

**Medical Devices: Are Current Regulations Doing Enough for Patients?
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Committee on Energy and Commerce
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Chairman Pallone and members of the committee, thank you for the opportunity to present our concerns about current problems with the regulation of medical devices by the Food and Drug Administration (FDA). Several serious weaknesses in the existing premarket review process impede the FDA's ability to ensure the effectiveness of devices and adequately protect American patients.

In our testimony today, we will focus on three problems in the review process, each illustrated by a paradigmatic case from recent regulatory proceedings. Other aspects of medical device regulation, such as postmarketing surveillance and compliance are beyond the scope of this testimony. Our testimony will also not address certain other premarket review issues including high-risk devices that the agency has not fully reviewed, despite a congressional mandate.¹ Furthermore, we will not discuss a group of over 200 overlooked devices that continue to reach the market through less-stringent review procedures.² We would be happy to provide the committee with more details on these subjects upon request.

Problem 1: Lower Approval Standard for Medical Devices than for Drugs

By statute, the approval standard for devices is lower than for drugs, regardless of how the device is reviewed. Before a new drug can be marketed, the sponsor must show “substantial evidence [of effectiveness],”³ whereas the sponsor of a new device need only demonstrate a “reasonable assurance of ... safety and effectiveness.”⁴ In practice, new drug applications (NDAs) typically contain two or more well-controlled clinical studies,⁵ whereas, even under the most stringent review process for devices, a single study is the norm.⁶ Furthermore, the FDA accepts lower-quality studies for devices compared to drugs; while for drugs, agency regulations state that “uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness,”⁷ for devices, even those reviewed under the most stringent review procedures, the regulations permit “reliance upon other valid scientific evidence ... even in the absence of well-controlled investigations.”⁸ Thus, data that would never be sufficient to support the approval of a drug can result in the approval of a device used to treat the same condition, potentially diverting patients from effective drugs to less-effective devices.

This concern is not merely theoretical. Consider Cyberonics’s vagus nerve stimulator (VNS), a surgically implanted device for treatment-resistant depression. In the only randomized, controlled trial, the device did not

demonstrate a statistically significant benefit on the primary depression measurement at ten weeks ($p=0.25$).⁹ However, the company relied on less-rigorous follow-up data at one year in which a group of VNS-treated patients improved more than a control group ($p<0.001$). Moreover, the control group was not randomized (patients were not assigned to their treatments at random); the study was unblinded (patients and doctors knew which patients were receiving VNS); patients in the treated and control groups were recruited at different times; and both groups were permitted to modify their antidepressant medications and to receive electroconvulsive therapy (ECT).¹⁰ An expert in the FDA's drug center advised the Center for Devices and Radiological Health (CDRH) that, with similar data for an antidepressant drug, the center would not have permitted even the filing of an NDA.¹¹ While CDRH initially issued a non-approvable letter, the director of CDRH reversed this decision and approved the device, overruling more than 20 FDA scientists and officials.¹¹ The Centers for Medicare and Medicaid Services subsequently declined reimbursement for the device under Medicare, saying that it did "not believe there is a treatment benefit directly attributable to VNS."¹²

In order to remedy this approval-standard inconsistency, Congress should raise the standard for device approval to that required for drugs: sponsors of devices that claim to treat diseases should produce "substantial evidence," rather than merely "reasonable assurance," of effectiveness. Such devices would have to

meet the same requirements as drugs, including more than one well-controlled trial.

Reliance upon Less-rigorous Review Mechanisms

As the committee is well aware, there are two general premarket review procedures for devices: the “premarket approval” (PMA) application and the “premarket notification” submission, often referred to as a “510(k)” submission. A PMA application, which is reserved for high-risk and novel devices, is analogous to a NDA. Sponsors must submit valid scientific evidence that directly establishes safety and efficacy, although, as we have seen in the VNS case, this need not be a randomized, controlled trial. In contrast, in a 510(k) submission, a sponsor need demonstrate only that the new device is “substantially equivalent” to an existing (“predicate”) 510(k) device.¹³

Compared to the PMA process, 510(k) review is “generally less stringent ... less expensive ... [and] faster.”¹ The average time until a decision on 510(k) submissions in fiscal year 2006 was 54 days, compared to 283 days for PMA applications.¹⁴ Only 10-15% of 510(k) submissions contain any clinical data.¹⁵ Instead, 510(k) submissions primarily contain performance characteristics comparing the new device to the predicate. In considering a PMA application, the FDA may consult with an advisory committee comprised of non-government

experts; this option is rarely pursued for 510(k) submissions. As the FDA acknowledges, it “does not attempt to address all of the issues [that] would be answered in a PMA in its review of 510(k)s.”^{13,*}

In the 510(k) pathway, new devices are compared to predicate devices with respect to their “intended uses” and “technological characteristics.”¹⁶ Less-rigorous interpretation of either element, and resultant review under 510(k), can permit manufacturers to evade the more-demanding requirements of PMA applications.

Problem 2: Permissive Interpretation of “Same Intended Use”

ReGen’s Menaflex Collagen Scaffold (MCS) is a device implanted during arthroscopic surgery to replace damaged knee cartilage (meniscus). After consulting with the FDA, which determined that the MCS was a novel device requiring a PMA,¹⁷ ReGen began a trial to support such an application^{18,19} – a two-year randomized, controlled trial comparing partial meniscus removal to partial meniscus removal with MCS. On all three primary clinical endpoints, however, the trial showed no benefit for the MCS.^{20,21}

* In addition, whereas the FDA has explicit authority to recall or temporarily suspend marketing of PMA-approved devices, corresponding statutory language for 510(k)-cleared devices does not exist.

With the trial complete,²² the FDA allowed the company to shift courses and submit a 510(k). ReGen was able to make this switch because current agency practices provide for permissive interpretations of “same intended use.” The FDA asserts that its “scientific expertise enables it to exercise considerable discretion in construing intended uses.”¹³

The company’s first two 510(k)s were rejected. In a third 510(k) submission, ReGen claimed that the MCS was a surgical mesh and that the intended use - to repair and reinforce soft tissue – was similar to other surgical meshes (e.g., rotator cuff mesh, anal fistula plug, and hernia repair graft). However, an FDA reviewer²⁰ pointed out that none of the twenty-two meshes cited by the company was implanted in a weight-bearing joint or intended to facilitate the regrowth of articular cartilage, both crucial aspects of the MCS.

The company downplayed the results of the randomized, controlled trial and argued that it was entitled to the less-rigorous review given to the MCS’s predicate devices. It claimed that bench testing data (e.g., suture retention strength and tensile strength) should provide the primary basis for establishing substantial equivalence.²³ Articulating this point before an FDA advisory committee, the company asserted that the committee’s decision should be based upon “the function of this device as a surgical mesh ... and not the ultimate

clinical outcome.”²⁴ The committee voted to endorse the MCS and the agency cleared it for commercial distribution in December 2008.

Subsequently, a number of irregularities in the advisory committee review of this device have come to light. Departing from usual agency practices, ReGen was permitted input into the questions posed to the advisory committee and into who made the FDA presentation at the meeting. Moreover, at the company's request, standing advisory committee members were replaced by clinicians thought more likely to favor the device.¹⁸ Currently, the FDA is reviewing the procedural and substantive aspects of this case.²⁵

To correct this problem, the agency could immediately tighten its working definition of “same intended use,” and begin directing novel devices with weak “same intended use” claims such as the MCS to the PMA pathway. This change in practice should also be formalized in either a regulation or statute.

Problem 3: “Different Technological Characteristics”

The second element of 510(k) review relates to the technological characteristics of the new device and its predicate. The 1990 amendments to the Food, Drug, and Cosmetic Act permit a new device to have “different technological characteristics” from its predicate as long as no new issues of safety or

effectiveness are raised.²⁶ Indeed, 14% of cleared 510(k) submissions have “different technological characteristics” from their predicates.¹ This provision has led to devices acting as predicates for devices from which they are plainly dissimilar, thus permitting use of the 510(k) pathway by devices that otherwise would have been reviewed as PMAs.

For example, transcranial magnetic stimulation (TMS) is a device intended to treat depression. The agency permitted TMS to be reviewed under the 510(k) process with ECT as the predicate device, even though ECT involves the administration of electrical currents to induce a generalized seizure and TMS applies a magnetic field to a specific region of the brain. The manufacturer, Neuronetics, conducted a nine-week randomized, controlled trial comparing TMS to a placebo.[†] The difference in depression severity between patients treated with TMS and those receiving a placebo was clinically minor (1.7 points on a 60-point scale) and statistically non-significant ($p=0.057$);²⁷ only the improper, after-the-fact exclusion of six patients yielded statistical significance ($p=0.038$).²⁸ An advisory committee concluded that, “the clinical effect was perhaps marginal, borderline, questionable, and perhaps a reasonable person could ask whether there was an effect at all.”²⁹

[†] Although the company claimed that TMS was substantially equivalent to ECT, it conducted no studies directly comparing the two devices and relied instead on less-rigorous historical data for ECT, which were mostly more than two decades old and used a different scale for depression.

The FDA ultimately determined that TMS was not substantially equivalent to ECT. But this debate (and the device's subsequent clearance as described in the footnote[‡]) would have been foreclosed if Congress were to repeal the "different technological characteristics" provision and thereby steer more devices like TMS toward the PMA route.

Conclusions

Advances in medical device technologies have translated into significant improvements in the health of patients. Yet cracks in the premarket device review system threaten to undermine this progress. In our testimony, we have focused on three specific problems in the review process for medical devices. But two overarching issues provide the context in which these deficiencies occur.

First, the 1997 amendments direct the agency, in certain circumstances, to consider the "least burdensome" means of showing effectiveness for devices,^{30,31}

[‡] TMS ultimately reached the market via a relatively obscure premarket review procedure, called the *de novo* process (21 USC §360c(f)(2)), reserved for devices rejected in the 510(k) pathway. Created in the FDA Modernization Act of 1997, the sponsor of a product rejected under 510(k) may use this process to request clearance without identifying a predicate device, thus circumventing another 510(k) or even a PMA. Here, the company requested clearance for a modified indication identified by another after-the-fact analysis of the negative randomized controlled trial (Lisanby, et al. *Neuropsychopharmacology*. 2009;34(2):522-34; Hines, et al. *Neuropsychopharmacology*. 2009;34(8):2053-4.). Such a statistical maneuver is typically regarded with considerable skepticism by most statisticians. Instead, for TMS it formed the basis for clearance by the FDA.

Importantly, Neuronetics could not have used the *de novo* process without the initial 510(k) designation, which itself was only made possible by the provision permitting technologically dissimilar devices to use the 510(k) pathway.

giving the industry recourse to challenge many requests it regards as onerous. For example, ReGen invoked this language when the FDA considered the unfavorable findings of its randomized, controlled trial, asserting that the agency was “required to consider the least burdensome information necessary to demonstrate substantial equivalence.”^{32,§}

Second, the FDA has permitted scientific approaches that fall well short of the rigorous. Approaches drawn from the examples in this testimony include a host of unacceptable practices as basic as failure to randomize,³³ after-the-fact looks at data,³⁴ comparing groups studied at different points in time,³⁵ failure to adjust for multiple statistical tests.²⁸ Depending on the specific case, these lax scientific standards can be the result of any combination of the lower standard for device approval, the inappropriate routing of devices through 510(k) instead of PMA, the “least burdensome” requirement, and lack of rigor at the agency level.

Thus, each of the issues identified in this testimony can be remedied by the combination of agency practice, regulation and legislation unique to that issue. Under the former, the agency can exercise its existing discretionary powers to require greater scientific rigor by sending more devices through PMA and by tightening the “same intended use” requirements. But legislation could also address all three of the problems identified in this testimony: the lower approval

[§] However, even this assertion was incorrect. The “least burdensome” language relevant to 510(k) submissions is only applicable to the “different technological characteristics” situation (21 USC §360c(i)(1)(D)), which did not apply to ReGen.

standards for devices than for drugs, the permissive interpretations of “same intended use,” and the “different technological characteristics” loophole. Most fundamentally, to reclaim its tarnished reputation for rigor, CDRH must place its decisions on a firm scientific base.

¹ Government Accountability Office. Medical devices: FDA should take steps to ensure that high-risk device types are approved through the most stringent premarket review process. Washington, DC: Government Printing Office, January 2009. Publication No. GAO-09-190. <http://www.gao.gov/new.items/d09190.pdf>. Accessed June 11, 2009.

² Center for Devices and Radiological Health. Medical device classification database [searched 'unclassified' under 'Device Class' field; searched '510(k)' under 'Submission Type' field]. Rockville, MD: Food and Drug Administration, Last June 8, 2009. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>. Accessed June 9, 2009.

³ 21 USC § 355(d).

⁴ 21 USC § 360c(a).

⁵ Center for Drug Evaluation and Research. Providing clinical evidence of effectiveness for human drug and biological products. Rockville, MD: Food and Drug Administration, May 1998. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf>. Accessed June 9, 2009.

⁶ 60 Fed Reg 39180-1 (August 1, 1995).

⁷ 21 CFR § 314.126(e).

⁸ 21 CFR § 860.7(e)(2).

⁹ Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry*. 2005;58(5):347-54.

¹⁰ Center for Devices and Radiological Health. FDA clinical review memorandum for Neurological Devices Panel for the Vagus Nerve Stimulator. Rockville, MD: Food and Drug Administration, June 15, 2004.

http://www.fda.gov/ohrms/dockets/ac/04/briefing/4047b1_00_FDA%20Clinical%20Review%20Memo.htm. Accessed June 11, 2009.

¹¹ United States Senate, Committee on Finance. Review of the FDA's approval process for the vagus nerve stimulation therapy system for treatment-resistant depression. Washington, DC: Government Printing Office, February 2006. Publication No. S. Prt. 109-45.

http://finance.senate.gov/press/Gpress/02_2006%20report.pdf. Accessed June 11, 2009.

¹² Coverage Analysis Group. Decision memo for vagus nerve stimulation for treatment of resistant depression (TRD). Baltimore, MD: Centers for Medicare and Medicaid Services, May 4, 2007.. <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?from2=viewdecisionmemo.asp&id=%20195&>. Accessed June 9, 2009.

¹³ Center for Devices and Radiological Health. Guidance on the CDRH premarket notification review program (k86-3). Rockville, MD: Food and Drug Administration, June 30, 1986. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm>. Accessed June 9, 2009.

¹⁴ Center for Devices and Radiological Health. Office of device evaluation: annual report fiscal year 2006 and fiscal year 2007. Rockville, MD: Food and Drug Administration, June 19, 2008. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm127516.pdf>. Accessed June 12, 2009.

¹⁵ Government Accountability Office. Medicare durable medical equipment: class III devices do not warrant a distinct annual payment update. Washington, DC: Government Printing Office, March 2006. Publication No. GAO-06-62. <http://www.gao.gov/new.items/d0662.pdf>. Accessed June 11, 2009.

¹⁶ 21 USC § 360c(i)(1).

¹⁷ 61 Fed Reg 15491-504 (April 8, 1996).

¹⁸ Mundy A. Political lobbying drove FDA process. *Wall Street Journal*. March 6, 2009:A1.

<http://online.wsj.com/article/SB123629954783946701.html>. Accessed June 11, 2009.

¹⁹ Waxman HA, Stupak B, Pallone F. Letter to Dr. Joshua M. Sharfstein regarding clearance of the ReGen Collagen Scaffold. Washington, DC: Committee on Energy and Commerce, House of

Representatives, May 11, 2009.

http://energycommerce.house.gov/Press_111/20090511/fdaregen.pdf. Accessed June 12, 2009.

²⁰ Center for Devices and Radiological Health. FDA summary for the Orthopedic and Rehabilitative Devices Panel for the ReGen Collagen Scaffold. Rockville, MD: Food and Drug Administration, November 14, 2008. <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4400b1-01FDA%20Summary%20and%20Questions%20.pdf>. Accessed June 9, 2009.

²¹ Hines J, Lurie P. Testimony before FDA on Collagen Scaffold medical device. Washington DC: Public Citizen, November 14, 2008. <http://www.citizen.org/publications/release.cfm?ID=7620>. Accessed June 9, 2009.

²² ReGen Biologics to present at the pacific growth equities life science conference in San Francisco on June 6, 2005 [press release]. Hackensack, NJ: ReGen Biologics, May 25, 2005. <http://www.regenbio.com/usa/en/pressroom/594/>. Accessed June 9, 2009.

²³ Premarket notification; ReGen Collagen Scaffold (CS). Hackensack, NJ: ReGen Biologics, July 22, 2008. [http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4400b1-01%20510\(k\)%20Intro%20K082079.pdf](http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4400b1-01%20510(k)%20Intro%20K082079.pdf). Accessed June 9, 2009.

²⁴ Center for Devices and Radiological Health. Transcript of the Orthopedic and Rehabilitative Devices Panel of the Medical Devices Advisory Committee: part 1. Rockville, MD: Food and Drug Administration, November 14, 2008. <http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4400t01.pdf>. Accessed June 9, 2009.

²⁵ Sharfstein JM. Letter from Dr. Joshua Sharfstein to Senator Charles Grassley regarding clearance of the ReGen Collagen Scaffold. Rockville, MD: Food and Drug Administration, May 8, 2009. http://www.thegraysheet.com/nr/FDC/SupportingDocs/gray/2009/051809_sharfstein_Letter_to_Senator_Grassley.pdf. Accessed June 9, 2009.

²⁶ 21 USC § 360c(i)(1)(A)(ii).

²⁷ O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007;62(11):1208-16.

²⁸ Lurie P, Park S. Testimony at meeting on repetitive transcranial magnetic stimulation, Duraseal and vagus nerve stimulation. Washington, DC: Public Citizen, January 26, 2007. <http://www.citizen.org/publications/release.cfm?ID=7499>. Accessed June 11, 2009.

²⁹ Center for Devices and Radiological Health. Transcript of the Neurological Devices Panel of the Medical Devices Advisory Committee. Rockville, MD: Food and Drug Administration, January 26, 2007. <http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4273t1.rtf>. Accessed June 9, 2009.

³⁰ 21 USC § 360c(i)(1)(D).

³¹ 21 USC § 360c(a)(3)(D)(ii).

³² Dichiara J. Letter to Mark N. Melkerson responding to request for additional information for ReGen's Collagen Scaffold. Hackensack, NJ: ReGen Biologics, 2007. <http://www.fda.gov/OHRMS/DOCKETS/ac/08/briefing/2008-4400b1-28-%20C.pdf>. Accessed June 9, 2009.

³³ Stine N, Lurie P, Wolfe S. Letter to FDA urging that the Vagus Nerve Stimulator not be approved for treatment of depression. Washington DC: Public Citizen, May 11, 2005. <http://www.citizen.org/publications/release.cfm?ID=7385>. Accessed June 9, 2009.

³⁴ Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009;34(2):522-34.

³⁵ Center for Devices and Radiological Health. FDA Summary for meeting of the Neurological Devices Panel for Neurostar TMS system. Rockville, MD: Food and Drug Administration, January 26, 2007.

http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4273b1_01-FDAExecutiveSummary.pdf. Accessed June 9, 2009.