



Medtronic

When Life Depends on Medical Technology

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DOCKET NO. 2004D-0410

November 29, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Docket No. 2004D -0410 - Draft Guidance for Industry and FDA Staff:
Application User Fees for Combination Products**

Dear Mr. Kramer:

Background

Medtronic Neurological, a division of Medtronic, Inc., is engaged in the research, development and marketing of restorative neuroscience products and therapies through site-specific, controlled delivery of electrical stimulation, drugs and biologics to the central and peripheral nervous system. Medtronic Neurological seeks to deliver innovative neurological therapies to patients with severe neurological disorders, typically orphan populations. Our products include implantable infusion systems and other drug delivery devices. Our therapies are often regulated as combination products as defined in 21 CFR 3.2 (e)(3)¹.

Drug delivery devices, such as those marketed by Medtronic Neurological, are labeled for infusion of specified drugs, for specified approved indications, and therefore are combination products under 21CFR 3.2(e)(3).¹ The regulatory path for combination

¹ 21 CFR 3.2 (e) 3 – Definition of a Combination Product –“ A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed; e.g. to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose....

products consisting of a drug/biologic intended for delivery via a drug delivery device and the unfilled drug delivery device is via two applications: an NDA/BLA for the new drug/biologic, reviewed by the respective CDER/CBER review division and a PMA or PMA/S for the device, reviewed by CDRH. This regulatory path was set forth in the CDER/CDRH Intercenter Agreement.² Post-approval changes to the device component are reviewed by CDRH, and post-approval changes to the drug component are reviewed by the respective CDER review center. This regulatory path is applicable whether a single sponsor holds both marketing applications, or if separate sponsors hold the marketing applications for the drug/biologic and the device components.

General Comments:

The Agency’s Draft Guidance of Application of User Fees for Combination Products (the “Draft Guidance”) is of substantial interest to our business. We applaud the Agency’s efforts in issuing this Draft Guidance to clarify the User Fee Assessment Process, especially the initiative proposing User Fee Waivers to reduce the additional fee burden associated with two separate applications.

Consideration of the Agency Review Effort in Determining Fees:

We respectfully propose that the Agency exercise flexibility in assessing User Fees for combination products, and consider not only whether one or two applications are required, but also the review burden on the Agency.

With regard to combination products such as drug delivery devices that require two applications covering the separate components (e.g., a drug NDA and a device PMA or PMA/S), the Agency historically has employed a collaborative review process similar to the process applicable to single applications.³ CDRH reviewed device-related issues and device labeling changes required to be mutually conforming with the new drug

² Section VII A.1.(a) of the Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for device and Radiological Health, effective 10/31/91.

³ Intercenter Consultive/Collaborative Review Process, Version 4, dated June 18, 2004, Manual of Standard Operating Procedures and Policies, <http://www.fda.gov/oc/ombudsman/intercentersop.pdf>, accessed November 23, 2004.

indication.⁴ CDER reviewed the safety and efficacy issues that were related to the drug and established by clinical data submitted to the NDA.

In such situations, where one Agency component performs the majority of the data review, we propose that the application fee for the secondary application (e.g. PMA/S) be significantly reduced to reflect the amount of resources expended for the secondary application.

We propose that this can be accomplished by aligning the type of marketing application to the expected review issues. For example, approval of a new drug for delivery by an approved delivery system would require an NDA for the new drug and a PMA/S to add the drug to the delivery system labeling. While the PMA/S technically may expand the delivery system indications for use, the Agency may categorize the PMA/S as either a 180-day supplement or a real time review PMA supplement, rather than as a panel-track PMA/S, as the clinical data is primarily reviewed under the NDA, and PMA Panel review is not necessary. Flexibility in aligning the market application category with the Agency review resource requirements may reduce the number of waiver requests and result in a more equitable allocation of fees. We suggest that the Agency and sponsor reach agreement on the appropriate category early in the process, either as part of the Request for Designation or in a pre-marketing submission meeting.

⁴ Section VII A.1.(a) (ii) of the Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for device and Radiological Health, effective 10/31/91.- “For a device intended for use with a category of drugs that are on the market, CDRH will be the lead center for regulation of the device under the device authorities. The effects of the device use on drug stability must be addressed in the device submission, when relevant. An additional showing of clinical effectiveness of the drug when delivered by the specific device will generally not be required. The device and drug labeling must be mutually conforming with respect to indications, general mode of delivery (e.g , topical, I.V.), and drug dosage/schedule equivalents.”

Specific Examples

We offer the following additional example for inclusion in Table 2: Examples of Fees Under Innovative Combination Products Waiver (FY05 Fee) of the Draft Guidance.

Table 2: Examples of Fees Under Innovative Combination Products Waiver (FY 05 Fees)

Application #1	Standard Fee for Standard Fee for Application #1	Application #2	Standard Fee for Application #2	Total Fee for both Applications (Without Waivers)	Proposed Total Fee (With Waivers)
Original PDUFA Application (BLA or NDA)	\$672,000	Panel-track PMA Supplement	\$239,237	\$911,237	\$672,000 (239,237 MDUFMA; 432,763 PDUFMA
PDUFA (NDA or BLA)	\$672,000	180 PMA Supplement	\$51,436	\$723,436	\$672,000: \$51,436 MDUFMA, \$610,664 PDUFA
<u>PDUFA (NDA or BLA)</u>	<u>\$672,000</u>	<u>Real-time PMA Supplement</u>	<u>\$17,225</u>	<u>\$689,225</u>	<u>\$672,000:</u> <u>\$17,225 MDUFMA,</u> <u>\$654,775 PDUFA</u>

As illustrated in Table 2, if a PMA/S were classified as a panel-track PMA/S, the MDUFMA fee would be \$239,237. If a waiver were granted, the PDUFA fee would be \$432,763 and the MDUFMA fee would be \$239,237.

In contrast, if the PMA/S were classified as a 180-day PMA/S, the MDUFMA fee would be \$51,436. If a waiver were granted, the PDUFA fee would be \$610,664 and the MDUFMA fee would be \$51,436.

If the PMA/S were classified as a Real Time PMA/S, the MDUFMA fee would be \$17,225. If a waiver were granted, the PDUFA fee would be \$654,775, and the MDUFMA fee would be \$17,225.

Innovative Combination Product Waiver

We request that the Agency clarify the third bullet point of Item III. E. (lines 259-264) as follows:

- The marketing application for each component includes only indications that require use of the other component ~~two components of the product include only indications for are specifically intended for and labeled only for use together.~~ Applications that include independent uses of one or both components outside the combination product generally would not be eligible for this waiver. However, applications for combinations of already approved, independent products generally would be eligible if two applications are required for approval of the new combined use.

We believe the intent of this provision is to avoid fee waivers where the combination product use is just one part of the marketing application. However, the proposed language could be an obstacle to legitimate fee waiver requests. For example, drug delivery devices may be labeled for delivery of more than one drug. A strict reading of the first sentence would suggest that a fee waiver would not be appropriate where both an NDA and a PMA/S are required to approve a new drug/biologic and to add it to the device label, as the device would not be labeled solely for use with that drug. We believe a fee waiver could be appropriate, if other conditions were met.

We thank the Agency for the opportunity to comment on this guidance, and look forward to providing input to the Agency on the development of additional guidances on combination products.

Sincerely,

Winifred C. Wu, RPh
Senior Regulatory Director
Medtronic Neurological