

that Bayer Co. has filed a petition proposing that the food additive regulations be amended both to provide for the safe use of dimethyl dicarbonate (DMDC) in noncarbonated juice beverages containing up to and including 100 percent juice and to also provide for a more descriptive term, in place of "inhibitor of yeast", for the safe use of DMDC.

FOR FURTHER INFORMATION CONTACT: Martha D. Peiperl, Center for Food Safety and Applied Nutrition (HFS-215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3077.

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 0A4718) has been filed by Bayer Co., c/o McKenna & Cuneo LLP, 1900 K St., NW., Washington, DC 20006-1108. The petition proposes to amend the food additive regulations in § 172.133 *Dimethyl dicarbonate* (21 CFR 172.133) both to provide for the safe use of DMDC in noncarbonated juice beverages containing up to and including 100 percent juice and also to provide for a more descriptive term, in place of "inhibitor of yeast", for the safe use of DMDC.

The agency has determined under 21 CFR 25.32(k) and 21 CFR 25.30(i) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Dated: February 22, 2000.

Alan M. Rulis,

*Director, Office of Premarket Approval,
Center for Food Safety and Applied Nutrition.*
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00F-0813]

Tritex Co., Inc.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that Tritex Co., Inc., has filed a petition proposing that the food additive regulations be amended to provide for

the safe use of sodium xylene sulfonated as a component of paper and paperboard intended to contact food.

FOR FURTHER INFORMATION CONTACT: Mark Hepp, Center for Food Safety and Applied Nutrition (HFS-215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3098.

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 0B4719) has been filed by Tritex Co., Inc., 1001 Boul. Industriel, Saint-Eustache (Quebec), CANADA J7H 6C3. The petition proposes to amend the food additive regulations in § 176.170 *Components of paper and paperboard in contact with aqueous and fatty foods* (21 CFR 176.170) to provide for the safe use of sodium xylene sulfonated as a component of paper and paperboard intended to contact food.

The agency has determined under 21 CFR 25.32(i) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Dated: February 22, 2000.

Alan M. Rulis,

*Director, Office of Premarket Approval,
Center for Food Safety and Applied Nutrition.*
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N-0018]

Orthopedic Devices; Reclassification of the Knee Joint Patellofemoral Metal/Polymer Porous-Coated Uncemented Prosthesis and the Knee Joint Femorotibial (Uni-compartmental) Metal/Polymer Porous-Coated Uncemented Prosthesis

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of panel recommendation.

SUMMARY: The Food and Drug Administration (FDA) is announcing for public comment two recommendations of the Orthopedic and Rehabilitation Devices Panel (the Panel) to reclassify the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented

prosthesis from class III into class II. The Panel made these recommendations after reviewing the reclassification petition submitted by the Orthopedic Surgical Manufacturers Association (OSMA) and other publicly available information. FDA is also announcing for public comment its tentative findings on the Panel's recommendations. After considering any public comments on the Panel's recommendations and FDA's tentative findings, FDA will approve or deny the reclassification petition by order in the form of a letter to the petitioner. FDA's decision on the reclassification petition will be announced in the **Federal Register**.

DATES: Submit written comments by June 7, 2000.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Peter G. Allen, Center for Devices and Radiological Health (HFZ-410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-2036.

SUPPLEMENTARY INFORMATION:

I. Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et seq.*), as amended by the Medical Device Amendments of 1976 (the amendments) (Public Law 94-295), the Safe Medical Devices Act of 1990 (the SMDA) (Public Law 101-629), and the Food and Drug Administration Modernization Act of 1997 (the FDAMA) (Public Law 105-115), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act, devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendment devices, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most

preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act) into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless and until the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, under section 513(i) of the act, to a predicate device that does not require premarket approval. The agency determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and 21 CFR part 807 of the regulations.

A preamendments device that has been classified into class III may be marketed, by means of premarket notification procedures, without submission of a premarket approval application (PMA) until FDA issues a final regulation under section 515(b) of the act (21 U.S.C. 360e(b)) requiring premarket approval.

Reclassification of classified postamendments devices is governed by section 513(f)(2) of the act. This section provides that FDA may initiate the reclassification of a device classified into class III under section 513(f)(1) of the act, or the manufacturer or importer of a device may petition the Secretary of Health and Human Services (the Secretary) for the issuance of an order classifying the device in class I or class II. FDA's regulations in § 860.134 (21 CFR 860.134) set forth the procedures for the filing and review of a petition for reclassification of such class III devices. In order to change the classification of the device, it is necessary that the proposed new class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

Under section 513(f)(2)(B)(i) of the act, the Secretary may, for good cause shown, refer a petition to a device classification panel. The Panel shall make a recommendation to the Secretary respecting approval or denial of the petition. Any such recommendation shall contain: (1) A summary of the reasons for the recommendation, (2) a summary of data upon which the recommendation is based, and (3) an identification of the risks to health (if any) presented by the device with respect to which the petition was filed.

II. Regulatory History of the Devices

The knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femoral tibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis intended to be implanted to replace the knee joint or part of the knee joint, respectively, are postamendments devices classified into class III under section 513(f)(2) of the act. Therefore, the devices cannot be placed in commercial distribution for implantation to replace the knee joint or part of the knee joint, respectively, unless they are reclassified under section 513(f)(2), or subject to an approved premarket approval application (PMA) under section 515 of the act.

This action is taken in accordance with section 513(f)(2) of the act and § 860.134, based on information submitted in a petition for reclassification by the OSMA received on July 28, 1997, requesting reclassification of the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femoral tibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis from class III into class II (Ref. 1). Consistent with the act and the regulation, FDA referred the petition to the Panel for its recommendation on the requested changes in classification.

III. Device Descriptions

The following device descriptions are based on the Panel's recommendation and the agency's review.

A. Knee Joint Patellofemoral Metal/polymer Porous-Coated Uncemented Prosthesis

A knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis is a device intended to be implanted to replace a knee joint. The device limits translation and rotation in one or more planes via the geometry of its articulating surfaces. It has no linkage across-the-joint. This generic type of device includes prostheses that have a femoral component made of a cobalt-chromium-molybdenum (Co-Cr-Mo) alloy or a surface hardened titanium-aluminum-vanadium (Ti-6Al-4V) alloy, a tibial component made of an ultra-high molecular weight polyethylene (UHMWPE) articulating bearing surface fixed to a metal base made of Co-Cr-Mo or Ti-6Al-4V alloy, and a patellar resurfacing component made of an UHMWPE component fixed to a metal base made of a Co-Cr-Mo- or a Ti-6Al-

4V alloy. The femoral component, tibial base, and patellar base have a substrate porous coating made of, in the case of Co-Cr-Mo components, beads of the same alloy or commercially pure titanium powder; and in the case of Ti-6Al-4V components, beads or fibers of commercially pure titanium or Ti-6Al-4V alloy, or commercially pure titanium powder. The porous coating has a volume porosity between 30 to 70 percent, an average pore size between 100 to 1,000 microns, interconnecting porosity, and a porous coating thickness of 600 to 1,500 microns. This generic type of device is designed to achieve biological fixation to bone without the use of bone cement. This device description does not include mobile bearing knee prostheses.

B. Knee Joint Femoral Tibial (Uni-compartmental) Metal/polymer Porous-Coated Uncemented Prosthesis

A knee joint femoral tibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis is a device intended to be implanted to replace part of a knee joint. The device limits translation and rotation in one or more planes via the geometry of its articulating surface. It has no linkage across the joint. This generic type of device includes prostheses that have a femoral component made of a cobalt-chromium-molybdenum (Co-Cr-Mo) alloy or a surface hardened titanium-aluminum-vanadium (Ti-6Al-4V) alloy and tibial component composed of an ultra-high molecular weight polyethylene fixed to a metal base made of a Co-Cr-Mo or a surface hardened Ti-6Al-4V alloy. The femoral component and tibial base have a substrate porous coating made of, in the case of Co-Cr-Mo components, beads of the same alloy or commercially pure titanium powder, and in the case of Ti-6Al-4V components, beads or fibers of commercially pure titanium or Ti-6Al-4V alloy, or commercially pure titanium powder. The porous coating has volume porosity between 30 to 70 percent, an average pore size between 100 to 1,000 microns, interconnecting porosity, and a porous coating thickness of 600 to 1,500 microns. This generic type of device is designed to achieve biological fixation to bone without the use of bone cement. This device description does not include mobile bearing knee prostheses.

IV. Recommendations of the Panel

At a public meeting on January 12 and 13, 1998, the Panel recommended unanimously that the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and recommended (five to three) that

the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis be reclassified from class III to class II (Ref. 2). The Panel believed that class II with the special controls (FDA recognized consensus standards and FDA guidance documents for both devices, and postmarket surveillance for only the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis) would provide reasonable assurance of the safety and effectiveness of the devices.

V. Risks to Health

After considering the information in the petition, the Panel's deliberations, the published literature, and the Medical Device Reports, FDA has evaluated the risks to health associated with the use of the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis. FDA now believes that the following are risks to health associated with use of the devices: infection, adverse tissue reaction, pain and/or loss of function, and revision. FDA notes that these risks to health are also associated with the use of the cemented versions of total and partial knee joint prostheses.

A. Infection

Infection is a potential risk to health associated with all surgical procedures and implanted devices, and it occurs equally in patients implanted with cemented and uncemented knee joint prostheses (Ref. 1). The best defenses against infection are preventative measures, including selection of patients without known local and/or systemic infection, administration of perioperative antibiotics, implantation of a sterilized device, and strict adherence to sterile surgical technique.

B. Adverse Tissue Reaction

Adverse tissue reaction is a potential risk to health associated with all implanted devices (Ref. 1). If the materials used in the manufacture of knee prostheses are not biocompatible, the patient could have an adverse tissue reaction. Knee prostheses are made of implant materials with an established long history of safe use. In addition, the biocompatibility of porous-coated implant materials has been shown to be comparable to those of the "as cast" noncoated material.

C. Pain and/or Loss of Function

Pain and loss of knee function can occur with any knee arthroplasty. Some

of the same kinds of device-related complications causing pain and/or loss of function are associated with the implantation of both cemented and uncemented knee prostheses. These complications include early loosening due to inappropriate patient and/or device selection, inappropriate surgical technique and/or poor bone quality; some forms of metal and/or polyethylene wear which may cause osteolysis (dissolution of bone); and component disassembly, fracture, and/or failure. Dislocation and instability of a knee prosthesis may be due to either inappropriate surgical technique and/or component design or failure. However, other device-related complications resulting in pain and/or loss of function are directly or uniquely related to the porous coating(s) of uncemented knee prosthesis components. These complications include incomplete and/or slow biological ingrowth of the porous coating, resulting in pain and dislocation/instability of the joint, and delamination of porous coating from the prosthesis components. Also, inadequate design and/or testing of the metal backing of the patellar component of uncemented knee prostheses may cause dislocation and instability, which may result in pain and/or loss of function.

D. Revision

The incidence of revision for uncemented knee prostheses is comparable to the revision rates of cemented total knee arthroplasty (Ref. 1). The major causes for revision of uncemented knee prostheses are failure of the metal-backed patellar component or incomplete tibial fixation.

VI. Summary of the Reasons for the Recommendations

After considering the data and information contained in the petition and provided by FDA, the open discussions during the Panel meeting, and the Panel members' personal knowledge of and clinical experience with the devices, the Panel gave the following reasons in support of its recommendations to reclassify the two generic type devices, the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis intended to replace a knee joint or part of a knee joint, respectively, from class III into class II. The Panel believed that both of these devices should be reclassified into class II because special controls, in addition to general controls, provide reasonable assurance of the safety and

effectiveness of the devices, and there is sufficient information to establish special controls to provide such assurance.

VII. Summary of Data Upon Which the Panel Recommendations Are Based

In addition to the potential risks to health of the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis, described in Section V., there is reasonable knowledge of the benefits of the devices. Both cemented and uncemented knee prostheses provide a decrease in pain or cessation of pain and increased mobility and function, post-operatively resulting in an overall improved quality of patient life. Specific benefits of uncemented knee prostheses are the absence of risks associated with the use of bone cement (e.g., embolism and bone cement breakdown) and easier revision, if revision should become indicated due to loosening.

VIII. Special Controls

FDA believes that the special controls identified below, in addition to general controls, are adequate to control the identified risks to health described for the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis. FDA agrees with the Panel that FDA recognized consensus standards and the FDA guidances are appropriate special controls to reasonably assure the safety and effectiveness of both devices. However, FDA disagrees with the Panel that postmarket surveillance is an appropriate special control to reasonably assure the safety and effectiveness of the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis.

In their deliberations, the panel stated that it was important that adverse device outcomes be reported to FDA. The panel thought that adverse device outcomes should be tracked through postmarket surveillance. FDA agrees with the Panel that adverse device outcomes should be reported to FDA. However, FDA believes that another postmarket mechanism better addresses the Panel's concern that adverse device outcomes should be reported to FDA. FDA believes that the existing mandatory medical device reporting (MDR) system is the appropriate mechanism to report such adverse

events. Therefore, postmarket surveillance is unnecessary to address the Panel's concerns and to reasonably assure the safety and effectiveness of the device.

Based on the available information, FDA identified the following 11 FDA recognized American Society for Testing and Materials (ASTM) consensus standards and 4 FDA guidance documents as special controls to reasonably assure the safety and effectiveness of both devices:

A. ASTM Consensus Standards

1. "ASTM F 67-95, Standard Specifications for Unalloyed Titanium for Surgical Implants Applications";
2. "ASTM F 75-98, Standard Specification for Cast Cobalt-28 Chromium-6 Molybdenum Alloy for Surgical Implant Applications";
3. "ASTM F 136-96, Standard Specification for Wrought Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) Alloy (R56401) for Surgical Implant Application";
4. "ASTM F 648-98, Standard Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants";
5. "ASTM F 1044-95, Standard Test Method for Shear Testing of Porous Metal Coatings";
6. "ASTM F 1147-95, Standard Test Method for Tension Testing of Porous Metal Coatings";
7. "ASTM F 1160-91, Standard Test Method for Constant Stress Amplitude Fatigue Testing of Porous Metal-Coated Metallic Materials";
8. "ASTM F 1377-98, Standard Specification for Cobalt-28 Chromium-6 Vanadium Powder for Coating of Orthopedic Implants";
9. "ASTM F 1580-98, Standard Specification for Titanium and Titanium-6% Aluminum-4% Vanadium Alloy Powders for Coatings of Surgical Implants";
10. "ASTM F 1672-95, Standard Specification for Resurfacing Patellar Prosthesis"; and
11. "ASTM F 1800-97, Standard Test Method for Cyclic Fatigue Testing of Metal Tibial Tray Components of Total Knee Joint Replacements."

The ASTM standards define material specifications and testing methods for the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femorotibial (uni-compartment) metal/polymer porous-coated uncemented prosthesis. Adherence to these standards and comparison of the results from these standard test methods can control the risks to health of adverse tissue reaction, pain and/or loss of

function, and revision, by having the manufacturer use surgical implant quality materials and assuring that the device has acceptable performance through mechanical testing.

ASTM standards may be obtained from ASTM Customer Services, 100 Barr Harbor Dr., West Conshohocken, PA 19428, telephone 610-832-9585. ASTM has a site on the Internet at the address <http://www.astm.org>.

B. Guidance Documents

1. "Guidance for the Preparation of Premarket Notifications (510(k)s) for Cemented, Semi-Constrained Total Knee Prostheses." (Facts-on-Demand #830);
2. "Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement." (Facts-on-Demand #827);
3. "Guidance Document for Testing Non-articulating, Mechanically Locked' Modular Implant Components." (Facts-on-Demand #916); and
4. "Preparation of Premarket Notification (510(k)) Applications for Orthopedic Devices." (Facts-on-Demand #832).

The FDA guidance documents provide guidance on how to meet general orthopedic device premarket notification (510(k)) requirements, including biocompatibility testing, sterility testing, mechanical performance testing, and physician and patient labeling for the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis. Use of the pre-clinical section of the FDA guidance documents can control the risks to health of adverse tissue reaction, infection, pain and/or loss of function, and revision by having manufacturers use surgical quality implant materials, adequately test and sterilize their devices, and provide adequate directions for use and patient information.

To receive a guidance via fax machine, telephone CDRH's Facts-on-Demand (FOD) system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. At the first voice prompt, press 1 to access DSMA Facts; at the second voice prompt, press 2, and then enter the document number (in parentheses in the list above) followed by the pound sign (#). Then follow the remaining voice prompts to compete your request.

Persons interested in obtaining a copy of these guidances may also do so using the Internet. The Center for Devices and Radiological Health (CDRH) maintains

an entry on the Internet for easy access to information including text, graphics, and files that may be downloaded to a personal computer with access to the Internet. The CDRH home page may be accessed at <http://www.fda.gov/cdrh>.

IX. FDA's Tentative Findings

FDA believes that the knee joint patellofemoral metal/polymer porous-coated uncemented prosthesis and the knee joint femorotibial (uni-compartmental) metal/polymer porous-coated uncemented prosthesis should be reclassified into class II because special controls, in addition to general controls, would provide reasonable assurance of the safety and effectiveness of the devices, and there is sufficient information to establish special controls to provide such assurance.

X. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m.

1. Petition for reclassification of the Patello-Femoro-Tibial Metal/Polymer/Metal Biologically Fixed Prosthesis submitted by the Orthopedic Surgical Manufacturers Association, July 28, 1997.
2. Transcript of the Orthopedic and Rehabilitation Devices Panel Meeting, January 12 and 13, 1998, Vol. II, pp. 1 to 227.

XI. Environmental Impact

The agency has determined under 21 CFR 25.34(b) that these reclassification actions do not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

XII. Analysis of Impacts

FDA has examined the impacts of the notice under Executive Order 12866 and the Regulatory Flexibility Act (Public Law 96-354) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104-121), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety and other advantages; distributive impacts; and equity). The agency believes that these reclassification actions are consistent

with the regulatory philosophy and principles identified in the Executive Order. In addition, the reclassification actions are not significant regulatory actions as defined by the Executive Order and so are not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Reclassification of the devices from class III to class II will relieve manufacturers of the cost of complying with the premarket approval requirements in section 515 of the act. Because reclassification will reduce regulatory costs with respect to this device, it will impose no significant economic impact on any small entities, and it may permit small potential competitors to enter the marketplace by lowering their costs. The agency therefore certifies that these reclassification actions, if finalized, will not have a significant economic impact on a substantial number of small entities. In addition, this reclassification action will not impose costs of \$100 million or more on either the private sector or State, local, and tribal governments in the aggregate, and therefore a summary statement of analysis pursuant to section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

XIII. Request for Comments

Interested persons may, on or before June 7, 2000, submit to the Dockets Management Branch (address above) written comments regarding this document. 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.

Dated: February 14, 2000.

Linda S. Kahan,

Deputy Director for Policy, Center for Devices and Radiological Health.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 99D-0297]

Guidance for Industry on Formal Dispute Resolution: Appeals Above the Division Level; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled "Formal Dispute Resolution: Appeals Above the Division Level." This guidance is intended to provide guidance for industry on procedures that will be adopted by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for resolving scientific and procedural disputes that cannot be resolved at the division level.

DATES: Submit written comments on agency guidances at any time.

ADDRESSES: Copies of this guidance for industry are available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/cber/guidelines.htm>. Submit written requests for single copies of the guidance to the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-3844, FAX 888-CBERFAX. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Patricia L. DeSantis, Center for Drug Evaluation and Research (HFD-2), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5400, or

Robert A. Yetter, Center for Biologics Evaluation and Research (HFM-10), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-0373.

SUPPLEMENTARY INFORMATION: FDA is announcing the availability of a guidance entitled "Formal Dispute Resolution: Appeals Above the Division

Level." The guidance is intended to provide guidance for industry on procedures that will be adopted by CDER and CBER for resolving scientific and procedural disputes that cannot be resolved at the division level. The guidance describes procedures for formally appealing such disputes to the office or center level and for submitting information to assist agency officials in resolving the issue(s) presented.

In the **Federal Register** of March 19, 1999 (64 FR 13587), FDA announced the availability of a draft guidance for industry entitled "Formal Dispute Resolution: Appeals Above the Division Level." The agency has finalized this guidance after considering comments received on the draft version. Few comments were received, and minor changes were made to the draft version in response to the comments in an effort to make the document more clear.

FDA regulations 21 CFR 10.75 provide a mechanism for any interested person to obtain formal review of any agency decision by raising the matter with the supervisor of the employee who made the decision. If the issue is not resolved at the primary supervisory level, the interested person may request that the matter be reviewed at the next higher supervisory level. This process may continue through the agency's entire supervisory chain of command, through the centers to the Commissioner of Food and Drugs. CDER and CBER regulations for dispute resolution during the investigational new drug process (21 CFR 312.48) and the new drug application/abbreviated new drug application process (21 CFR 314.103) establish similar procedures for the resolution of scientific and procedural matters at the division level and subsequent formal review of decisions through center management.

On November 21, 1997, President Clinton signed into law the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) (Public Law 105-115). Section 404 of the Modernization Act creates new section 562 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360bbb-1). Section 562 of the act provides that if, regarding an obligation concerning drugs or devices under the act or section 351 of the Public Health Service Act (42 U.S.C. 262), there is a scientific dispute between the agency and a sponsor, applicant, or manufacturer and no specific provision of the act or regulation provides a right of review of the matter in controversy, FDA shall, by regulation, establish a procedure under which such sponsor, applicant, or manufacturer may request a review of the controversy, including