DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Combination Products
15800 Crabbs Branch Way (HFG-3)
Suite 200
Rockville, MD 20855

Food and Drug Administration
Rockville MD 20857

May 22, 2009

Dr. Michael L. Basara
EPIEN Medical, Inc.
4225 White Bear Parkway, Suite 600
St. Paul, MN 55110

Re: Request for reconsideration
Epien Root Canal Cleanser
Our file: RFD 2009.0004
Dated: May 8, 2009
Received: May 8, 2009
Filed: May 8, 2009

Dear Dr. Basara:

The Food and Drug Administration (FDA) has completed its review of your request dated May 8, 2009, for reconsideration of the designation for the EPIEN Root Canal Cleanser (ERCC) as a combination product. We made this designation, presented in our letter of April 29, 2009, in response to your February 27, 2009 request for designation (RFD). You now request that we reconsider that designation and find, instead, that ERCC is a device.

We have considered the arguments offered in your request, and consulted with FDA's Center for Drug Evaluation and Research, Center for Devices and Radiological Health (CDRH), and Office of Chief Counsel. For the reasons provided below, we affirm our designation of the product as a device-drug combination product.

Product Description

According to the RFD, ERCC is a moderately viscous and dense liquid, consisting of water and three acids, hydroxybenzenesulfonic acid, hydroxymethoxybenzenesulfonic acid, and sulfuric acid, in addition to a colorant. The product is intended to be used by dental practitioners to irrigate tooth root canals to remove dentinal debris, smear layer, and dental plaque remaining after endodontic instrumentation, in preparation for endodontic obturation procedures.

FDA's April 29, 2009 Designation

FDA determined that ERCC is a combination product consisting of device and drug constituent parts, with a primary mode of action (PMOA) attributable to the device constituent part. In making this determination, FDA concluded that the three acids included in the product were drugs because they achieved their primary intended purposes through chemical action within or on the body, including through hydrogen bonding between these acids and water molecules from the dentinal debris.

Request for Reconsideration

The request for reconsideration asserts, as did the RFD, that hydrogen bonding is not a chemical action, noting that these bonds are "readily reversible" and that "their formation does not lead to the creation of new molecular entities." The request states that "recognized authorities in the field of Chemical Technology have characterized the mechanism of action of sulfuric acid as a dessicant as being a form of 'Physical Absorption.'"

In addition, the request argues that a series of QuickClot products cleared under section 510(k) of the Federal Food, Drug, and Cosmetic Act (FFDCA) offer a precedent for classifying ERCC as a device, "because the mechanisms by which both products absorb water from the tissues is the same—through the formation of hydrogen bonds . . . ." The request argues that FDA should, therefore, classify ERCC as a device "in order to be consistent with the precedent and not arbitrary in classification."

Decision upon Reconsideration: Device-drug combination product

Our analysis of whether hydrogen bonding is a form of chemical action begins with the statutory definition of a device. Section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 USC 321(h)) states that a device "does not achieve its primary intended purposes through chemical action within or on the body . . . ." The Act does not qualify the term "chemical action" to include, for example, only covalent or ionic bonding, and the Agency believes it is appropriate to interpret the term to include electrostatic interactions, including hydrogen bonding.

In addition, hydrogen bonding and other electrostatic interactions are commonly described in chemistry and other scientific sourcebooks as examples of interactions between chemical entities. Most drug effects depend on underlying electrostatic interactions between molecules, including hydrogen bonding. For example, receptor-ligand interactions are mediated electrostatically, including through hydrogen bonding. This bonding, including hydrogen bonding, is essential to drug-receptor interactions because it is the initial chemical interaction in a chain of chemical actions needed to achieve the ultimate drug effect. See, for example, Foye's Principles of Medicinal Chemistry: Receptors and Drug Action, 6th Ed. (2008); Levine's Pharmacology: Drug Actions and Reactions, 7th Ed. (2005); Bruice's Organic Chemistry: The Organic Chemistry of Drugs, 3d Ed. (1995). In the case of ERCC, the acids loosen debris by desiccating it through one of these forms of chemical action, namely hydrogen bonding, as you acknowledge.

Further, we note that it would be reasonable to conclude that the acids in ERCC participate in additional chemical actions besides hydrogen bonding, including acid reactions or tissue acidification through dissociation of sulfuric acid ions. The data discussed in the RFD regarding acid effects on the surface of teeth do not demonstrate that chemical actions would not occur in the root canal. In fact, those data indicate that ERCC could act as an acid in a more aqueous environment, and such an environment might reasonably be expected to exist in the root canal when ERCC is used as described in the RFD.

Moreover, the QuickClot products are distinguishable from your product on a number of grounds. For example, they are comprised of different ingredients and have different indications than your product. Further, as noted above, there is reason to believe, based upon the data presented in your RFD, that ERCC relies on other chemical actions in addition to hydrogen bonding.

Neither the information provided in your RFD or your request for reconsideration, nor any other information available to FDA, supports a conclusion that the acids in ERCC meet the device definition. The acids included in ERCC achieve their primary intended purposes through chemical action and ERCC is, therefore, a combination product. Accordingly, we affirm our designation that it is a combination product and the assignment of ERCC to the Dental Devices Branch of CDRH's Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices.

Next Steps

For further information about review requirements, please contact the Branch Chief, Susan Runner, DDS, MA at 240-276-3776 or susan.runner@fda.hhs,gov.

You may request further internal agency review of this decision under 21 CFR § 10.75. The Office of Combination Products reports to Dr. Murray M. Lumpkin, Deputy Commissioner for International and Special Programs. Dr. Lumpkin would be the appropriate reviewing official if you choose to request further review. Dr. Lumpkin's address is 5600 Fishers Lane (HF-3), Rockville, MD 20857. There is no time limit for submittal of a request for internal agency review.

Sincerely,

Thinh X. Nguyen
Director
Office of Combination Products

cc: Murray M. Lumpkin, M.D.
Susan Runner, DDS MA

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April 29, 2009

Drs. Michael L. Basara and Reg Dupre
EPIEN Medical, Inc.
4225 White Bear Parkway, Suite 600
St. Paul, MN 55110

Re: Request for Designation
Epien Root Canal Cleanser
Our file: RFD 2009.0004
Dated: February 27, 2009
Received: February 27, 2009
Filed: March 4, 2009

Dear Drs. Basara and Dupre:

The Food and Drug Administration (FDA) has completed its review of the request for designation (RFD) for the EPIEN Root Canal Cleanser (ERCC), which you submitted on behalf of EPIEN Medical, Inc. We have determined that the product is a combination product, and we have assigned it to the Center for Devices and Radiological Health (CDRH) as the lead agency center for premarket review and regulation based on our determination of the product's primary mode of action (PMOA).

Description of the Product

According to the RFD, ERCC is a moderately viscous and dense liquid, generally administered by irrigation syringe through a burr hole. It consists of hydroxybenzenesulfonic acid, hydroxymethoxybenzenesulfonic acid, sulfuric acid, and water, in addition to a colorant.

The product is intended to be used by dental practitioners to irrigate tooth root canals in preparation for endodontic obturation procedures. The RFD explains that by removing dentinal debris, smear layer, and dental plaque remaining after endodontic instrumentation, [redacted].

You recommend that ERCC be assigned to CDRH for premarket review and regulation. You assert that the product's PMOA is that of a device, specifically a mechanically rinsing action. You state that a secondary action loosens debris by desiccating it, to facilitate this rinsing function. You argue that this secondary action is also a device action and that the product should, therefore, be classified as a device.

Product Classification: Combination Product

While we agree, as explained below, that the product is appropriately assigned to CDRH for review, we do not agree that it is a device. Rather, we conclude that it is a combination product consisting of device and drug constituent parts. Specifically, based on the information provided in your RFD, we conclude that the water constitutes a device constituent part providing a mechanical, irrigation mode of action. We also conclude that the three acids are drug constituent parts because they achieve their primary intended effects through chemical action.

As the RFD states, these acids loosen debris through desiccation. We believe this desiccation occurs as a result of chemical actions. For example, the addendum to the RFD states that it is achieved through hydrogen bonding between these acids and water molecules from the debris, which is a form of chemical action. Therefore, these acids do not meet the statutory definition of a device at section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 USC 321(h)) for this intended purpose, but do meet the statutory definition of a drug at section 201(g) of the Act (21 USC 321(g)).[1]

We have determined that, because the product is comprised of both device (water) and drug (the three acids) constituent parts, it is a combination product within the meaning of section 503(g) of the Federal Food, Drug, and Cosmetic Act (Act) and Title 21 of the Code of Federal Regulations (CFR) section 3.2(e)(1).

Assignment of Lead Center: CDRH

In accordance with section 503(g)(1) of the Act and 21 CFR section 3.4, assignment of a lead Center to conduct the review of a combination product is based on the Agency's determination of the product's PMOA.

As discussed above, this product has two modes of action. We have considered the information in the RFD, and discussed the issues with staff in both CDRH and the Center for Drug Evaluation and Research (CDER). Based on the information in the RFD and other relevant information available to the Agency at this time, we have determined that your product's primary mode of action is attributable to the device component, which provides a mechanical irrigation action, while the drug constituent parts play a secondary role, facilitating the mechanical irrigation action of the device constituent part.

Accordingly, we are assigning the combination product to CDRH for premarket review and regulation under the medical device provisions of the Act.

Next Steps

CDRH's Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices, Dental Devices Branch will have lead responsibility for the combination product's premarket review and regulation. For further information about review requirements, please

[1] Section 201(h) of the Act states in pertinent part that a device " . . . does not achieve its primary intended purposes through chemical action within or on the body . . . ."

contact the Branch Chief, Susan Runner, DDS, MA at 240-276-3776 or susan.runner@fda.hhs,gov. Please include a copy of this letter with your initial submission to CDRH.

CDRH will coordinate with CDER as appropriate regarding the drug constituent parts of your product. Any clinical investigations of the combination product are subject to the Investigational Device Exemption (IDE) requirements found in 21 CFR 812 and should be conducted in conformity with those regulations. For your information, FDA published a draft guidance document "Current Good Manufacturing Practice for Combination Products," available at http://www.fda.gov/oc/combination/default.htm, which provides information about the applicability of current good manufacturing practice regulations for combination products. We encourage you to discuss with CDRH these and other regulatory requirements applicable to your combination product.

You may submit a written request for reconsideration of the classification or assignment of your product within 15 days of receipt of this letter, in accordance with 21 CFR 3.8(c). If you wish to request reconsideration, or have any other questions about this letter, please contact John Barlow Weiner at (301) 427-1934 or john.weiner@fda.hhs.gov. Finally, the Office of Combination Products is also available to you as a resource for questions or issues that may arise throughout the development of your product. You may reach us at the above address or by email at combination@fda.gov.

Sincerely,

Barlow Weiner for

Thinh X. Nguyen
Director
Office of Combination Products

cc: S. Runner