

Unless otherwise noted, comments regarding each of these applications must be received not later than August 11, 1995.

A. Federal Reserve Bank of Chicago (James A. Bluemle, Vice President) 230 South LaSalle Street, Chicago, Illinois 60690:

1. *Olympia Bancorporation, Inc. Employee Stock Ownership Plan*, Chicago Heights, Illinois; to become a bank holding company by acquiring 50.01 percent of the voting shares of Olympia Bancorporation, Inc., Chicago Heights, Illinois, and thereby indirectly acquire Heritage Olympia Bank, Chicago Heights, Illinois.

B. Federal Reserve Bank of Dallas (Genie D. Short, Vice President) 2200 North Pearl Street, Dallas, Texas 75201-2272:

1. *FCT Bancshares, Inc.*, Mart, Texas; to become a bank holding company by acquiring 100 percent of First Central Holdings, Inc., Dover, Delaware, and thereby indirectly acquire The First National Bank of Mart, Mart, Texas.

In connection with this application, First Central Holdings, Inc., Dover, Delaware; also has applied to become a bank holding company by acquiring 100 percent of the voting shares of The First National Bank of Mart, Mart, Texas.

Board of Governors of the Federal Reserve System, August 12, 1995.

Jennifer J. Johnson,

Deputy Secretary of the Board.

[FR Doc. 95-17560 Filed 7-17-95; 8:45 am]

BILLING CODE 6210-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 95N-0200]

Public Hearing: Products Comprised of Living Autologous Cells Manipulated ex vivo and Intended for Implantation for Structural Repair or Reconstruction

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public hearing to discuss the regulation of products that are comprised of living autologous cells manipulated ex vivo and intended for implantation for structural repair or reconstruction of the source tissue or other tissue, including products used for cosmetic reconstruction and augmentation. The products to be discussed at this hearing are described in further detail in this document.

In view of the emergence of new autologous cell products and the potential enhancement to the public health, the purpose of the hearing is to solicit information and views from interested persons, including scientists, clinical investigators, professional groups, trade groups, commercial enterprises, and consumers, on the issues and concerns relating to regulation of such products.

Preregistration by written notice is advised to ensure participation. The procedures governing the hearing are found in 21 CFR part 15.

DATES: Submit written notices of participation by October 26, 1995. The public hearing is scheduled for November 16 and 17, 1995, from 9 a.m. to 5 p.m. Written comments will be accepted until February 16, 1996.

ADDRESSES: The public hearing will be held at the Gaithersburg Hilton, 620 Perry Pkwy., Gaithersburg, MD 20877, 301-977-8900. Submit written notices of participation and comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. Transcripts of the hearing also will be available for review at the Dockets Management Branch.

FOR FURTHER INFORMATION CONTACT:

Andrea E. Chamblee, Office of the Commissioner (HF-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1306.

SUPPLEMENTARY INFORMATION:

I. Background

Over the last several years, FDA has worked to clarify its approach to the regulation of products that are comprised in whole or in part of living cellular materials. The agency's approach has been embodied in several recent policy statements. The agency's statement on somatic cell therapy was published in a notice in the **Federal Register** of October 14, 1993 (58 FR 53248). The agency's position on banked human tissue was outlined in an interim rule published in the **Federal Register** on December 14, 1993 (58 FR 65514).

As noted, the agency described its policies for the regulation of somatic cell therapies in an October 1993 notice. The somatic cell statement defined

somatic cell therapy products as autologous (i.e., self), allogeneic (i.e., intra-species), or xenogeneic (i.e., inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo (i.e., outside the body) to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries. FDA defined "manipulation" as the ex vivo propagation, expansion, selection, or pharmacological treatment of cells, or other alteration of their biological characteristics.

The statement outlined the regulatory controls over somatic cell therapy products, and explained that the degree of regulatory control reflected the extent and intent of cell processing ex vivo. Thus, in accordance with the statement, cells manipulated in a way that changed the biological characteristics of the cell population would be subject to product licensure as final biological products. The statement also made clear that such products would be subject to all other pertinent regulatory requirements, including provisions governing drug listing and registration, and rules governing misbranding and adulteration.

In contrast, the October 1993 notice on somatic cell products stated that applications for premarket approval were not presently required for certain other cellular products, including minimally manipulated or purged bone marrow, and certain minimally processed cell transplants.

The statement also indicated that the field of somatic cell therapy was dynamic and rapidly expanding, and stated that, "[a]s scientific knowledge in the area of somatic cell therapy continues to accumulate and evolve, the agency's approach may also evolve" (58 FR 53248). The agency also acknowledged the need to reconsider periodically its approach to these evolving products in an article by FDA's Commissioner David Kessler, entitled "Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration" that published in the *New England Journal of Medicine* on October 14, 1993. That article observed that, "[a]s these novel therapeutic applications are explored and knowledge about risks and benefits accumulates, the FDA's regulatory approach may be modified."

In the **Federal Register** of December 14, 1993 (58 FR 65514), FDA established certain requirements for banked human tissue intended for transplantation. Banked human tissue products are described in the interim final rule as

any tissue derived from a human body which: (1) Is intended for administration to another human for the diagnosis, cure, mitigation treatment, or prevention of any condition or disease; (2) is recovered, processed, stored, or distributed by methods not intended to change tissue function or characteristics; (3) is not currently regulated as a human drug, biological product, or medical device; (4) excludes kidney, liver, heart, lung, pancreas, or any other vascularized human organ; and (5) excludes semen or other reproductive human tissues, human milk, and bone marrow. The interim final rule specifically excluded autologous products.

Thus, the agency's policies on somatic cell therapy, gene therapy, and banked human tissue for transplantation contemplated that changes in the products, and greater understanding of the benefits and risks of new products, might lead to modifications in the agency's regulatory approach.

II. Development of Autologous Cellular Products for Structural Repair and Reconstruction

The agency is aware of an increasing number of reports in the scientific literature of the clinical use of autologous cells manipulated *ex vivo* that are intended for implantation. One recent article reported a Swedish study of autologous chondrocyte transplantation in 23 patients with deep cartilage defects in the knee (Ref. 1). Another article reported that mesenchymal cells harvested for expansion *ex vivo* and implanted in experimental animals can differentiate into bone, muscle, cartilage, and other mesenchymal tissues (Ref. 2). In recent years, other articles have described the use of autologous skin cells for burns and wounds (Refs. 3 and 4), and the use of cultured melanocytes for vitiligo (Refs. 5 and 6). Still other articles reported the *ex vivo* culturing of autologous skin to treat burns and vitiligo (Refs. 7 and 8).

References

1. Brittberg, M. et al., "Treatment of Deep Cartilage Defects in the Knee With Autologous Chondrocyte Transplantation," *New England Journal of Medicine*, 331:889-895.
2. Mesenchymal Stem Cells in Bone Development, Bone Repair, and Skeletal Regeneration Therapy, *Journal of Cellular Biochemistry* 56:283-294, 1994.
3. Navsaria, H. A., S. R. Myers, I. M. Leigh, and I. A. McKay, "Culturing Skin In Vitro for Wound Therapy," *Trends in Biotechnology*, 13(3): 91-100, March 1995.
4. Malakhov, S. F., B. A. Paramonov, A. V. Vasiliev, and V. V. Tersikh, "Preliminary

Report of the Clinical Use of Cultured Allogeneic Keratinocytes," *Burns*, 20(5):463-466, October 1994.

5. Olsson, M. J., G. Moellmann, A. B. Lerner, and L. Juhlin, "Vitiligo: Repigmentation With Cultured Melanocytes After Cryostorage," *Acta Dermato-Venereologica*, 74(3):226-228, May 1994.
6. Zachariae, H., C. Zachariae, B. Deleuran, and P. Kristensen, "Autotransplantation in Vitiligo: Treatment With Epidermal Grafts," *Acta Dermato-Venereologica*, 73(1):46-48, February 1993.
7. Navsaria, H. A., S. R. Myers, I. M. Leigh, and I. A. McKay, "Culturing Skin In Vitro for Wound Therapy," *Trends in Biotechnology*, 13(3):91-100, March 1995.
8. Tissue Engineering and the Human Body Shop: Encapsulated-cell Transplants Enter the Clinic, *Journal of NIH Research*, 47-51, 1995.

In addition to these reports from the scientific literature, the agency has received an increasing number of inquiries from companies about the regulation of autologous products intended for implantation. The inquiries have been made for a variety of products intended to replace or repair tissue that is nonfunctioning or diseased, including cosmetic augmentation, dermal wound healing, and cartilage replacement for damaged knees. The products may have characteristics of drugs, biological products, and devices, and some may be combination products. (See 21 CFR part 3.)

These reports in the literature and inquiries to the agency may reflect changes in what is understood about the science of autologous cell transplantation. The reports also signal a significant evolution in the nature of the products. As technologies are developing, these products increasingly are being commercialized and made available on a larger scale to patients.

III. Purpose and Scope of the Hearing

The promise of products that use autologous cells for implantation is great, and the demand for them is expected to be correspondingly high. Successful development and marketing of these products may be slowed by questions about the scope of regulatory requirements. In light of the potential public health significance of the new products, the growth of a commercial industry, and the need to develop an appropriate regulatory framework for products comprised of autologous cells for implantation for repair or reconstruction, the agency has decided to hold a public hearing to solicit information on the nature and diversity of these products, and comments on the formulation and implementation of appropriate regulatory requirements.

The hearing will be limited to discussion of autologous cells

manipulated *ex vivo*, and intended for implantation for structural repair or reconstruction of the source tissue or other tissue, including products intended for cosmetic reconstruction and augmentation. Examples of these products include cartilage, fat, and skin cells, removed, manipulated *ex vivo*, and implanted in the patient, either at the site where the cellular material was removed or at another site. These products will be referred to hereinafter as "manipulated autologous structural cells (MAS cells)."

Allogeneic and xenogeneic products are beyond the scope of the hearing. In addition, the hearing will not consider products intended for nonstructural purposes, including, for example, autologous pancreatic cells to produce insulin following total pancreatectomy, autologous stem cells for functional replacement of muscle, and autologous lymphocytes activated to induce immune function.

Gene therapy products also are beyond the scope of this hearing. Gene therapy products are products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells.

IV. Issues for Discussion

The agency recognizes the importance of facilitating the introduction of useful new technologies while minimizing regulatory burdens. The agency notes that there are a variety of products covered by this hearing (see section III. of this document) and that different regulatory approaches may be appropriate for different types of MAS cells. Participants should address appropriate distinctions among MAS cells. To assist in the development of an appropriate regulatory strategy, the agency invites information and comments on the following:

(a) What are the public health benefits of products in this group? What alternative therapies exist?

(b) What are the public health risks of products in this group? What are the risks of contamination associated with the *ex vivo* processing of the cellular material? What other potential risks exist?

(c) Some of the MAS cells may have characteristics of biological products, drugs, or devices. What are the mechanism(s) of action of these products?

(d) The 1993 interim final rule for banked human tissue did not require premarket review and approval or provide for FDA oversight of tissue as regulated drugs, devices, or biological

products. In contrast, many somatic cell products are subject to premarket review and approval and to all other pertinent requirements, including provisions governing misbranding and adulteration. The agency is interested in information and views on the relative strengths and weaknesses of these approaches as they relate to the regulation of MAS cells. In particular, the agency is interested in the following:

(1) What are the advantages and disadvantages of an approach that would require premarket product approval?

(2) If premarket approval is not required, what would be the advantages and disadvantages of an approach that required licensing of each establishment involved in the processing of the material?

(3) If premarket product approval is required, what safety and efficacy information should the agency seek in a premarket submission? What issues are important in clinical trial design (e.g., efficacy measurements, endpoints)?

(4) What role should institutional review boards or other third party review organizations play in the oversight of these products?

(e) Autologous cells manipulated ex vivo for implantation for structural repair or reconstruction may involve intraoperative procedures to remove the cellular material from the patient, shipment of the cellular material to a distant site, processing of the material at that site, and the return of the processed material to the physician for implantation. In light of these practices, the agency seeks comment on the need for the following:

(1) Recordkeeping, to enable audits, tracking, or recall, if necessary;

(2) Precautions to help prevent errors and accidents, such as wrong-donor infusion, or potential infectious disease transmission;

(3) Process controls and validation, to help ensure the appropriate characterization of the product before, during and after processing;

(4) Labeling, to help ensure that users are adequately informed of uses and risks associated with the product;

(5) Current good manufacturing practices (CGMP's), to help ensure the consistency and control of the process and product;

(f) What amount of time should be allowed for compliance after adoption of new regulatory frameworks? Are there widely-practiced procedures, e.g., recordkeeping or other GMP's, that could be implemented sooner than others?

V. Current Regulatory Status of Pending and Approved Applications

This notice is not intended to affect the status of any approved or pending investigational or marketing application.

Pending the hearing and its outcome, FDA does not at this time intend to actively regulate products comprised of human living autologous cells manipulated ex vivo and intended for implantation for structural repair or reconstruction.

The agency recommends that any facility that currently distributes or plans to distribute such products pending the outcome of this hearing use appropriate process controls and validation and adhere to current good manufacturing practices. Informed consent from the patient should be obtained, and labeling should be truthful and not misleading.

In addition, recordkeeping and tracking should be performed to facilitate the distribution of any appropriate information, and recall if indicated. To guard against transmission of infectious disease, the facilities should take precautions to prevent errors and accidents such as wrong-donor infusion.

VI. Outcome of the Hearing

After the hearing, FDA will consider the information presented at the hearing, all written comments submitted to the docket, and all other relevant information in determining the appropriate regulation of these products. As the agency has indicated, FDA will provide appropriate time for compliance with any regulatory requirements.

VII. Notice of Hearing Under 21 CFR Part 15

For the reasons stated above, the Commissioner of Food and Drugs is announcing that a public hearing will be held in accordance with 21 CFR part 15. The purpose of hearing is to solicit information and views, under § 15.1(a), from interested persons on the public health issues and concerns relating to regulation of products that are comprised of living autologous cells manipulated ex vivo and intended for implantation for structural repair or reconstruction, including repair or reconstruction of the source tissue.

Every effort will be made to accommodate each person who wants to participate in the public hearing. However, those who want to ensure participation in the hearing are encouraged to submit: (1) A written notice of participation containing the name, address, phone number, facsimile number, affiliation (if any), topic of the presentation, and approximate amount of time requested for the presentation; and (2) a brief description or outline of their presentation. The information should be submitted to the Dockets

Management Branch (address above) by close of business on the date specified above. Interested persons attending the public hearing who did not request in advance an opportunity to make a presentation will have an opportunity to be heard as time permits and at the discretion of the presiding officer.

After reviewing the notices of participation and accompanying information, FDA will schedule each appearance and notify each participant by letter, telephone, or facsimile, with the amount of time assigned to each person and the approximate time his or her presentation is scheduled to begin. A hearing schedule will be available at the hearing and will be filed with the Dockets Management Branch (address above).

In order to enable all interested persons to submit data, information, and views on this subject, the administrative record of the hearing will remain open until February 16, 1996. Any person may submit written comments to the Dockets Management Branch (address above) no later than February 16, 1996. The agency will consider these comments in formulating its conclusions. In formulating the appropriate regulatory framework for products involving MAS cells, the agency may also consider information that cannot be made public by the agency, e.g., confidential commercial information. The agency does not intend to respond to or summarize the comments received.

The presiding officer will be the Chief Mediator and Ombudsman. The presiding officer will be accompanied by a panel of Public Health Service employees with relevant expertise.

Under § 15.30, the hearing is informal, and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer or members of the panel may question any person during or at the conclusion of the presentations.

Public hearings, including hearings under part 15, are subject to FDA's guideline on the policy and procedures for electronic media coverage of FDA's public administrative proceedings (21 CFR part 10, subpart C). Under § 10.205, representatives of electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. The hearing will be transcribed as stipulated in § 15.30(b). Orders for copies of the transcript can be placed at the meeting, or through the Dockets Management Branch (address above).

Any handicapped persons requiring special accommodations in order to attend the hearing should inform the contact person listed in order for FDA to be prepared to meet those needs.

To the extent that the conditions for the hearing as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h)

Dated: July 10, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95-17535 Filed 7-17-95; 8:45 am]

BILLING CODE 4160-01-F

[Docket No. 95F-0174]

H.B. Fuller Co.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that H.B. Fuller Co. has filed a petition proposing that the food additive regulations be amended to provide for the safe use of nonanoic acid, lactic acid, citric acid, sodium 1-octane sulfonate, tertiary butylhydroquinone, and the sodium salt of tetrapropylene-1,1-oxybis-benzenesulfonic acid as components of a sanitizing solution intended for general use on food-contact surfaces.

DATES: Written comments on the petitioner's environmental assessment by August 17, 1995.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Diane E. Robertson, Center for Food Safety and Applied Nutrition (HFS-216), Food and Drug Administration,

200 C St. SW., Washington, DC 20204, 202-418-3089.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 5B4462) has been filed by H.B. Fuller Co., c/o SRS International Corp., 1625 K St. NW., suite 1000, Washington, DC 20006-1604. The petition proposes to amend the food additive regulations in § 178.1010 *Sanitizing solutions* (21 CFR 178.1010) to provide for the safe use of nonanoic acid, lactic acid, citric acid, sodium 1-octane sulfonate, tertiary butylhydroquinone, and the sodium salt of tetrapropylene-1,1-oxybis-benzenesulfonic acid as components of a sanitizing solution intended for general use on food-contact surfaces.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental assessment submitted with the petition that is the subject of this notice on public display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before August 17, 1995, submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the **Federal Register**. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the

notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the **Federal Register** in accordance with 21 CFR 25.40(c).

Dated: July 5, 1995.

Alan M. Rulis,

Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 95-17639 Filed 7-17-95; 8:45 am]

BILLING CODE 4160-01-F

[Docket No. 95N-0206]

Richmar International, Inc., et al.; Withdrawal of Approval of 2 Abbreviated Antibiotic Applications and 15 Abbreviated New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing approval of 2 abbreviated antibiotic applications (AADA's) and 15 abbreviated new drug applications (ANDA's). The holders of the applications notified the agency in writing that the drug products were no longer marketed and requested that the approval of the applications be withdrawn.

EFFECTIVE DATE: AUGUST 17, 1995.

FOR FURTHER INFORMATION CONTACT: Lola E. Batson, Center for Drug Evaluation and Research (HFD-360), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1038.

SUPPLEMENTARY INFORMATION: The holders of the applications listed in the table in this document have informed FDA that these drug products are no longer marketed and have requested that FDA withdraw approval of the applications. The applicants have also, by their request, waived their opportunity for a hearing.

Application No.	Drug	Applicant
AADA 60-446.	Tetracycline Oral Suspension, U.S.P	Richmar International, Inc., 1706 Birch Rd., McLean, VA 22101.
AADA 62-502.	Nystatin Vaginal Tablets, U.S.P., 100,000 units	Lemmon Co., 650 Cathill Rd., Sellersville, PA 18960.
ANDA 70-438.	Propranolol Hydrochloride Tablets, U.S.P., 10milligrams (mg) ..	Warner Chilcott, 201 Tabor Rd., Morris Plains, NJ 07950.
ANDA 70-439.	Propranolol Hydrochloride Tablets, U.S.P., 20 mg	Do.
ANDA 70-440.	Propranolol Hydrochloride Tablets, U.S.P., 40 mg	Do.
ANDA 70-441.	Propranolol Hydrochloride Tablets, U.S.P., 60 mg	Do.