DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Ombudsman
5600 Fishers Lane (HF-7)
Room 14B-03
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

September 9, 2002

Cary J. Reich, Ph.D.
Vice President, Research and Development
[ ]
34175 Ardenwood Blvd.
Fremont, California 94555

Re: Request for Designation – Decision Upon Reconsideration
FloSeal [ ]
Our file: 2002.018

Dear Dr. Reich:

This letter responds to your letter on behalf of [ ] Inc.,[1] dated May 24, 2002, requesting reconsideration of the Food and Drug Administration's (FDA) decision that FloSeal [ ] would be regulated by the Center for Biologics Evaluation and Research (CBER) under the device premarket application (PMA) provisions of the Food, Drug, and Cosmetic Act (the Act). As discussed below, we now conclude that the Center for Devices and Radiological Health (CDRH) will have primary review responsibility for FloSeal [ ] CBER will review and regulate the human thrombin component under a biologics license application for further manufacture. CDRH will review and regulate the product as a whole under the device provisions of the Act. A full discussion follows.

FloSeal [ ] is an absorbable hemostatic agent containing bovine gelatin granules and human thrombin. In December 1999, CDRH approved a PMA covering [ ] [ ] FloSeal, which contains identical bovine gelatin granules, but bovine rather than human thrombin. The human thrombin component of FloSeal [ ] is the same human thrombin contained in [ ], manufactured by [ ] and approved by CBER under a BLA in 1998. In its March 11, 2002 request for designation, [ ] recommended that CDRH have primary jurisdiction for the review and regulation of FloSeal [ ]

By letter dated May 13, 2002. FDA concluded that CBER would have primary jurisdiction for the review of FloSeal [ ] under the device provisions of the act. The reason for the assignment was that CBER has been responsible for the premarket review and regulation of human thrombin products.

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[1] According to the request for reconsideration, [ ] was acquired by Baxter Healthcare Corporation, effective May 3, 2002. The original request for designation, dated March 11, 2002, was submitted by [ ]; and the request for reconsideration was submitted on [ ]; letterhead. This letter refers to Baxter (which includes [ ]) as appropriate to reflect current ownership.

[redacted] request for reconsideration stated that CDRH should have primary responsibility for reviewing and regulating FloSeal[redacted] under the device provisions of the Act. Among other things, the Company argued that the primary mode of action of FloSeal [redacted] is identical to the primary mode of action of FloSeal. Since assignment of the FDA Center with lead review responsibility is based on the product's primary mode of action, CDRH's review and approval of FloSeal means that the primary mode of action of FloSeal (and of FloSeal[redacted], by extension) is due to the device component.

We have considered the information contained in the request for reconsideration and information presented at a meeting between representatives of Baxter and the agency on July 30, 2002. We now conclude that FloSeal [redacted] is a combination product consisting of a device component (bovine gelatin) and a biologics component (human thrombin), but given the contribution of both components to hemostasis, we are unable to determine the primary mode of action of FloSeal [redacted] at this time. When the primary mode of action of a product cannot be determined, the agency must rely on other factors to assign primary jurisdiction. In this case, because of CDRH's past experience with FloSeal, we are assigning primary responsibility for the review and regulation of FloSeal [redacted] to CDRH.

The thrombin component of all device – thrombin combination hemostatic agents approved to date has been covered by a BLA containing an indication for use with an approved device for hemostasis. While we recognize that the thrombin component of FloSeal [redacted] has been evaluated in the context of the [redacted] BLA, it has not been reviewed for use with a device for hemostasis. Accordingly, CBER will review and regulate the human thrombin component of FloSeal [redacted] under a BLA for further manufacture. The BLA for further manufacture will be required to contain only chemistry, manufacturing, and controls (CMC) information. Much, if not all, of the CMC information necessary to support the human thrombin BLA for further manufacturer may already be contained in the [redacted] BLA. Baxter may extract relevant information from the [redacted] BLA and re-submit that information in the human thrombin BLA.

It is our understanding that at this time, Baxter [redacted] We further understand that Baxter has not yet determined whether it will [redacted] CBER requests that [redacted] it notify the CBER Ombudsman, Ms. Sherry Lard-Whiteford, at 301-827-0379. Ms. Lard-Whiteford will contact appropriate Center management [redacted]

It is our understanding that a user fee will not be assessable on the BLA for further manufacture. To confirm this understanding, Baxter may contact Ms. Carla Vincent, Regulatory Information Specialist, Office of Management, CBER, at 301-827-4357.

CDRH will review and regulate the product as a whole under a supplement to the PMA covering FloSeal. Baxter should submit all information other than CMC information related to human thrombin to the PMA supplement for review by CDRH. Please note that CBER and CDRH must approve the BLA for further manufacture and the PMA supplement simultaneously.

The statutory review time for a BLA for further manufacture is ten months. The statutory review time for a PMA supplement is six months. Baxter may submit either application as soon as it is ready. However, Baxter should not submit the BLA for further manufacture more than 45 days before the PMA supplement will be ready to be submitted. CBER must decide whether it is able to file a BLA 45 days after it is submitted; CBER has concluded that the PMA supplement must have been submitted in order to file the BLA for further manufacturing covering human thrombin.

Baxter should communicate with CBER directly about the BLA, both prior to submitting the BLA and as the BLA is undergoing review. For further information about the BLA, contact Sayah Nedjar, Ph.D., Chief, Regulatory Projects Management, Division of Blood Applications, OBRR, Center for Biologics Evaluation and Research (HFM-380), at 301-827-3524.

Baxter should direct all other communication to David Krause, Ph.D., Biologist/Reviewer, Plastic and Reconstructive Surgery Devices Branch, Division of General, Restorative, and Neurological Devices, CDRH, at 301-594-3090.

If you have any questions about this letter, please contact Suzanne O'Shea, of this office, at 301-827-3390.

Sincerely,

Suzanne O'Shea for

Steven H. Unger
Ombudsman

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May 13, 2002

Cary J. Reich, Ph.D.
Vice President, Research and Development
[redacted]
34175 Ardenwood Blvd.
Fremont, California 94555

Re: Request for Designation
FloSeal Hemostatic Matrix
Our file: RFD # 2002.018

Dear Dr. Reich

The Food and Drug Administration has completed its review of [redacted] request for designation (RFD) covering FloSeal [redacted] Hemostatic Matrix (FloSeal [redacted], filed by this office on March 11, 2002.

FloSeal [redacted] is an absorbable hemostatic agent containing bovine gelatin granules and human thrombin. The product will be a kit; the gelatin and thrombin components will be mixed in the operating room at the time of use. FloSeal [redacted] will be indicated in surgical procedures (other than in ophthalmic) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

In December 1999, FDA's Center for Devices and Radiological Health (CDRH) approved [redacted] premarket approval application 990009 covering FloSeal, consisting of bovine gelatin granules and bovine thrombin. FloSeal [redacted] will be essentially identical to FloSeal, except that FloSeal [redacted] will use human rather than bovine thrombin. [redacted] FDA's Center for Biologics Evaluation and Research (CBER) has already licensed this human thrombin [redacted]

[redacted] recommends that CDRH have primary jurisdiction for the premarket review and regulation of FloSeal [redacted] suggests that FloSeal is not a combination product, but argues that even if it is a combination product,

CDRH would have primary jurisdiction because the gelatin component is responsible for the product's primary mode of action. According to [ ] the gelatin component acts to seal the wound; the thrombin allows the product to effect hemostasis more quickly. In addition, according to [ ] the fact that the thrombin component is derived from human plasma does not determine the designation of FloSeal[ ].[1]

We have considered the information provided in the RFD, reviewed the Intercenter Agreement between CBER and CDRH, and discussed the issues raised with the staff in both centers. We conclude that FloSeal [ ] is a combination product consisting of a device component (bovine gelatin) and a biologic component (human thrombin).[2]

Assignment of a lead Center to conduct the review of a combination product is based on the Agency's determination of the product's primary mode of action.[3] In this case, there is not a full consensus among our scientists about the component responsible for the primary mode of action of FloSeal [ ]. It is clear that both components contribute to the product's function as a hemostatic agent. To date, CDRH has been responsible for the premarket review and regulation of combination products containing bovine thrombin, while CBER has been responsible for the premarket review and regulation of human thrombin products. Consistent with the existing division of responsibility, we are assigning primary jurisdiction for the premarket review and regulation of FloSeal [ ] to CBER.

We recognize the similarities between FloSeal and FloSeal [ ]. As [ ] points out, for [ ] product, CBER approved a change from a bovine thrombin component to a human thrombin component by relying heavily on data from animal studies. CBER anticipates that it will be able to rely on similar kinds of data with FloSeal [ ] Moreover, because the premarket review of FloSeal was accomplished under the device provisions of the act, CBER will review FloSeal [ ] under the device provisions of the act as well. [ ] should note however, that the human thrombin component of this product may be subject to certain biologic licensing requirements as well. CBER will provide guidance on which biologic requirements apply.

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[1] [ ] states that CDRH should "retain" jurisdiction over FloSeal [ ] and argues that there is no justification for changing the designation under 21 CDR § 3.9(b). This argument is based on an incorrect premise – that FloSeal and FloSeal [ ] are the same product. FloSeal [ ] is a different product from FloSeal, and is subject to a separate jurisdictional determination.

[2] See section 503(g) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 353(g)).

[3] See 21 U.S.C. § 353(g)(1) and 21 CFR 3.4.

The Division of Blood Applications will be the primary review group within CBER. For submission and review information, contact Sayar Nedjar at 301-827-3524.

You may request reconsideration of the designation decision set forth in this letter within 15 days of its receipt. See 21 CFR § 3.8(c). If you have any questions concerning this matter, please contact Richard Lawlor of this office at 301-827-3390.

Sincerely yours

Steven H. Unger
Ombudsman