



Medtronic

AUGUST 19, 2004

BY FEDERAL EXPRESS

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

Re: Docket No. 2004N-0194 – Definition of Primary Mode of
Action of a Combination Product

Dear Sir or Madam:

Medtronic Neurological, a division of Medtronic, Inc., is engaged in the research, development and marketing of drug delivery systems, implantable neurostimulation devices, and other devices and therapeutic systems for neurologic disorders. Given Medtronic Neurological's focus, which often includes combination products and drug delivery system technology, the Agency's proposed regulation further defining "primary mode of action" for combination products is of direct and substantial interest to our present and future activities.

As recognized by FDA in recent years, delivery system technology is essential to medical innovation and to our public health system. In January of last year, FDA announced an initiative to "help make certain innovative medical technologies available sooner, and to reduce the costs of developing safe and effective medical products, while maintaining FDA's traditional high

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standards of consumer protection.”^{1/} Medtronic Neurological applauds the Agency for identifying novel drug delivery systems as one of the core areas of attention for this initiative. Novel delivery systems were identified as a priority area for FDA’s initiative because they represent a promising area of technological development, yet are often slow to reach market due to the complexities and uncertainty in the premarket review process—including at the initial stage of establishing jurisdiction.

These comments focus primarily on those aspects of FDA’s proposed rule that may inadvertently impede future development of novel delivery system technology, or otherwise affect this important class of products.

I. Primary Mode of Action Pathway Principles for Delivery Systems and Related Intercenter Agreement Issues

There are three principles that have guided jurisdictional decisions for delivery systems over the years, that Medtronic Neurological believes are essential to the continued jurisdictional framework for this category of products. The first of these principles is that unfilled delivery systems are considered devices, and not combination products, when drug labeling is determined not to require change. The second principle is that, even when delivery systems are deemed combination products, FDA’s Intercenter Agreements have allowed primary jurisdiction under device authorities when device issues predominate. The final principle is that, when FDA determines that drug issues will predominate in a combination delivery system review, FDA’s

^{1/} FDA News, FDA Launches Initiative to Improve the Development and Availability of Innovative Medical Products (Jan. 31, 2003).

Intercenter Agreements have preserved the parallel path option, allowing separate device filings in a number of circumstances. As described below, Medtronic is concerned that these longstanding guiding principles, all of which derive from the Intercenter Agreements, may be adversely impacted by the primary mode of action proposal.

The importance of these three jurisdictional principles for delivery systems is described in more detail below.

A. Unfilled Delivery Systems That Are Devices

The Intercenter Agreement between the Center for Drug Evaluation and Research (“CDER”) and the Center for Devices and Radiological Health (“CDRH”) makes clear that delivery systems that are distributed unfilled and are determined not to require conforming changes to drug labeling, are devices.^{2/} Over the years, FDA has applied this principle flexibly,^{3/} allowing certain minor changes to be made through device labeling without a corresponding change in drug

^{2/} Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health, at Section VII.A.1.(a) (Oct. 31, 1991) (the “CDER/CDRH Intercenter Agreement”).

^{3/} The CDER/CDRH Intercenter Agreement states that, if device labeling is generally consistent with indications, mode of delivery, and dosage/schedule equivalents, the essential elements of mutual conformance will be assumed. CDER/CDRH Intercenter Agreement, at Section VII.A.1.(a). When there is general mutual conformance, the Agreement states that FDA should do two things—it should grant CDRH jurisdiction for the product, and it generally should waive an additional clinical showing of drug effectiveness. The Intercenter Agreement also affords CDRH flexibility to consult with CDER and to resolve drug issues through device labeling. Under this interpretation, less significant drug labeling issues historically have been able to be addressed through device labeling and review. *Id.*

labeling that would alter the device pathway.^{4/} This flexibility has allowed delivery system technology to progress quickly, bringing improved standards of patient care and significant cost savings to our health economy. Examples include the evolution of drug infusion technology from hospital to home-based or ambulatory patient use; the development of miniaturized and less invasive delivery systems; and the opening up of new possibilities of effectiveness for older generation drugs.

Medtronic Neurological is concerned that, as currently drafted, the proposed rule's definition of primary mode of action could redefine jurisdiction for delivery systems. If the combination proposal is applied to these products, the majority of delivery systems would be regulated as drugs or biologics. The proposed rule defines "primary mode of action" as the "mode of action" that provides "the most important therapeutic action" of the combined product, and defines "mode of action" as the "means by which a product achieves a therapeutic effect."^{5/} This standard undervalues the importance of the delivery system technology and its contribution, and instead would look to the drug or biologic component as providing the most important therapeutic action. Because it is likely that FDA would make these conclusions "with reasonable

^{4/} For example, FDA has regulated as devices numerous elastomeric infusion pumps for continuous infusion of anesthetics in either the hospital or home environment, even though anesthetic labeling does not specifically identify home use. See, e.g., Accufuser/Accufuser Plus System (K023098); MPS Acacia Pump Kit (K003476); Freedom Infusion System (K992015); PainBuster (K980558). See also Personal Infusor Local Pain Management Procedural Kit (K010824) (referencing continuous infusion of local anesthetic with portable device suitable for ambulatory patients); Pain Care 200L (K002321) (referencing patient controlled infusion of local anesthetic); I-Flow Variable Rate Elastomeric Pump (K023883) (referencing continuous delivery of local anesthetics); McKinley SP Disposable Infusion Pump (K990461) (referencing continuous infusion of a local anesthetic).

certainty,” consideration of second-tier issues such as precedents, would not be permitted to affect the analysis.

We do not believe that the Agency intended such a result, and, indeed, Agency officials have referred to the Intercenter Agreement language defining these products as devices, and not combination products, in discussions with stakeholders. Because delivery systems can be either combination products (subject to the proposed rule) or single entity devices, clarification is needed regarding the ongoing effect of the Intercenter guidance on this point. Accordingly, Medtronic requests that the preamble to the primary mode of action final rule confirm that this important Intercenter Agreement jurisdictional guidance will remain in effect.^{6/}

B. Combination Delivery Systems Regulated Under Device Authorities

Another principle described in the CDER-CDRH Intercenter Agreement is that, even when a delivery system is considered a combination product, jurisdiction is determined based on the technology and issues that predominate. As stated in the Intercenter Agreement, the lead Center for delivery systems will be determined as follows:

For a drug delivery device and drug that are developed for marketing to be used as a system, a lead [C]enter will be designated If a drug has been developed and marketed and the development and studying of device technology predominates, the princip[al] mode of action will be deemed to be that of the device,

^{5/} 60 Fed. Reg. 25527, 25532 (May 7, 2004) (proposed Section 3.2(m), (k)).

^{6/} Although Medtronic Neurological understands that the Intercenter Agreements continue to be referenced at 21 C.F.R. § 3.5, in order to avoid uncertainty and confusion regarding the effect of the new rule on delivery systems, Medtronic Neurological believes that clarification is needed in the preamble.

and CDRH would have the lead. If a device has been developed and marketed and the development and studying of drug predominates, then, correspondingly, CDER would have the lead.^{7/}

Preservation of this language granting CDRH lead jurisdiction is particularly important for delivery systems intended to deliver generic drugs, drugs with specifications that are well defined in the USP/NF or other recognized compendia, DESI drugs, “grandfathered” drugs, and other drugs for which the safety and efficacy have been established via decades of medical use.

Medtronic, therefore, requests that this Intercenter Agreement language—like the Intercenter device language described above—remain in effect, and that the preamble for the primary mode of action final rule acknowledge its continuing importance in determining delivery system jurisdiction.

C. Parallel Path

A third and final principle referenced in the Intercenter Agreements that could be impacted by the primary mode of action rule, is that the Agreements permit a parallel review path option, even for those combination delivery systems where a drug is investigational and CDER assumes the lead. For device companies developing innovative, platform technologies, a device filing—separate from any drug or biologic filing for the agent(s) delivered—is extremely useful for both regulatory and business reasons. A parallel filing may be useful, for example: (1) when the

^{7/} CDER/CDRH Intercenter Agreement, at Section VII.A.1.(a). As noted above, even in instances where new conforming labeling changes are needed to reflect the combined drug-device product, the CDER/CDRH Intercenter Agreement provides flexibility, allowing CDRH to consult with CDER and resolve minor and secondary drug issues through device labeling. CDER/CDRH Intercenter Agreement, at Section VII.A.1.(a).

delivery system is a platform technology intended to be used with a variety of therapeutics, each having separate CDER review divisions; (2) where the device component of the delivery system is capable of being separately defined and reviewed; (3) where delivery system components are expected to have separate distribution and use/reuse patterns; and/or (4) where two different companies—for example, a drug company and a device company—are involved in the manufacture of a combination drug delivery system. In these circumstances, Medtronic Neurological believes that separate filings are appropriate, and should be permitted, at the discretion of the sponsor.

While not directly pertinent to primary mode of action, this parallel path principle is important and relevant to jurisdictional decisions. Because the proposed rule and accompanying flowchart leave the impression that the decision on jurisdiction must be Center-specific, without any parallel path options, the Intercenter Agreement's guidance should be retained, with preamble language specifically citing this point.

D. New Guidance

Finally, given that delivery systems have their own unique jurisdictional issues, as described above, Medtronic Neurological also strongly recommends development and issuance of separate guidance for this category of products. This recommendation is consistent with a similar recommendation by FDA concerning the importance of guidance for these products.^{8/} In

^{8/} Statement of Mark B. McClellan, M.D., Ph.D, Commissioner of Food and Drugs, "Technology and Innovation: Their Effects on Cost Growth of Healthcare." Before the Joint Economic Committee of the United States Congress, July 9, 2003.

particular, at a recent NIH-FDA conference, Agency officials stated that premarket guidance is essential for delivery systems, if the Agency is to meaningfully “foster and promote these new kinds of technology.”^{9/}

II. Other Comments

A. Administrative Comments to Facilitate Jurisdictional Decisionmaking

1. Flow Charts

Medtronic Neurological recommends that the Agency include the flow chart, provided with the proposed rule, in a guidance document, rather than in the rule itself. The flow chart is not material to the definition of primary mode of action, and would be more appropriate for inclusion in guidance, consistent with the Agency’s practice for other flow charts and decision trees it has developed over the years.^{10/}

2. Additional Examples

Medtronic Neurological believes that additional examples, demonstrating how the proposed rule will be applied particularly to delivery systems, are essential to a full understanding of the rule’s potential impact. Because technology in this area will continue to evolve at a rapid pace, Medtronic Neurological recommends that examples be included in a guidance document (along with the flow chart), to avoid having outdated examples locked into law. Medtronic

^{9/} Local Interest: FDA Surveys Targeted Drug-Delivery Device Landscape, M+D-D-I Reports (“The Gray Sheet”), June 7, 2004. See also FDA Improving Innovation in Medical Technology: Beyond 2002, Executive Summary (Jan. 2003) (recommending development of guidance for novel drug delivery systems).

Neurological acknowledges and applauds the Office of Combination Products website publication of Request for Designation (upon approval of the products) results and other combination product approvals. To date, however, the precedents displayed have been few in number. Development of a guidance document on combination product jurisdiction that includes examples could provide a mechanism to supplement the published precedents.

B. Endorsement of AdvaMed Comments

Medtronic Neurological strongly endorses AdvaMed's comments and recommendations, and, in particular, encourages consideration of the following issues:

1. Medtronic Neurological agrees that the critical role of precedents should be acknowledged in both the preamble and the regulation. As with many in industry, we have built our delivery system business, based on a long and consistent history of precedent regulation. Thus, it is important to Medtronic Neurological and other delivery system manufacturers that this regulatory history remain in place and that it inform and guide future jurisdictional decisions.
2. Medtronic Neurological also agrees with AdvaMed that, as part of the two-tier assignment algorithm, the Agency's goal of fostering innovation should be an important factor in the decisionmaking process. FDA has sought and continues to seek through both its "Improving Innovation in Medical Technology" and its "Critical Path Initiative" to "more actively support the development of innovative new technologies" including novel drug delivery

^{10/} See, e.g., FDA, Deciding When to Submit a 510(k) for a Change to an Existing Device (Jan. 10, 1997).

systems.^{11/} Novel delivery systems have been the subject of a July 8, 2003 stakeholders meeting^{12/} and a recent NIH-FDA conference,^{13/} as part of the Agency's innovation agenda to smooth the premarket path for these promising technologies. In order to ensure consistent application of FDA policies and initiatives, these themes should be incorporated into jurisdictional decisionmaking analyses.

In considering innovation, we believe it important for FDA to acknowledge that existing device laws and regulatory mechanisms foster innovation. The device laws, unlike those governing drugs and biologics, require FDA to consider "the least burdensome appropriate means of evaluating the device effectiveness that would have a reasonable likelihood of resulting in approval."^{14/} Over the past several years, devices, including novel delivery systems, have also benefited from regulatory mechanisms available only to products regulated under device authorities. These include: early collaboration meetings; Day 100 meetings; modular reviews; third party reviews; real time reviews; and humanitarian device

^{11/} FDA News, FDA Launches Initiative to Improve the Development and Availability of Innovative Medical Products (Jan. 31, 2003); FDA News, Advancing America's Health, Advancing Medical Breakthroughs. "Critical Path" Paper Calls for Academic Researchers, Product Developers, and Patient Groups to Work with FDA to Help Identify Opportunities to Modernize Tools for Speeding Approvable, Innovative Products to Improve Public Health (Mar. 16, 2004).

^{12/} 68 Fed. Reg. 33723 (June 5, 2003).

^{13/} Local Interest: FDA Surveys Targeted Drug-Delivery Device Landscape M-D-D-I Reports ("The Gray Sheet") (June 7, 2004)

^{14/} Food and Drug Modernization Act, § 205, 21 U.S.C. § 360c(a)(3)(D)(ii).

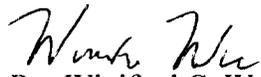
exemptions.^{15/} Similarly, the device review framework is better suited to accommodate the faster momentum of postmarket modifications typically seen in the device industry. For example, device laws have Special 510(k)s and similar post-approval mechanisms that allow regulation to keep pace with quickly moving device innovation.

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We thank the Agency for its critical assessment of combination product jurisdictional issues, and the opportunity to comment on its proposal, and look forward to collaborating with the Agency on the development of guidances on combination products jurisdiction and on delivery systems.

Sincerely,

Medtronic Neurological



By: Winifred C. Wu, RPh
Senior Regulatory Director

^{15/} As a corollary theme, Medtronic Neurological encourages the Agency to utilize the resources available to it, to better leverage its internal expertise to resolve combination product issues. For example, if CDRH jurisdiction is chosen, resources include use of external consultants, advisory committees, multi-Center collaborations and consultations, and related mechanisms. Related to this notion, however, if CDRH jurisdiction is chosen, any CDER consultative or collaborative process should not be permitted—directly or indirectly—to set the review standards for the composite product. CDRH product jurisdiction, if it is to be meaningful, necessarily must involve device authorities defining the combined product.