	18	20	19	42	17	54.99	
				6	20	31	23	42	27	64.57	
				9	20	38	15	30	27	55.74	
				15	21	56	35	34	38	76.88	
				30	22	55	28	40	41	78.77	
				47	22	48	31	34	41	74.14	
142	Brooke	C-1	Putts, William	Pre	22	12	12	26	7	37.77	
				3	18	12	19	30	6	41.15	1.09
				6	21	25	12	22	7	38.85	1.03
				36	22	33	35	32	27	65.09	1.72
				50	19	51	26	20	29	58.57	1.55
144	Brooke	C-1	Corcoran, Robert	Pre	22	38	20	24	26	54.73	
				3	22	--	--	38	--	33.86†	
				6	22	39	16	30	26	57.05	1.04
				12	22	33	32	30	21	60.43	1.10
				47	22	35	34	44	21	70.69	1.29
146	Brooke	C-1	Coad, Kelly	Pre	22	39	38	24	31	64.65	
				3	20	18	23	42	19	57.73	0.89
				6	22	35	18	42	31	65.94	1.02
				9	21	39	23	42	37	71.00	1.10
				12	21	57	44	38	45	86.07	1.33
				34	22	64	46	30	56	88.41	1.37
				47	22	65	46	40	58	95.68	1.48
				55	21	59	44	38	--	70.98†	
149	Brooke	C-1	Walker, Fred	Pre	20	12	0	22	11	30.50	
				3	20	8	10	28	8	36.34	1.19

*C-1, ACL only
C-2, ACL + one or both collateral ligaments

†Incomplete score

CONTROL CASES
Acute Cases

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TREATMENT	TIME (Mos.)	SCCRF Deform.	SCCRF Funct.	SCCRF Sympt.	SCCRF Stab.	SCCRF Pt.Ev.	ORTHO. STATUS	HEALING INDEX
1	LSUMC	A-2	Warren, Monnie	PT	Pre	18	5	2	34	8	34.75	
					26	20	42	26	34	33	66.38	1.91
					67	15	39	28	26	26	56.58	1.63
6	LSUMC	A-1	Kirkman, Greg	Conservative treatment	Pre	22	19	29	40	25	62.42	
					68	20	41	31	42	--	61.75†	
10	LSUMC	A-1	Williams, Marvin	PT	Pre	18	3	2	40	17	41.02	
					12	17	48	47	44	43	85.80	2.09
					27	18	64	33	42	50	86.31	2.10
					44	18	62	46	46	46	92.48	2.25
11	LSUMC	A-1	Jennings, Joe	Conservative treatment	Pre	18	1	0	36	4	32.49	
					12	21	62	44	44	52	93.82	2.89
					24	21	65	38	40	54	90.32	2.78
					42	20	65	42	44	55	94.47	2.91
23	LSUMC	A-2	Roberson, Ralph	PT	Pre	22	3	10	24	2	31.10	
					20	21	62	39	44	47	89.89	2.89
					25	21	51	30	42	43	79.89	2.57
					38	17	54	41	42	47	85.19	2.74
					55	19	64	43	36	47	86.34	2.78
24	LSUMC	A-1	Perkins, Dave	Conservative treatment	Pre	14	0	0	44	2	34.65	
					25	22	59	39	38	44	84.61	2.44
					40	21	47	42	38	39	79.99	2.31
26	LSUMC	A-3	Breakenridge, Robert	PT	Pre	15	0	0	24	2	22.59	
					3	22	27	43	32	20	64.28	2.84
					9	22	50	41	28	45	76.78	3.40
					19	22	59	46	28	46	82.11	3.63
					37	21	63	46	44	49	93.96	4.16
					57	17	62	46	20	52	77.84	3.44
34	LSUMC	A-1	St. Aubyn, Ron	PT	Pre	14	0	0	22	11	24.02	
					3	22	27	20	44	22	62.44	2.60
					6	22	--	--	44	--	37.62†	
					9	22	52	33	44	33	79.73	3.32
					12	22	52	33	44	38	81.48	3.39
					28	22	63	41	38	52	89.52	3.73
					43	21	64	36	44	53	91.30	3.80
					54	19	64	36	42	52	88.78	3.70
49	LSUMC	A-1	Sellers, Roderick	Sutured	Pre	22	0	0	40	2	35.81	
					24	15	55	40	44	40	87.96	2.32
					41	16	50	33	44	45	80.55	2.25

CONTROL PATIENTS (Acute Cases), continued

NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TREATMENT	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Fv.	ORTHO. STATUS	HEALING INDEX
50	LSUMC	A-1	Warren, Angela	PT	Pre	14	0	0	20	2	19.63	
					6	22	28	44	44	34	77.42	3.94
					9	22	52	44	44	46	89.07	4.54
					12	22	59	32	44	48	86.70	4.42
					18	22	60	30	44	49	86.49	4.41
					23	22	57	46	44	41	89.76	4.57
					45	22	55	37	44	48	87.65	4.46
53	LSUMC	A-1	Sloan (Hurt), Betty	Conservative treatment	Pre	19	26	20	44	--	53.07†	
					9	22	60	23	40	47	80.23	
					12	16	56	20	40	45	74.23	
					24	19	61	23	38	55	80.71	
					36	21	65	44	42	58	95.60	
					50	22	65	46	42	--	76.68†	
56	LSUMC	A-1	Koebke, Claus	PT	Pre	22	0	--	8	2	15.78†	
					20	19	49	44	40	43	83.22	
					36	17	54	46	40	41	84.03	
					51	19	59	46	42	45	89.15	
59	LSUMC	A-1	Tillman, Donald	PT	Pre	22	--	--	40	10	38.61†	
					3	17	12	16	44	11	49.89	
					12	22	48	32	36	34	73.39	
					26	21	56	39	40	49	86.22	
					40	21	49	26	34	37	70.42	
64	LSUMC	A-3	Messer, Gerren	Sutured	Pre	--	0	0	26	2	16.97†	
					12	20	37	29	38	24	65.50	
					25	19	51	35	--	41	54.17†	
					37	20	48	34	30	35	69.94	
69	LSUMC	A-2	Bowermeister, Steve	PT	Pre	22	0	0	38	2	34.56	
					8	19	30	21	32	24	55.62	1.61
					12	22	--	--	40	--	35.12†	
					17	22	46	40	40	28	76.67	2.22
					34	21	39	16	40	29	63.90	1.85
72	LSUMC	A-1	Crooks, Douglas	PT	Pre	22	0	0	40	2	35.81	
					10	21	61	46	46	50	94.94	2.65
					20	22	62	38	26	55	81.44	2.27
					34	22	65	46	36	56	92.47	2.58
94	Iowa	A-2	Davis, Brian	Sutured	Pre	18	0	0	28	3	26.82	
					3	20	14	17	38	12	48.92	1.82
					6	22	46	23	38	42	72.88	2.72
					8	22	46	23	36	42	71.63	2.67
					11	22	59	38	36	50	85.02	3.17

CONTROL PATIENTS (Acute Cases), continued

NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TREATMENT	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Fv.	ORTHO. STATUS	HEALING INDEX
96	Iowa	A-1	Oliver, Robert	Semitendinosis	Pre	22	0	0	32	2	30.81	
					4	18	22	14	40	21	53.57	1.74
					6	18	33	20	38	28	60.81	1.97
					9	22	44	46	40	32	80.07	2.60
					12	22	61	46	42	45	91.15	2.96
					46	--	55	38	38	42	72.16†	
99	Iowa	A-1	Booker, Scott	Sutured	Pre	18	6	0	36	11	36.48	
					3	22	31	23	44	20	64.29	1.76
					6	22	48	23	44	39	76.21	2.09
					9	22	49	23	44	41	77.22	2.12
					12	22	61	46	44	50	94.14	2.58
102	Iowa	A-1	Kimber, Lloyd	Semitendinosis	Pre	12	0	0	36	4	29.43	
					3	16	9	17	40	14	47.48	1.61
					6	20	19	21	42	14	55.42	1.88
					9	20	53	23	44	44	78.59	2.67
					12	21	57	46	44	52	93.14	3.16
					20	17	--	42	42	28	62.20†	
106	Iowa	A-1	Dierks, Steven	Semitendinosis	Pre	18	20	11	24	15	39.53	
					3	20	19	20	38	18	53.88	1.36
					6	22	--	--	30	21	36.18†	
					9	18	11	23	40	15	51.99	1.32
					15	21	55	44	38	39	83.35	2.11
					50	19	47	41	28	36	71.33	1.80
107	Iowa	A-1	Troia, Tom	Semitendinosis	Pre	20	3	0	26	8	29.16	
					3	20	16	22	42	8	52.83	1.81
					6	22	37	46	40	34	78.59	2.70
					9	22	52	46	40	53	89.89	3.08
					15	22	59	46	40	53	92.06	3.16
					24	22	59	46	40	56	93.11	3.19
135	Brooke	A-1	Lewis (Horace), Clory	PT	Pre	22	2	7	30	14	37.42	
					3	22	19	19	44	26	60.91	1.63
					6	--	28	20	30	40	50.19	1.34
					9	22	30	37	32	35	67.82	1.81
					16	21	48	42	34	40	78.14	2.09
					46	20	51	39	26	30	68.81	1.84
					58	21	54	39	30	41	76.54	2.04
143	Brooke	A-1	Thomas, Solomon	PT	Pre	--	0	0	32	2	20.73†	
					3	17	14	20	44	20	55.40	
					6	21	26	19	40	26	60.12	
					9	21	40	20	40	28	65.61	
					13	21	45	38	40	35	77.47	
					33	16	32	16	44	20	58.80	

†Incomplete score

CARBON-FIBER CASES
Acute Cases

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Fv.	ORTHO. STATUS	HEALING INDEX
3	LSUMC	A-2	Hightower, Richard	Pre	20	10	0	32	2	33.00	
				9	22	49	44	38	46	84.38	2.56
				12	22	61	44	44	51	93.62	2.84
				33	22	65	46	44	55	97.13	2.94
				46	22	63	46	42	54	94.91	2.88
				60	22	65	46	38	56	93.72	2.84
5	LSUMC	A-2	Wittenburg, Steven	Pre	11	0	0	24	2	20.76	
				9	22	57	46	40	45	88.65	4.27
				12	22	65	46	44	50	95.39	4.59
				26	21	65	44	38	53	91.35	4.40
				42	19	65	46	40	57	93.95	4.52
				58	17	65	44	38	56	90.56	4.36
8	LSUMC	A-2	Garner, James	Pre	13	0	0	30	2	25.43	
				9	22	54	39	42	47	86.61	3.40
				12	22	64	46	44	55	96.82	3.81
				31	22	53	38	38	40	80.91	3.18
				42	21	50	34	34	40	75.27	2.96
				55	17	59	33	28	45	73.79	2.90
9	LSUMC	A-3	Jackson, Archie	Pre	20	0	2	0	2	10.73	
				24	20	62	44	38	48	88.21	8.22
				43	17	59	44	38	44	84.51	7.88
				60	20	58	41	44	45	88.36	8.23
13	LSUMC	A-1	Taylor, Dan	Pre	20	5	0	24	11	29.58	
				3	--	--	--	44	--	27.54†	
				9	22	63	46	44	51	95.11	3.22
				12	22	65	46	44	56	97.48	3.30
				33	22	65	46	44	56	97.48	3.30
				42	--	64	46	40	54	83.89†	
				66	22	65	46	40	56	94.98	3.21
19	LSUMC	A-2	Toney, Lawrence	Pre	21	9	19	24	8	38.54	
				6	22	20	27	44	11	59.48	1.54
				29	21	33	28	40	30	67.63	1.75
				42	19	37	28	40	26	66.56	1.73
				62	17	42	15	44	37	67.86	1.76
21	LSUMC	A-1	Pease, Randall	Pre	22	10	17	38	14	49.29	
				3	22	35	23	40	30	66.52	1.35
				6	22	52	44	40	43	85.52	1.74
				12	21	53	35	40	49	83.54	1.69
				24	21	59	21	40	49	79.28	1.61
				45	20	63	44	42	54	93.12	1.89
				60	21	63	46	44	50	94.31	1.91

CARBON-FIBER PATIENTS (Acute Cases), continued

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
45	LSUMC	A-1	Collins, Jimmy	Pre	19	7	19	42	2	46.17	
				3	18	--	--	44	--	35.79†	
				12	19	64	46	44	45	91.96	1.99
				25	22	65	41	40	55	92.44	2.00
				41	19	64	42	42	55	92.45	2.00
51	LSUMC	A-2	Bultynck, James	Pre	20	0	0	24	7	26.63	
				14	17	30	20	40	27	60.32	2.26
				49	--	--	--	--	36	12.56†	
				51	22	44	39	32	--	60.84†	
52	LSUMC	A-1	Brown, Gary	Pre	19	0	0	36	3	32.28	
				14	21	62	46	32	55	88.23	2.73
				24	20	64	46	44	56	96.25	2.98
				39	22	62	46	40	56	94.04	2.91
54	LSUMC	A-2	Bradberry, Wilson	Pre	10	0	0	26	2	21.55	
				18	21	61	46	40	50	91.18	4.23
				32	16	64	46	44	52	93.03	4.32
				44	15	65	46	36	56	89.27	4.14
63	LSUMC	A-1	Melton, Roderick	Pre	16	0	0	34	2	29.31	
				6	22	56	22	44	40	78.61	2.68
				12	22	64	46	44	52	95.77	3.27
				27	22	65	46	44	58	98.18	3.35
				39	22	65	46	44	58	98.18	3.35
65	LSUMC	A-2	Wyatt, Mark	Pre	--	0	0	32	2	20.73†	
				7	16	58	39	34	46	79.75	
				18	22	61	43	44	46	91.44	
				31	21	51	27	40	36	74.88	
				42	21	--	--	44	41	51.47†	
70	LSUMC	A-1	Mitchell, David	Pre	22	0	0	34	6	33.45	
				16	21	55	46	18	48	74.84	2.24
				37	21	52	42	36	46	82.73	2.47
75	LSUMC	A-1	Williams, Christian	Pre	22	0	0	36	2	33.31	
				3	20	22	20	44	16	57.87	1.74
				6	22	28	21	44	17	61.44	1.84
				12	22	50	46	44	33	84.79	2.54
84	Iowa	A-2	Briggs, Cynthia	Pre	20	0	0	28	2	27.39	
				3	19	18	9	44	15	51.01	1.86
				6	20	36	21	44	24	65.45	2.39
				9	22	--	--	32	--	30.11†	
				14	21	54	38	38	40	80.77	2.95
				32	18	56	44	38	46	84.73	3.09
				54	18	56	37	38	47	82.02	2.99

CARBON-FIBER PATIENTS (Acute Cases), continued

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Fv.	ORTHO. STATUS	HEALING INDEX
87	Iowa	A-1	Christison, Marlene	Pre	22	0	0	26	2	27.05	
				3	18	12	6	44	11	45.98	1.70
				6	20	42	23	44	34	71.68	2.65
				9	20	52	23	44	41	77.24	2.86
				12	22	27	20	30	14	50.88	1.88
				24	20	57	44	40	54	90.00	3.33
				35	22	61	46	36	52	89.83	3.32
104	Iowa	A-1	Krueger, Holly	Pre	22	7	31	36	9	51.48	
				3	19	11	23	40	15	52.45	1.02
				6	19	27	23	32	11	51.02	0.99
				9	20	35	46	40	24	73.56	1.43
				12	17	51	46	38	45	83.24	1.62
				24	17	64	48	40	45	89.41	1.74
				52	--	62	46	30	--	58.16†	
108	Iowa	A-1	Schlicher, Corey	Pre	20	0	0	22	34	34.80	
				3	20	43	18	34	44	67.04	1.93
				6	22	43	23	38	46	73.34	2.11
				9	21	51	23	26	45	67.51	1.94
				12	21	59	46	24	53	81.59	2.34
				38	21	63	46	44	57	96.75	2.78
111	Iowa	A-2	Sekafetz, Robin	Pre	22	0	0	36	2	33.31	
				3	20	6	23	44	10	52.11	1.56
				12	21	57	44	42	45	88.57	2.66
				30	20	61	37	38	45	83.79	2.52
114	Iowa	A-1	Ellis, Bill	Pre	19	0	0	36	2	31.94	
				3	20	6	20	40	11	48.64	1.52
				12	20	58	46	36	44	85.19	2.67
				34	20	58	44	16	51	74.24	2.32
115	Iowa	A-1	Wanckett, Anthony	Pre	22	0	0	18	2	22.04	
				3	22	25	22	38	20	58.23	2.64
				6	20	33	22	34	28	60.09	2.73
				12	22	45	21	40	31	69.11	3.14
				26	20	52	42	44	34	83.10	3.77
				45	16	57	42	34	43	79.70	3.62
116	Iowa	A-1	Ravenscroft, Robert	Pre	20	0	0	26	--	25.44†	
				3	18	2	8	40	7	39.84	
117	Iowa	A-1	Sennott, Timothy	Pre	14	0	0	24	2	22.13	
				3	22	23	23	42	17	59.50	2.69
				6	22	50	46	32	43	80.77	3.65
				8	22	59	46	40	53	92.06	4.16
				12	22	63	46	40	53	93.31	4.22
				24	22	59	46	42	53	93.32	4.22
				46	22	59	40	44	43	88.46	4.00

CARBON-FIBER PATIENTS (Acute Cases), continued

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
118	Iowa	A-2	Murphy, David	Pre	14	0	0	34	2	28.39	
				3	22	8	23	28	8	42.94	1.51
				6	22	42	44	28	46	75.95	2.68
				9	19	55	46	40	46	87.00	3.06
				15	15	55	42	34	53	82.11	2.89
				37	21	57	42	36	53	86.73	3.05
121	Iowa	A-1	Green, Steve	Pre	22	0	0	30	2	29.55	
				3	17	2	3	42	8	38.80	1.31
				6	22	24	46	42	38	77.20	2.61
				9	22	--	--	38	46	49.92†	
				11	22	56	46	38	52	89.53	3.03
				36	21	63	46	40	56	93.90	3.18
136	Brooke	A-3	Clough, Sam	Pre	22	59	37	24	7	62.06	
				3	--	14	20	--	7	15.54†	
				9	19	25	21	34	7	49.38	0.80
				12	21	28	19	36	7	51.61	0.83
				44	22	58	44	44	28	84.66	1.36
137	Brooke	A-1	Robbins, Kenneth	Pre	16	17	0	30	25	40.12	
				3	--	28	21	--	19	24.52†	
				6	21	29	19	40	19	58.61	1.46
				9	22	51	40	38	42	81.86	2.04
				45	20	62	46	42	50	92.20	2.30
140	Brooke	A-1	Leeper, Dale	Pre	--	0	0	24	15	20.26†	
				3	19	20	23	40	32	61.18	
				9	22	36	15	28	42	60.01	
				40	22	59	46	30	44	82.66	
				54	21	51	38	30	41	75.17	
147	Brooke	A-1	Hubbard, Rodney	Pre	18	7	0	26	16	32.28	
				3	21	27	14	40	21	56.50	1.75
				9	20	40	22	40	41	70.56	2.18
				46	22	65	46	40	55	94.63	2.93
151	Brooke	A-1	Edwards, Pilly	Pre	22	8	0	28	16	35.68	
				3	21	32	22	36	25	60.44	1.69
				6	21	43	23	38	36	69.39	1.94
				9	20	57	46	38	45	86.48	2.42
				30	22	65	46	38	56	93.72	2.63
				46	19	65	46	34	56	89.85	2.52

* A-1, ACL only
A-2, ACL + one or both collateral ligaments
A-3, ACL + PCL

†Incomplete score

NON-RANDOMIZED GROUP
Chronic Cases

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHC. STATUS	HEALING INDEX
27	ISUMC	C-3	Plemmons, Debra	Pre	18	8	8	44	9	44.91	
				6	22	32	22	44	24	65.56	1.46
				9	22	32	22	40	26	63.76	1.42
				22	19	42	36	40	31	73.36	1.63
				41	15	35	29	38	36	66.78	1.49
				53	17	39	30	12	33	52.05	1.16
				64	18	44	39	40	32	75.18	1.67
38	ISUMC	C-3	Packard, James	Pre	22	19	9	22	12	37.88	
				6	--	21	27	--	21	25.66†	
				23	10	9	8	18	14	27.03	0.71
60	ISUMC	C-3	Boobar, Mark	Pre	22	31	14	26	19	48.74	
				14	21	29	16	26	22	49.58	1.02
				26	17	56	44	--	43	59.44†	
				40	17	46	42	8	39	59.06	1.21

†Incomplete score

NON-RANDOMIZED GROUP
Acute Cases

PT. NO.	SERIES	*EXTENT OF INJURY	PATIENT NAME	TIME (Mos.)	SCORE Deform.	Funct.	Sympt.	Stab.	Pt.Ev.	ORTHO. STATUS	HEALING INDEX
30	LSUMC	A-3	Herold, James	Pre	17	0	0	26	2	24.76	
				6	22	35	40	38	25	70.95	2.86
				9	22	45	32	38	25	70.57	2.85
				21	22	59	46	40	50	91.02	3.68
				40	22	61	44	44	51	93.62	3.78
				59	--	61	45	36	--	61.17†	
33	ISUMC	A-3	Burns, Jimmy	Pre	4	0	0	0	2	2.53	
				6	22	24	14	44	25	59.93	23.69
				16	21	26	18	40	26	59.68	23.59
				23	17	21	20	38	17	52.78	20.86
				35	16	35	30	44	26	67.94	26.85
				46	17	42	23	36	33	64.95	25.67
46	LSUMC	A-3	Harris, Flora	Pre	13	0	0	14	2	15.42	
				3	10	13	15	--	18	21.46†	
				6	21	29	15	44	29	62.86	4.08
				9	20	46	20	40	41	71.56	4.64
				12	19	40	22	40	40	69.76	4.52
				19	21	35	20	42	24	63.91	4.14
				30	18	16	14	38	15	48.36	3.14
				42	16	28	15	36	23	53.15	3.45
48	ISUMC	A-3	Pittman, Maurice	Pre	12	0	0	0	2	6.19	
				6	22	53	23	20	50	66.58	10.76
				9	22	62	46	40	51	92.30	14.91
				12	22	61	46	20	52	79.82	12.89
				17	22	49	22	40	39	73.58	11.89
				24	22	65	46	42	53	95.18	15.38
				38	21	60	44	14	54	75.12	12.14
71	ISUMC	A-3	Jones, Emma	Pre	22	0	0	0	2	10.77	
				7	15	--	--	38	--	30.66†	
				9	--	18	18	--	14	18.35†	
				16	17	30	18	42	26	60.35	5.60
				29	15	32	14	--	34	34.81†	
82	ISUMC	A-3	Jessie, William	Pre	--	0	0	--	--	0.00†	
				18	20	55	38	40	32	79.08	
				31	20	58	34	40	32	78.26	
83	ISUMC	A-3	Walker, Maurice	Pre	12	0	0	0	2	6.19	
				44	15	55	43	26	37	71.96	11.62

†Incomplete score

RANDOMIZED STUDY

Average Pre-op Scores

CHRONIC CATEGORY

	CARBON	NO. OF PTS.	CONTROL	NO. OF PTS.
Deformity	21.17 ± 1.25	42/43	20.03 ± 2.54	34/36
Function	25.28 ± 15.76	43/43	26.61 ± 14.62	36/36
Symptoms	16.49 ± 12.15	43/43	15.89 ± 10.71	36/36
Stability	27.53 ± 6.48	43/43	28.00 ± 6.01	32/36
Patient Evaluation	19.02 ± 11.36	43/43	17.14 ± 9.78	36/36
Orthopaedic Status	48.78 ± 15.01	42/43	49.38 ± 12.66	31/36

ACUTE CATEGORY

	CARBON	NO. OF PTS.	CONTROL	NO. OF PTS.
Deformity	18.96 ± 3.54	29/31	18.82 ± 3.29	22/24
Function	4.48 ± 11.05	31/31	3.83 ± 7.36	23/24
Symptoms	4.03 ± 9.73	31/31	3.68 ± 7.62	22/24
Stability	28.52 ± 7.76	31/31	31.83 ± 8.84	24/24
Patient Evaluation	6.83 ± 7.86	30/31	6.61 ± 6.34	23/24
Orthopaedic Status	32.44 ± 10.45	28/31	33.60 ± 9.02	19/24

RANDOMIZED STUDY

Average Post-op Scores (≥24 mos.)

CHRONIC CATEGORY

	CARBON	NO. OF PTS.	NO. OF FOLLOW-UPS	CONTROL	NO. OF PTS.	NO. OF FOLLOW-UPS
Deformity	20.60 ± 2.60	41/43	78	19.62 ± 2.17	33/36	56
Function	47.30 ± 13.94	42/43	80	52.53 ± 12.40	33/36	55
Symptoms	33.48 ± 12.52	42/43	80	38.16 ± 9.80	33/36	56
Stability	35.92 ± 7.51	41/43	77	37.82 ± 5.39	32/36	55
Patient Evaluation	37.96 ± 12.17	41/43	76	43.04 ± 11.46	31/36	50
Orthopaedic Status	74.64 ± 16.17	39/43	72	80.28 ± 14.11	30/36	50
Healing Index	1.60 ± 0.57	39/43	70	1.74 ± 0.76	27/36	44

ACUTE CATEGORY

	CARBON	NO. OF PTS.	NO. OF FOLLOW-UPS	CONTROL	NO. OF PTS.	NO. OF FOLLOW-UPS
Deformity	20.23 ± 1.94	29/31	53	19.58 ± 2.08	20/24	36
Function	59.09 ± 7.27	29/31	54	55.11 ± 8.86	21/24	37
Symptoms	41.76 ± 6.84	29/31	54	37.14 ± 8.04	21/24	37
Stability	38.87 ± 5.22	29/31	55	38.33 ± 6.19	21/24	36
Patient Evaluation	48.50 ± 8.26	29/31	54	44.17 ± 9.29	20/24	35
Orthopaedic Status	87.34 ± 8.44	26/31	51	81.70 ± 10.64	19/24	33
Healing Index	3.24 ± 1.50	26/31	48	2.70 ± 0.79	14/24	25

RANDOMIZED STUDY

Average Follow-up Times (≥24 mos.)

CHRONIC CATEGORY

	CARBON	CONTROL
Deformity	40.95 ± 12.17	41.75 ± 12.24
Function	40.96 ± 12.27	41.49 ± 12.20
Symptoms	40.96 ± 12.27	41.75 ± 12.24
Stability	41.04 ± 12.22	41.34 ± 11.97
Patient Evaluation	40.18 ± 12.15	40.58 ± 11.61

ACUTE CATEGORY

	CARBON	CONTROL
Deformity	39.68 ± 11.46	39.28 ± 12.56
Function	39.91 ± 11.47	39.46 ± 12.43
Symptoms	39.91 ± 11.47	39.46 ± 12.43
Stability	39.94 ± 11.37	39.86 ± 12.36
Patient Evaluation	39.68 ± 11.32	38.34 ± 11.62

NON-RANDOMIZED GROUP

Average Pre-op Scores

	CHRONIC	NO. OF PTS.	ACUTE	NO. OF PTS.
Deformity	20.67 ± 2.31	3/3	13.33 ± 5.99	6/7
Function	19.33 ± 11.50	3/3	0.00 ± 0.00	7/7
Symptoms	10.33 ± 3.21	3/3	0.00 ± 0.00	7/7
Stability	30.67 ± 11.72	3/3	6.67 ± 11.00	6/7
Patient Evaluation	13.33 ± 5.13	3/3	2.00 ± 0.00	6/7
Orthopaedic Status	43.84 ± 5.51	3/3	10.98 ± 8.09	6/7

Average Post-op Scores (≥24 mos.)

	CHRONIC	NO. OF PTS.	NO. OF FOLLOW-UPS	ACUTE	NO. OF PTS.	NO. OF FOLLOW-UPS
Deformity	16.50 ± 1.00	2/3	4	18.20 ± 2.82	7/7	10
Function	44.00 ± 7.97	2/3	5	46.64 ± 16.69	7/7	11
Symptoms	36.80 ± 6.91	2/3	5	32.00 ± 13.42	7/7	11
Stability	19.33 ± 16.29	2/3	3	35.56 ± 9.79	6/7	9
Patient Evaluation	36.60 ± 4.50	2/3	5	35.80 ± 13.24	7/7	10
Orthopaedic Status	63.27 ± 9.96	2/3	4	72.06 ± 15.94	5/7	9
Healing Index	1.38 ± 0.24	2/3	4	12.75 ± 9.51	5/7	8

Average Follow-up Times (>24 mos.)

	CHRONIC	ACUTE
Deformity	40.00 ± 11.04	35.90 ± 7.26
Function	44.80 ± 14.38	38.00 ± 9.80
Symptoms	44.80 ± 14.38	38.00 ± 9.80
Stability	44.67 ± 7.23	36.67 ± 7.26
Patient Evaluation	44.80 ± 14.38	35.90 ± 7.26

LSUMC

				COMPLICATIONS/ADVERSE REACTIONS								
NAME	CATEGORY & CLASS	CP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Hightower, R.	A-2, CF	4/15/83	Keating	Delayed healing	4/16/83	1 wk.		2	1	5	Mild drainage from wound for 3-4 days post-op., but now healing
Gloer, M.	C-1, CF	4/11/83	Keating	Intermittent pain and instability	6/83	2 mos.					Arthroscopy, debridement of lateral meniscal tear. Found Grade I chondromalacia. Cleared 2 weeks later.
Cooper, B.	C-2, CF	7/11/83	Keating	Infection	noted 2/14/85						No details given.
Winkler, S.	C-1, CF	7/21/83	Waddell	Pain				2			1/18/89: Treatment: Aspirin, work with more care, less exertion and sometimes wrap with Ace bandage.
Larson, I.	C-1, CF	7/6/83	Waddell		noted 10/7/83						30 cc straw colored fluid aspirated from knee. No sign of infection.

ISUMC

				COMPLICATIONS/ADVERSE REACTIONS							
NAME	CATEGORY & CLASS	CP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Toney, I.	A-2, CF	7/29/83	Keating	Adhesions in supra-patellar pouch	noted 10/26/83			3		1	Diagnostic arthroscopy with lysis of adhesions (probably due to having polio as a child) -- CFs not involved.
Jenkins, L.	C-1, CF	9/22/83	Keating	Pain	1985 (noted 2/15/88)			2			Treated at least 3 years with Motrin 600 mg. No induration or edema.
Pease, R.	A-1, CF	9/21/83	Keating	Swelling, stiffness	6/88			2			ROM from 20-90°. Knee appears stable. 1/3 effusion. No evidence of infection. Appears to have synovitis. Treated with anti-inflammatories.
Packard, J. (NR)	C-3, CF	1/29/84	Keating	Osteomyelitis left proximal tibia	1/85	2 mos.	2	2	1	5	Treated with Keflex orally for 10 days for "bone infection"; no sequelae.

LSUMC

				COMPLICATIONS/ADVERSE REACTIONS								
NAME	CATEGORY & CLASS	CP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Packard, J. (NR)	C-3, CF	1/29/84	Keating	Degenerative arthritis left knee, moderate ACL & MCL instability							Arthroscopy, arthrotomy 1/27/88
Harris, F. (NR)	A-3, CF	5/5/84	Keating	Tenderness due to neuromas (mild to moderate) at light touch							Non-steroidal anti-inflammatory drugs for pain. Patient also had apparent osteochondral fracture of femur.

BAMC

COMPLICATIONS/ADVERSE REACTIONS

NAME	CATEGORY & CLASS	OP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Toney, R.	C-1, CF	8/25/83	Markey	Popping (one episode)	11/17/83			1			Patient heard "pop" while descending stairs. No effusion or tenderness.
Barfield, J	C-1, Con	9/22/83	Markey	Soreness, stiffness, articular (?) phenomenon	12/84						Re-operated 12/7/84 for debridement patella lateral (?) retinacular (?) release.
Tolley, I.	C-1, CF	9/29/83	Markey	Knee pops out 2-3 times a week							+ Lachmann; +pivot; - pain; - effusion; + (?). No synovitis.
Duke, C.	C-1, Con	10/12/83	Markey	Pain (mild continual, occasionally sharp)							Can't straighten leg. No explanation tion or comments.

BAMC				COMPLICATIONS/ADVERSE REACTIONS							
NAME	CATEGORY & CLASS	OP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Landry, A.	C-1, CF	10/13/83	Markey	Mild synovitis	noted 1/26/84						Valgus stress to knee with suture "pop" probable. Iliotibial tract (?) and first-degree MCL sprain with partial peroneal palsy.
					4/18/84						Still has palsy, but knee stable.
Bassett, D.	C-1, CF	11/17/83	Markey	Re-injury	5/86 (approx)						Subsequent pain and instability, not relieved with brace. Reoperated, CF removed 7/20/88.
Clough, S.	A-3, CF	11/7/83	Markey	Bollard removal	10/15/84						Well-healed; no inflammation. Prominent bollards require removal. Very tender at bollard of PCI (medial) femoral condyle.

BAMC

COMPLICATIONS/ADVERSE REACTIONS

NAME	CATEGORY & CLASS	OP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Leeper, D.	A-1, CF	12/12/83	Markey	Re-injury	noted 7/84						Person stomped on back of knee; buckled & swelled for 3 days.
				Giving way	noted 8/84						Running with brace, turned corner to right, knee gave way.
Walker, F.	C-1, CF	4/5/84	Markey	Meniscal repair	noted 6/25/84						Healed; mild warmth with bogginess to synovium. Pain all the time. Meniscal repair -- but (?)
Byrd, J.	C-1, Con	2/13/84	Markey	Contracture	11/7/84						Poor motion. 25° flexion contracture. Casted to release contracture.
					2/15/85						Casted for one month during Nov.-Dec. 13. 20° flexion contracture.
Butts, W.	C-1, CF	1/1/84	Markey	Inflammation	soon after surgery	3-4 days	1	1	1	1	Noted 2/3/87

Iowa

				COMPLICATIONS/ADVERSE REACTIONS							
NAME	CATEGORY & CLASS	CP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Grenon, G.	C-2, CF	10/4/83	John Albright	Pain, Inflammation			3	2,3	3	2	Severe medial and lateral chondromalacia with large lateral flap.
Edwards, T.	C-2, Con	8/22/84	John Albright	Injury	10/84	1.5 mos.	2	2	3	1	Patient fell while fishing 5-6 weeks ago, causing knee to go into further flexion. It is felt that this has helped to loosen up the ACL & medial capsule. Put into knee immobilizer.
				Delayed healing	10/84	4.5 mos.	2	2	3	1	Knee has continued to loosen. Put in LLC at 40° flexion for next 4-6 wks.
				Mild ant-anterior medial joint line pain	Noted 9/8/86			2	3	1	PLRI. Physical therapy for gastrocnemius strengthening, Iowa knee brace

Iowa

NAME	CATEGORY & CLASS	OP. DATE	SURGEON	COMPLICATIONS/ADVERSE REACTIONS: TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Schlicher, C.	A-1, CF	10/30/84	John Albright	Increased laxity	Noted 2/7/85		2	2	3	3	Pt. has begun to stretch out his rx(?). This is believed to be caused by (1) the carbon fibers becoming mechanically inactive and (2) because patient has not been using his crutches and using quadriceps more than advisable. Will be put in immobilizer to see if it tightens up.
				Increased laxity	Noted 2/7/85	3 mos.	2	2	3	3	Further increase in laxity from 2/7/85. ROM: 0-135°. Anterior drawer: 7-8 mm, L>R; Lachman's: 6-7 mm, L>R. Desire is to put pt. back into a cast but pt. is against this.

Iowa

				COMPLICATIONS/ADVERSE REACTIONS								
NAME	CATEGORY & CLASS	OP. DATE	SURGEON	TYPE	DATE OF OFSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Sanderson, J.	C-1, Con	12/13/83	John Albright	Inflammation	6/1/84	1 wk.	2	1	3	1	Has sense of median parapatellar "pinching." Very rigorous activity school. Diagnosis: Mild overuse syndrome.
Sanderson, J.	C-1, Con	12/13/83	John Albright	Increased laxity	Noted 1/10/85			2	3	3	1 yr. assessment - Doing well functionally and stability-wise. Has developed very mild pivot recently.
Kimber, I.	A-1, Con	4/6/84	John Albright	Pain	Noted 10/18/84		1	1	2	1	Skin scar appears to be adhesed to the deep fascial layers where semitendinosis has been adhered. Adhesion of skin to hamstring tendons. Mild.

COMPLICATIONS/ADVERSE REACTIONS

NAME	CATEGORY & CLASS	OP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Kimber, I.	A-1, Con	4/6/84	John Albright	Adhesion	12/10/84	2 mos.	2	3	3	1	Well healed - there is scar adhesion to the hamstrings on the posteromedial aspect that will be removed this Fri. Also "see note on exam of surgical site" (unavail.)
					1/15/87		Mild	3	3	1	Post-capsular retinacular flexion contracture. Problem was and still is ankylosis, not laxity.
Briggs, C.	A-2, CF	5/15/83	John Albright	Skin flap necrosis	5/17/83	8 wks.	1	1	1	1	Medial skin flap necrosis (superficial-epidermal). Negative cultures. Straight incision, probably 7° to staples. Knee OK.
				Skin slough	5/17/83	6 mos.	1	1	1	1	Tiny area granulation left - wound healing well (still pink scar). No effusion; no tenderness.

Iowa

				COMPLICATIONS/ADVERSE REACTIONS							
NAME	CATEGORY & CLASS	CP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Hill, J.	C-1, CF	5/16/83	John Albright	Cast neuro-praxia	5/18/84	5 days	?	1	1	1	Post-op mild cast neuropraxis. 4 day relayed casting. Relayed (neuro-pathy?) 4 days post-op. Resolved.
				Decreased sensation	5/18/84	9 mos.	1	1	3	1	Still wearing Iowa brace, still experiencing neuropraxia (small area).
Burriola, M.	C-2, Con	7/18/83	John Albright	?	7/21/83	5 days	1	2	1	1	None.
Burriola, M.	C-2, Con	7/18/83	John Albright	Auto accident	10/23/83		1	1	2	1	Development of posterolateral rot-atory instability and reverse pivot after auto accident (dashboard to tibia with posterolateral pain at 4 mos. post-op). +/- brace foot plate in 15° extension rot. - Has been noncom-pliant about knee brace.

Iowa

				COMPLICATIONS/ADVERSE REACTIONS								
NAME	CATEGORY & CLASS	OP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Burriola, M.	C-2, Con	7/18/83	John Albright	Episode of instability (reverse pivot) with pain, laxity	2/28/84	2 mos.	2	2	3	1	PIRI with reverse pivot. Has pain. 2° chondromalacia.

Others

COMPLICATIONS/ADVERSE REACTIONS

NAME	CATEGORY & CLASS	CP. DATE	SURGEON	TYPE	DATE OF ONSET	DURATION	MAXIMUM SEVERITY (since last report)	TREATMENT 1=None 2=Medical treatment 3=Surgical treatment	OUTCOME 1=Recovered 2=Residual effects 3=Currently under treatment	RELATED TO CF IMPLANT? 1=No 2=Possibly 3=Probably 4=Definitely 5=Unknown	COMMENTS
Boobar, M. (ISU) (NR)	C-3, CF		Keating	Pain, tenderness of medial condyle of femur							Toggle removed in office.
Singletary, A. (Iowa)	C-1, CF	1/14/85	John Albright	Moderate patello-femoral pain							Moderate pain has delayed rehabilitation.
Murphy, D. (Iowa)	A-2, CF	10/13/85	John Albright	Increased laxity	4/3/86	2 mos.	Mild	2	1		Increased translation anteriorly - reduced activity and use immobilizer at night.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

NOV 2 1 1990

3X

Andrew A. Marino, Ph.D.
President
Plastafil, Inc.
P.O. Box 268
Belcher, Louisiana 71004

Re: IDE NUMBER G820122/S13
Plastafil CFS™ Carbon Fiber System
Dated: October 12, 1990
Received: October 23, 1990

Dear Dr. Marino:

The Food and Drug Administration (FDA) has reviewed the sections in your PMA application which you refer to for the fulfillment of the requirement to submit an annual progress report to your investigational device exemptions (IDE) application and has determined that additional information is required. Please address the following concerns:

1. It appears from the study design reported in the PMA that several changes and deviations from the original protocol occurred in violation of 21 CFR Part 812.35(a). Proper compliance to the investigational plan is the responsibility of the sponsor as described in Part 812.46. For instance, there is no explanation why you include an open phase with no control patients when there was no provision for such a trial in the original design and also there is no explanation why the randomization scheme was changed to result in a 3:2 ratio of device treated to controls instead of 1:1 ratio. In addition, implants were used in nine patients which had injuries only to the posterior cruciate ligament which was not one of the subgroups approved for this study.

2. Additional information is needed on the complications reported. The incidence of synovitis, extra-articular infections, intra and extra-articular failures, graft laxity, septic arthritis, and presence of carbon particles are not reported. Although you state that these occurred at low levels, the variability in the frequency of follow-up visits among patients may have made it impossible to detect the actual incidence of complications.

3. Patient accountability is extremely poor. It is not possible to identifiy all patients entered in the study who remained through its completion. A flow chart showing all patient groups from the initiation of study through its termination would clarify this. All withdrawals, losses, formation of new sub-groups should be clearly indicated in the chart.

4. Patient follow-up information is incomplete and confusing as reported. The "random-sampling model" suggested is not acceptable. Information for each parameter measured should be presented in life tables to include data for each time point as specified in the study protocol (that is, 0, 3, 6, 9, 12, and 24 months) plus any length of time beyond 2 years. The intervals should be selected in such a way that each patient is represented once in each interval. The following information should be included in such a table:

    a. patients in each category;

    b. patients lost to follow-up;

    c. patients due for follow-up visit;

    d. complications;

    e. withdrawals;

    f. deaths; and

    g. missing data.

A patient is considered lost to follow-up beginning at the time when he/she first missed a visit and the patient did not later have an evaluation after that time period.

Since the IDE regulation does not specify the information to be submitted in the annual progress report, we are enclosing the guidance document entitled "Suggested Format for IDE Progress Report" which highlights the type of information to be included.

This information must be submitted to FDA within 30 days from the date of this letter. It should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

If you do not provide this information within 30 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

If you have any questions, please contact Michael J. Blackwell, D.V.M., M.P.H., at (301) 427-1036 or Ms. Nancy F. Teague at (301) 427-1190.

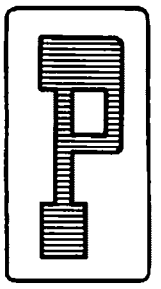
Sincerely yours,

for Carl A. Larson, Ph.D.
Director, Division of Surgical
and Rehabilitation Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

PLASTAFIL, INC.

P. O. Box 268
Belcher, Louisiana 71004



ANDREW A. MARINO, PH. D.
PRESIDENT

February 21, 1991

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

RE: IDE NUMBER G820122/S13
Plastafil CFS™ Carbon Fiber System

Dear Sirs,

This letter and its appendices are in response to FDA's letter dated November 21, 1990. My delay in response was occasioned by the need for me to reply to FDA's letter dated June 22, 1990 requesting further information regarding Plastafil's Pre-market Approval application (PMA). I have responded to FDA's letter dated June 22, 1990, and a copy of that response together with its enclosures are included with this letter. Below, I provide specific replies to each of the points raised in FDA's letter dated November 21, 1990; where the points raised were identical to those raised in FDA's previous letter, I have provided the same response here that I did previously.

In what follows, "I" refers to both Plastafil, which is the sponsor of the CFS™ Carbon Fiber System, and to me personally. "PMA" refers to Plastafil's Pre-Market Approval application listed above. "IDE" refers to Plastafil's investigational device exemption #G820122/S13. "Device" refers to either the portion of the CFS™ Carbon Fiber System consisting of the carbon-fiber implant itself, or to the carbon-fiber implant together with the fixation devices, whichever is appropriate in the circumstances in which the term is used. "Cases" refers to patients who received the Device; "Controls" refers to patients who received standard therapy. "Guidance Document" refers to Guidance Document for the Preparation of Investigational Device Exemptions and Pre-Market Approval Applications for Intra-Articular Prosthetic Knee Ligament Devices, Division of Surgical and Rehabilitation Devices, Center for Devices and Radiological Health, USFDA, 1987.

In each instance, FDA's comment is reproduced verbatim, followed by Plastafil's reply.

FDA: Page 1, Paragraph 1: "It appears from the study design reported in the PMA that several changes and deviations from the original protocol occurred in violation of 21 CFR Part 812.35(a). Proper compliance to the investigational plan is the responsibility of the sponsor as described in Part 812.46. For instance, there is no explanation why you include an open phase with no control patients when there was no provision for such a trial in the original design and also there is no explanation why the randomization scheme was changed to result in a 3:2 ratio of device treated to controls instead of 1:1 ratio.

In addition, implants were used in nine patients which had injuries only to the posterior cruciate ligament which was not one of the subgroups approved for this study.

PLASTAFIL REPLY: The aforementioned section requires: "a statement that each study was conducted in compliance with Part 812 or Part 813 concerning sponsors of clirical investigations and clinical investigators, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance." The term "study" is not defined in Part 814, but from 21 CFR 814.20 (b)(6)(ii) it seems that the term refers to clirical investigations involving human subjects with the Device, whether or not conducted under an IDE. Plastafil's clinical investigation under the IDE was conducted in compliance with Part 812. It was also conducted in compliance with the Institutional Review Board regulations in Part 56, and in compliance with the informed consent regulations in Part 50.

The clinical studies conducted by Drs. Mare, Demmer, Botha, and Penny reported in the PMA application were not conducted in compliance with the Institutional Review Board regulations (Part 56), the informed consent regulations (Part 50), or regulations concerning sponsors of clinical investigations and clinical investigators (Part 812). The reason for noncompliance was that the investigators had no legal or other obligation to comply with the aforementioned Parts. This information has previously been furnished (4E-1*, 2; 4E-21). In brief, the surgeons, each of whom is a citizen of a foreign country, provided the results of their clinical studies because the FDA staff felt that the information would be useful with regard to evaluating Plastafil's PMA, notwithstanding the fact that it was not generated under Plastafil's IDE.

Staff raises the issues of (1) an open phase with no control patients; (2) the use of the implant in patients who had injuries only to the posterior cruciate ligament; and (3) the use of the 3:2 ratio, not a 1:1 ratio. I will reply to the first two issues together, and the third issue separately.

Non-IDE Device Use. In mid-1983, Dr. John Albright expressed a desire to use the Device in some patients who had an injured posterior cruciate ligament or who had a totally dislocated knee (salvage patients). During the summer of 1983 I presented Dr. Albright's proposals to FDA staff during several telephone conversations. I explained Plastafil's willingness to provide the Device, and Dr. Albright's willingness to undertake the responsibility for its use. Plastafil's concern was that our actions might be construed as marketing the Device in violation of Section 301 of the Food, Drug and Cosmetic Act (FD&C) -- which was not the case. I asked: (1) Did the proposed uses amount to requests for approval of a modification of the IDE so as to include two additional study groups; (2) for the purposes of the proposed uses, was the Device a Custom Device within Section 520(b) of the FD&C Act and therefore exempt from Section 515? Initially, it was suggested that the proposal amounted to the inclusion of additional study groups, and that some formal steps were needed for the inclusion to be valid. But I pointed out: (1) The Device was

*Volume 4E, page 1 of the PMA. Subsequent references in this form similarly refer to the indicated volume and page numbers of the PMA.

not offered for commercial distribution to Dr. John Albright (or anybody else). (2) The Device was used to meet the unique needs of Dr. Albright's patients; Plastafil neither requested nor received a list of inclusion or exclusion criteria for use of the Device, nor did Plastafil make any recommendations regarding either criteria. The Device was used in particular patients whose clinical and anatomical features were, in Dr. Albright's discretion, suitable for use of the Device. (3) The Device was not commercially distributed, and no fee was charged for the Device. (4) Plastafil was not regularly engaged in providing Custom Devices, and that we would not do so for any individual other than Dr. John Albright. When Plastafil was satisfied that its actions would not be viewed as commercial distribution of an unlicensed medical device in interstate commerce, it provided the Devices to Dr. Albright to use as he thought appropriate. Plastafil never advocated the Device for use in salvage procedures because our rationale for the use of the Device did not extend to such an application; furthermore, we never advocated use of the Device for isolated PCL injuries because we had no intention of conducting a study that would directly test that hypothesis. Despite these facts, Plastafil made no attempt to impose its judgment on Dr. Albright, and made the Device available to him at his request, based on our respect for his efforts and his judgment.

21 CFR Part 812.46 describes the sponsor's responsibility in the situation in which an investigator fails to comply with the investigational plan. No investigator in Plastafil's IDE clinical study failed to comply with the investigational plan because each investigator, insofar as I am aware, substantially adhered to the investigational plan with regard to all its pertinent and substantive aspects including entry criteria, randomization, surgical procedures employed, handling and treatment of the device, and conduct of follow-up examinations.

In summary, for the abovementioned reasons, it is a mischaracterization of Plastafil's activities to assert that the issues raised were "deviations from the original protocol ... in violation of 21 CFR Part 812.35." The first issue related to a use of the Device that was thoroughly discussed with Staff at the time the use was carried out, and which was justified by considerations not pertinent to the IDE. The second issue related to an appropriate use of the Device that did not involve the hypotheses considered in the IDE study.

3:2 Allocation of Patients. In the IDE we said: "The randomization scheme used to allocate patients to treatment groups will result in approximately one experimental for each control" (emphasis added). The question posed by Staff therefore amounts to whether our use of a patient ratio of 1.5:1, and not 1:1 is a "change" within the meaning of the applicable version of Section 812.35. We concluded at the inception of the study that it was not such a change and that the use of 1.5:1 rather than 1:1 was scientifically desirable and justified. There were several bases for our conclusions.

Not a change within the meaning of Section 812.35. On January 18, 1980 the FDA promulgated a final rule regarding Section 812.35 (supplemental application), effective July 16, 1980 (45 FR 3755) that provided in pertinent part: "(a) Changes in Investigational Plan. A sponsor shall (1)

submit to FDA a supplemental investigation if the sponsor or an investigator proposes a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects, and (2) obtain IRB and FDA approval of the change before implementation...."

In adopting this final rule FDA made it clear that it was intended to apply only to changes affecting the safety of subjects or the validity of the investigation: "Supplemental applications are required only for the addition of new institutions to an investigation and for changes in the investigational plan that may affect the scientific soundness of the study or the rights, safety, or welfare of subjects" (45 FR 3745).

On January 27, 1981 the FDA adopted an amendment to Section 812.35, effective July 27, 1981 which read in pertinent part: "(a) Changes in Investigational Plan. A sponsor shall: (1) Submit to FDA a supplemental investigation if the sponsor or an investigator proposes a change in the investigational plan and (2) obtain IRB approval (see Section 56.110(b)) and FDA approval of the change before implementation."

FDA again amended this Section, effective April 12, 1983 (48 FR 15621) to provide, in pertinent part: "(a) Changes in Investigational Plan. A sponsor shall: (1) Submit to FDA a supplemental investigation if the sponsor or an investigator proposes a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects and (2) obtain FDA approval of any such change and IRB (institutional review board) approval when the change involves the rights, safety, or welfare of subjects (see Sections 56.110 and 56.111), before implementation."

The Section was modified again (50 FR 25909, June 24, 1985; 50 FR 28932, July 17, 1985) and presently reads as follows: "(a) Changes in Investigational Plan. A sponsor shall: (1) Submit to FDA a supplemental investigation if the sponsor or an investigator proposes a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects and (2) obtain FDA approval under Section 812.30(a) of any such change, and IRB approval when the change involves the rights, safety, or welfare of subjects (see Sections 56.110 and 56.111), before implementation...."

Even if use of a patient ratio of 1.5:1 were to be considered a "change", the only aspect of the study to which it could reasonably be viewed as pertinent is that of the study's scientific soundness. That is, use of this ratio has no direct link with the question whether the device in any particular patient is more or less safe, or more or less efficacious. Thus, if there were a "change" within the meaning of Section 812.35, it affected "scientific soundness". But our IDF study was authorized by letter dated March 4, 1983, and the version of Section 812.35 that was in effect as of that date specifically removed "scientific soundness" as a "change" that must be submitted to FDA for prior approval. As a consequence of these considerations, I interpreted the law to mean that even if there were a "change", it was not a change that required a formal supplemental application.

Affirmative reasons for the choice of the 1.5:1 ratio. Assume that two surgical therapies are available to treat a particular disease, and that both procedures are performed routinely but that there is no scientific evidence to indicate which procedure is superior. The uncertainty could be resolved by randomizing subjects to the two procedures, and performing suitable follow-up determinations. If the investigating surgeon routinely performed both procedures, the study would contain no a priori bias regarding degree of surgical skill. However, if the patients randomized to one arm were operated on by a surgeon experienced in that procedure, and the surgeon had no experience with the second procedure, then any difference between the two patient groups might be due to either the relative merits of the procedures, or the relative skills of the surgeon. A similar difficulty in experimental design occurs whenever a new therapy is to be tested against a standard therapy; in such instances, surgeons have experience with one procedure, but not the new procedure, and consequently any measured decrement in efficacy in the new procedure might be due to relative inexperience. One acceptable strategy to overcome this difficulty is to provide, in advance, that the number of subjects receiving the new treatment will be greater than those who receive the standard treatment. The rationale is that the relative inexperience will be averaged over a larger subject population than would otherwise have been the case, thereby lessening the impact of this confounding variable on mean performance. Based on this consideration, and after reviewing other clinical studies in which a similar rationale was invoked, we chose to conduct this study at a case:control ratio of 1.5:1.

FDA: Page 1, Paragraph 2: "Additional information is needed on the complications reported. The incidence of synovitis, extra-articular infections, intra and extra-articular failures, graft laxity, septic arthritis, and presence of carbon particles are not reported. Although you state that these occurred at low levels, the variability in the frequency of follow-up visits among patients may have made it impossible to detect the actual incidence of complications."

PLASTAFIL REPLY: The listed clinical states are not defined in the IDE, and I do not understand how the absence of information regarding undefined clinical states can be considered a violation of the CFR. I cannot provide specific information unless the requests are posed using terms that have a meaning within the context of our study -- each of the listed terms have no such specific meaning because they are judgments, not dependent variables.

The phrasing of Staff's comment creates an irresolvable conflict between the meaning of a scientific term and the pattern of clinical practice. "Incidence" means frequency of occurrence of an event in a population within a particular time interval. Carbon fibers are not radio-opaque, and the presence of carbon-fiber debris (which is what I assume to be the issue raised here by Staff) cannot be determined unless the patient is arthroscoped (and even that may not be sufficient). It is not acceptable to conduct routine arthroscopic examinations in the absence of symptomatology, and in our IDE we expressed no intention to do so. Thus, it is impossible for me to report the incidence of carbon particles.

In alleging the deficiency, I think there has been a failure to recognize the change in the nature of decision-making within the surgical specialties which the FDA, itself, spearheaded. The public record shows that sponsors routinely presented the results of uncontrolled clinical studies in which clinical endpoints were evaluated using subjective criteria: Patients did "excellent", "good", or "poor", and they had "graft laxity", "synovitis", and they were "satisfied" or "unsatisfied." Since it is the practitioner that is the ultimate consumer of the research, the attempt to express both the design of the study and its results in clinical terms makes eminently good sense. The drawback in this approach is that it does not provide an objective basis for the degree of confidence that one may place in the conclusion of the study.

There is another procedure for conducting a clinical study. Groups representative of patients with a specific pathology are treated using alternative therapies, and the results are compared using acceptable clinical and statistical methods, stipulated in advance. These methods must be clinical, otherwise the study has no meaning; they must be statistical, otherwise the study is not superior to the alternative methodology. The basic process for implementing this procedure is to focus on a clinical state, define it in terms of a symptomatology, ascertain the grades or levels of the symptomatology, create a realistic a priori classification scheme, and finally, determine whether treatment affects distribution within the scheme (by analyzing the mean or median of the scorecharacterizing the symptom used to define the clinical state, or the frequency distribution of patients in the various states as a function of treatment). This procedure removes (or goes a long way toward removing) the objection that the conclusion of a clinical study using the anecdotal method was too subjective. The price paid when the scientific method is used is that some clinical states, while remaining of crucial importance with regard to clinical judgment, patient management, diagnosis, and treatment, simply have no well-defined meaning within the decision-making process wherein the investigator seeks to ascertain the superior therapy. In this process, the clinical state has been replaced by the sum total of the symptoms deemed pertinent.

FDA has repeatedly made it clear that it prefers and expects well-designed clinical studies involving appropriate control groups assessed with regard to well-defined objective endpoints using appropriate statistical methodology. This is the kind of study Plastafil promised to perform when the IDE was approved in 1983, and it is the kind of study that Plastafil did, in fact, perform. Plastafil did not perform an anecdotal study, and therefore we cannot provide anecdotal evidence.

(1) With respect to "synovitis". Synovitis is a clinical condition involving inflammation of the synovial lining of the joint; its presence or absence (except in a florid condition) is a matter of clinical judgment. I am unaware of any methodology by which the presence or absence of the pathology can be uniquely determined. Moreover, the incidence of synovitis itself is not a meaningful number because, however the condition may actually be defined, it is expected to occur in all patients to some extent. The pertinent question is whether the incidence of synovitis in the Cases (patients who received carbon fibers) differs from that in the Controls (patients who received standard therapy). The best response

consists in characterizing the Cases and Controls with regard to parameters that were accepted prior to the study as being characteristic of the pathology. This was done in Volume 4F, Tables 9-14 for pain, and Tables 21-26 for swelling for all the patients in the study. The format employed in the preparation of the Tables was that specified in the Guidance Document. A pertinent response to Staff's question is also contained in the parameter SYMPTOMS defined in the IDE. The data from our study in the format SYMPTOMS is given in Enclosure 1 with this response.

(2) With respect to extra-articular infections. On page 4D-17 we reported "Mark Boobar (non-randomized study, ISU) experienced pain and tenderness in the area of the toggle, and it was removed in his physician's office under local anesthesia. Bryan Cooper (ISU) underwent removal of both medial bollards after he developed an abscess two weeks postoperatively." These were the only extra-articular infections (or possible infections) noted in our study.

(3) Intra-articular failures. I am unable to provide a definitive reply because I do not know what Staff means by "failures". If "failure" means a situation in which an initial treatment did not satisfactorily resolve an initial complaint, resulting in a second procedure for the same complaint, then the treatment failures in the Plastafil study were described on pages 4D-15 and 4D-16. There were four intra-articular treatment failures in the controls and four intra-articular treatment failures in the carbon-fiber patients in the chronic category; there were no other treatment failures.

(4) With regard to graft laxity. I am unable to provide a definitive reply because I do not know what Staff means by "graft laxity." Moreover, I do not understand the pertinence of a request for information regarding graft laxity because we have performed a controlled clinical study; consequently, no dependent variable has specific meaning except with relation to the magnitude of the corresponding variable in the control group. We provided information regarding numerous clinical tests and signs (see Tables 57-68, 103-107) that are pertinent to laxity. The tables were prepared according to the "distribution of scores for each objective item from Appendix 6 and subjective item from Appendix 5 for the entire population, at each time point of data collection according to the format of Appendix 11" as required in the Guidance Document. The data from our study in the format STABILITY is given in Enclosure 1 with this letter.

(5) Septic arthritis. We think none, but the limitations and ambiguities described in our response to the four previous clinical states applies with equal force here.

(6) Presence of carbon fibers. We were unable to report the fact or extent of presence of carbon fibers in the knee joint in any scientifically objective manner. Such a determination would have required arthroscopic surgery, tissue biopsy, and a validated quantitative procedure for analyzing the biopsy specimens. Such a strategy was not proposed in our IDE, and would probably have been ethically unacceptable. The objective information that is available which bears on the issue, and which may be evaluated to make judgments about the existence of carbon fibers in the

joint consists of (1) observations regarding patient symptoms (under the hypothesis that a significant presence of carbon-fiber debris would have produced symptoms); (2) an analysis of the pertinent animal studies regarding the issue of carbon-fiber debris; and (3) the arthroscopic examinations made by Dr. Penny in a series of patients who agreed to be arthroscoped. This information has previously been presented to FDA, and we believe it supports the conclusion that trace presence of carbon fibers may be expected in the joint, but the debris does not have functional significance. I know of no countervailing evidence nor any objective method by which the question might be more adequately assessed.

FDA: Page 2, paragraph 3: "Patient accountability is extremely poor. It is not possible to identify all patients entered in the study who remained through its completion. A flow chart showing all patient groups from the initiation of the study through its termination would clarify this. All withdrawals, losses, formation of new sub-groups should be clearly indicated in the chart."

PLASTAFIL REPLY: I am unable to provide a definitive reply because I do not know what Staff means by "completion", "termination", "withdrawal", "losses". None of these terms are defined in our study; consequently there is no unambiguous method to determine whether they occurred, or when.

We dealt with human beings who had their own likes, dislikes, priorities, and ambitions. When a patient chose not to return for a follow-up examination, I lacked both the legal and moral authority to require compliance. When faced with this difficulty, which occurred frequently, we accepted the patient's decision, and tried again later. No patient (with the exception discussed below) is "lost" or "terminated", and no patient "completes" the study in any absolute sense. It cannot be assumed that all subjects dutifully appear when requested to do so by their doctor, because this did not occur in the real world in which we performed our study. Indeed, any study performed on subjects who appear on command is probably worthless with regard to establishing inferences for the general population. Our study centers were chosen to provide a representative patient sample; frequently, the patients did not conform to a schedule that suited Plastafil. Banal as it may sound, patients do not respond to a physician's request like automatons, and implementation of the federal regulatory scheme for medical devices must recognize this fact. As difficult as the problem was at one year postoperative, it became increasingly more difficult as time passed.

Staff's assertion "patient accountability is extremely poor" is factually erroneous, and it is my hope that the error will be apparent when Staff evaluates our data in the format provided in this letter (Enclosure 1). The facts will show that our study is the best study involving an orthopaedic implant that has yet been performed and reported, and is probably near the theoretical limit on patient accountability for a study involving a cross-section of the population. The major difficulties I faced in reporting our data occurred because the IDE, the Guidance Document, and the categories defined in FDA's deficiency letters frequently conflict with one another.

FDA: Page 2, Paragraph 4, Sentence 1: "Patient follow-up information is incomplete and confusing as reported."

PLASTAFIL REPLY: All follow-up information obtained during the course of this study has been summarized in the PMA; a copy of all case reports is included with this letter. Not every patient was followed at 3, 6, 9, and 12 months post-operatively for the reason that was described in the preceding Replies. The consequences of this fact are discussed below. The format of the follow-up information provided in the PMA was mandated by the Guidance Document -- it was not a format that we chose, nor a format that we proposed in the IDE. Confusion engendered by the preparation of data in the Guidance-Document format is not reasonably attributable to shortcomings on the part of Plastafil.

Plans describing (1) the format in which data would be presented for scientific evaluation, and (2) the statistical methodology that would be employed in evaluating the data were contained in the approved IDE. Below, I present: (1) the pertinent parts of the approved plan dealing with the format of the data and the decisional process to be employed in evaluating device efficacy; (2) the data obtained pursuant to this plan (Enclosures 1 and 2); (3) an analysis of pertinent changes in the implementation of this plan (compared with the plan as originally approved); and (4) the results of analysis of the data performed according to the approved methodology.

(1) The Approved Plan. The plan that Plastafil proposed for evaluating the data from the clinical study is contained in pages 13-15 in the IDE. The part of the approved plan dealing with the data format and the decisional process to be employed in evaluating device efficacy is:

Data Management

...

Efficacy: The success of the carbon-fiber treatment will be determined on the basis of statistical analysis of the results of Orthopaedic Examinations of the patients. Each patient will be evaluated with regard to the five categories listed in Table 3, using the Forms contained in APPENDIX A of this Protocol. The categories will be weighted, as shown in Table 3, to give the greatest weight to Stability (30%), equal rights to Symptoms, Function, and Patient's Evaluation (20% to each category), and the least to Deformity (10%).

Data for Symptoms and Function will be entered by the Investigator (or an appropriate assistant) at the time of the Orthopaedic Examination based on answers provided by the patient. A maximum total of 46 and 65 points respectively can be achieved in the two categories; as will be the case for all categories shown in Table 3, the actual values measured will be adjusted, using the appropriate scale factors, to obtain the desired weighting of each category.

...

Let O(t) be the orthopaedic status of the patient at time t. O(t) is defined to be the sum of the weighted scores from each of the categories

as follows:

$$O(t) = Ss + Ff + Dd + Xx + Yy.$$

Where S, F, D, X, and Y, are the raw scores for each category as defined in Table 3, and the lower case symbols are the appropriate scale factors as defined in Table 3. For a patient with no knee disability, O(t) = 100.

O(t) will be measured at the time of the pre-operative visit (O(o)), and at 3-12 months post-operative. A Healing Index, HI, may be defined as the ratio of the patient's status at any particular time, compared to that found at the pre-operative visit.

$$HI = O(t)/O(o), \quad t = 3, 6, 9, 12 \text{ months}.$$

Table 3. Categories to be Evaluated During Orthopaedic Examination, and Assigned Weight.

CATEGORY	CATEGORY SYMBOL	MAXIMUM RAW POINTS	FACTOR TO CONVERT TO 0-100 SCALE	RAW POINTS 0-100 SCALE	ASSIGNED WEIGHT	FACTOR TO PRODUCE ASSIGNED WEIGHT	FACTOR SYMBOL	EFFECTIVE SCALE FACTOR
Symptoms	S	46	0.42	19.2	20%	1.04	s	0.437
Function	F	65	0.42	27.2	20%	0.74	f	0.311
Deformity	D	22	0.42	9.2	10%	1.09	d	0.458
Stability	X	48	0.42	20.1	30%	1.49	x	0.626
Patient's Evaluation	Y	58	0.42	24.2	20%	0.83	y	0.349

HI(t) will be computed in the manner described above for each patient in this study, and the values from the carbon-fiber patients will be compared, using the independent t-test, at 3, 6, 9, and 12 months with those found from the corresponding control group.

(2) The Data. The data collected in this study is presented in Enclosure 1 on a patient-by-patient basis prepared according to the format described above. Enclosure 2 consists of averages obtained using the data in Enclosure 1. Enclosure 2, page 1, contains the average scores for each orthopaedic category defined in the IDF as a dependent variable, as assessed pre-operatively. Page 2 contains comparable average values obtained using all data in Enclosure 1 that was obtained more than 24 months post-operatively; also indicated or page 2 is the number of patients who contributed to the average. For example, there were 43 patients in the chronic category that received carbon fibers, and we had data regarding deformity on 41 patients that were at least 24 months post-operative; the mean Deformity score was 20.6, compared with 19.6 in the control group (for which data was obtained on 33 of the 36 patients enrolled). The

average follow-up times for each of the orthopaedic categories is listed on page 3. Page 4 of Enclosure 2 contains comparable information regarding the non-rardomized group.

(3) The Changes. The decisional process itself is an essential part of the investigational plan. Wholesale or arbitrary a posteriori changes in the investigational plan would make it impossible to perform valid scientific studies, but changes in some aspects of design, conduct, or data evaluation may be necessitated by changed circumstances or unforeseen events. If so, the question whether the experimental hypotheses can still validly be assessed is raised. As discussed previously, not all patients were examined at 3, 6, 9, and 12 months post-operatively, because some patients refused to appear for scheduled clinical appointments. If a patient chose not to submit to a clinical examination at a particular time or within a particular time interval, there existed no legal nor moral force that could require compliance. There probably was not a single instance in which a patient was not requested to appear for a timed follow-up at 3, 6, 9, and 12 months post-operatively. Nevertheless, this situation constituted a change from the original plan.

What are the scientific consequences of the absence of data at the timed intervals? If a patient failed to appear at a timed interval, and also failed to appear at all subsequent times, the patient would be lost to follow-up. Every patient lost to follow-up compromises, to some extent, the confidence that one might have in decisions based on the study data, because of the possibility of bias associated with decision-making using only part of the sample. The difficulty is that the investigator could not be certain that the patients still available for follow-up reflected or characterized those that were unavailable. Thus, the existence of patients lost to follow-up inexorably injects uncertainty into the decisional process, thereby weakening any conclusion.

If no patient is lost to follow-up -- that is, if there is some data for every patient, even if the data is not obtained at the same post-operative time poirt for each patient, then the potential bias associated with lost patients does not exist. With only a few exceptions (discussed at length in the PMA), this situation applies to the Plastafil IDE study. That is, we have follow-up data for almost every patient (Enclosure 1). Since follow-up data beyond 24 months post-operatively was obtained for essentially every patient enrolled in the study, the question of potential bias due to lost patients becomes irrelevant and the performance of the Case and Control groups can be formally evaluated using appropriate statistical methods.

(4) Data Analysis. The healing index in the Cases in the chronic category (1.60 ± 0.57, page 2 of Enclosure 2) did not differ significantly from the Control value (1.74 ± 0.76) using the unpaired t test. The healing index in the Cases in the acute category (3.24 ± 1.50) did not differ significantly from the Control value (2.7 ± 0.79) using the unpaired t test.

FDA: Page 2, Paragraph 4, Sentence 2: "The 'random-sampling model' suggested is not acceptable."

PLASTAFIL REPLY: The basic value of a statistical approach is that, under the appropriate conditions, data obtained from a sample may be used to characterize the parent population. Indeed, in our PMA we urged that data taken on fewer than 150 patients could be used to make inferences regarding efficacy in a population (those having injured anterior cruciate ligaments) of more than 150,000/year. As established by Fisher (R.A. Fisher: J. Ministry of Agriculture of Gr. Brit. 33:503-513, 1926) and endorsed by subsequent authorities (W.J. Dixon and F.J. Massey: Introduction to Statistical Analysis, 4th Ed., McGraw-Hill: New York, 1983; B.J. Winner: Statistical Principles and Experimental Design, 2nd Ed., McGraw-Hill: New York, 1962), the validity of the inferential process depends upon establishing that the sample is representative of the population. The method of randomly choosing subjects is one process by which "representativeness" is assured. Surely if 150 subjects can characterize 150,000 subjects, then 15 subjects can (under appropriate circumstances) characterize 30 subjects. It would therefore be inconsistent to hold that, regardless of all other considerations, it is "not acceptable" to rely on a sample of a sample for the purposes of categorizing the latter; such an assertion is unscientific, and lacks both authority and a logical basis. Not only is the random-sampling model proper, it is probably the only acceptable model because it alone permits a clinical study on the true population -- all patients (not merely those whose socioeconomic, cultural, and medical backgrounds are such that they are certain to dutifully obey the orders of a physician regarding follow-up).

The pertinent question posed by a sample-of-a-sample methodology involves an *a priori* determination of the probability of occurrence of error. For our PMA, however, this consideration is not important because the sample-of-a-sample methodology is not part of the approved a priori decisional process.

FDA: Page 2, Paragraph 4, Sentences 3 and 4: "The information for each parameter should be presented in life tables to include data for each time point as specified in the study protocol (that is, 0, 3, 6, 9, 12, and 24 months) plus any length of time beyond two years. The intervals should be selected in such a way that each patient is represented once in each interval."

PLASTAFIL REPLY: I reject the notions that (1) a study exhibiting rigid chronological regularity is possible in a representative patient group, and (2) chronological regularity is a *sine qua non* of statistical validity. If Staff disagrees I request that FDA take whatever definitive and final steps that are necessarily entailed by its view, because it is neither necessary nor possible for us to provide data at each of the specified time points.

A life table is a table showing the proportion of a group of patients with a chronic disease that survive beyond a specific time chosen as the initial point of observation (J.A. Ingelfinger, F. Mosteller, L.A. Thibodeau and J.H. Ware: Biostatistics in Clinical Medicine, 2nd Ed., Macmillan: New York, 1987). Life tables may be used to evaluate survival as a function of differing treatments for an underlying disease (N. Eng. J. Med. 311:1333-1339, 1984). I have been unable to find any scientific authority describing the use of life tables for evaluating the efficacy of an implant, compared with standard therapy. Death is not a useful

endpoint, and it is unclear what Staff has in mind as a substitute. I can find no indication of either a format or a method of decision using "life tables" in the information disclosed by FDA under the FOI laws regarding previous ligament devices that were the subject of PMAs. I request that Staff specifically apprise me of (1) what it understands by "a life table" in the context of our study; (2) a scientific or legal authority wherein the method of computation of the life table acceptable to FDA is performed; (3) scientific or legal authority by which life tables for the Cases and Controls are to be compared for the purpose of determining any differences.

If Staff is seeking information regarding treatment failures, this information has previously been provided (4D-15).

FDA: Page 2, Paragraph 4, Sentence 5: "The following information should be included in such a table: (a) patients in each category; (b) patients lost to follow-up; (c) patients due for a follow-up visit; (d) complications; (e) withdrawals; (f) deaths; (g) missing data."

PLASTAFIL REPLY: (a) The patients in each category are listed in Table 1, Volume 4D; the Table lists the name, category, class, grade, and group of each patient. (b) I am unable to provide a definitive response to Staff's request because I do not understand what is meant by the term "lost to follow-up". If Staff means patients regarding whom Plastafil has irreversibly decided that no further follow-up can be obtained, our answer is none. If Staff means patients regarding whom follow-up information directly bearing on the decisional processes regarding safety and efficacy have received no contribution, our reply is contained in detail in Appendix 3, Volume 4D "Accounting for Patients for which the Longest Follow-up was Fewer than 24 Months"). (c) All patients are due for a follow-up visit because we are attempting to follow the group on a permanent basis. (d) I am unable to provide a definitive response because I do not understand what Staff means by "complications." If Staff means complications that clearly involved the Device, the two such instances that occurred during the study are described on page 4D-17. If the question refers to information obtained by investigators during follow-up visits ("Complications/Adverse Reactions" section of the "Follow-up Evaluation" form), all such replies received during this study are listed in Enclosure 3. The original data forms are contained in the case records which accompany this letter. (e) None. (f) William Hall was killed in an automobile accident on February 1, 1984 (4D, Appendix 3). (g) I am unable to respond because I do not understand what Staff means by "missing data." If by this term Staff means a list of follow-ups from which it may be determined when data was not obtained at 3, 6, 9, and 12 months post-operatively, this information is described in Enclosure 1.

Also on page 7 of its letter, Staff wrote "a patient is considered lost to follow-up beginning at the time when he/she first missed a visit and the patient did not later have an evaluation after that time period." This position is inadequate to define the notion of lost to follow-up because "later" is undefined; it is therefore not possible to determine whether the event has

occurred. In my judgment, a patient is not lost in any absolute sense until the patient either dies or obtains a court order enjoining Plastafil from attempting to obtain a follow-up examination.

Sincerely,

Andrew A. Marino

Ardrew A. Marino, Ph.D.

AAM:pab

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville MD 20850

JUL 12 1991

Andrew A. Marino, Ph.D.
Plastafil, Inc.
P.O. Box 268
Belcher, Louisiana 71004

RE: P900020
Plastafil CFS™ (Carbon Fiber System)
Received: February 25, 1991

Dear Dr. Marino:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA) and your response to FDA's June 22, 1990 non-filing letter. We regret to inform you that your application remains incomplete and cannot be filed at this time. This means that the PMA will not undergo further review by CDRH until the deficiencies listed below are corrected or adequate justification for the omission of any item is submitted.

In order for the PMA to be filed, you must address the following:

1. The following information on complications must be provided for each time interval (post-op, 3, 6, 9, 12, 24, and 24+ months) following surgery:

   a. the incidence of synovitis. If synovitis is present in all patients as you claim, then those which experienced a severe or chronic condition should be listed separately from those who experienced a mild condition;

   b. the incidence of intra-articular failures. This includes incidences where the prosthesis ruptured for any reason which required its removal;

   c. the incidence of graft laxity. This includes incidences where excess laxity in the graft required surgery to correct or as according to the "Guidance Document for the Preparation of Investigational Device Exemptions and Premarket Approval Applications for Intra-Articular Posthetic Knee Ligament Devices", a post-surgical Lachman score which remains greater than or equal to 2 or in your corresponding test, remained in Class 3 or higher in the Anterior Drawer-30° test; and

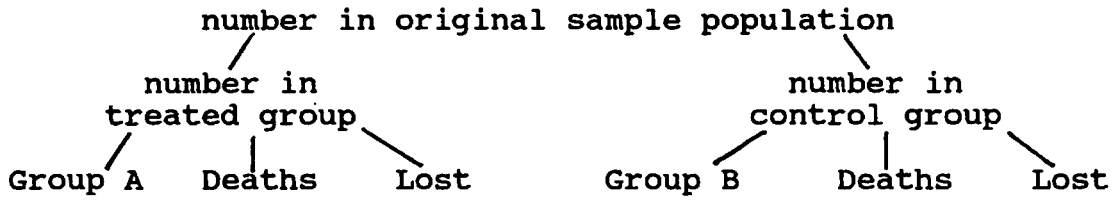
d. the incidence of carbon fiber particles being observed intra-articularly during arthroscopic examination or revision surgery due to prosthesis rupture or other concomitant complications.

2. You state that you cannot provide life table summaries for your study because data for the specific time points are not available. It is the responsibility of the study monitor to take measures to assure that there is compliance with the study protocol. The results of a particular study may show statistically significant differences between groups, but it must also be shown that the data were derived from a well designed, well implemented study. Non-compliance with the study protocol cannot be ignored and compliance is critical for the interpretation of the results and an assessement of their reliability. Therefore, you must provide summary life tables for each parameter (i.e., anterior drawer, Lachman test, etc.). The following table must be completed for patients in the randomized portion of the study (controls and treated patients separately) and for the non-randomized portion of the study.

	Interval of Time Post-Treatment (Months)							
	post-op	3	6	9	12	24	36	48	60
Number of Patients in Each Score Category									
Missed Visits									
Lost to follow-up									
Deaths									
Revisions									
Withdrawals									
Incomplete data									
Complications									
Failures									

You must also define the limits selected for each time interval and designate with NA when there is no available data at a specific time point. Each interval can have only one evaluation per patient. Since patients, according the study protocol, were to be followed for 1 year after surgery, missed visits need to be considered only within the first year.

3. It is difficult to assess the composition of the study population in terms of the patient groups at any given time. You must provide a flow chart showing the original sample population and all groups through the completion of the study as in the following example (the nomenclature for these groups will be specific for your study and is not limited to the groups shown below):



4. You must discuss how the possibility of bias in your randomization scheme was avoided. In addition, you must explain the rationale for using different randomization methods and p values at each one of the three centers.

5. The total strength of the Carbon Fiber System is reported to be 289 N which is well below that of other artificial ligament designs and of the natural human ligament. The suggestion that the strength of the carbon fiber system is augmented by tissue ingrowth to be within the range of the natural ligament is not supported by the animal test data. According to the goat model you presented, the ultimate tensile strength achieved after 18 months is only 25% of the natural ACL of the goat. It is, therefore, necessary that you demonstrate that the Carbon Fiber System can withstand mechanical testing in bending fatigue and tensile fatigue with load levels comparable to physiologic conditions. If tissue ingrowth is to be considered a factor in significantly improving the strength of this ligament system, animal test data must be provided to support this claim. In addition, you must perform abrasion testing and creep testing with the ligament in a similar position as when it is implanted. The carbon particles formed from the abrasion testing must be quantified and compared to what has been seen in vivo.

6. Your justification for the omission of complete information in the Manufacturing Section to validate the sterilization process for this device and to determine whether this process adversely affects the device's physical and mechanical properties is inadequate. You must provide complete sterilization information which includes:

a. the sterility assurance level of the device for the radiation sterilization process, the radiation dose, and the radiation source;

b. the results of dose mapping including a diagram of the product loading pattern and a description of the dosimeters; and controls for routine monitoring of the sterilization cycle;

c. the names and contracts with the sterilization facilities; and your plan for collecting validation data and the data themselves; and

d. complete information concerning the test methods and frequency for bioburden and pyrogenicity testing.

For guidance concerning the types of sterilization information to be submitted, you should refer to Chapters 61, 71, 85, 151, 1035, and 1211 of The United States Pharmacopeia XXII, the Association for the Advancement of Medical Instrumentation Standard Process Control Guidelines for Gamma Radiation Sterilization of Medical Devices, and the enclosure which is FDA's Guideline on Validation of the Limulus Amoebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices.

As provided by 21 CFR 814.42(d), you may resubmit the PMA with the additional information necessary to correct the above deficiencies or you may request in writing within 10 working days of your receipt of this letter an informal conference with the Director of the Office of Device Evaluation (ODE) to review the decision not to file the PMA. Any review will be based only on information within the existing PMA and will be limited to a reconsideration as to whether any of the not filing criteria in 21 CFR 814.42(a) apply. The Director of ODE will hold this informal conference within 10 working days of receipt of the request and will render a decision on filing within 5 working days after the informal conference. If, after the informal conference, FDA accepts the PMA for filing, the filing date will be the date of the decision to accept the PMA for filing. If the Director of ODE does not reverse this decision not to file the PMA, the applicant may request reconsideration of the decision from the CDRH Director.

A request for reconsideration by the Director of CDRH must be submitted in writing within 30 working days of your receipt of a denial for filing from the Director of ODE. The request must contain written descriptions of your positions on the issues critical to filing. The Director of CDRH will render a written decision within 60 days of receipt of your request. If, after the review by the Director of CDRH, FDA accepts the PMA for filing, the

filing date will be the date of the decision to accept the PMA for filing. If, after his review, the Director of CDRH does not reverse this decision not to file, that denial constitutes final administrative action for the purpose of judicial review.

The following additional deficiencies were noted in this initial review. While they did not directly relate to our decision to not file your PMA, you should make every effort to address them in your next amendment:

1. You must provide historical and literature support for what is considered a successful ligament reconstruction procedure in terms of the parameters used in your study.

2. You must submit justification for the large effect size difference (0.55) which is used to calculate the sample sizes.

3. You must provide a summary of complication rates for each investigator, not simply the complications/adverse reactions reporting forms.

4. You must provide revised chi square test analyses to compare distribution of data at time intervals that meet the conditions described in major deficiency #2 where each patient has only one visit reported in each time interval.

If you need to obtain clarification regarding any of the above deficiencies and the measures required to correct them, a request for an informal conference with the Director of ODE is inappropriate. Instead, we suggest that you contact or meet informally with the reviewing ODE division.

Any resubmission of the PMA to correct the above deficiencies, any request for an informal conference with the Director of ODE to review this decision not to file the PMA, or any other correspondence pertaining to this PMA should be identified as a PMA amendment and should include the above PMA reference number to avoid unnecessary delays in its processing. Please submit 6 copies, or 3 copies in the case of a request for an informal conference. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, Maryland 20850

FDA must consider the PMA to have been voluntarily withdrawn if you do not respond in writing to this request for an amendment within

180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to CDRH approval and must justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) respond the above deficiencies or (2) request an extension of time to respond and have the request approved, FDA will close this file and not accept any amendments referencing this PMA number. Under these circumstances, any resubmissions will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

This letter reflects the current progress of our review of your application. It should be noted that the time allotted for the agency to perform a filing review and the condition of your PMA may not have permitted us to identify all deficiencies that the application may contain. Please be advised that continued review of your application and/or your response to this letter may result in additional deficiencies.

If you have any questions concerning the deficiencies listed above, please contact Thomas J. Callahan, Ph.D., at (301) 427-1036 or Ms. Kathleen Lundsten at (301) 427-1186.

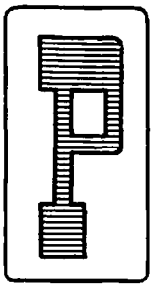
Sincerely yours,

Deborah Lewis

for Charles H. Kyper
Chief, Premarket Approval Section
Program Operations Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

PLASTAFIL, INC.

P. O. Box 268
Belcher, Louisiana 71004



ANDREW A. MARINO, PH. D.
PRESIDENT

July 25, 1991

Director, Office of Device Evaluation
PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

RE: IDE NUMBER G820122/S14
Plastafil CFS™ (Carbon Fiber System)

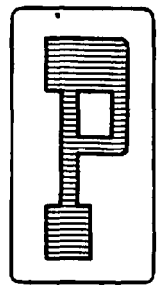
Dear Sir,

In accordance with information provided in FDA's letter to me dated July 12, 1991, received July 17, 1991, I am requesting an informal conference with the Director of the Office of Device Evaluation (ODE) to review the decision not to file the PMA.

Approximately eight years ago I began work on this project with the goal of evaluating the use of carbon fibers for the treatment of injuries to the anterior cruciate ligament. Throughout this period, I have consistently followed the highest scientific standards and practices, and have responded to every request, direction, or suggestion made to me by the staff of ODE with whom I have dealt (ODE-S). In response, ODE-S, and particularly Nirmal Mishra have consistently lied and misled me, and the latest deficiency letter is a further example of ODE-S abusive behavior. The scientific facts, the law, and common decency require that the deficiency allegations be withdrawn, and my PMA be accepted for filing.

ODE-S is distorting the rules regarding PMA filing to make it impossible for me to obtain a decision on the scientific merits. Instead, ODE-S makes endless illegal, irrelevant, or trivial requests, thereby avoiding its responsibility to decide. I have supplied thousands of pages of documentation, hundreds of tables of data, and responded to myriad requests for more information. Despite this, I am continually met with further repetitive demands. Each new round of ODE-S employees, rather than reading information previously supplied, simply issue a new demand.

ODE-S repeatedly demands that I perform tests, conduct statistical analyses, and take other steps that are unscientific and have no rational basis. It alleges, for example, that the absence of mechanical testing constitutes a scientific deficiency. Such tests, however, are irrelevant with regard to our device. No matter what data was obtained from such tests, they could neither support nor obviate the conclusions that we reached on the basis of appropriate scientific procedures. Thus, ODE-S demands that I spend time and money performing tests that are useless.



Reasonable men may differ regarding the results and implications of various scientific studies. If a panel of my scientific peers reaches a scientific conclusion that is contrary to mine, and states the reasons as required by law, then I would regard the system as designed by Congress as having functioned properly. Congress, however, never intended the rules regarding filing to be used by the ODE-S as a vehicle to avoid making substantive scientific decisions. Indeed, in more than eight years of experience with the ODE-S, I have not met individuals who have written books, published scholarly articles, conducted scientific studies involving animals, performed and published the results of mechanical tests, conducted clinical studies, or written scholarly reviews. Consequently, the ODE-S may be legally incompetent to make the substantive scientific judgments inherent in the alleged deficiencies.

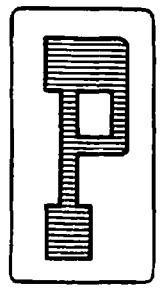
ODE preaches to me in a patronizing fashion when I make the smallest deviation from the original experimental plan submitted in 1983, and it simply refuses to consider that such changes were both necessary and appropriate. Thus, if I follow the 1983 protocol, I am unscientific, whereas if I do not follow it I am noncompliant.

I am weary of explaining to ODE-S that I do not have data at the specific times planned in my 1983 protocol. There are good reasons why the data does not exist; most importantly, the nonexistence of the data does not vitiate the scientific soundness of the study. But each time I explain that the material does not exist, I am met with a further request for the same data. Common decency requires ODE-S to recognize that I have in fact answered its request, and to make whatever decision on the merits ODE-S feels is justified by my answer.

No one at ODE-S seems to understand the difference between a controlled clinical study and a collection of case reports. I am continually asked for anecdotal information and, when I respond that I performed a controlled study and did not collect anecdotal information, my response is ignored and the initial request is iterated. When ODE-S makes requests using language that has no meaning within the context of the study, it is impossible for me to respond substantively. If then, ODE demands that I respond substantively before it accepts the PMA for filing, then clearly I will never receive a decision on the merits.

Other abusive tactics have also been employed by ODE-S. I was asked, for example, to explain how the subjects in my study were randomized, and I did so in great detail. However, ODE ignored my response and in the subsequent deficiency letter I was asked to "discuss how the possibility of bias in your randomization scheme was avoided." ODE-S did not reject my previous explanation because it was unclear, they simply acted as if I hadn't responded in the first instance.

A further ODE tactic has been to mischaracterize information previously proferred, and posit questions on the basis of the misunderstanding. I was



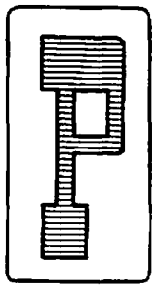
asked, for example, to "rationalize using different randomization methods and P values for each of the three centers" but I never used different randomization methods or P values at the three centers, so how, rationally, can the question be addressed?

Questions involving mechanical testing are particularly aggravating. I will not perform mechanical testing involving abrasion and creep because the data is irrelevant to my study. Now, if ODE-S concludes that it is relevant and must be performed, then there would exist an actual decision that could be examined by some independent authority. I have repeatedly told ODE that I will not perform the tests because they are irrelevant, yet, I am continually asked to perform the tests. The distinction between the two conditions involves the question whether the tests are nonsensical, as I believe, or whether they have some value. Until ODE-S makes a substantive decision, however, I can never have the issue reviewed.

ODE-S repeatedly demands animal test data, but does not appear to have any idea about its purpose or utility. I was told, for example, "if tissue ingrowth is to be considered a factor in significantly improving the strength of this ligament system, animal test data must be provided to support this claim." But I have already provided data showing that the artificial ligament performs as well as harvesting the patient's own tissue and reconstructing the joint. What then, does it matter what takes place in an animal study?

Another example of ODE-S's bad faith regarding my PMA is its handling of issues involving manufacturing. Those issues are trivial, and should be dealt with by engineers after the important scientific questions have been resolved. There is no reason for ODE-S to press questions regarding manufacturing matters now, except for a desire to erect roadblocks in my path. It should be obvious to anyone that the product can be adequately sterilized, but I simply do not have the money to hire a quality-control engineer who can supply ODE-S with the standard verbal formulas for sterilization. On the other hand, if ODE-S makes a decision on the merits and it is favorable to me, I would have no difficulty whatsoever in raising sufficient capital to hire the engineer who could supply the verbal formulas that are needed. If ODE-S's goal is to foster initiative and the development of small businesses, then it is self-defeating to commingle manufacturing and scientific issues. On the other hand, if ODE-S would like to destroy small companies, it can do so by the simple expedient of demanding trivial (but expensive) information. Again, I have requested that the manufacturing issues be postponed but ODE-S simply ignores my request -- not refuses, but ignores -- and propounds it in the next round of paper.

I am at a loss to understand how ODE-S could have developed such hostility toward carbon fibers, and such reluctance to make a substantive decision. Throughout my eight years of dealing with ODE in this area, I have tried to hard to understand ODE-S's concerns, and to accommodate its every wish. Originally, a decision regarding the study was supposed to be made after one year following surgery. Nirmal Mishra, however, told me that he had changed



the rules and that a two-year follow-up would be needed. Later, he required a follow-up of 2-5 years, and he directed me to go overseas and determine what had happened to patients who received carbon fibers prior to the initiation of my study. I did as I was ordered, and supplied the information; in response, Mishra listed it as a deficiency that the foreign physicians had not followed American law in treating their patients.

No one at ODE-S seems to have an overall conception of the work we have performed, as described in the PMA. Bits and pieces of the work have been assigned to various individuals who frequently quit or are transferred, and hence are replaced by someone who knows even less than they did.

The ODE-S staff, and particularly Mishra have treated me poorly: his advice and comments during various "informal discussions" have, in retrospect, led me in exactly the wrong direction -- a direction that maximizes my grief and minimizes my opportunity to pass successfully through the review process.

I was contacted on April 26, 1991 by Rebecca Asente, of FDA, who told me that my IDE had been lost; she told me to send another copy immediately. When I asked for a written request for the information she informed me that she would not do so, and that I must respond to her oral request -- or else. This episode well exemplifies the arrogance of the ODE-S.

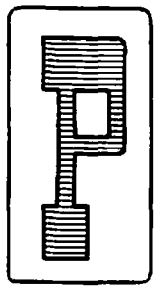
It's clear that there is nothing I can say nor do that will win filing of the PMA from Mishra and the other decision-makers at ODE-S, regardless of the law, the merits of my application, or basic principles of fairness and decency. ODE-S is misusing the rules governing filing to enforce the personal philosophy and opinion of individuals who are hostile to innovation and afraid to make a decision.

After eight years of dealing with Mishra, both directly and through his staff, I have formed an opinion concerning his motivation. He has decided that the use of artificial ligaments in acute cases can never be approved by ODE because it may lead to complaints in the future, thereby jeopardizing his career. In my case, he cannot fabricate reasons for rejecting the PMA on its merits because such fabrications would be inconsistent with facts when the case was presented to a judge or the general scientific community in the form of scientific publications. Consequently, Mishra has ordered the proffering of an endless series of irrelevant questions, and has made filing contingent upon the furnishing of answers to all such questions. Thus, under him, the simple procedural task of filing has grown cancerously to become an Odyssey without end.

I ask:

(1) that the PMA be filed;

(2) that individuals at ODE-S with records of demonstrated hostility toward



artificial ligaments be removed from the adjudicative process of evaluating the merits of the PMA;

(3) that all scientific questions propounded to me be clear and susceptible of being answered;

(4) that any valid scientific questions be resolved prior to a consideration of issues involving manufacturing or quality control;

(5) that questions regarding the PMA should be propounded by persons who have a basic understanding of the content of the entire application (because, otherwise, the questions frequently make no sense within the context of the PMA);

(6) that the basic rules of science, experimental design and law be applied, and applied consistently;

(7) that the basic principles of fairness be applied, and applied consistently.

I request that the informal conference be held on a face-to-face basis in an open forum with due notice to all interested industry representatives, and that an official record of the hearing be obtained to facilitate further review. If "informal conference" means that I would be closeted in a private room with 6-12 ODE staff with you, then I waive my right to a face-to-face meeting and request a decision on the basis of the paper that has been submitted.

Sincerely,

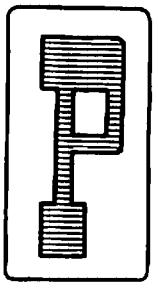
Andrew A. Marino

AAM:pab

cc: Commissioner David Kessler
President Bush

PLASTAFIL, INC.

P. O. Box 268
Belcher, Louisiana 71004



ANDREW A. MARINO, PH. D.
PRESIDENT

July 25, 1991

David Kessler
Commissioner
Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Dear Commissioner Kessler,

I am the President of a small biomedical company, and I am attempting to file a PMA for an artificial ligament. In the process, I have fallen into a cesspool consisting of some of your employees who work in the Office of Device Evaluation. These employeee are misusing FDA's statutory power to regulate filing of a PMA to enforce their personal and unscientific opinions.

I am a well-published scientist, a tenured professor, and a lawyer. I have worked eight years and spent several million dollars performing the best studies regarding an implant material that have ever been performed. I have performed the first controlled clinical study regarding an orthopaedic implant. The quality and scope of the scientific data contained in my PMA is not exceeded or equalled in the world's published literature. Despite this, the ODE has refused to even consider evaluating the scientific merits of my data. Their actions are arbitrary and capricious, and I think motivated by improper considerations.

I ask you to review the facts concerning my application, and to bring about a just resolution.

Sincerely,

Andrew A. Marino

AAM:pab
encl.

CURRICULUM VITAE

ANDREW A. MARINO, Ph.D., J.D.

President
Plastafil, Inc.
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Belcher, Louisiana 71004
(318) 674-6177

Personal Data	Born January 12, 1941, Philadelphia, PA; married; four children; U.S. citizen
Home address	P.O. Box 127, Belcher, Louisiana 71004 (318) 378-4431
Education	B.S., Physics, St. Joseph's College, Philadelphia, PA, 1962
	M.S., Biophysics, Syracuse University, Syracuse, NY, 1965
	Ph.D., Biophysics, Syracuse University, Syracuse, NY, 1968
	J.D., Law, Syracuse University College of Law, 1974
Positions Held	Research Biophysicist, Veterans Administration Medical Center, Syracuse, New York, 1964-1981
	Assistant Professor, Department of Orthopaedic Surgery, SUNY Upstate Medical Center, Syracuse, New York, 1972-1981
	Assistant Professor, Department of Orthopaedic Surgery, Louisiana State University Medical Center, Shreveport, Louisiana, 1981-1985
	Associate Professor, Department of Orthopaedic Surgery, Louisiana State University Medical Center, Shreveport, Louisiana, 1985-1989
	Associate Professor, Department of Bioengineering, Louisiana Tech University, Ruston, Louisiana, 1988-present
	Professor: Department of Orthopaedic Surgery, Louisiana State University Medical Center, Shreveport, Louisiana, 1989 to present
	Department of Cellular Biology and Anatomy, Louisiana State University Medical Center, Shreveport, Louisiana, 1989 to present
	Chairman, LSU Medical School Institutional Review Board for Human Research, June, 1986-1990
	Chairman, Committee on Promotions Guidelines, I990-present
	Chairman, Medical Communications Committee, I990-present
	President of the Faculty of the Medical School, 1991-
	Member, Elected Faculty Council, LSUMC, June, 1986-present

Andrew A. Marino, Ph.D., J.D.

	Member, Institutional Animal Care and Use Committee, 1990-present
	Member, Standing Appeal Committee, 1990-present
	Vice-President, International Society for Bioelectricity, 1981-1983
	President, International Society for Bioelectricity, 1983-1991
	Editorial Consultant in Biophysics and Medical Physics, Encyclopedia of Applied Physics, 1990-present
Editor	Journal of Bioelectricity, 1980-1991
Bar Membership	New York, 1975-present

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