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March 14, 2002

Dale Carlson  
Associate Director, Regulatory Affairs  
American Pharmaceutical Partners, Inc.  
2152 West Potomac Avenue  
Chicago, IL 60622

Re: Docket No. 01P-0061/CP1

Dear Mr. Carlson:

This formally responds to your Citizen Petition, dated January 31, 2001, requesting the Food and Drug Administration (FDA) to determine whether IFEX (ifosfamide for injection) was withdrawn from sale by Bristol-Myers Squibb (BMS) for safety or effectiveness reasons.

The FDA has reviewed its records and determined that IFEX was not withdrawn for reasons of safety or effectiveness. Accordingly, FDA will continue to list IFEX (ifosfamide for injection) in the "Discontinued Drug Product List" section of *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book").

Enclosed is a copy of the Federal Register notice that announces the FDA determination. If you need further information, do not hesitate to contact me at 301-594-2041.

Sincerely,

S. Mitchell Weitzman  
Office of Regulatory Policy (HFD-7)  
Center for Drug Evaluation and Research

Enclosure

OIP-0061

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Government, or individuals. FDA

estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN<sup>1</sup>

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
530.22(b)	2	1	2	4,160	8,320

<sup>1</sup>There are no capital costs or operating and maintenance costs associated with this collection of information.

The Center for Veterinary Medicine (CVM) has not found circumstances to require the establishment of a safe level and subsequent development of an analytical methodology. However, CVM believes there will be instances when an analytical methodology will be required.

Dated: May 3, 2002.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 02-11934 Filed 5-13-02; 8:45 am]

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. 01P-0061]

#### Determination That IFEX (Ifosfamide for Injection), 1-Gram and 3-Gram Vials, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing its determination that IFEX (ifosfamide for injection), 1 gram (g) and 3 g, was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for ifosfamide.

**FOR FURTHER INFORMATION CONTACT:** Mitchell Weitzman, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5670.

**SUPPLEMENTARY INFORMATION:** In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA sponsors must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength

and dosage form as the "listed drug," which is a version of the drug that was previously approved. Sponsors of ANDAs do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products with Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA's regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

IFEX is the subject of NDA 19-763, held by Bristol-Myers Squibb Co. (BMS). FDA approved NDA 19-763 on December 30, 1988. Used in combination with other approved antineoplastic agents, IFEX is indicated for third line chemotherapy of germ cell testicular cancer. In the IFEX clinical studies, it was observed that urotoxic side effects, especially hemorrhagic cystitis, were frequently associated with the administration of IFEX. The approved labeling for IFEX stated that IFEX "should ordinarily be used in combination with a prophylactic agent for hemorrhagic cystitis, such as mesna." FDA separately approved BMS's NDA for MESNEX (mesna) Injection on December 30, 1988. BMS

never marketed IFEX alone; instead, it elected to market IFEX exclusively in a combination package with MESNEX.

IFEX as a single agent is currently listed in the "Discontinued Drug Product List" section of the Orange Book. IFEX is also listed as part of a copackaged kit with MESNEX in the Orange Book's prescription drug product list. The relocation of IFEX as a single agent to the "Discontinued Drug Product List" coincided with a labeling modification on October 10, 1992, to reflect changes in storage conditions for IFEX and an approval of copackaging with MESNEX.

On January 31, 2001, Tom Stothoff submitted a citizen petition (Docket No. 01P-0061/CP1) to FDA under 21 CFR 10.30, requesting that the agency determine whether IFEX (as a single agent) was withdrawn from sale for reasons of safety or effectiveness. The petitioner seeks this determination in preparation for filing an ANDA for ifosfamide for Injection, U.S.P.

On March 9, 2001, BMS filed a comment to the citizen petition requesting that FDA find that IFEX has not been withdrawn from sale and is not separately marketed by BMS for reasons of safety or effectiveness. With respect to safety and effectiveness, BMS argued that regardless of whether IFEX was withdrawn, FDA should deny the petitioner permission to file an ANDA for ifosfamide as a single agent because, as stated in the label, ifosfamide can only be administered safely in conjunction with a uroprotective agent such as mesna. BMS cited both the medical literature and the potential for urotoxic reactions if ifosfamide is used alone in support of this claim.

BMS contends that it has never withdrawn or ceased to market IFEX because it has marketed IFEX in a combination package with MESNEX since the time of their approval. However, IFEX was approved under its own NDA as a single agent. In previous instances (see, e.g., 61 FR 25497, May 21, 1996) (addressing a relisting request for glyburide tablets), FDA has concluded that never marketing an approved product is equivalent to withdrawing the drug from sale.

Therefore, even though BMS has never marketed IFEX alone, it is appropriate to categorize IFEX (as a single agent) as having been withdrawn from sale. Once a listed drug has been withdrawn from sale, FDA must make a determination that the withdrawal from sale was not for reasons of safety or effectiveness before it can approve any ANDAs referencing the listed drug.

The agency has determined that IFEX as a single agent has not been withdrawn for reasons of safety or effectiveness. FDA agrees with BMS that ifosfamide should be used with a uroprotective agent like mesna. However, that does not preclude the safe use of ifosfamide as a single agent with MESNEX or a generic version of mesna. FDA approved two ANDAs for mesna in April 2001. The FDA has no requirement that coadministered products must also be copackaged. There are many drugs whose labeling identifies them for use in combination with other drugs with which they are not copackaged, including Taxol and Taxotere. Neither the petitioner nor BMS identified any data suggesting that marketing IFEX alone would compromise patients' safety. Moreover, the relevant literature and adverse event reports do not bear out BMS's claim that marketing IFEX as a single agent would be unsafe. In the absence of data suggesting a safety risk, and because IFEX was approved as a single agent, we conclude that FDA may approve ANDAs referencing IFEX alone.

After considering the citizen petition and the comments thereon and reviewing its records, FDA determines that, for the reasons outlined previously in this document, IFEX as a single agent was not withdrawn for reasons of safety or effectiveness. Accordingly, the agency will continue to list IFEX in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to IFEX, 1-g and 3-g vials, may be approved by the agency.

Dated: May 6, 2002.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 02-11971 Filed 5-13-02; 8:45 am]

BILLING CODE 4160-01-S

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. 02D-0113]

#### Medical Devices; Draft Guidance for Industry and FDA on Class II Special Controls: Root-Form Endosseous Dental Implants and Abutments; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of the draft guidance entitled "Class II Special Controls Guidance Document: Root-form Endosseous Dental Implants and Abutments; Draft Guidance for Industry and FDA." This draft guidance document was developed as a special control guidance to support the reclassification of the root-form endosseous dental implant device from class III to class II and the reclassification of the endosseous dental implant abutment device from class III to class II. Elsewhere in this issue of the *Federal Register*, FDA is issuing a proposed rule to reclassify these device types. This guidance is neither final nor is it in effect at this time.

**DATES:** Submit written or electronic comments on the draft guidance by August 12, 2002.

**ADDRESSES:** Submit written requests for single copies on a 3.5" diskette of the draft guidance document entitled "Class II Special Controls Guidance Document: Root-form Endosseous Dental Implants and Abutments; Draft Guidance for Industry and FDA" to the Division of Small Manufacturers, International, and Consumer Assistance (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850. Send two self-addressed adhesive labels to assist that office in processing your request, or fax your request to 301-443-8818. Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

#### FOR FURTHER INFORMATION CONTACT:

Angela E. Blackwell, Center for Devices and Radiological Health (HFZ-480), Food and Drug Administration, 9200

Corporate Blvd., Rockville, MD 20850, 301-443-8879.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

This draft guidance document describes a means by which the root-form endosseous dental implant device and the endosseous dental implant abutment device may comply with the requirement of special controls for class II devices. A root-form endosseous dental implant device is intended to be surgically placed in the bone of the upper or lower arches to provide support for prosthetic devices, such as artificial teeth, in order to restore the patient's chewing function. An endosseous dental implant abutment device is a separate component that is attached to the implant and is intended to aid in prosthetic rehabilitation.

##### II. Significance of Guidance

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on root-form endosseous dental implant and endosseous dental implant abutment devices. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

##### III. Electronic Access

In order to receive the draft guidance entitled "Class II Special Controls Guidance Document: Root-form Endosseous Dental Implants and Abutments; Draft Guidance for Industry and FDA" via your fax machine, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system. At the second voice prompt press 1 to order a document. Enter the document number (1389) followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

Persons interested in obtaining a copy of the draft guidance may also do so using the Internet. 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 Internet access. Updated on a regular basis, the CDRH home page includes the civil money penalty guidance documents package, device safety alerts, *Federal Register* reprints, information on premarket submissions (including lists of approved applications and manufacturers' addresses), small manufacturers'