THE JOURNAL OF THE AMERICAN DENTAL ASSOCIATION

J A D A

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J Am Dent Assoc 2008;139;1192-1199

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The safety of bone allografts used in dentistry

A review

Dan Holtzclaw, DDS, MS; Nicholas Toscano, DDS, MS; Lisa Eisenlohr, PhD; Don Callan, DDS

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ABSTRACT

Background. Recent media reports concerning "stolen body parts" have shaken the public's trust in the safety of and the use of ethical practices involving human allografts. The authors provide a comprehensive review of the safety aspects of human bone allografts.

Methods. The authors reviewed U.S. government regulations, industry standards, independent industry association guidelines, company guidelines and scientific articles related to the use of human bone allografts in the practice of dentistry published in the English language.

Results. The use of human bone allografts in the practice of dentistry involves the steps of procurement, processing, use and tracking. Rigorous donor screening and aseptic proprietary processing programs have rendered the use of human bone allografts safe and effective as a treatment option.

Conclusions. When purchasing human bone allografts for the practice of dentistry, one should choose products accredited by the American Association of Tissue Banks for meeting uniformly high safety and quality control measures.

Clinical Implications. Knowledge of human bone allograft procurement, processing, use and tracking procedures may allow dental clinicians to better educate their patients and address concerns about this valuable treatment option.

Key Words. Bone; bone grafting; disclosure; doctor-patient relationship; documentation; patient education.

JADA 2008;139(9):1192-1199.

Although clinicians have used human bone allografts safely in the practice of dentistry for more than four decades, recent media reports have shaken the public's confidence in this treatment option. In late 2005, the New York Police Department investigated Biomedical Tissue Services (BTS, Fort Lee, N.J.), a human tissue recovery firm, for allegedly selling "stolen human body parts."[1] Ensuing police investigations uncovered a ghastly operation in which BTS employees dismembered dozens of human corpses for allograft tissue that they sold to be used in a multitude of medical and dental operations. According to government witnesses, between the years 2001 and 2005, BTS struck monetary agreements with a number of New York– and Pennsylvania-based funeral homes for access to the bodies of recently deceased people.[2] On acquisition of these cadavers, BTS employees systematically harvested high-value body parts, often in unsanitary conditions. In most cases, they obtained human allograft tissue without authorized consent and did not test the tissue for diseases according to U.S. Food and Drug Administration (FDA) regulations. To cover their

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tracks, BTS employees forged a variety of documents, including death certificates, and they even went so far as to replace harvested bones with polyvinyl chloride pipes to fool unsuspecting family members of the deceased people.

This story gained international exposure when police investigations determined that the remains of the acclaimed British broadcaster Alistair Cooke were among those violated by BTS. To make matters worse for the practice of dentistry, the media widely publicized that the mastermind behind this gruesome operation was Michael Mastromarino, a former New Jersey–based oral surgeon.

While the FDA has since ordered BTS to cease all manufacturing operations, and multiple defendants have stood trial for scores of criminal offenses, the damage caused by this scandal may affect the medical and dental professions for years to come. Ultimately, the burden of restoring the public's trust in the safety of human bone allografts likely will fall on the shoulders of clinical providers. The purpose of this article is to review safety aspects of human bone allografts as they apply to the practice of dentistry.

INDUSTRY REGULATION

A combination of government and industry entities currently regulate U.S.-based human allograft acquisition, processing and use. Although federal agencies such as the FDA retain ultimate authority over such matters, independent nonprofit associations like the American Association of Tissue Banks (AATB) and corporate self-governance help ensure the safe and ethical use of donated human tissues.

FDA. The FDA Center for Biologics Evaluation and Research (CBER) regulates human cells, tissues and cellular-based products under federal law, specifically title 21 of the U.S. Code of Federal Regulations (CFR), parts 1270 and 1271.[3] The CFR is a systematic codification of general and permanent rules published in the Federal Register. CFR Title 21 part 1271 created a unified registration and listing system for establishments that manufacture human cellular and tissue-based products (HCT/Ps). Additionally, this regulation established donor eligibility, good tissue practice and other guidelines to prevent the introduction, transmission and spread of communicable diseases via HCT/Ps. CFR Title 21 part 1271 requires HCT/P manufacturers to register their companies and products with the FDA CBER and comply with applicable FDA regulations such as the donor eligibility final rule (DEFR) and the current good tissue practice rule (CGTPR).

The CGTPR satisfied requirements in subpart D of CFR Title 21 part 1271 that govern the methods used in, and the facilities and controls used for, the manufacture of HCT/P; this includes, but is not limited to, all steps in tissue recovery, donor screening, donor testing, processing, storage, labeling, packaging and distribution.[4] To determine compliance with the CGTPR and applicable provisions in CFR Title 21 part 1271, the FDA conducts inspections of tissue banks in which its inspectors examine all aspects of HCT/P processing. Unsatisfactory performance during these inspections may lead to FDA orders of product retention, recall, destruction or cessation of manufacturing.

The DEFR requires all HCT/P manufacturers to screen and test donors for risk factors and clinical evidence of relevant communicable disease agents or diseases as defined in CFR Title 21 part 1271.[5] Examples of such diseases include human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), *Treponema pallidum* and human T-lymphotropic virus (HTLV).

AATB. Although the FDA is the paramount regulatory agency for U.S.-based HTC/P manufacturers, other organizations, such as the AATB, contribute significantly to the industry. The AATB is an independent nonprofit organization

ABBREVIATION KEY. AATB: American Association of Tissue Banks. **BTS:** Biomedical Tissue Services. **CBER:** Center for Biologics Evaluation and Research. **CFR:** Code of Federal Regulations. **CGTPR:** Current good tissue practice rule. **CLIA:** Clinical Laboratory Improvement Amendment. **DEFR:** Donor eligibility final rule. **DFDBA:** Demineralized freeze-dried bone allograft. **FDA:** U.S. Food and Drug Administration. **FDBA:** Freeze-dried bone allograft. **HBcAb:** Hepatitis B core antibody. **HBsAg:** Hepatitis B surface antigen. **HBV:** Hepatitis B virus. **HCT/P:** Human cellular and tissue-based product. **HCV:** Hepatitis C virus. **HCVAb:** Hepatitis C antibody. **HIV:** Human immunodeficiency virus. **HIV-1/2Ab:** Human immunodeficiency virus 1 antibody/human immunodeficiency virus 2b antibody. **HTLV:** Human T-lymphotropic virus. **HTLV-1/2Ab:** Human T-cell lymphotrophic virus 1 antibody and human T-cell lymphotrophic virus 2 antibody. **ISO:** International Organization for Standardization. **NAT:** Nucleic acid test. **RPR/STS:** Rapid plasma reagin/serologic test for syphilis. **SAL:** Sterility assurance level.

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BOX 1

Human bone allograft preprocurement steps.

STEP 1. NOTIFICATION OF PROSPECTIVE DONOR'S DEATH
Hospitals or morgues notify tissue recovery agencies of human deaths.

STEP 2. DETERMINATION OF INITIAL DONOR ELIGIBILITY
The tissue recovery agency determines donor eligibility on the basis of readily available information (for example, age, cause of death, evidence of infection, history of systemic disease, evidence of drug use).

STEP 3. CONSENT
If a potential donor is deemed acceptable, the tissue recovery agency obtains and documents consent according to U.S. Food and Drug Administration regulations and state anatomical gift laws.

STEP 4. DISPATCH OF RECOVERY TEAM
Most tissue recovery agencies use their own recovery teams to evaluate and procure potential donor tissues.

STEP 5. ASSIGNMENT OF TRACKING NUMBER TO PROSPECTIVE DONOR
The dispatched tissue recovery team assigns a unique tracking number to the potential donor.

STEP 6. DETERMINATION OF ADDITIONAL DONOR ELIGIBILITY
The tissue recovery team confirms donor identity, reviews medical records, performs a full-body physical assessment, reviews critical time limits and verifies the temperature of the cadaver's storage.

STEP 7. TISSUE PROCUREMENT
The tissue recovery team must procure the tissue within 12 hours of death for nonrefrigerated cadavers or within 24 hours for refrigerated cadavers.

STEP 8. AUTOPSY
Some tissue procurement agencies perform autopsies on potential donors as an additional screening procedure.

STEP 9. TRANSPORT
The tissue recovery team transports harvested donor tissue, blood samples and relevant medical records to the tissue processing center.

dedicated to ensuring and maintaining the safety, consistency and availability of human allografts in the United States. To fulfill this mission, the AATB publishes tissue-banking industry standards and offers rigorous accreditation for institutional members as well as a certification program for people working in the field. Although membership in the AATB is not legally required for U.S.-based human tissue banks, the FDA's CGTPR for human cell, tissue, and cellular- and tissue-based product establishments indicates that 75 to 80 percent of tissue-banking agencies follow the voluntary industry standards established by the AATB.[4] By accepting AATB accreditation, tissue banks agree to comply with on-site inspections of processing facilities, annual audits and other various AATB-prescribed safety regulations.[6] Additionally, by satisfying AATB accreditation, tissue banks help ensure their compliance with FDA HTC/P regulations. The AATB publishes a list of its accredited tissue banks on a quarterly basis. Copies of this list are available from the AATB and are easily accessible online at "www.aatb.org".

DONOR SCREENING

Conditions of participation regulations of the Centers for Medicare and Medicaid Services require hospitals receiving care reimbursements to report all human deaths promptly to organ procurement organizations or tissue banks (Box 1).[7] Accordingly, more than 90 percent of all donor referrals to AATB-accredited tissue banks come from hospitals.[8] Once a tissue bank receives a referral, it sends a trained screening team to determine initial donor eligibility on the basis of readily available information such as age, cause of death and evidence of infection. If the screening team deems a potential donor acceptable, they must obtain consent and document it according to FDA regulations and state anatomical gift laws. Documentation of donor consent may include signed organ donation cards, signed driver's licenses positively indicating organ donation or various other legal documents. If the deceased person had no written documentation of an organ donation decision or if the deceased person was a minor, the person's next of kin may give consent for donation.

On acquisition of consent, the tissue bank dispatches a tissue recovery team to the location of the deceased person, where they assign the potential donor a unique tracking number before performing a multitude of preprocurement procedures. Preceding invasive tissue retrieval, the team confirms donor identity, reviews medical records, performs a full-body physical assessment, reviews critical time limits and verifies time-critical temperature of the cadaver's storage. Most tissue banks also require their recovery teams to satisfy a combination of FDA, AATB and company-

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specific donor eligibility criteria before acquiring the donor tissue. LifeNet Health (Virginia Beach, Va.), for example, requires potential bone donors to be between 12 and 80 years of age and weigh a minimum of 88 pounds.

Once the team has satisfied preprocurement donor eligibility criteria, they retrieve and prepare desired tissues for transport. This process requires expediency, because the tissue recovery team must accomplish excision of donor tissue within the first 12 hours after death for nonrefrigerated cadavers or within 24 hours if the cadaver has been refrigerated.[9] Donor tissue retrieval may occur in a variety of locales. A 1996 survey of tissue bank procurement services indicated that 39 percent of organ or tissue acquisitions occurred in the hospital morgue, 33 percent in an operating room, 22 percent in a coroner's facility and 14 percent at actual tissue banks.[10] Although the location of initial tissue recovery varies, the team must use clean environments and follow established aseptic protocols.

TABLE

Human bone allograft preprocessing microbiological and serological testing.

TEST	PURPOSE OF TEST
Bacteria Test	Detects and identifies contamination with various bacteria
Fungi Test	Detects and identifies contamination with various fungi
HIV-1/2Ab* Test	Detects HIV-1, HIV-2 antibody
HIV/HCV NAT†	Detects HIV and hepatitis C virus
HTLV-1/2Ab‡ Test	Detects HTLV-1 antibody and HTLV-2 antibody
HBsAg§ Test	Detects hepatitis B surface antigen
HBcAb¶ Test	Detects hepatitis B core antibody
HCVAb# Test	Detects hepatitis C antibody
RPR/STS	Detects syphilis antibody

* HIV-1/2Ab: Human immunodeficiency virus 1 antibody/human immunodeficiency virus 2 antibody.
† HIV/HCV NAT: Human immunodeficiency virus/hepatitis C virus nucleic acid test.
‡ HTLV-1/2Ab: Human T-lymphotropic virus 1 antibody and human T-lymphotropic virus 2 antibody.
§ HBsAg: Hepatitis B surface antigen.
¶ HBcAb: Hepatitis B core antibody.
# HCVAb: Hepatitis C antibody.
** RPR/STS: Rapid plasma reagin/serologic test for syphilis.

With procurement complete, the team forwards the donor's tissue, blood samples and all available relevant medical records to a tissue processing center and then reconstructs and transports the donor's body to its requested destination.[11] Some organizations, such as the University of Miami Tissue Bank, also perform donor autopsies to add a further measure of safety. The benefits of donor autopsies are evident in a recent study in which the investigator directly attributed 3.1 percent of donor rejections to autopsy findings that uncovered conditions that had been unrecognized previously.[12]

On receipt of donor material, FDA regulations require tissue processing facilities to quarantine the harvested tissue and perform further donor screening and testing procedures to ensure donor suitability.[13] The processing facility conducts a behavioral risk assessment and medical history review by interviewing the donor's next of kin or other close acquaintances and comparing the feedback with available medical records. The processing facility sends donor blood samples to FDA-registered laboratories certified under the 1988 Clinical Laboratory Improvement Amendment (CLIA) where they are tested for HIV, HBV, HCV, HTLV and syphilis. Many processing facilities have their own on-site CLIA-certified laboratories. Finally, as dictated by FDA and AATB regulations, the processing facility samples and tests all recovered tissues for both bacterial and fungal contamination (Table).[13] Once qualified personnel have determined donor eligibility, they release acceptable tissue for processing and either destroy or dispose of unacceptable tissue according to FDA regulations.

Donor screening programs such as those advocated by the AATB significantly reduce the possibility of inadvertently obtaining contaminated human bone allografts from people who had disease. In a previous study in which researchers used exclusionary methods similar to those used by the AATB, the investigators calculated the risk of harvesting bone from a donor with HIV at one in 1.67 million.[14] Further evidence of effective donor screening is apparent in the low acceptance rate for potential human organ and tissue donors.

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BOX 2

Steps in the processing of freeze-dried bone allograft.

PROCESSING STEP 1. SOFT-TISSUE STRIPPING
The technician removes residual muscle, tendon, ligament and so forth.

PROCESSING STEP 2. INITIAL SIZE REDUCTION
The technician reduces the bone to pieces of approximately 5-millimeter diameter for easier processing.

PROCESSING STEP 3. INITIAL CLEANSING AND DECONTAMINATION
The technician flushes, agitates, centrifugates or does all of these to the bone particles, using various solutions such as saline, acetone, ethanol or hydrogen peroxide to remove residual bioburden and reduce antigenicity.

PROCESSING STEP 4. MICROBIOLOGICAL TREATMENT
The technician treats the bone particles with antimicrobial, antimycotic and antifungal solutions.

PROCESSING STEP 5. FREEZING
The technician freezes the bone particles in liquid nitrogen of a temperature as low as –80°C.

PROCESSING STEP 6. DEHYDRATION
The technician lyophilizes or treats the bone particles with repetitive solvent washes to eliminate moisture content and reduce antigenicity.

PROCESSING STEP 7. SECONDARY SIZE REDUCTION
The technician reduces the bone particles to final particulate sizes ranging between approximately 250 and 750 micrometers.

PROCESSING STEP 8. PACKAGING
The technician packages the bone allograft in sterile containers.

PROCESSING STEP 9. TERMINAL STERILIZATION
The technician applies low-dose γ irradiation at low temperatures to ensure sterility (sterility assurance level, 10^{-6}).

According to the AATB, accredited institutions accepted less than 5 percent of all screened donors for tissue donation within the past year (unpublished AATB statistics, Debbie Butler Newman, director of accreditation and education, AATB, e-mail communication, February 2008). Although these donor screening programs are successful, the risk of human allograft contamination still exists.

DONOR TISSUE PROCESSING

One of the foremost goals in the processing of human bone allografts is preventing contamination of aseptically harvested donor tissue. Therefore, tissue-processing facilities use "clean rooms," which are hyperclean environments achieved via strict control of temperature, humidity, ionization, electrostatic discharge, air pressure, air ventilation and air filtration.[15] The industry determines cleanliness largely by the quantity of airborne particulate matter per cubic meter: the International Organization for Standardization (ISO) universally measures cleanliness according to ISO standard 14644,[16] which covers classification of air cleanliness in rooms and associated clean environments through the assignment of nine class levels. Most U.S.-based human bone allograft processing facilities manufacture their products in ISO Class 6 clean rooms that have air quality 10 times cleaner than that of many hospital operating rooms.[16] To operate in an ISO Class 6 clean room, HCT/P technicians must wear full-body electrostatic discharge garments, foot coverings, hair coverings, gloves, masks and eye protection. Although cumbersome, such precautions reduce the risk of human bone allograft contamination from airborne particulate during processing.

The act of processing human bone allografts can be a secretive endeavor, as most tissue banks employ proprietary methods in the creation of their products. Zimmer Dental's Puros bone allograft products (Carlsbad, Calif.), for example, uses the patented Tutoplast process,[17] whereas LifeNet Health uses its patented Allowash XG process.[18] Although these processes differ in many technical aspects, in generic terms, most tissue-processing procedures are based on similar underlying concepts (Boxes 2 and 3). Initial processing of human bone allografts typically involves stripping the bone of its soft tissue and sectioning it into smaller, more manageable pieces of approximately 5 millimeters in diameter. Next, technicians rigorously cleanse the bone and solubilize residual lipids, marrow and other bioburden in solutions such as acetone or ethanol. They then remove solubilized contaminants via agitation, centrifugation and repeated washings. Processing technicians also typically treat the bone allograft with antibiotic, antimycotic and antiviral agents. After the technician has cleansed the bone of soft tissue and has decontaminated it, proprietary processing takes place via one of many paths; some tissue processing techniques involve liquid nitrogen freezing followed by lyophilization,

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whereas others involve repetitious wash treatments with solvents such as acetone. Although different, these procedures produce similar results by eliminating nearly all of the moisture content from the bone, reducing antigenicity and facilitating extremely lengthy shelf storage at room temperature.

If the final product is a freeze-dried bone allograft (FDBA), processing technicians reduce the processed bone to a particle size usually ranging between 250 and 750 micrometers, resample it for quality control, package it in sterile containers and may terminally sterilize it with low-dose γ irradiation (Box 4 and Figure 1).

If the final product is intended to be a demineralized freeze-dried bone allograft (DFDBA), the technician typically immerses the bone in a hydrochloric acid bath for various lengths of time to demineralize the bone by removing calcium. The next step depends on the philosophy of the tissue bank; some companies reduce the bone to its final particle size before acid demineralization, whereas others prefer to accomplish this task after demineralization. After acid treatment, the technician washes the newly demineralized bone allograft in various buffer solutions to remove residual acid, rinses it to remove the buffer and terminally processes it in a fashion similar to that used for FDBA (Box 3).

The net result of human bone allograft processing is an exponential reduction in the potential for graft contamination, disease transfer or both. With proper processing, human bone allografts for dental purposes routinely achieve a sterility assurance level (SAL) of $10^{-6.19}$ SAL is the probability that an item will not be sterile after it has been subjected to a validated sterilization process.[20] With a SAL of 10^{-6}, the odds of an

BOX 3

Steps in the processing of demineralized freeze-dried bone allograft.

PROCESSING STEP 1. SOFT-TISSUE STRIPPING
The technician removes residual muscle, tendon, ligament and so forth.

PROCESSING STEP 2. INITIAL SIZE REDUCTION
The technician reduces the bone to pieces of approximately 5-millimeter diameter for easier processing.

PROCESSING STEP 3. INITIAL CLEANSING AND DECONTAMINATION
The technician flushes, agitates, centrifugates or does all of these to the bone particles, using various solutions such as saline, acetone, ethanol or hydrogen peroxide to remove residual bioburden and reduce antigenicity.

PROCESSING STEP 4. MICROBIOLOGICAL TREATMENT
The technician treats the bone particles with antimicrobial, antimycotic and antifungal solutions.

PROCESSING STEP 5. FREEZING
The technician freezes the bone particles in liquid nitrogen of a temperature as low as –80°C.

PROCESSING STEP 6. DEHYDRATION
The technician lyophilizes or treats the bone particles with repetitive solvent washes to eliminate moisture content and reduce antigenicity.

PROCESSING STEP 7. SECONDARY SIZE REDUCTION
The technician reduces the bone particles to final particulate sizes ranging between approximately 250 and 750 micrometers.

PROCESSING STEP 8. DEMINERALIZATION
The technician immerses the allograft particles in a hydrochloric acid bath at concentrations ranging from 0.5 to 0.6 normal for various lengths of time.

PROCESSING STEP 9. BUFFERING
The technician again immerses the demineralized allograft particles in buffering solution to remove residual acid.

PROCESSING STEP 10. FINAL RINSE
The technician again rinses the demineralized allograft with various solutions (for example, distilled water) to remove residual buffer solution.

PROCESSING STEP 11. PACKAGING
The technician packages the bone allograft in sterile containers.

PROCESSING STEP 12. TERMINAL STERILIZATION
The technician applies low-dose γ irradiation at low temperatures to ensure sterility (sterility assurance level 10^{-6}).

BOX 4

Human bone allograft postprocessing procedures.

VISUAL INSPECTION TEST
Visual detection for such problems as gross graft contamination, packaging defects and product mislabeling.

RESIDUAL MOISTURE TEST
Testing of freeze-dried allografts to ensure residual moisture is 6 percent or less.

RESIDUAL CALCIUM TEST
Testing of demineralized freeze-dried bone allograft to ensure residual calcium content is 8 percent or less.

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Figure 1. Human bone allograft final product (particulated).

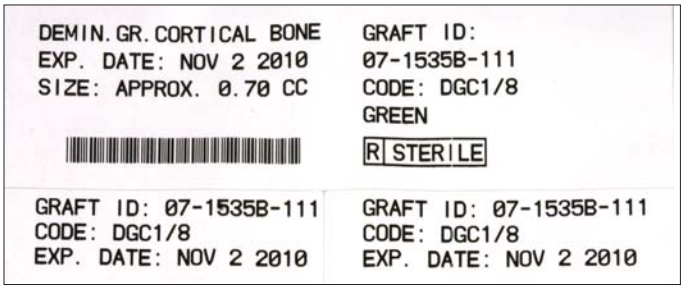

Figure 2. Sample label from human bone allograft packaging. Note the multiple tracking stickers for the patient's record, the practitioner's records and the tissue-processing facility's records.

organism's surviving allograft processing are less than one in 1 million.[21] For a specific organism such as HIV, processing can decrease this risk even further. If a tissue bank uses the aforementioned donor screening process coupled with the act of graft freezing, the risk of producing an HIV-contaminated human bone allograft decreases to 1 in 8 million.14 If the tissue bank demineralizes the allograft, this risk plummets to a calculated one in 2.8 billion.[22] In the processing of DFDBA, investigators have demonstrated that exposing allografts to low-pH solutions such as hydrochloric acid inactivates numerous viruses such as HIV, HBV, HCV, cytomegalovirus and poliovirus.[23-25]

HUMAN BONE ALLOGRAFT TRACKING

Although human bone allografts have a safe track record in the practice of dentistry, and the calculated odds of disease transfer are infinitesimal, it is impossible to assign a risk of absolute zero to these products. Because of this, FDA regulations require that human bone allografts must be tracked so that tissue banks and clinicians can notify recipients in the event of a product recall. CFR Title 21 part 1271.290 addresses tracking protocols for human bone allografts to facilitate the investigation of actual or suspected transmission of communicable diseases.[3] According to this regulation, HCT/P processing facilities must label each manufactured HCT/P with a unique alphanumeric identification code that does not contain the donor's name or Social Security number (Figure 2). This code allows each manufacturer to record and track the donor graft to its recipient and vice versa. Most tissue banks supply a self-addressed prepaid postage tracking form with each human bone allograft. These forms typically consist of triplicate copies: one for the patient's record, one for the practitioner's record and one for the tissue bank. Although FDA and AATB regulations require retention of these records for 10 years beyond the date of allograft transplantation, many tissue banks retain their records indefinitely. In the event of an HCT/P recall, tissue banks refer to these records to notify practitioners who have used the products in question. Clinicians who have used recalled allografts should immediately notify patient recipients and test them for suspected pathogens for a minimum of six months after implantation of the product.[9]

CONCLUSION

Use of human bone allografts in the practice of dentistry and medicine in the United States is safe. Since 1972, the use of human bone allografts has increased more than 400-fold, with more than 800,000 transplantations performed annually in the United States.[26] The ever-increasing use of human bone allografts reflects positively on the usefulness and safety of these products. Progressive FDA policies and industry self-regulation through agencies such as the AATB have allowed reputable tissue-processing facilities to uphold their fiduciary responsibility to the public. As is recommended for medical surgeons, when using human bone allografts in the practice of dentistry, practitioners should investigate carefully and be familiar with the institutions that they are patronizing.[27] Purchasing products from HCT/P manufacturers such as those accredited by the AATB may provide practitioners with peace of mind, knowing that these institutions accept and adhere to strict and reliable safety measures in the creation of their products. ■

Disclosure. At the time this article was written, Dr. Eisenlohr was an employee of LifeNet Health (Virginia Beach, Va.), a company that is

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mentioned in this article. She is no longer employed by LifeNet Health and currently is the publication planning manager for Genentech (South San Francisco, Calif.).

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The opinions expressed in this article are those of the authors and do not reflect the views or the endorsement of the U.S. Government, Department of Defense, Navy Medicine or Naval Hospital Pensacola, Fla.

For their assistance in the preparation of this article, the authors thank Billy E. Buck, MD, University of Miami Miller School of Medicine, Miami; Ralph Powers, DDS, LifeNet Health, Virginia Beach, Va.; and Debbie Newman, American Association of Tissue Banks, McLean, Va.

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