

**REVIEW OF THE
CLINICAL SAFETY EXPERIENCE WITH
GRAFTON® DEMINERALIZED BONE MATRIX**

Prepared for:

OSTEOTECH

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EXECUTIVE SUMMARY

The WEINBERG GROUP INC. was asked to review the clinical safety experience with Osteotech Inc.'s human demineralized bone matrix (DBM) products Grafton® DBM Gel, Grafton® DBM Putty and Grafton® DBM Flex. These materials have been on the market since the early 1990's, and an estimated 350,000 treatments have been performed to date. The purpose of the review was to evaluate the human safety information for Grafton® products based on Osteotech's clinical trial experience, spontaneous reports to Osteotech from the marketplace, and the literature. Of particular interest was specific evaluation for adverse events suggestive of glycerol toxicity.

Clinical trial materials available for analysis included the Grafton® usage database for a total of 659 patients treated with demineralized allogeneic bone matrix gel, bone matrix putty and bone matrix flex in company-sponsored studies, and the various clinical protocols employed. Base line and post-operative laboratory data were available from 73 patients. Data for 173 patients in various control arms was also available for comparison. The spontaneous adverse report database consisted of 26 spontaneous reports submitted to Osteotech Inc. from 1992 to the present, and represents the entirety of the spontaneous feedback. A search of the published literature (1965 to present) for case descriptions involving Grafton® products yielded 24 original articles from which it was possible to derive safety conclusions on 417 patients.

Our analysis identified a broad range of adverse events associated with the use of Grafton® products, from which we conclude:

- # The frequencies of specific adverse events recorded from Osteotech trials, spontaneous adverse event reports, and the literature are consistent with expected adverse experiences in surgical cohorts undergoing graft procedures;
- # Of the most serious events in the clinical trials, including myocardial infarction, congestive heart failure, stroke, seizures and death, none were suggestive of a causal relation to Grafton® DBM specifically;
- # The range of serious and non-serious adverse events in the Grafton®-treated patients was similar to that of control patients, without any suggestion of events specifically related to demineralized bone matrix;
- # Investigators in Osteotech clinical trials identified only solitary cases of urinary anastomosis, leg edema, fever, operative site infection, and graft failure as possibly or likely related to Grafton® DBM;
- # A broad range of laboratory abnormalities were observed, consistent with expected adverse laboratory values in surgical cohorts;
- # Of the noted laboratory abnormalities, only transient hyperglycemia is suggestive of glycerol-related effects;
- # There was no clinical or laboratory evidence for renal failure;
- # Spontaneous adverse event reports were very uncommon;
- # Of the spontaneous reports, all events other than one case of death from sepsis are anticipated complications of the orthopedic procedures employed;

- # Clinical studies reported in the literature indicate Grafton® DBM is well tolerated; no unanticipated adverse experiences were reported; and
- # There were no adverse events suggestive of glycerol toxicity.

In conclusion, our analysis of Osteotech's clinical trial database, spontaneous reports, and the literature did not raise any concerns about the safety of Grafton® products for human bone grafting. The range and frequencies of adverse experiences noted would be anticipated for the types of surgical procedures utilized whether grafting involved glycerol-containing Osteotech demineralized bone matrix (i.e., Grafton® DBM), other forms of demineralized bone matrix, or autograft bone. There is no suggestion from Osteotech's clinical trials, spontaneous adverse event reports, or from the published literature that Grafton® DBM preparations pose safety risks to patients. No adverse experiences were identified that would suggest glycerol toxicity.

INTRODUCTION

The WEINBERG GROUP INC. was asked to review the clinical safety experience with Osteotech Inc.'s human demineralized bone matrix (DBM) Grafton® Grafton® DBM Gel, Grafton® DBM Putty and Grafton® DBM Flex. The purpose of the review was to evaluate the human safety information for Grafton® products based on Osteotech's clinical trial experience, spontaneous reports to Osteotech from the marketplace, and the published and unpublished clinical literature. The safety evaluation was intended to provide an objective overall assessment of product safety, as well as a directed evaluation for potential adverse reactions that might be attributable to glycerol, the carrier excipient which distinguishes Grafton® products from other preparations of human demineralized bone matrix.

Bone grafting is used extensively to treat bone defects sufficient in size to prevent optimal spontaneous healing. Grafting of critical bone defects is common for a wide range of clinical situations including fractures, trauma, bone infections, osteotomies, arthrodesis reconstructive procedures, and augmentation of periodontal defects. Particularly common are spinal procedures for disk herniation and degenerative derangements, scoliosis, post-laminectomy instability, and other fusion procedures. Sources of bone materials are from autografts, allografts, xenografts or synthetic bone substitutes. Autografts are considered the gold standard in terms of clinical experience, demonstrated utility, and safety. However, autografting characteristically involves additional operative time and post-operative morbidity including donor site pain, pseudarthrosis and instability, infection, fracture, sensory loss and increased blood loss. Fear of antigenic responses and inadequate mineralization have limited the use of xenografting and artificial bone substitutes, respectively. In contrast, allografts (bone tissue transplanted from one individual to another) using demineralized bone are well tolerated, without immune rejection, and exhibit both osteoconductive and osteoinductive properties. Consequently, allograft bone grafts have become increasingly popular as an alternative to autografting. Known complications of allograft surgery include operative site infections, insufficient mechanical strength, and graft failure.

Grafton® demineralized bone matrix is prepared from donated human bone, mostly cadaveric in origin. Hydrochloric acid demineralization of ethanol-cleansed bone chips or powder results in demineralized bone matrix (DBM), containing less than five percent residual calcium phosphate mineral content and lacking cellular components. DBM is composed primarily of collagen and various non-collagenous proteins, and in Grafton® is combined with glycerol to increase viscosity and lubricity for optimal handling and dispersion. The absence of a cellular component and type II collagen result in a non-immunogenic preparation unlikely to result in graft rejection. Other processing steps eliminate the potential to transmit donor-derived infectious pathogens. Quantitative removal or inactivation of a variety of clinically relevant viruses and bacteria has been documented. Grafton® DBM has been formulated for different applications as gel, putty, or flexible sheet-like (flex) products.

Grafton® DBM has been used in over 350,000 procedures to date, spanning nearly ten years. It is used in some surgical situations as the sole source of grafted bone and in other situations in combination with autograft material. Its use has been investigated for a number of different orthopedic applications, as will be summarized in this report. Human safety information is

available from a comprehensive Osteotech clinical database of adverse events, spontaneous reports of adverse experiences, and the published literature. This human experience forms the content of this report. When appropriate to the discussions of product safety, considerations of pertinent manufacturing details are also noted. Pre-clinical toxicity evaluations of Grafton® products has been considered elsewhere (expert opinion by Dr. Ronald W James).

METHODS OF THIS REVIEW

The following materials were used by THE WEINBERG GROUP for this review:

CLINICAL DATABASE FROM GRAFTON® STUDIES

This database consists of clinical follow-up of all patients involved in Grafton® studies. The protocols, which also were reviewed, are listed below. Altogether, this patient database documents the clinical follow-up of 659 individual patients who received Grafton® products and 173 untreated patients in control arms. Available for review were the original clinical complication/adverse event forms as well as a tabular summary of findings. Information from the adverse event forms included descriptions of the events, treatments if needed, and clinical outcomes. The comprehensive database also included a causality (relatedness) statement for some of the adverse events as concluded by the Osteotech Clinical Research Department. In addition to the comprehensive adverse event database, laboratory tests were available from 73 patients who had received ≥ 20 cc of Grafton® products.

- # Protocol 0193: The utility of Grafton® allogeneic bone matrix in the formation of new bone following lumbar spinal fusion (*DBM + autologous bone vs. autologous bone only*).
- # Protocol 0294: A pilot study of a specific form of Demineralized Bone Matrix (Grafton® Allogeneic Bone Matrix (ABM)) in long bone grafting procedures (*DBM + bone marrow aspirate*).
- # Protocol 0395: Analysis of spine fusion utilizing demineralized bone matrix (*DBM + local autologous bone +/- other allograft bone vs. iliac crest autograft alone*).
- # Protocol 0495: A randomized controlled trial of a specific form of demineralized bone matrix (Grafton® Demineralized Bone Matrix Putty) plus bone marrow aspirate versus autologous bone (autograft) in long bone grafting procedures (*DBM putty + bone marrow aspirate vs. iliac crest autograft*).
- # Protocol 0795: A randomized controlled trial of a specific form of demineralized bone matrix (Grafton® Demineralized Bone Matrix Putty) versus autologous bone in lumbar spinal fusion procedures (*DBM putty + iliac crest autograft vs. iliac crest autograft alone*).
- # Protocol 0996: A randomized controlled trial of core decompression versus core decompression augmented with Grafton® Demineralized Bone Matrix Gel for the surgical management of osteonecrosis of the femoral head (*DBM gel + decompressions vs. decompression alone*).
- # Protocol 1096: The utility of Grafton® in acetabular reconstruction for revision hip arthroplasty (*DBM gel + morselized femoral head bone*).

- # Protocol 1598: A retrospective assessment of the performance of a composite graft of cancellous allograft and Grafton® DBM Gel compared to iliac crest autograft, in treating long bone osseous defects and non-unions secondary to trauma or infection (*DBM gel + cancellous allograft bone vs. iliac crest autograft*).
- # Protocol 1798: A retrospective assessment of the performance of Grafton® DBM as a substitute to iliac crest bone graft in treating bone defects from acute fractures, osteotomies, arthrodeses, and non-unions (*DBM gel or putty + cancellous allograft or cortical chips vs. DBM alone*).
- # Protocol 1899: A retrospective study of the use of Grafton® demineralized bone matrix putty in lumbar interbody fusion with the Ray TFC™ or BAK™ interbody cage devices (*DBM putty + local autologous bone*).
- # Protocol 1999: A retrospective assessment of the performance of a composite Grafton® DBM putty and local autologous bone in instrumented posterolateral spine fusion procedures (*DBM putty + local autologous bone*).
- # Protocol 1196: A case study of a specific form of Demineralized Bone Matrix (Grafton® Demineralized Bone Matrix Flex) used in burr hole defects resulting from craniotomy procedures (*alternating layers of DBM flex and bone dust autograft*).
- # Protocol 0595: A retrospective study of a specific form of demineralized bone (Grafton® Demineralized Bone Matrix Gel) versus autologous bone in anterior cervical discectomy and arthrodesis (*DBM gel + fibula allograft bone vs. autologous iliac crest autograft*).
- # Protocol 1698: A randomized controlled trial of Grafton® Demineralized Bone Matrix Putty versus iliac crest autologous bone in lumbar spine fusion procedures (*DBM putty + autologous bone marrow aspirate + local bone autograft vs. DBM putty + iliac crest autograft vs. iliac crest autograft alone*).

SPONTANEOUS ADVERSE EVENTS DATABASE

This database consists of all spontaneous reports of adverse events received by Osteotech from 1992 to the present. Spontaneous reports were submitted from either the treating physician or from the client tissue banks. Altogether, this database documents adverse experiences communicated to Osteotech Department of Compliance from 26 patients treated during this time period. Available for review were the original Incident Report forms as well as a tabular summary of findings. Information from the incident reports included descriptions of the events, treatments if needed, and clinical outcomes. The comprehensive database also included a causality (relatedness) statement for each adverse event as concluded by the Osteotech Quality Systems Department, and comments regarding the investigation in each case for evidence of a product defect.

PUBLISHED AND UNPUBLISHED LITERATURE

A search was performed for English language literature describing the clinical experience with Grafton® products. Search criteria included the terms “demineralized bone matrix”, “Grafton” and “Osteotech”, and papers were restricted to those with “clinical” characteristics. The databases searched were MEDLINE (1966-2000), Toxline (1965-2000), Biosis Reviews (1969-2000), EMBASE (1974-2000), and SciSearch (1990-2000). Additional unpublished literature based on clinical studies and case reports was provided by Osteotech Inc. All literature was included for review, including single case reports. Also obtained were selected review articles concerning the potential toxicities that could be anticipated from glycerol, the excipient used in the Grafton® formulations.

FINDINGS FROM ANALYSIS OF THE GRAFTON® STUDIES CLINICAL DATABASE

CLINICAL ANALYSIS

The experience of Osteotech's various prospective and retrospective clinical investigations includes procedures that are representative of the range of clinical applications of Grafton®. Procedures used Grafton® in gel, putty, and flex formulations. Surgeries involved the lumbar spine, cervical spine, long bones, hip, and cranium. Some studies involved combination of Grafton® with autologous bone marrow, autologous bone dust, local site autograft bone, iliac crest autograft bone or other allograft bone preparations. Several studies included a control arm using autograft bone as the gold standard procedure. Protocols included periodic clinical follow-up examinations for safety and efficacy evaluations for 12-24 months after surgery.

Safety data have been collected for patients enrolled in the various Osteotech clinical trials, many of which are still ongoing. Data have been received from 1992 to the present. The following tables summarize all the adverse events documented from the various Osteotech clinical trials involving altogether 659 individual patients to date, all of which received a Grafton® product (gel, putty or flex). Safety results from 173 patients in the control arms of the various trials were also available for review.

A total of 303 adverse events were recorded from 201 patients who received Grafton® DBM products. These adverse events were broadly distributed between clinical protocols in which Grafton® volumes used ranged from 1 cc to 30 cc. Interestingly, no adverse events were recorded for three patients in the spine putty study (protocol 1698, lumbar fusion procedures) who received the highest doses of Grafton® (60 cc). In some instances, more than one adverse event was noted per patient. Multiple adverse events reports were in some cases from the same follow-up date, and in other cases from different times during the clinical follow-up periods. In some studies, a causality assessment was made by the reporter concerning the relationship between the Grafton® product used and the specific event noted (62 percent of adverse event reports included causality assessments). In other instances, causality assessments were not available. Complete summaries of each adverse event, with description of the reaction, reporter causality assessment and clinical outcome, are presented in Appendix 1.

Frequency lists of the adverse events reported from patients who received Grafton® products, listed as COSTART terms according to body system, are presented below. A comparison of frequency lists for Grafton® patients vs. control patients is presented in Appendix 2. For evaluation of the reported adverse experiences as relate to Grafton®, it is necessary to consider the range of adverse events that would be anticipated due to the orthopedic procedures involved as well as potential toxicities specifically related to Grafton® products. As discussed in more detail in the section of this report entitled "Overall Consideration of the Adverse Events Associated with DBM in Orthopedic Procedures", recognized adverse outcomes of bone grafting procedures in general include blood loss, infection, hematoma, deep venous thrombosis, pulmonary embolus, neural injury, donor site complications (pain, infection, instability), and graft failure. Serious complications from Osteotech's clinical trials are thus discussed in the following body system frequency tables.

**Table 1.
BODY AS A WHOLE**

<u>COSTART TERMS</u>	<u>Total Terms Reported</u>
Accident	4
Addiction - pain killers	1
Allergic Reaction	1
Back Injury	3
Burning and Numbness	1
Death	4
Edema	1
Fall	11
Fever	3
Fluid collection	1
Graft complications/failure	7
Hardware complications/failure	43
Headache	3
Infection, wound	39
Infection, not otherwise specified	12
Infection, site	2
Injection, inadvertent	1
Laceration - accidental operative	1
Narcotic withdrawal	1
Nonunion	3
Pain	23
Pain control - use of heroin	1
Painful Retained Hardware	7
Stiffness	1
<u>Transitional symptoms</u>	<u>1</u>
<i>Total Events (percent of all terms reported)</i>	<i>175 (57%)</i>

As shown in Table 1, 175 total adverse events (57 percent of all events) were documented, the most common of which were hardware complications or failure, wound infections, and pain. The range of complications is similar to those reported in the control arms of these trials (Appendix 2). Most of the listed adverse events in this table are expected complications of the types of orthopedic procedures involved in these studies. In approximately two-thirds of cases, reporter causality assessments were available. Causality was concluded “Unrelated” in 88 percent of these assessments. Of the remaining events, one instance of graft failure was felt related to the Grafton® Gel used. Three events were felt possibly related to Grafton®: one each of fever, leg edema, and hip infection. An additional 18 adverse events were reported with “Unknown” causality. These included one case of deep infection, two of graft failure, three non-unions, four operative site infections, three device failures, loss of height, two reports of degenerative joint disease, and two reports of ectopic bone. None of these adverse events are beyond the scope of anticipated complications for bone graft procedures in general.

Four deaths were reported. In the first case, a patient received Grafton® Flex for a craniotomy procedure. More than 26 weeks after the procedure, the patient died with metastatic meningioma. The investigator concluded that the death was unrelated to Grafton®. In the second case, a patient died from a massive cerebral artery stroke at an unspecified time after spinal fusion. Causality was not assessed for this case, but the narrative presented no reason to

suspect that death was due to either of the bone grafting materials utilized in this surgery, Grafton® or iliac crest autograft bone. In the third case, the patient died from a self-inflicted gunshot wound to the head. In the fourth case, the patient died from a ruptured aneurysm an unspecified time after receiving Grafton® Flex for a craniotomy procedure. The investigator concluded that the death was unrelated to Grafton®.

Table 2.
CARDIOVASCULAR SYSTEM

<u>COSTART Terms</u>	<u>Total Terms Reported</u>
Blood pressure drop	1
Cerebral vascular accident, stroke	4
Congestive heart failure	1
Fibrillation, Atrial	1
Hypertension	1
Myocardial infarction	2
Thrombophlebitis	1
<u>Vascular necrosis</u>	<u>1</u>
<i>Total Events (percent of all terms reported)</i>	12 (4%)

Cardiovascular complications were rare (4 percent of all events), and in no case was the event believed related to Grafton®. Six cases of serious cardiovascular adverse reactions were reported without a reporter causality statement. Atrial fibrillation, congestive heart failure and hypertension each developed in a single patient at unknown times after surgery. Strokes occurred at unknown times after surgery in three patients, one of whom had previously been treated by carotid endarterectomy. These cardiovascular events can occur as general post-operative sequelae, and none of these cases suggest an adverse experience related to Grafton® or its glycerol excipient specifically.

Table 3.
DIGESTIVE SYSTEM

<u>COSTART Terms</u>	<u>Total Terms Reported</u>
Crohns Disease	1
Gastrointestinal reflux	1
GI bleed, upper	1
<u>Stomach biopsy</u>	<u>1</u>
<i>Total Events (percent of all terms reported)</i>	4 (1%)

Digestive system complications were rare (1 percent of all events). All but an event of gastrointestinal reflux (causality assessment unavailable) were concluded by the reporter to be unrelated to Grafton®. Reflux developed at an unknown time related to the surgical procedure (lumbar spinal fusion), and resolved with medical therapy. None of these adverse experiences suggest a specific relationship to Grafton®.

**Table 4.
HEMIC & LYMPHATIC SYSTEM**

<u>COSTART Terms</u>	<u>Total Terms Reported</u>
Anemia	3
Coagulopathy	2
Deep venous thrombosis	3
Elevated platelet	1
Hematuria	1
High white blood count	1
Leukocytosis – chronic	1
Low blood count	1
Seroma	5
<u>Thrombocytopenia</u>	<u>2</u>
<i>Total Events (percent of all terms reported)</i>	20 (6%)

A variety of hematologic abnormalities were reported, comprising 6 percent of all adverse events. One quarter of these events were considered unrelated to the Grafton® products utilized. For the remainder, causality assessments were not available.

Hematologic abnormalities are of particular interest because Grafton® products contain glycerol as the sole excipient. As discussed in more depth in the section entitled “Other Issues in the Consideration of Grafton® Safety”, glycerol is capable of inducing a variety of clinical abnormalities. Principal among them are hematologic consequences of hemolysis, including anemia, hemoglobinemia, and hemoglobinuria. Rarely, hemolysis can result in a disseminated coagulopathy, characterized by thrombocytopenia and prolonged clotting times. Review of laboratory test results showed that these laboratory abnormalities typically were mild in the Grafton® studies, and would not have been of clinical significance. Although the hematologic findings of anemia, coagulopathy, and thrombocytopenia observed rarely in the Osteotech clinical studies are of unclear etiology, it should be recognized that each of these laboratory abnormalities is frequently observed secondary to common surgical complications such as blood loss, infection, and anticoagulation with either coumadin or heparin. Similarly, thrombocytosis and leukocytosis are common occurrences in the post-surgical setting with generalized inflammatory or infectious processes, and are not necessarily related to Grafton® per se. Also not clearly related to Grafton® use were the three cases suggestive of deep venous thrombosis. Reported from these studies in approximately 0.5 percent of patients, this constitutes a rate similar to that of orthopedic operations in general.

**Table 5.
METABOLIC & NUTRITIONAL**

<u>COSTART Terms</u>	<u>Total Terms Reported</u>
Diabetes	1
<u>Electrolyte imbalance</u>	<u>1</u>
<i>Total Events (percent of all terms reported)</i>	2 (1%)

One case of diabetes was reported. Although hyperglycemia can be a consequence of glycerol administration by means of glycerol metabolism, this particular patient required insulin treatment for this complication which was felt by investigators to be unrelated to Grafton®. Mild electrolyte imbalance, reported in a different patient, can be seen with surgical procedures in general, and cannot be assumed related to Grafton®.

Table 6.
MUSCULOSKELETAL SYSTEM

<u>COSTART Terms</u>	<u>Total Terms Reported</u>
Acetabular cyst	1
Arthritis	2
Arthroplasty, knee	1
Bone formation	1
Bone resorption	2
Bursitis	3
Carpal Tunnel syndrome	3
Degeneration	2
Degenerative joint disease	2
Disc injury (new) - L4-L5	1
Dislocation	8
Fibular tetherin	1
Fracture	8
Failed back syndrome	1
Fibromyalgia symptom	1
Herniation	2
Hip replacement	1
Knee stiffness	2
Meniscus injury	2
Osteoarthritis	1
Osteophyte formation	1
Pseudoarthrosis – possible	2
Spondylosis	1
Stenosis	2
Thoracic outlet syndrome	1
<u>Weakness, lower extremity</u>	<u>1</u>
<i>Total Events (percent of all terms reported)</i>	<i>53 (17%)</i>

Musculoskeletal events were relatively common, occurring in 17 percent of cases. These sorts of events are common as either underlying conditions or as sequellae of the orthopedic procedures employed, and nearly all of these events were considered “Unrelated” to Grafton® by the clinical investigators. Adverse events for which causality assessment was unavailable include bursitis, possible new disc injury, degenerative joint disease, two fractures, and two possible pseudoarthroses. Due to their common occurrence in orthopedic patients receiving the surgical procedures in these trials, it is impossible to conclude them related to Grafton®.

**Table 7.
NERVOUS SYSTEM**

<u>COSTART Terms</u>	<u>Total Terms Reported</u>
Cerebral Spinal Fluid Leak	2
Cognitive disorders	1
Facial Twitching	1
Foot drop – right	1
Hemorrhage – intracerebral (secondary to self-inflicted gunshot wound)	1
Leg goes out – Left	1
Nerve Root Compression	1
Neural injury	1
Occipital neuralgia	1
Paresthesia	4
Perineural fibrosis	1
Radiculopathy	2
<u>Seizure</u>	<u>2</u>
<i>Total Events (percent of all terms reported)</i>	19 (6%)

Nervous system events were infrequent, 6 percent of total adverse events. The majority of these events were felt by the clinical investigators to be unrelated to Grafton®, and are relatively common adverse outcomes in orthopedic surgical procedures. Among serious events, seizure presents an adverse experience potentially related to Grafton®. In one case, investigators ascribed this reaction to Xanax withdrawal; in the other case, investigators concluded the seizures were not related to Grafton® but did not identify a suspected etiology.

**Table 8.
RESPIRATORY SYSTEM**

<u>COSTART Terms</u>	<u>Total Terms Reported</u>
Acute respiratory distress syndrome	1
Bronchospasms intraoperatively	1
<u>Pneumonia, aspiration</u>	<u>1</u>
<i>Total Events (percent of all terms reported)</i>	3 (1%)

Respiratory events were uncommon, comprising 1 percent of all recorded adverse events. Aspiration pneumonia was considered unrelated to Grafton® by the investigators, whereas no causality assessments were presented for the cases of respiratory distress syndrome and intraoperative bronchospasm. Each of these complications, however, is relatively frequent for operative procedures in general, and do not suggest a relationship to Grafton®.

Table 9.
SKIN & APPENDAGES

<u>COSTART Terms</u>	<u>Total Terms Reported</u>
Hematoma	2
Lipoma	1
Ulcer, heel/ankle	1
<u>Wound dehiscence</u>	<u>1</u>
<i>Total Events (percent of all terms reported)</i>	5 (1%)

Skin system events were uncommon, comprising 1 percent of all recorded adverse events. Lipoma is a common underlying cutaneous condition, cutaneous ulcers are common in the population undergoing bone graft procedures, and hematomas and wound dehiscence are recognized complications of operative procedures in general. None of these events were felt related to Grafton® by the clinical investigators.

Table 10.
UROGENITAL SYSTEM

<u>COSTART TERMS</u>	<u>Total Terms Reported</u>
Bowel and bladder problems	2
Erectile dysfunction	2
Incontinence	1
Kidney stones requiring hospitalization	1
Prostate enlargement	1
Prostatitis, chronic	1
Urinary anastomosis	1
<u>Urinary retention</u>	<u>3</u>
<i>Total Events (percent of all terms reported)</i>	12 (4%)

Urogenital system events were fairly uncommon, comprising 4 percent of all recorded adverse events. Of these events, only one instance of urinary anastomosis during a lumbar spinal fusion study was felt by investigators to be related to Grafton® (mechanism unstated). The other adverse experiences are fairly common as underlying conditions or as consequences of surgical procedures, and are not suggestive of a reaction to Grafton® specifically. Notably, there were no reports of renal failure, an anticipated potential complication from the glycerol excipient in Grafton® products. A screening for subclinical renal abnormalities is described in the following section, Laboratory Analysis.

LABORATORY ANALYSIS

In addition to baseline and post-operative general clinical and radiographic data, the studies comprising the Grafton® clinical database may have included baseline and routine follow-up laboratory evaluations. In many instances, organ toxicity can be detected by appropriate laboratory testing even when clinical signs and symptoms are insufficient to result in an overt adverse event. For the specific evaluation of Grafton® safety, it could be anticipated that many patients not identified with adverse events in the clinical database may have laboratory abnormalities and, reciprocally, that many clinical adverse events may fail to demonstrate corresponding laboratory changes. In order to obtain an independent safety assessment based on laboratory abnormalities potentially associated with the use of Grafton® DBM, available laboratory data were analyzed for patients most likely to have exhibited changes between baseline and post-operative measurements, i.e., those who received substantial (≥ 20 cc) quantities of Grafton® products. All laboratory data made available from investigators were evaluated.

Both baseline pre-operative and post-operative laboratory data were available for analysis from 73 patients treated with Grafton® DBM. Laboratory data from control arm patients were not available for comparison. Grafton® products used were gel (59 cases), putty (13 cases) and flex (1 patient, 14 layers). Quantities of gel or putty used ranged from 20-50 cc. In 68 patients laboratory data were available both pre-operatively and post-operatively within 7 days of surgery. In the other 5 cases, post-operative lab data were obtained within 2-3 weeks after surgery. Available laboratory data included some or all of the following: electrolytes and other chemistries, complete blood counts and differentials, coagulation assays, urine analysis, microbiology culture results and transfusion product logs. Blood gas data were available in some cases but were not evaluated because of uncertain temporal relationships with surgeries and use of anesthetics. Laboratory tests of potential clinical significance were tabulated; results are presented in Table 11.

A broad range of laboratory abnormalities were observed post-operatively. Most commonly observed were anemia, hyperglycemia, and leukocytosis. Other chemistry and hematology abnormalities were also noted. None of the laboratory abnormalities were life-threatening, and most were shown to be resolving by subsequent follow-up laboratory assays.

In general, the spectrum of laboratory abnormalities would be anticipated as a consequence of the surgical procedures themselves, post-operative organ dysfunction, or as a result of anesthesia. Anemia is common due to blood loss during orthopedic surgery. Hyperglycemia can be seen as a general metabolic response, in settings of infection or exacerbated diabetes, or can be iatrogenic in nature (i.e., intravenous glucose infusion or as a drug reaction). Leukocytosis is common with stress, as in surgery or general inflammatory states, or as a response to infection. The less common laboratory abnormalities detected are similarly non-specific, and do not provide any particular insight for potential Grafton® toxicities. In many instances, multiple laboratory abnormalities were present in a single case associated with infection, serious cardiovascular events, or other significant adverse events.

Table 11.
LABORATORY ANALYSIS

LABORATORY ABNORMALITIES*	TOTAL NUMBER OF ABNORMALITIES REPORTED (from 73 patients with available data**)
Low hemoglobin/hematocrit	34
Leukocytosis	20
Leukopenia	2
Thrombocytosis	6
Thrombocytopenia	6
Hypernatremia	1
Hyponatremia	5
Hyperkalemia	1
Hypokalemia	10
Hyperchloremia	11
Hypochloremia	1
Hyperglycemia	36
Hypocalcemia	12
Hyperphosphatemia	1
Hypophosphatemia	1
Hypomagnesemia	3
Hypoferremia	7
Increased ALAT and/or ASAT	5
Increased LDH	8
Increased creatine phosphokinase	2
Hypoproteinemia	9
Increased PT and/or PTT	7
Urine red blood cells and/or hemoglobinuria	3

* Laboratory abnormalities are relative to pre-operative values, and all represent values above the normal range for that laboratory

** Not all laboratory tests were obtained for every patient

With particular regard to potential kidney toxicity due to glycerol, 57 patients had renal function measurements (BUN and creatinine) both pre-operatively and post-operatively within 1-7 days. Three additional cases had post-operative labs from 1-3 weeks after surgery. No patient showed worsening of their renal function status. Of the 57 patients evaluated within 7 days of surgery, 56 had normal BUN and creatinine measurements both pre- and post-operatively. The entire laboratory test database contained only a single patient with renal function abnormalities. This patient had elevated BUN and creatinine levels both pre-surgery and post-surgery, but without significant changes through post-operative day 3 (the last day with available data). Therefore, no evidence exists suggesting glycerol-induced renal disease.

Two other possible abnormalities that could represent glycerol toxicity would be hemolysis secondary to hyperosmolality, and hyperglycemia. Hemolysis would be suspected on the basis

of hematuria or newly developed anemia. Hematuria was rare, and in no instances was hemolysis considered. Although anemia was common, there was no suggestion that this represented hemolysis (i.e., schistocytic or spherocytic red blood cells were not noted) due to glycerol-related hyperosmolality. However, definitive laboratory assays for hemolysis, such as serum haptoglobin or urinary hemosiderin, were not obtained in any instance.

Hyperglycemia, as a potential result of glycerol load, was common, and is the sole laboratory abnormality suggestive of a glycerol effect. Most commonly, hyperglycemia was mild to moderate (10-50 mg/dL above the upper limit of normal) and transient. When occurring on the day of surgery, modest hyperglycemia may have been related to glycerol absorption, whereas hyperglycemia developing later in the post-operative course would be unlikely related to glycerol in Grafton®. In two cases, more severe hyperglycemia (greater than 100 mg/dL above the upper limit of normal) was detected. Neither case listed an adverse event near the time of surgery, although one of the cases reported a cerebrospinal fluid leak two years later. In one case, hyperglycemia peaked one day after surgery and resolved within three days, and in the other hyperglycemia peaked the day of surgery, then declined to near normal by the following morning. Glycerol cannot be excluded as causing these hyperglycemic reactions.

CONCLUSIONS DERIVED FROM ANALYSIS OF THE CLINICAL TRIAL DATABASE

Known intra- and post-operative serious complications for the types of orthopedic procedures in the various Osteotech clinical trials include blood loss, infection (surgical or graft-derived), hematoma, deep venous thrombosis, pulmonary embolus, neural injury, donor site complications (pain, infection, instability), and graft failure. Many non-serious complications of surgical procedures would also be anticipated. A variety of laboratory abnormalities would be expected associated with the types of orthopedic procedures in the various Osteotech trials. From consideration of anticipated complications of these various surgical procedures and the observed adverse events and laboratory abnormalities from the clinical database, we conclude:

- # The total number of patients involved (659) and wide array of orthopedic procedures studied provide a useful assessment of Grafton® DBM safety;
- # A broad range of adverse events were observed, spanning all the major body systems;
- # The frequencies of specific adverse events recorded are consistent with expected adverse experiences in surgical cohorts;
- # The frequencies of specific adverse events observed in Grafton®-treated patients were similar overall to the adverse events in control patients. When there were differences in specific adverse events between groups, it was equally likely that either the control group or the Grafton® group had the greater frequency.
- # Most commonly observed events were anticipated complications of the orthopedic surgical procedures employed, or of orthopedic surgeries in general. Of the most serious events, including myocardial infarction, congestive heart failure, stroke, seizures and death, none were suggestive of a causal relation to Grafton® specifically;
- # Investigators identified only solitary cases of urinary anastomosis, leg edema, fever, operative site infection, and graft failure as possibly or likely related to Grafton®;

- # A broad range of laboratory abnormalities were observed, consistent with expected adverse laboratory values in surgical cohorts;
- # Of the noted laboratory abnormalities, only transient hyperglycemia is suggestive of glycerol-related effects;
- # There was no clinical or laboratory evidence for renal failure; and
- # There is no suggestion from the clinical trial database that Grafton® DBM preparations pose safety risks to patients.

**FINDINGS FROM ANALYSIS OF THE GRAFTON®
SPONTANEOUS ADVERSE EVENTS DATABASE**

Spontaneous reports of Grafton®-related events have been collected from 1992 to the present, during which time an estimated 350,000+ surgical procedures using Grafton® were conducted. During this eight-year time period, a total of 26 spontaneous reports have been received. Adverse event frequency rates should not be calculated based on these reports since surgery-related complications are clearly underreported. One of the 26 spontaneous reports was submitted directly by a surgeon, and the remainder by Osteotech’s client tissue banks who distribute Grafton®. Summaries of these individual reports are presented in Appendix 3.

**Table 12.
SUMMARY OF SPONTANEOUS ADVERSE EVENT REPORTS,
1992-PRESENT**

<u>COSTART Term</u>	<u>TOTAL EVENTS REPORTED</u>
Death	1
Infection	20
Exudate, post-operative	1
Fever	2
Fluid at Implant	1
<u>Immune Response</u>	<u>1</u>
TOTAL REPORTS	26

Although Osteotech conducted investigations in each case for possible product defects (in all cases negative), adverse event causality assessments typically were not provided by the submitting agencies. However, in five instances, case narratives indicate that the involved physicians did not believe that the Grafton® products were the cause of the observed complications. Grafton® was specifically not implicated for four of the cases of infection and the report of the patient death, which was concluded to be due to sepsis.

CONCLUSIONS DERIVED FROM ANALYSIS OF THE SPONTANEOUS REPORTS DATABASE

- # Spontaneous adverse event reports submitted to Osteotech were extremely uncommon, although it is generally recognized that underreporting is typically 10-fold or greater;
- # All events other than the case of death from sepsis are anticipated complications of the orthopedic procedures employed; and
- # There is no suggestion from the spontaneous adverse events database that Grafton® DBM preparations pose safety risks to patients.

FINDINGS FROM ANALYSIS OF THE GRAFTON® LITERATURE

Review of the human clinical literature during the past 30 years yielded only 24 original articles that provided safety assessments for Grafton® DBM products. These studies reported results from a range of orthopedic and dental procedures, altogether involving 417 patients. Most studies used Grafton® gel, with lesser number of procedures involving flex or putty. Literature on demineralized bone matrix not prepared by Osteotech was excluded from this review as the processing steps were not identical, and only Osteotech Grafton® DBM preparations contained glycerol.

Whereas each of the studies presented some form of quantitative assessment of graft efficacy (graft survival, healing rates, new bone formation, implant stability, etc.), safety assessments were in general much less detailed. In many reports, safety assessment consisted of the brief statement that no problems were noted. However, in 4 reports specific adverse events including wound infections, graft failure, and non-unions were listed, as described in the table below. These adverse outcomes would each be anticipated from the types of orthopedic procedures involved, and do not suggest specific adverse reactions to Grafton® products. The overall complication rate calculated from these reports, 3 percent, is lower than that anticipated and likely represents underreporting due to opinion of the authors that post-operative adverse experiences were not related to the graft material.

Table 13.
ADVERSE REACTIONS FROM THE GRAFTON® DBM LITERATURE

DESCRIPTION OF PRODUCT	NUMBER OF PATIENTS TREATED	FOLLOW-UP PERIOD	ADVERSE REACTIONS	REF.
DBM ¹	21	52 mo	None	1
DBM	11	14-24 mo	None	2
DBM PUTTY	2	1 yr	Wound Infection (1)	3
DBM GEL	6	1 yr	None	4
DBM GEL	34	7-24 mo	Delayed union (1), non-union (1)	5
DBM GEL	7	6-7 mo	None	6
DBM	36	1 yr	None	7
DBM	36*	2 yr	None	8
DBM	61	9-28 mo	None	9
DBM GEL, PUTTY OR FLEX	40	3 yr (ongoing)	None	10
DBM	56	2 yr	None	11
DBM FLEX OR PUTTY	13	10-24 mo	None	12
DBM GEL	13	5-14 mo	None	13
ABM ²	1	4 mo	None	14
DBM GEL	1	8 mo	None	15
DBM GEL	1	3 mo	None	16
DBM PUTTY	7	11 mo	Infection (2)	17
DBM GEL	12	1 yr	None	18
DBM GEL	1	1 yr	None	19
DBM GEL	6	2-6 mo	None	20
DBM	37	6-33 mo	None	21
DBM	39	12-31 mo	Graft failures (5), Infection (1)	22
DBM	1	6 mo	None	23
DBM gel	11	6 mo	None	24

¹ Demineralized Bone Matrix

² Allogeneic Bone Matrix, not otherwise described

* These patients were the same (longer-term follow-up) as for the previous citation.

Several additional publications touch upon Grafton® safety without specifically describing patient safety outcomes. A study of Grafton® DBM in lumbar spine fusion described clinical success in 61 patients but did not mention any aspects of safety (25). In addition, review descriptions of Grafton® DBM attest to general safety of these products (26-29).

CONCLUSIONS DERIVED FROM ANALYSIS OF THE GRAFTON® LITERATURE

- # Clinical studies reported in the literature indicate Grafton® DBM is well tolerated;
- # Adverse events noted are expected and consistent with those observed in Osteotech clinical trials;
- # Adverse events considered relevant for reporting by the authors are very infrequent; and
- # There is no suggestion from the published literature that Grafton® preparations pose safety risks to patients.

OVERALL CONSIDERATION OF THE ADVERSE EVENTS ASSOCIATED WITH GRAFTON® DBM IN ORTHOPEDIC PROCEDURES

A general picture of Grafton® DBM safety can be pieced together from consideration of the Osteotech clinical trials, the spontaneous adverse event reports, and the literature. From these sources, safety information is available for approximately 1,100 individuals undergoing a variety of orthopedic procedures involving Grafton® products. These safety data provide a quantitative view to supplement the overwhelming but objectively unsubstantiated user opinions in the orthopedic and dental literature that: “DBM can be used safely” and “DBM grafting is a suitable alternative to autologous iliac crest bone grafts.” In this regard, review of the literature on Grafton® DBM did not identify even a single comment questioning the general safety of Grafton® products.

It is important to recognize the inherent biases from each of these sources of information. The clinical summary from Osteotech’s trials provides the most complete assessment of possible adverse experiences because safety and efficacy are equivalent concerns of the investigations. Each of the studies included as a major objective the determination of type, frequency, and severity of postoperative complications and adverse events. The unfortunate limitation to this source of information is the unavailability of safety information from the various control arms of these studies in which Grafton® DBM was not used. Thus, it is not possible to compare adverse event frequency rates for Grafton®-treated and untreated cohorts. The spontaneous consumer reports suffer from the typical deficiencies of spontaneous adverse event reporting, i.e., that reporting of adverse experiences is uncontrolled, spotty, biased by the interests and concerns of consumers, and inadequate for frequency determinations. Evaluation of the literature using Grafton® products suffers from similar limitations because most studies reported were small and typically focused on specific issues of efficacy rather than safety. In general, literature reports of this type refer only to unexpected safety findings, and do not specify the anticipated and common events.

Despite these limitations to the data, the following safety-related conclusions concerning adverse event scope and frequency can be drawn concerning the clinical use of Grafton® DBM:

- # The scope of complications reported for Grafton® DBM is similar to the known intra- and post-operative complications for these types of orthopedic procedures using other forms of bone graft material. Recognized adverse outcomes of major orthopedic procedures, both with or without bone grafting, include blood loss, infection (surgical or graft-derived), hematoma, deep venous thrombosis, pulmonary embolus, neural injury, donor site complications (pain, infection, instability), and graft failure. Rarely, patients experience serious cardiovascular events, coagulation abnormalities, renal dysfunction (most commonly acute tubular necrosis) or death following such major surgical procedures. None of the adverse events associated with use of Grafton® DBM fall outside of this range of anticipated outcomes.
- # The frequency of complications reported for Grafton® DBM is also similar to the known intra- and post-operative complications for these types of orthopedic procedures. The most common adverse events noted, hardware complications, infections and pain, were observed

in 3-6 percent of patients in the Osteotech clinical trials. Serious events such as death, myocardial infarction, stroke, thrombosis and respiratory distress were each observed in less than 0.5 percent of patients. For comparison, the following tables present published morbidities and complication rates for lumbar spinal fusions and autograft donor sites. None of the adverse events associated with use of Grafton® in the Osteotech clinical trials fall outside of an anticipated range of adverse outcomes based on the tables below.

Table 14.
REPORTED COMPLICATIONS OF LUMBAR FUSION*

<u>Complication</u>	<u>Mean, percent (range, %)</u>
In-hospital mortality	0.2 (0-2.3)
Deep Infection	1.5 (0-5.2)
Superficial Infection	1.6 (0-4.0)
Deep vein thrombosis	3.7 (0-11.2)
Pulmonary Embolus	2.2 (0-6.1)
Neural Injury	2.8 (0-16.5)
Donor site Infection	1.5 (0-5.2)
Donor site pain	8.7 (0-37.1)
Donor site pelvic instability	1.9 (1.1-2.6)
Other	8.7 (1.0-42.6)

Source: Turner JA, et al. (Reference 30)

* This compilation is a literature review illustrating the frequency of complications associated with lumbar fusion surgery. Data were obtained from 47 articles, each with at least one year follow-up time for at least 30 patients. Specific complications were reported in anywhere from 2 to 29 of the articles reviewed.

Table 15.
REPORTED DONOR SITE COMPLICATIONS
ILIAC CREST OR LONG BONE AUTOGRAFTS*

<u>Complication</u>	<u>Frequency</u>
Deep Wound Infection	2.5%
Major hematoma	1.2%
Prolonged pain	2.5%
Sensory loss	1.2%
Wound breakdown	0.4%
Osteomyelitis	0.4%
Superficial Infection	N/A
Wound drainage	N/A

Source: Younger EM and Chapman MW. (Reference 31)

* This report was from a retrospective review of the medical records of 239 patients with orthopedic procedures that involved obtaining 243 total autologous bone grafts. The overall complication rate (serious and non-serious) in this study was 8.6 percent.

Table 16.
INCIDENCE OF SERIOUS COMPLICATIONS
AFTER LUMBAR DISCECTOMIES

<u>Complication</u>	<u>Frequency</u>
Death from all causes	0.06%
Wound Infection	0.19%
Septicemia and Meningitis	0.12%
Neurological complications	0.30%
Stroke	0.4%
Myocardial Infarction	0.06%
Arrhythmia	0.02%
Pulmonary Embolus	0.11%

Source: Ramirez LF and Thisted R (Reference 32)

* This report was from a retrospective review of patient discharge abstracts of 28,395 patients with lumbar discectomies in 1980. The overall rate of serious complications was 1.6 percent. Non-serious complications were not reported.

OTHER ISSUES IN THE CONSIDERATION OF GRAFTON® DBM SAFETY

Three additional issues require consideration for assessing Grafton® DBM safety: risk of pathogen contamination, risk of immunologic reaction, and the risk of excipient-related toxicity, in particular glycerol. The first two of these issues pertain to allograft materials in general, whereas the potential for glycerol toxicity is specific to the Grafton® preparations marketed by Osteotech.

Pathogen contamination of human allograft products is the greatest potential risk for product safety. Contamination is possible via infected donor material or can be acquired during processing of the cadaveric graft material. To minimize the potential for inadvertent inclusion of donor-contaminated material, donor bone tissue is initially screened by a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Such screening involves testing a blood sample from the donor for HIV (antibody to HIV types 1 and 2, HIV p24 antigen testing by PCR), hepatitis B (surface antigen and core antibody serologies), hepatitis C (antibody serology), HTLV-1 (antibody), HIV-2 (antibody), and syphilis (RPR or FTA). Additional HIV and hepatitis C assays using recently available but still unlicensed nucleic acid testing procedures are currently being evaluated for use in cadaveric sera, and may lessen even further the potential for unsuspected donor positivity. These screening procedures make the risk of donor positivity for these various pathogens at less than 0.001percent (data from Short Topics: Making Plasma Safer, American Association of Blood Banks 52nd Annual Meeting, November, 1999).

Once bone tissues are obtained, the processing to prepare demineralized bone matrix provides an additional guarantee of safety by incorporating validated viral and other pathogen inactivation steps. Processing steps such as acid demineralization and solvent extractions are known to inactivate enveloped and non-enveloped viruses, bacteria, fungi and other pathogens. Process validation studies conforming with Good Laboratory Practice (GLP) regulations have shown that these bone processing steps generate 5 to greater than 9 log reductions in HIV, hepatitis B, hepatitis C, cytomegalovirus (CMV) and polio virus, thus demonstrating the additional safety ensured beyond that of donor screening. The level of viral inactivation by processing steps far exceeds any reasonable estimates of potential viral burden in donor bone. Any Grafton® DBM products returned to date to Osteotech because of recipient infections post-operatively have proven to be sterile. To date, there is no evidence from clinical trials, spontaneous reports or the literature that Grafton® DBM products have transmitted infectious diseases to recipients.

The risk of immunologic reaction is based on the allogeneic source of Grafton® DBM. However, the demineralization process removes all cellular elements as well as acid-soluble proteins, leaving a protein matrix consisting of collagen, bone morphogenic protein and other non-collagenous proteins. These proteins are known to be at most weakly immunogenic, and the specific bone protein known to be capable of generating a sufficient immune response to potentially lead to autoimmune conditions (type II collagen) is not present in the donor bone used for Grafton® DBM. Neither preclinical testing nor the human clinical experience has produced evidence that Grafton® DBM elicits an immune response capable of resulting in autoimmunity or graft rejection. In no instance has Grafton® DBM graft failure been ascribed to

rejection, and soft tissues surrounding graft implants do not demonstrate changes suggestive of an active nearby immunologic process.

The greatest theoretic risk associated with Osteotech Grafton® products is from the excipients in the preparations. Small quantities of residual alcohol could produce local irritation, although such a situation has not been observed in animal studies or from the human experience. Similarly, trace amounts of residual antibiotics used to maintain sterility could theoretically produce an allergic reaction in a susceptible recipient. This potential adverse reaction has not been recognized despite the use of Grafton® DBM in over 350,000 treatments to date.

The excipient of greatest potential risk is glycerol. Lyophilized demineralized bone matrix preparations are suspended in glycerol to increase the product's viscosity, surface tension, stability and lubricity. Glycerol added to Osteotech bone products is USP grade and has Generally Recognized as Safe (GRAS) status according to the FDA. Glycerol is widely used as an excipient in foods, pharmaceuticals, and cosmetic products as well as a direct therapeutic agent for glaucoma and many neurological disorders based on its hyperosmolar properties. However, because glycerol in high doses can have toxicity, the risks of this particular excipient have been carefully considered.

Known adverse reactions of glycerol in man include hyperosmolality, intravascular hemolysis, renal damage, hyperglycemia, and a neurolytic effect when injected locally around nerves (33, 34). The systemic toxicities have been observed with >0.5 g/kg infusions of glycerol intravenously given for treatment of elevated cerebrospinal fluid pressure in settings of stroke or other cerebral trauma, brain tumors, Reye's syndrome, central nervous system infections, and glaucoma. Lesser reactions (headache, dizziness, and gastrointestinal distress) can be observed with oral ingestion of glycerol in amounts >1 g/kg. In Osteotech's various clinical trials, all of which were conducted in adults, glycerol-based Grafton® DBM was administered extravascularly and in doses of approximately 0.01-0.5 g/kg. Literature reports are equivalent in terms of approximate dosing when volumes and body weights are available. The largest doses were used in spine procedures. From the literature, children have received similar doses on a weight basis for healing of bone cysts. Glycerol absorption with orthopedic applications would not be anticipated to generate blood glycerol levels near those associated with systemic toxicity. Therefore, from a theoretical perspective glycerol toxicity should be considered extremely unlikely with Grafton® DBM.

The most consistent adverse reaction to glycerol observed in preclinical studies specifically investigating glycerol toxicity are hemolysis, acute renal failure, and symptoms related to hyperosmolality (33). When observed in humans given toxic levels of glycerol, the usual signs are hemoglobinemia, hemoglobinuria, and decreased urine production (33). These abnormalities are easy to detect, and are not likely to be missed during clinical investigations. Non-specific signs and symptoms of hemolysis and hyperosmolality such as fever, chills, nausea, headache, back pain, prostration, jaundice, dizziness, and altered consciousness are also likely to be noted by health care professionals, and appropriate laboratory workup initiated for their assessment. Therefore, the absence of such abnormalities in the Osteotech clinical studies, spontaneous adverse event reports, and published literature strongly suggests that serious glycerol-related toxicity was not occurring. There also are no suggestions that any of the lesser, non-specific

reactions like headache or gastrointestinal distress were associated with Grafton® DBM administration. Therefore, from the perspective of clinical experience with Grafton® products, glycerol toxicity should be considered extremely unlikely.

CONCLUSIONS DERIVED FROM CONSIDERATION OF THE OTHER ISSUES OF GRAFTON® DBM SAFETY

- # Pathogen contamination is likely to be extremely low due to donor screening and product processing steps, and there is no documented instance of transmission of infection from graft material to the recipient;
- # Risks of immunologic reaction to Grafton® DBM are extremely low due to bone processing, and there is no evidence that autoimmune or graft rejection processes occur; and
- # Glycerol toxicity, though potentially a risk, is unlikely given the doses of Grafton® DBM utilized and the route of clinical administration of Grafton® DBM. There is no evidence that any patient undergoing grafting procedures with Grafton® products has experienced glycerol toxicity.

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