DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

December 2, 2004

Gerda P. Resch, MT, RAC
Regulatory Affairs Manager
Medtronic MiniMed
18000 Devonshire Street
Northridge, CA 91325-1219

Re: Docket No. 94P-0268

Dear Ms. Resch:

This letter responds to your citizen petition dated July 11, 1994 and filed by the Food and Drug Administration (FDA) on July 18, 1994, and the additional information that you provided in a letter dated June 23, 2004.

Petition

In your petition, you request that the Food and Drug Administration (FDA), in accordance with § 601(8) (42 U.S.C. 7671(8)) of the Clean Air Act (CAA)), amend § 2.125(e) (21 CFR 2.125(e)) to include the use of the MiniMed Implantable Infusion Pump (MIP) as essential and exempt from the CAA ban on products that contain Class I and Class II ozone-depleting substances. You state that the MIP utilizes the chlorofluorocarbon trichlorotrifluoroethane (CFC-113), a Class I ozone-depleting substance (ODS).[1] You also state that the MIP is being evaluated in human clinical trials under Investigational Device Exemption (IDE) G860065, and request an interim exemption pending a decision on the petition.

In an interim response to your petition dated March 21, 2003, FDA explained that it was not clear what happened after FDA received your petition in 1994, but we did a thorough search and did not find that we had issued a response. We then began a review of your petition. As part of this review process, we referred your petition to the Environmental Protection Agency (EPA) to obtain an opinion on whether your device is "an aerosol product or other pressurized dispenser" that is subject to the ban on nonessential products containing ODSs under 40 CFR 82.66(d). In a letter dated December 9, 2003, EPA determined that your device is subject to the ban. (See the enclosed letters).

[1] ODS is defined in § 2.125(a) as "any class I substance as defined in 40 CFR part 82, appendix A to subpart A, or class II substance as defined in 40 CFR part 82, appendix B to subpart A." CFC-113 is listed in 40 CFR part 82, appendix A to subpart A as a class I substance.

You provided additional information on the MIP in letter dated June 23, 2004. In that letter, you informed FDA that the MIP is currently under clinical investigation in the United States for treatment of Type 1 (insulin-dependent) diabetes. You noted that Medtronic MiniMed has completed enrollment of all subjects in its ongoing clinical trial and no more new implants are anticipated. The only possible exception is in the event of a device failure, in which case current subjects would be eligible for an immediate pump replacement.

Your letter also stated that because of the environmental issues surrounding use of CFCs, Medtronic MiniMed is currently engaged in conducting the verification and validation activities necessary to switch the pump design to use cyclopentane. Emergency pump replacement occurring prior to the completion of validation will involve CFC-containing pumps; however, pumps using cyclopentane will be introduced once the verification and validation activities associated with the change are complete.

As explained further below, FDA is denying your petition because the available information does not support designating the MIP an "essential" use under 21 CFR 2.125(f). However, under its enforcement discretion, FDA does not intend to object to your use of a MIP device containing CFC-113 as an emergency replacement for a patient enrolled in the MIP clinical trial, consistent with your June 23, 2004 letter.

Background

The CAA (42 U.S.C. 7671) provides EPA with the authority to issue regulations that prohibit the sale or distribution in interstate commerce of certain nonessential products that release class I ODSs into the environment and any aerosol or pressurized dispenser that contains a class II substance. Section 610(b) of the CAA authorizes EPA to determine which products that release class I substances are nonessential. Section 610(d) of the CAA sets forth the nonessential use ban for class II substances and authorizes EPA to grant exceptions to the class II ban in certain circumstances.

EPA's regulations define nonessential Class I products to include: "Any aerosol product or other pressurized dispenser . . .which contains a chlorofluorocarbon." EPA has determined that your device, which you describe as an "implantable infusion pump" that uses a CFC to create negative pressure in the pump's insulin reservoir, meets this definition. (See attached letter).

Under § 601(8) of the CAA, a medical device that utilizes a class I or class II ODS for which no safe or effective alternative has been developed is exempt from EPA's nonessential use ban provided that FDA, in consultation with EPA, has determined that the use is essential. The "essential uses" that are exempt from the CAA's ban are listed in 21 CFR § 2.125(e).

Criteria for Essential Use Determination

At the time you submitted your petition, § 2.125(f) stated that any person may file a petition under § 10.30 (21 CFR 10.30) to request that FDA initiate rulemaking to amend 21 CFR 2.125(e) to add an essential use. To demonstrate that the use of a CFC was essential, the petition needed to be supported by an adequate showing that:

1. There are no technically feasible alternatives to the use of a CFC in the product;

2. The product provides a substantial health, environmental, or other public benefit that would not be obtainable without the use of the CFC; and

3. The use does not involve a significant release of CFCs into the atmosphere or, if it does, the release is warranted by the consequence if the use were not permitted.

In the Federal Register of July 24, 2002 (67 FR 48370), FDA published a final rule amending its regulation on the use of CFC propellants in self-pressurized containers (enclosed). Revised § 2.125 uses the phrase "ozone-depleting substance" instead of the word "chlorofluorocarbon" in the title and text of the regulation. The new rule also changes the scope of the regulation to include medical products that release an ODS rather than limiting the definition to those products that use CFCs as a propellant.

In addition, the revised rule provides a separate process with distinct criteria for adding investigational uses to § 2.125(e). Under this amended rule, FDA decides whether to add an investigational use to § 2.125(e) in response to a petition submitted under § 10.30 and after notice-and-comment-rulemaking. If FDA amends § 2.125(e) to include an investigational use, that determination does not allow commercial manufacture and marketing of the medical product. Instead, following approval, a sponsor needs to file a separate petition under § 10.30 seeking a new essential use determination for commercial marketing of the medical product.

Under the new § 2.125(f) (2), any person may file a petition under § 10.30 to request that FDA amend § 2.125(e) to add the use of an investigational product. The new rule requires compelling evidence in support of a petition for a new essential use. Specifically, the petition must present compelling evidence that:

1 <u>Substantial technical barriers exist to formulating the investigational product without the use of ODSs.</u>

The term "technical barriers" refers to difficulties encountered in chemistry and manufacturing. A petitioner should establish that it evaluated all available alternative technologies and explain in detail why each alternative was deemed to be unusable to demonstrate that substantial technical barriers exist to formulating the investigational product without the use of ODSs. 67 FR at 48373.

2. A high probability exists that the investigational product will provide an unavailable important public health benefit.

The petitioner must provide compelling evidence that there is a high probability that the investigational product will provide an unavailable important public health benefit. "High probability" is defined in the preamble to mean that it is substantially more likely than not that the investigational product will provide an unavailable important public health benefit. "Unavailable important public health benefit" is construed to include benefits such as saving lives, significantly reducing or preventing an important morbidity, or significantly increasing patient quality of life. The petitioner must also show that patients cannot access non-ODS products and that no technology is readily available to produce and distribute non-ODS products. *Id.*

3. Use of the investigational product does not release cumulatively significant amounts of ODSs into the atmosphere or the release is warranted in view of the high probability of an unavailable important public health benefit.

A petitioner should submit a well-documented statement of the number of products to be manufactured and the amount of ODSs to be released by each product. Alternatively, a petitioner may show that the release is warranted in view of a high probability of an unavailable important public health benefit.

These revisions became effective January 20, 2003.

In your petition, you certify that:

1. There are no technologically feasible alternatives to the use of CFCs in the MIP. You base this statement on the conclusion that "There are no other gaseous substances currently available to create a negatively pressurized chamber needed for the insulin reservoir." However, your June 23, 2004 letter indicates that there are non-CFC alternatives to the use of CFC-113 in the MIP, and that you are currently switching pump designs to use cyclopentane. As a result, you have not met the standard in §2.125(f)(2)(i).

2. The MIP provides a substantial health benefit that would not be obtainable without the use of a CFC. In your petition, you reference several studies. You conclude, based on this data, that "the use of the MIP will provide the benefits of intensive therapy, which includes slowing or reversal of diabetic retinopathy, nephropathy, and neuropathy, without the increased risk of hypoglycemia." In your June 23, 2004 letter, you reiterate that there is no other therapy available for patients who have difficulty gaining glycemic control using standard methods of care. However, your letter also indicates that the MIP is being redesigned to use

cyclopentane, which will allow it to provide the same health benefit without the use of a CFC. On this basis, you have not provided compelling evidence that there is a high probability that the investigational product will provide an important public health benefit that is otherwise unavailable given other marketed insulin pumps and other modalities, as required by new §2.125(f)(2)(ii); and

3. The use of a CFC in the MIP does not involve a significant release of a CFC into the atmosphere. Your petition does not include a well-documented statement of the number of products to be manufactured and the amount of ODSs that may be released in the manufacture and use of each product. Your June 23, 2004 letter provides some information on the likelihood of release under ordinary usage, stating that the gas chamber of the device is hermetically sealed; that returned MIP devices are quarantined as hazardous and stored for analysis without compromising the hermetic chamber containing the CFC-113; and that once analyzed, the devices are sent to an approved disposal site, handled in accordance with EPA regulations, and disposed of by a licensed hazardous materials processor. However, without information on the amount of ODS that may be released in the manufacture of the product and the number of products manufactured, your petition does not meet the requirements of new §2.125(f)(2)(iii).

Conclusion

In order to add a new essential use to § 2.125 (e) for your device as you request in your petition, FDA would have to undertake notice and comment rulemaking. FDA does not believe that the available information supports adding an essential use for your device. You stated in your June 23, 2004 letter that you do not intend to implant any more devices containing CFC unless it is necessary as an emergency replacement for a device already implanted. Furthermore, you stated that you will not implant any device containing CFCs after you have completed the verification and validation activities necessary to switch to a pump design using cyclopentane.

FDA has determined that the available information does not support granting essential use status to the MIP device at this time and is denying your petition. However, FDA has determined that the MIP device, when used under the limited circumstances set forth in your June 23, 2004 letter, presents minimal, if any, risk to the environment from the use of CFC. Therefore, in its enforcement discretion, FDA does not intend to object to your use of the MIP device containing CFC for limited emergency replacement as described in your letter of June 23, 2004.

If you have any questions about this response, please contact Joseph M. Sheehan at 301-827-2974.

Sincerely Yours,

Linda S. Kahan
Deputy Director,
Center for Devices and
Radiological Health

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
AIR AND RADIATION

Mr. Joseph M. Sheehan
Chief, Regulations Staff
Food and Drug Administration
Center for Devices and Radiological Health (HFZ-215)
1350 Piccard Drive
Rockville, MD 20850

Dear Mr. Sheehan

Thank you for your letter of October 23, 2003, regarding the applicability of the Clean Air Act Section 610 rule and 40 CFR 82.66 to the MiniMed implantable infusion pump. You had requested EPA's opinion as to whether the device would be considered an "aerosol product or other pressurized dispenser" within the meaning of the CAA Section 610 rule and 40 CFR 82.66.

EPA has determined that the MiniMed implantable infusion pump is a "pressurized dispenser" and is therefore subject to the CAA Section 610 non-essential product ban and 40 CFR 82.66. EPA based this decision upon the fact that the MiniMed implantable infusion pump uses CFC-113 to create a negative pressure in the device to avoid over-filling of the insulin reservoir during refillll procedures. We therefore consider the sale and distribution of this product to be prohibited by the rule unless it is listed as a medical device in 21 CFR 2.125(e).

If you have further questions about the content of this letter, please do not hesitate to contact Jabeen Akhtar of my staff at (202) 343-9313.

Sincerely,

Drusilla Hufford

Drusilla Hufford, Director
Global Programs Division