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A Humanitarian Device Exemption For Deep Brain Stimulation

Joseph Fins and his coauthors (Feb 2011) raise several points regarding the humanitarian device exemption that the Food and Drug Administration granted to Medtronic Inc.'s deep brain stimulation therapy for the treatment of severe, treatment-resistant obsessive-compulsive disorder (OCD). It is useful to consider some important context about the exemption, as well as Medtronic's commitment to bringing new therapies to underserved patient populations.

The pool of severe, treatment-resistant OCD patients for which Medtronic received the exemption is precisely the type of population intended to be helped by humanitarian-use devices. Fewer than 1,000 OCD patients in the United States are eligible for the therapy each year, based on published epidemiological data and criteria from physicians who specialize in treating OCD. This is well under the exemption limit of 4,000 patients per year. Since Medtronic's device was approved in 2009, fewer than fifty US patients have received it for OCD. These patients are carefully monitored by dedicated and trained inter-

disciplinary teams.

Regulations provide oversight to ensure that only eligible patients receive the therapy, and that they do so with support from an expert team of health care providers. Centers must have approval from their Institutional Review Board, providing oversight similar to that for an investigational device exemption. The board must provide documentation approving the use of deep brain stimulation therapy for OCD before Medtronic will provide its device to the center.

Medtronic provides training and education for centers with expertise in managing psychiatric conditions and implanting deep brain stimulation systems. The humanitarian device exemption regulations require Medtronic to submit a yearly detailed report to the Food and Drug Administration, updating the safety and probable benefit of the therapy for OCD. All of these measures are in place to assure patient safety and to achieve the best possible clinical outcomes.

Developing innovative medical technologies for underserved patient populations is critical to Medtronic's mission to alleviate pain, restore health, and extend life.

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Humanitarian Device Exemptions: The Authors Reply

We appreciate Medtronic's desire to engage in a dialogue about the humanitarian device exemption that the Food and Drug Administration (FDA) granted the company for deep brain stimulation in cases of severe, treatment-resistant obsessive-compulsive disorder.

With respect to eligibility for the exemption and epidemiology, we stand by the peer-reviewed data we cited in our paper (Feb 2011) and note that the number of eligible subjects, rather than the number who enroll in a study, is the criterion for an exemption. Multiple factors beyond the yearly incidence of disease can influence who enrolls.

Moreover, the science of estimating demographics is generally the purview of a clinical epidemiologist, not a clinician. It would behoove patients and industry alike if the FDA brought greater transparency to these calculations and ensured that its consultants had no conflicts of interest.

We disagree that the stringency of Institutional Review Board oversight is the same for the humanitarian device exemption as for the investigational device exemption. Only with the latter is informed consent monitored by the board. Indeed, an FDA spokesperson said that additional

oversight is not necessary "because it is part of the practice of medicine."¹ We disagree and see this work as scientific inquiry that should be regulated as research, lest we promulgate a therapeutic misconception.

The problem is more one of regulation than compliance, and of how best to advance science and meet the needs of the underserved whose conditions, if not orphans, are economically disinherited by market forces.

It is our hope that this case proves instructive to the FDA as its new Innovation Pathway seeks to rebalance the competing needs of innovation and safety. We need to work together to find better ways to ensure patient safety, promote innovation, and achieve sustainable funding through improved public-private partnerships.

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NOTE

¹ Hurley D. Should the FDA rescind the humanitarian exemption for DBS? *Neurology Today*. 2011;11(5):10.

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The FDA's Humanitarian Device Exemption Program

Joseph Fins and coauthors (Feb 2011) maintain that the humanitarian device exemption of the Food and Drug Administration (FDA) is being misused by the medical device industry for commercial gain and to avoid the time- and resource-intensive efforts of conducting appropriately sized and statistically powered clinical trials. The example that the authors cite is a recently approved humanitarian device exemption for deep brain stimulation to treat obsessive-compulsive disorder. The authors call for greater regulatory stringency and oversight by the FDA of the humanitarian device exemption process so as not to put patients at risk.

The article contains factual errors, omissions, and misconceptions regarding the humanitarian device exemption pathway. It misstates the governing approval standard, makes no reference to the required demonstration of safety, and deemphasizes certain safeguards that help protect patients and guard against misuse of the program. In this letter we provide clarification on the humanitarian device exemption program and address some of the concerns raised by Fins and coauthors in their article.

The humanitarian device exemption pathway was created by Congress to provide an incentive for the development of devices for the treatment or diagnosis of rare diseases or conditions (that is, conditions that affect small patient populations). Patients who receive humanitarian device

exemption devices have no other comparable device available to diagnose or treat their disease or condition.¹ A device is eligible for a humanitarian exemption if, among other criteria, it is designed to diagnose or treat a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.²

The FDA agrees with the general proposition in Fins and colleagues' article that, wherever possible, deep brain stimulation studies for neuropsychiatric illness should "progress through a series of logical steps" (p. 307), with well-designed, well-controlled, hypothesis-driven studies.

By law, humanitarian device exemptions are exempt from the effectiveness approval requirement governing premarket approval applications for devices.³ They are not exempt from the requirement to demonstrate a reasonable assurance of safety. The safety standard for humanitarian device exemptions and premarket approval applications, therefore, is the same. However, because of the smaller population size for humanitarian device exemptions, the amount of data submitted in the two applications may not be the same.

Furthermore, even though humanitarian device exemption applicants are by statute exempt from having to demonstrate a reasonable assurance of effectiveness, the data to support humanitarian device exemption approval must demonstrate the following: (1) that there is a probable benefit to health from the use of the device (which is often based on data from clinical investigations); and (2) that the probable benefit outweighs the

risk of injury or illness from the use of the device, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

The applicant must also certify that no comparable device, other than another device approved under a humanitarian device exemption or a device approved under an investigational device exemption, is available to diagnose or treat the disease or condition, and must explain why the device would not be available for that disease or condition without the humanitarian device exemption approval.

The authors create confusion for the reader by suggesting that manufacturers are pursuing the humanitarian device exemption pathway in lieu of the investigational device exemption pathway. For high-risk Class III devices such as deep brain stimulation systems, there are only two legal pathways to market: a premarket approval application or a humanitarian device exemption. Submission of an investigational device exemption application, in contrast, is a precursor to obtaining marketing approval. The FDA's approval of such an application allows investigational devices to be used in a clinical study to collect the data necessary to support a premarket application to the FDA, but it does not authorize commercial marketing of the device.

Investigational device exemptions have been used to gather data to support the approval of both premarket approval applications and humanitarian device exemptions, rather than as an alternative pathway to either. Thus, one should not assume that approval of a humanitarian device exemption device implies that data were not collected in an investigational device exemption clinical trial.

Indeed, it is not unusual for humanitarian device exemption applications to contain limited clinical data collected under an investigational device exemption. Although

the statistical power and size of clinical trials performed to support humanitarian device exemptions may differ from those performed to support premarket approval applications, largely because the affected population is smaller, the FDA does review all of the data in a humanitarian device exemption application to determine if the device can be approved.

The article states that “the purpose of the humanitarian device exemption is to provide access to therapy in cases where there are too few patients for a large, randomized clinical trial to be practical” (p. 304). The authors claim that “there are 440,000–660,000 people with chronic, severe, treatment-resistant obsessive-compulsive disorder in the United States” (p. 304). We note that for the humanitarian device exemption device the authors refer to in their article (the Medtronic Reclaim Deep Brain Stimulation therapy for obsessive-compulsive disorder), the FDA-approved indication for use is far narrower than treatment of all patients severely afflicted with the disorder.

The approved indication for the device is “bilateral stimulation of the anterior limb of the internal capsule, AIC, as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant [obsessive-compulsive disorder] in adult patients who have failed at least three selective serotonin reuptake inhibitors.” This indication represents a small patient population of severely affected patients with the disorder who are highly resistant to treatment, and thus meets the humanitarian device exemption criterion of fewer than 4,000 patients per year.

Furthermore, clinical data were submitted in support of the humanitarian device exemption application for the device in question. The data demonstrated an average 40.7 percent reduction in the Yale-Brown Obsessive Compulsive Scale score at twelve months. According to the expert consensus panel on the disorder, a full responder is considered a subject who demonstrates a 35 percent reduction in this score, and a partial

responder is a subject with a 25 percent reduction. As the authors themselves note, “Clinical studies of deep brain stimulation for obsessive-compulsive disorder have shown objective improvement of symptoms and indications of long-term benefits for...patients who do not respond to conventional therapies” (p. 303).

The article states, incorrectly, that the Safe Medical Devices Act of 1990 “requires that the safety of a device used under a humanitarian exemption be assessed by what is called analogic reasoning of equivalence” (p. 304). The authors mistakenly equate the premarket notification process—known as the 510(k) clearance process—with the humanitarian device exemption approval process.

The 510(k) and humanitarian device exemption pathways are separate marketing pathways governed by different review standards. Under the 510(k) clearance process, certain low- and moderate-risk devices can be legally marketed after showing that they are “substantially equivalent” to a legally marketed predicate device—in other words, that they are at least as safe and effective as the predicate device.⁴ The humanitarian device exemption approval pathway, in contrast, does not rely on “substantial equivalence” or any showing of comparable safety and effectiveness.

Comparability is relevant in humanitarian device exemption applications only insofar as applicants must certify that no comparable device, other than another device approved under a humanitarian device exemption or a device approved under an investigational device exemption, is available to diagnose or treat the disease or condition.⁵ The humanitarian device exemption pathway is instead most similar to the premarket approval pathway—the most stringent type of device premarket application that the FDA requires.

Humanitarian device exemptions require the same safety performance as premarket approvals—a reasonable assurance of safety—but by statute are exempt from the premarket approval effectiveness requirement. Nonetheless, as described above, probable benefit of a humanitarian device

exemption must be shown to outweigh any risks, and humanitarian device exemption applications often contain clinical data collected under an investigational device exemption to support this finding.

The authors deemphasize certain safeguards of the humanitarian device exemption program that help protect patients and guard against misuse of the program. Humanitarian device exemption devices are subject to strict limitations on their use and profit. Before such a device is used at a facility to diagnose or treat patients, an Institutional Review Board must approve that use—except in certain emergencies, as provided by statute and described in FDA guidance.⁶

In approving such use, the board may choose to require informed consent that is consistent with the approved humanitarian device exemption labeling. The board may impose additional limitations on the use of the device at the facility—for example, requiring prior use and failure of alternative treatment modalities or follow-up precautions and evaluations, as appropriate.

A prohibition on profit generally applies to devices under a humanitarian device exemption. Such devices cannot be sold for profit except, as provided by Congress, in narrow circumstances for certain pediatric indications. In addition, the FDA may withdraw humanitarian device exemption approval if the eligibility criteria are no longer met—if, for example, comparable devices become available to diagnose or treat the disease or condition in question.

In sum, humanitarian device exemptions have been, and will continue to be, reserved for devices that serve small, underserved patient populations and satisfy all regulatory and scientific criteria for approval. We appreciate the opportunity to provide clarification on the program.

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NOTES

1 Applicants must certify that no comparable device, other than another device approved under a

humanitarian device exemption or a device approved under an investigational device exemption, is available to diagnose or treat the disease or condition. 21 CFR, sec. 814.104(b)(2).

2 21 CFR, sec. 814.100(a).

3 Section 520(m)(2) of the Federal Food, Drug, and Cosmetic Act, 21 US Code, sec. 360j(m)(2).

4 Sections 510(k) and 513(i) of 21 US Code, secs. 360(k) and 360c(i).

5 21 CFR, sec. 814.104(b)(2).

6 Food and Drug Administration. Guidance for HDE holders, Institutional Review Boards (IRBs), clinical investigators, and Food and Drug Administration staff: humanitarian device exemption (HDE) regulation: questions and answers [Internet]. Silver Spring (MD): FDA; 2010 Jul 8 [cited 2011 May 9]. Available from: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110203.pdf>

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NOTE

1 Medtronic, Inc. v. Lohr, 518 US 470 (1996).

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FDA Exemptions: The Authors Reply

We are pleased that the Food and Drug Administration (FDA) “agrees with the general proposition in Fins and colleagues’ article that, wherever possible, deep brain stimulation studies for neuropsychiatric illness should ‘progress through a series of logical steps,’ with well-designed, well-controlled, hypothesis-driven studies.” Because we are proponents of good science and subject safety, this is the major focus of our argument (Feb 2011).

Where we continue to disagree with the FDA is when such an approach is obligatory or discretionary. We maintain that the use of an approved device directed at a new brain target or clinical condition requires an investigational device exemption, consistent with the aforementioned general proposition and with the FDA’s own regulations calling for such an exemption when there is a new device or new indication.

We appreciate that as a Class III device, a deep brain stimulation device is not eligible for the 510(k) clearance process and requires a premarket approval application to advance to market. We never invoked the 510(k) process in our argument. We did appeal to associated equivalence arguments (in light of *Medtronic v. Lohr*, which involved a cardiac stent, a Class III device).¹ We believed that analogic reasoning was implicitly undergirding an equivalence construct essential for humanitarian device exemption approval because of the Reclaim device’s

closely shared lineage with its predecessor Aptiva unit.

Had there been a new device used to target the putative target, there would have been an unequivocal call for an investigational device exemption. We believe that the FDA staff’s familiarity with the device might have distracted them from seeing the novelty of the brain target and clinical indication—the key reason why an investigational device exemption was the preferred pathway to market.

But beyond the regulatory issues is the more important question of how best to do rigorous, systematic science and learn about complex brain mechanisms. Given limited resources for scientific discovery, the early state of our knowledge, and the need to demonstrate both safety and efficacy during this era of health care reform, it seems imprudent to have any subject outside a properly designed clinical trial. The ethical mandate to learn as much as possible is especially compelling because objective preliminary data suggest efficacy—an outcome we note and celebrate.

Our tasks now are to appreciate that deep brain stimulation is as much a therapy as a tool of discovery, and to secure the resources that will allow us to develop treatments and imagine next-generation hypotheses to serve patients now and in the future.

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