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A Risky Shortcut

Proposal to Permit the FDA to Rely on Journal Articles
to Approve High-Risk Medical Devices Is Misguided

Acknowledgments

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Executive Summary

To protect the health and well-being of the American public, the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), examines scientific evidence to evaluate the effectiveness and safety of certain high risk medical devices through a process known as premarket approval (PMA).¹

In July 2015, the U.S. House of Representatives passed the 21st Century Cures Act (H.R. 6), which has generated strong criticism from the public health community. Independent patient advocacy groups and former FDA officials have expressed concerns that the bill would carve out shortcuts that could lead to the approval of drugs and devices that are not effective or pose unacceptable safety risks.^{2,3,4}

This report is the second in a series covering specific provisions in the bill.⁵ Here, we focus on section 2222 of the legislation, and specifically the part of that section that would encourage the FDA to rely on articles published in peer-reviewed journals to determine the effectiveness of a medical device. While peer-reviewed journals can provide valuable information related to the use of medical devices, the evidence within these studies is not validated by the FDA, and many peer-reviewed articles contain errors, omissions, misrepresentations or fraudulent information. Conflicts of interests between authors of peer-reviewed journal articles and device manufacturers may increase the likelihood of such problems occurring.

This report summarizes the potential problems with relying on peer-reviewed articles for FDA approval, and describes case studies involving two devices: Medtronic Infuse and the CardioMEMS Champion Heart Failure Monitoring System. Initially, these devices were the subjects of glowing reports in peer-reviewed journals, but information casting doubt on the safety or efficacy of them later emerged.

The FDA already grants approval of a very small percentage of high-risk devices based on information in peer-reviewed journals. The proposal pending in Congress would serve to pressure the agency to rely more on this unsound practice. Public Citizen opposes the 21st Century Cures Act because of the contents of section 2222, as well as numerous other issues. We strongly recommend that section 2222 be removed from the bill and that peer-reviewed journals not be relied upon as a basis for determining the effectiveness or safety of medical devices.

¹ *Premarket Approval (PMA)*, FOOD AND DRUG ADMINISTRATION (Aug. 19, 2014), <http://1.usa.gov/yxo3FS>.

² Alec MacGillis, *Would Washington's FDA Fix Cure the Patients or the Drug Industry?* PROPUBLICA (Oct. 20, 2015), <http://bit.ly/1OaUYuD>.

³ Susan F. Wood and Diana Zuckerman, *The 21st Century Cures Act Could be a Harmful Step Backward*, THE WASHINGTON POST (Nov. 19, 2015), <http://wapo.st/1jvQJnY>.

⁴ Gregg Gonsalves, Mark Harrington and David A. Kessler, *Don't Weaken the F.D.A.'s Drug Approval Process*, THE NEW YORK TIMES (June 11, 2015), <http://nyti.ms/1Oj6KyE>.

⁵ PUBLIC CITIZEN, HOUSE ORPHAN DRUG PROPOSAL: A WINDFALL FOR PHARMA, FALSE 'CURE' FOR PATIENTS (Dec. 8, 2015), <http://bit.ly/1m6QF9m>.

Background on Regulation of Medical Devices

Current Regulation of Medical Devices

Medical devices are categorized into three classes: I, II or III. As the Government Accountability Office (GAO) summarized in a 2011 report on FDA oversight of devices, these classifications generally are based on the level of risk the devices pose and the “controls necessary to provide reasonable assurance of its safety and effectiveness.”⁶ In general, class I medical devices pose the least risk and class III medical devices pose the greatest risk.⁷ Examples of class I medical devices include tongue depressors, elastic bandages, reading glasses and forceps.⁸ Class II medical devices include electrocardiographs, powered bone drills and mercury thermometers.⁹ Class III medical devices include pacemakers and replacement heart valves.¹⁰

In general, class III devices require premarket approval (PMA) from the FDA before being marketed in the United States.¹¹ For a manufacturer to obtain PMA from the FDA, as the GAO summarized, it “must submit evidence, typically including clinical data, providing reasonable assurance that the new device is safe and effective.”¹² As is appropriate for the highest-risk devices, the PMA process is the most stringent type of review.¹³ Makers of Class III devices must demonstrate reasonable assurance of safety and effectiveness of the products prior to approval, whereas Class II devices are generally cleared for marketing by establishing similarity to other devices already on the market, and class I devices may be marketed without any FDA assessment.¹⁴

Even Class III review frequently falls short of the standard needed to protect patients from dangerous devices. At least four out of every five devices approved for marketing through the PMA process do not undergo testing in even a single randomized, double-blind clinical trial, the gold standard for medical research.^{15,16} The testing that is conducted is often too small, short, or poorly designed to detect important safety risks.

Danger of Proposed Provision in 21st Century Cures Act

Given all of the problems with the current PMA process, patient groups have repeatedly pressed Congress for heightened FDA scrutiny of medical devices. Yet the 21st Century Cures Act would do

⁶ GOVERNMENT ACCOUNTABILITY OFFICE, MEDICAL DEVICES FDA SHOULD ENHANCE ITS OVERSIGHT OF RECALLS (June 2011), p. 6, <http://1.usa.gov/1QXyRZi>.

⁷ *Id.*

⁸ *Id.*

⁹ *Id.*

¹⁰ *Id.*

¹¹ *Id.*

¹² *Id.*

¹³ *Id.*

¹⁴ *Id.*

¹⁵ SS Dhruva, LA Bero and RF Redberg, *Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices*. 302 JAMA 2679-2685, 2683 (2009).

¹⁶ VK Rathi, HM Krumholz, FA Masoudi and JS Ross, *Characteristics of clinical studies conducted over a total product life cycle of high-risk therapeutic medical devices receiving FDA premarket approval in 2010 and 2011*, 314 JAMA 604-612.

the opposite, endorsing dangerous practices that would further degrade the quality of the FDA's review of the highest-risk medical devices.

Prior to approving a PMA application, the FDA must find that there is reasonable assurance that the device is safe and effective.^{17,18} Currently, the Federal Food Drug and Cosmetics Act specifies that proof of effectiveness is to be determined “on the basis of well-controlled investigations, including 1 or more clinical investigations where appropriate...”¹⁹ (generally, one or more controlled trials in humans²⁰). However, the statute allows for an exception to this requirement if the FDA determines that there exists “valid scientific evidence:”

- (i) Which is sufficient to determine the effectiveness of a device, and
- (ii) From which it can fairly and responsibly be concluded by qualified experts that the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommend, or suggested in the labeling of the device[.]²¹

The 21st Century Cures Act passed by the House of Representatives would remove clauses (i) and (ii), quoted above, and explicitly state instead that the “valid scientific evidence” used to determine efficacy “may include ... evidence described in well-documented case histories, ... studies published in peer-reviewed journals; and data collected in countries other than the United States.”²²

Many commentators have already critiqued this proposed change in the law for encouraging the FDA to approve high-risk devices based on “well-documented case histories,” which are essentially medical anecdotes.^{23,24} Yet few have noted the provision instructing the FDA to consider studies published in peer-reviewed journals as sufficient proof of a device's effectiveness. Such studies often suffer from numerous flaws, and can differ dramatically in quality from the data more commonly submitted to the FDA in support of a PMA application.

The FDA has issued guidance highlighting the flaws with such articles and describing the limited circumstances under which certain peer-reviewed articles may be used as the basis for approval of

¹⁷ *Design Considerations for Pivotal Clinical Investigations for Medical Devices – Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff*, FOOD AND DRUG ADMINISTRATION (Nov.7, 2013), <http://1.usa.gov/1OLTweg>.

¹⁸ Determination of Safety and Effectiveness, 21 CFR § 860.7(c)(1) (2012).

¹⁹ 21 U.S.C. § 360c (a)(3)(B).

²⁰ *PMA Clinical Studies*, FOOD AND DRUG ADMINISTRATION, <http://1.usa.gov/1QcefLG>.

²¹ 21 U.S.C. § 360c (a)(3)(B).

²² The 21st Century Cures Act, H.R. 6, 114th Cong. (2015), p. 207.

²³ Jerry Avorn and Aaron Kesselheim, *The 21st Century Cures Act – Will It Take Us Back in Time?* 372 THE NEW ENGLAND JOURNAL OF MEDICINE 2473-2475, 2473 (2015).

²⁴ Rita F. Redberg And Sanket S. Dhruva, *The F.D.A.'s Medical Device Problem*. THE NEW YORK TIMES (July 17, 2015), <http://nyti.ms/1lsPfon>.

a PMA supplement for an already-marketed device.²⁵ While some peer-reviewed articles have now been used in this way, it remains rare for the FDA to rely solely on such evidence to support an original PMA (i.e., a device that has never before been marketed). Public Citizen reviewed the 43 approvals of original PMAs issued by the FDA in 2015 for which information is publicly available. Public Citizen was able to identify only two that relied exclusively on published peer-reviewed research.²⁶ One of these approvals involved a pacemaker that had been previously cleared in 1991 under the review process generally used for Class II devices, prior to a new FDA decision requiring the submission of a PMA application.²⁷

As this report details, reliance on peer-reviewed literature as the sole basis for approval of high-risk devices puts patients in harm's way because such publications often include biased presentation of the evidence, serious mistakes and omissions, and even outright fraud. As such, the insidious provision in the 21st Century Cures Act that would serve to pressure the FDA to approve Class III devices more often based only on peer-reviewed articles will weaken further the already dangerously low quality of the FDA review process for the highest-risk medical devices.

Problems Commonly Afflicting Peer-Reviewed Journal Articles

Journals vary significantly in their credibility and rigor. But even among the most respected journals, the peer-review process suffers from shortcomings that can permit fraudulent or otherwise incorrect articles find their way into publication. This means that relying on articles published in journals, without digging deeper into the underlying data, may lead to the approval and rapid adoption of unsafe medical devices.

In the peer-review process, authors submit articles to be evaluated for publication. Typically, an article is reviewed by people in the relevant area of expertise. If the article is accepted and published by the journal, this generally indicates that the peer reviewers have not found significant flaws in the article. But these peer reviewers rarely have access to the source data used by the author. They simply evaluate the author's argument, information, summary data and conclusions. If flaws are found in articles following publication, journals seek to protect their reputations and the accuracy of information on record by retracting articles that are revealed to contain information that is inaccurate, misrepresentative or fraudulent.

²⁵ Food and Drug Administration. Guidance for industry – supplements to approved applications for class III medical devices: use of published literature, use of previously submitted materials, and priority review. May 20, 1998.

²⁶ Public Citizen analysis of devices granted initial PMA in 2015. A total of 43 devices were approved. Two of these were approved solely on the basis of analysis of peer-reviewed journal articles. These were: Algovita spinal cord stimulation system – P130028 (issued November 20, 2015), <http://1.usa.gov/1PYLSUv> and Myopore sutureless myocardial pacing lead – P130012 (issued April 30, 2015), <http://1.usa.gov/20wwtzl>.

²⁷ *Id.*

Problems with the Reliability of Peer-Reviewed Journal Articles

Many types of problems have been discovered in studies published in peer-reviewed journals. These problems have included enrolling unqualified subjects, backdating information, failing to report adverse events, deviating from protocol, failing to obtain informed consent, covering up mistakes, and submitting false data for publication.²⁸

Journal editors and peer reviewers are unlikely to detect these flaws because they are not present during the collection of research data and do not typically audit records related to studies. By contrast, the FDA has the authority to audit trial sites, review protocols and analyze or exclude raw data based on questions about the conduct of the trial or analysis carried out by the trial sponsor (although, it does not always exercise this authority).^{29,30}

Selective Reporting

A pervasive problem with peer-reviewed literature is the practice of selectively reporting study findings that are favorable for medical products. For example, a study published in 2015 in the *British Medical Journal (BMJ)* compared the results of clinical trials for recently approved high-risk cardiovascular devices as reported to the U.S. Food and Drug Administration (FDA) with the results published in peer-reviewed publications.³¹

The BMJ study found that in 11 percent of cases there were substantial differences between the primary results submitted to the FDA and those published in peer-reviewed journals, and in another 20 percent of cases, the primary results were so different they could not be compared.³² The authors noted that these discrepancies echoed findings of previous studies of new drugs, explaining that, “The selective publication of favorable results for drugs includes several types of reporting bias, including failure to publish entire studies, failure to publish unfavorable outcomes, and publication of only selected prespecified outcome analyses.”³³

²⁸ Michael R. Hamrell, *Raising Suspicions With the Food and Drug Administration: Detecting Misconduct*, 16 SCIENCE AND ENGINEERING ETHICS 697-704, 699 (Sept. 15, 2010).

²⁹ See, e.g., *Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors FDA Inspections of Clinical Investigators*, FOOD AND DRUG ADMINISTRATION (June 2010), <http://1.usa.gov/1ZpVcIq>.

³⁰ For example, in 2014, FDA reviewers considering the ResQCPR System noted that a substantial number of subjects in clinical testing did not receive the device they were randomly assigned to receive. The FDA re-analyzed the data to take this fact into account, and the results of this re-analysis were not entirely consistent with the results originally presented by the device sponsor. See, *FDA Executive Summary Prepared for the May 6, 2014 Meeting of the Circulatory System Devices Panel. P110024 ResQTrial*, FOOD AND DRUG ADMINISTRATION, <http://1.usa.gov/1OLU0kF>.

³¹ Lee Chang, Sanket S Dhruva, Janet Chu, Lisa A Bero, Rita F Redberg, *Selective Reporting in Trials of High Risk Cardiovascular Devices: Cross Sectional Comparison Between Premarket Approval Summaries and Published Reports*, 350 BRITISH MEDICAL JOURNAL H2613, p. 1 (June 10, 2015).

³² *Id.*, p. 5.

³³ *Id.*, p. 1.

Insufficient Vetting of Peer Reviewers

The quality of peer review is no better than the reviewers themselves. While FDA reviews are conducted by qualified public servants, the editors of peer-reviewed journals do not necessarily exercise great care in selecting individuals to review journal articles.

Some journals routinely request that authors provide recommendations on potential peer reviewers for their manuscript. The flaws in the process of selecting peer reviewers were dramatically illustrated in revelations of peer-review fraud by South Korean researcher Hyung-in Moon. Moon admitted to having invented e-mail addresses so that he could provide “peer reviews” for his own manuscripts. And Moon’s case is not an isolated one. Dr. Charlotte Haug recently compiled a list of similar reviewer-fraud schemes for a commentary in the *New England Journal of Medicine*.³⁴ Since Moon’s confession three years ago, more than 250 articles have been retracted because of the fake reviews, about 15 percent of the total number of retracted articles.³⁵ Such cases of blatant fraud reveal how little care some journals put into vetting and selecting peer reviewers. Haug concluded, “As long as authors are (mostly) rewarded for publishing many articles and editors are (mostly) rewarded for publishing them rapidly, new ways of gaming the traditional publication models will be invented more quickly than new control measures can be put in place.”³⁶

Increase in Retractions of Peer-Reviewed Articles

A recent analysis carried out by British researchers showed that retractions of articles in journals indexed in Medline/PubMed (a database of journal citations and abstracts for biomedical literature from around the world) have increased considerably since 1980.³⁷ Separately, a 2012 study of the same database found that the percentage of articles retracted due to fraud had “increased [about] 10 fold since 1975.” Notably, 67 percent of retractions were due to fraud or suspected fraud, while only 21 percent of retractions were attributable to error.³⁸ The authors noted that retracted articles continued “to be cited as if still valid work.”³⁹ Further, the authors noted that not all articles suspected of fraud have been retracted. “The current number of articles retracted because of fraud represents an underestimation of the actual number of fraudulent articles in the literature,” they wrote.⁴⁰

³⁴ *Peer-Review Fraud – Hacking the Scientific Publication Process*, 373 THE NEW ENGLAND JOURNAL OF MEDICINE 2393-2395, 2393 (Oct. 21, 2015).

³⁵ *Id.*

³⁶ *Id.*, p. 2394.

³⁷ *Id.*, p. 567.

³⁸ Ferric C. Fang, R. Grant Steen and Arturo Casadevall, *Misconduct Accounts for the Majority of Retracted Scientific Publications*, 109 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES 17028-17033, 17028 (2012).

³⁹ *Id.*, p. 17029.

⁴⁰ *Id.*, p. 17030.

Case Studies of Faulty Peer-Reviewed Literature on Medical Devices

The following sections describe two cases involving medical devices that cast doubt on the reliability of the peer-review process. In these cases, safety problems or study design flaws emerged after the publication of peer-reviewed articles that reported glowing results. These cases illustrate the difference in quality between FDA reviews informed by full access to the original data from medical device studies and those that would rely solely on the limited information available in peer-reviewed publications.

Both of the devices discussed in this report were approved by the FDA. Public Citizen often disagrees with FDA's decisions on medical device approvals and is on the record as opposing the approval of one of the devices discussed in this report (CardioMEMS). Despite our view that the FDA's approval process already is far too lax, we believe that encouraging the FDA to rely only on the peer-reviewed literature in making these decisions would render the agency less effective at fulfilling its duties than it already is.

Case Study One: Medtronic Infuse (rh-BMP-2) LT-CAGE Lumbar Tapered Fusion Device

Degenerative conditions of the spine can cause back and leg pain.⁴¹ Many patients suffering from these ailments undergo surgery to stabilize their spine through a spinal fusion procedure. For years, surgeons performing these procedures routinely used bone graft material taken from patients' hips.

In the late 1990s, medical device company Medtronic developed a new spinal fusion medical device that incorporated a protein called recombinant human bone morphogenetic protein (rhBMP-2). (Hereafter, the rhBMP-2 will be referred to as the "bone-growth protein.") The device, called Infuse Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device (hereinafter, "Infuse"), involved embedding a small metallic cage in a patient's spine and filling the cage with an absorbable collagen sponge that had been treated with bone-growth protein.⁴² The product developers' theory was that the bone-growth protein would promote bone formation, thus eliminating the need to harvest bone from the patient's hips to achieve spinal fusion.⁴³

⁴¹ J. Kenneth Burkus, Matthew F. Gornet, Curtis A. Dickman and Thomas A. Zdeblick, *Anterior Lumbar Interbody Fusion Using rhBMP-2 With Tapered Interbody Cages*, 15 JOURNAL OF SPINAL DISORDERS & TECHNIQUES 337-349, 338 (2002).

⁴² *Summary of Safety and Effectiveness Data: InFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device*, FOOD AND DRUG ADMINISTRATION (July 2, 2002), <http://1.usa.gov/1ZzGK8D>.

⁴³ Ashely R. Poynton and Joseph M. Lane, *Safety Profile for the Clinical Use of Bone Morphogenetic Proteins in the Spine*, 27 SPINE S40-S48, S40 (2002) and J. Kenneth Burkus, Matthew F. Gornet, Curtis A. Dickman and Thomas A. Zdeblick, *Anterior Lumbar Interbody Fusion Using rhBMP-2 With Tapered Interbody Cages*, 15 JOURNAL OF SPINAL DISORDERS & TECHNIQUES 337-349, 338 (August 2002).

From August 1998 to July 1999 Burkus et al. conducted a clinical trial of Infuse involving 279 spinal fusion patients who had surgery to treat degenerative disc disease. In the study, which was published in 2002, 143 patients received the experimental Infuse treatment and 136 patients (the control group) received the traditional bone graft treatment for spinal fusion.⁴⁴ In reporting the results in 2002, Burkus et al. characterized the Infuse device as a “promising method of facilitating [...] spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion.” Additionally, they wrote, “The use of [Infuse] is associated with high fusion rates without the need for harvesting bone from the iliac crest and exposing the patient to the adverse effects associated with that procedure.”⁴⁵

Subsequent peer-reviewed journal articles described Infuse as a safe treatment that was superior to the traditional treatment. A 2003 article on Infuse, written by three of the four authors of the 2002 article referenced above, combined data from the original Infuse trial with data from “two additional patient data sets” that had not previously been published in full.⁴⁶ The combined analysis involved 679 spinal fusion patients, of whom 277 received the bone-growth protein treatment. The patients treated with the bone-growth protein “had statistically superior outcomes with regard to length of surgery, blood loss, hospital stay, reoperation rate, median time to return to work, and fusion rates at 6, 12, and 24 months,” Burkus et al. wrote.⁴⁷ “With its superiority, INFUSE Bone graft may now become the new gold standard.”⁴⁸ A co-author of both articles was Thomas A. Zdeblick, who invented the Infuse device. Zdeblick was editor of the *Journal of Spinal Disorders & Techniques* when these studies were published.⁴⁹

In 2002, the FDA approved Medtronic’s PMA application for Infuse.⁵⁰ With the endorsement of many peer-reviewed journals, Infuse was rapidly adopted for spinal fusions. Use of the product “jumped from less than 1% of all fusions in 2002 to 25% in 2006.”⁵¹

⁴⁴ J. Kenneth Burkus, Matthew F. Gornet, Curtis A. Dickman and Thomas A. Zdeblick, *Anterior Lumbar Interbody Fusion Using rhBMP-2 With Tapered Interbody Cages*, 15 JOURNAL OF SPINAL DISORDERS & TECHNIQUES 337-349, 338 (2002).

⁴⁵ *Id.*, p. 348.

⁴⁶ J. Kenneth Burkus, Stephen E. Heim, Matthew F. Gornet and Thomas A. Zdeblick, *Is INFUSE Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-Cage Lumbar Tapered Fusion Device*, 16 JOURNAL OF SPINAL DISORDERS & TECHNIQUES 113-122, 114 (2003).

⁴⁷ *Id.*, p. 113.

⁴⁸ *Id.*, p. 122.

⁴⁹ John Fauber, *Spinal Fusion Device: A Bone of Contention for FDA*, MEDPAGE TODAY (Aug. 29, 2010), <http://bit.ly/1OLW1gP> and Thomas Zdeblick, *Editorial Commentary*, 15 JOURNAL OF SPINAL DISORDERS & TECHNIQUES 1 (February 2002), <http://bit.ly/1V8IQuA>. (Commentary article documents that Zdeblick was editor of the Journal Of Spinal Disorders & Techniques as of February 2002. The initial Zdeblick co-authored Infuse article published in the Journal was in August 2002. The MedPage Today article reports that Zdeblick was still the editor of the publication as of 2010.)

⁵⁰ Medtronic Sofamo Danek USA, INC., *PMA for Infuse Bone Graft/LT-Cage Lumbar Tapered Fusion Device* (approval date July 2, 2002), <http://1.usa.gov/1Pfj8Xg>.

⁵¹ John Fauber, *Spinal Fusion Device: A Bone of Contention for FDA*, MEDPAGE TODAY (Aug. 29, 2010), <http://bit.ly/1OLW1gP>.

As a condition of approval of Infuse, the FDA required that a six-year post-approval study be conducted on the long-term efficacy and safety of the product.⁵² In 2009, Burkus (the lead author of the 2002 and 2003 studies cited above), Infuse inventor Zdeblick, and others published a follow up article on the post-approval study. Burkus et al. reported in the post-approval study that the use of the Infuse for spinal fusions resulted in “improved clinical outcomes” and “reduced pain” in patients with degenerative lumbar disk disease.⁵³

Conflicting Evidence on Infuse Emerges

In time, however, serious questions were raised about the safety and efficacy of Infuse. In 2010, a letter to the editor of the *Journal of Bone and Joint Surgery* contrasted the presentation of the post-marketing study dataset in the 2009 article by Burkus et al. with data from the study posted on the FDA’s web site.⁵⁴ The authors alleged that Burkus et al. omitted key data on adverse events in their paper.

“Although [...] data on the FDA website demonstrate that eleven patients managed with [the bone-growth protein] (7.9% of 140 male patients) developed retrograde ejaculation [ejaculation into the bladder instead of through the penis], the six-year follow-up report did not mention a single patient with permanent retrograde ejaculation, nor did it mention ectopic bone formation [proliferation of bone in an abnormal place] anterior to the instrumented disc spaces.”⁵⁵

Others began questioning whether researchers who had reached such rosy conclusions about Infuse had conflicts of interest. John Fauber, a reporter for the *Milwaukee Journal-Sentinel*, authored an investigative series of articles on Infuse in conjunction with *MedPage Today*. “Over the last year, an ongoing series of *Journal Sentinel/MedPage Today* investigations has raised questions about annual payments made to a core of prominent surgeons [...] who were involved either in the clinical testing of Infuse or co-authoring positive medical journal articles that failed to link the product to serious complications,” Fauber wrote.⁵⁶

In 2011, *The Spine Journal* dedicated an entire issue to Infuse.⁵⁷ One of the *Spine Journal* articles identified 13 industry-sponsored studies of Infuse published between 2000 and 2009 that did not report any adverse events associated with its use. “With each new industry-sponsored trial publication, the safety findings were identical: no adverse events associated with [bone-growth

⁵² Letter to Richard W. Treharne, FOOD AND DRUG ADMINISTRATION (July 2, 2002), <http://1.usa.gov/1RS2Xja>.

⁵³ JK Burkus, MF Gornet, TC Schuler, TJ Kleeman and TA Zdeblick, *Six-Year Outcomes of Anterior Lumbar Interbody Arthrodesis With Use of Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein-2*, 91 THE JOURNAL OF BONE & JOINT SURGERY 1181-1189, 1181 (2009).

⁵⁴ Tomislav Smoljanovic, Franjo Siric and Ivan Bojanic, Letter to the Editor, *Six-year Outcomes of Anterior Lumbar Interbody Arthrodesis with Use of Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein-2*, 92 THE JOURNAL OF BONE AND JOINT SURGERY 2614-2615, 2614 (2010).

⁵⁵ *Id.*

⁵⁶ John Fauber, *Senators Investigate Medtronic Spine Device*, MEDPAGE TODAY (June 22, 2011), <http://bit.ly/1ZzuwyC>.

⁵⁷ Barry Meier and Duff Wilson, *Spine Experts Repudiate Medtronic Studies*, THE NEW YORK TIMES (June 28, 2011), <http://nyti.ms/22Hsejk>.

protein] were reported to be observed.”⁵⁸ The authors went on to suggest that these 13 industry-sponsored trials may have led to the rapid adoption of Infuse as a safe and effective treatment.⁵⁹

However, after analyzing adverse event data obtained from databases and follow-up publications, the authors concluded that the actual risk to patients was dramatically greater than portrayed in the industry-sponsored publications. “Retrospective review of complications and adverse events as reported in FDA and other documents suggests the true risk to patients receiving [bone-growth protein] is conservatively 10 to 50 times the original estimates calculated from industry-sponsored publications.”⁶⁰ The authors concluded that the true likelihood of a patient experiencing complications resulting from treatment with Infuse was approximately 10 percent to 50 percent.⁶¹

After the series of critical articles was published, Thomas Zdeblick, the inventor of the Infuse device, submitted a letter to the editor of *The Spine Journal* in defense of Infuse, claiming that, “although interesting, a single publication in the medical literature does not constitute a ‘truth’.”⁶²

2012 U.S. Senate Committee on Finance Investigation Into Infuse Finds Conflicts of Interest

The U.S. Senate Committee on Finance, at the direction of committee chair Sen. Max Baucus (D-Mont.) and ranking member Charles Grassley (R-Iowa), in June 2011 opened an investigation into Medtronic’s conduct relating to Infuse.⁶³ This investigation lasted 16 months.⁶⁴ On Oct. 25, 2012, the Finance Committee released a report,⁶⁵ concluding that, “The Committee’s investigation discovered troubling evidence that Medtronic officials influenced the content of articles in peer-reviewed scientific publications to present Infuse in the best possible light.”⁶⁶ To this end, “Medtronic was heavily involved in drafting, editing, and shaping the content of medical journal articles authored by its physician consultants who received significant amounts of money through royalties and consulting fees from Medtronic.⁶⁷ Specifically, the committee charged, Medtronic encouraged paid physicians to omit adverse events from study publications and to attribute more pain to the patients who received the traditional [non-Infuse] treatment, which involved harvesting bone from a patient’s hip and inserting it into his or her spine.”⁶⁸

⁵⁸ Eugene Carragee, Eric Hurwitz and Bradley Weiner, A Critical Review of Recombinant Human Bone Morphogenetic Protein-2 Trails in Spinal Surgery: Emerging Safety Concerns and Lessons Learned, 11 THE SPINE JOURNAL 471-491, 472 (2011).

⁵⁹ *Id.*, p. 472-473.

⁶⁰ *Id.*, p. 487.

⁶¹ *Id.*, p. 471.

⁶² Thomas Zdeblick, *Science Please*, 11 THE SPINE JOURNAL 686 (2011).

⁶³ John Fauber, *Senators Investigate Medtronic Spine Device*, MEDPAGE TODAY (June 22, 2011), <http://bit.ly/1ZzuwyC>.

⁶⁴ Press release, U.S. Senate Committee on Finance, *Baucus-Grassley Investigation into Medtronic Reveals Manipulated Studies, Close Financial Ties with Researchers* (Oct. 25, 2012), <http://1.usa.gov/1OX1EbS>.

⁶⁵ *Id.*

⁶⁶ U.S. SENATE COMMITTEE ON FINANCE, STAFF REPORT ON MEDTRONIC’S INFLUENCE ON INFUSE CLINICAL STUDIES (October 2012), p. 18.

⁶⁷ *Id.*, p. 2.

⁶⁸ *Id.*, p. 8-9 and p. 11.

The committee found that “Medtronic, which describes itself as ‘the world’s largest independent medical technology company,’ also maintained significant, previously-undisclosed financial ties with physicians who authored studies about Infuse, making \$210 million in payments to physicians over a 15-year period.”⁶⁹ Zdeblick and Burkus, authors of two of the earliest peer-reviewed articles touting Infuse, received \$34.2 million and \$6.4 million, respectively, from Medtronic, according to the Finance Committee report.⁷⁰

Medtronic-Funded Investigation Into Infuse Finds Bias in Studies

In response to criticism, Medtronic in 2011 commissioned Yale University to conduct an independent review of Infuse.⁷¹ The company reportedly provided researchers with complete access to its data. Yale, in turn, contracted with two universities to conduct the review. Researchers concluded in 2013 that the device provided little benefit, if any, to patients over the traditional treatment.⁷²

Moreover, the researchers concluded that previous peer-reviewed studies were reported improperly. “We found substantial evidence of reporting bias and no evidence that [bone-growth protein] is more effective than [traditional bone graft] in spinal fusion,” they wrote.⁷³

Case Study Two: CardioMEMS Champion Heart Failure Monitoring System

CardioMEMS is a wireless, battery-less medical device about the size of a paper clip with one large loop at each end that is implanted in the pulmonary artery to monitor and guide management of heart failure patients.⁷⁴ By sending periodic pulmonary artery pressure readings to the patient’s physician, the device is intended to enable physicians to optimally adjust their patients’ treatment.⁷⁵

A study dubbed “CHAMPION” (CardioMEMS Hearth Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients) was completed in 2010, with results presented at the European Society of Cardiology Heart Failure Congress in Berlin that May. According to a press

⁶⁹ Press release, U.S. Senate Committee on Finance, *Baucus-Grassley Investigation into Medtronic Reveals Manipulated Studies, Close Financial Ties with Researchers* (Oct 25 2012), <http://1.usa.gov/1OX1EbS>.

⁷⁰ U.S. SENATE COMMITTEE ON FINANCE, STAFF REPORT ON MEDTRONIC’S INFLUENCE ON INFUSE CLINICAL STUDIES (October 2012), p. 5.

⁷¹ James Walsh, *Long-Awaited Yale Study Raises Questions About Integrity of Previous Studies of Medtronic’s Infuse*, MINNEAPOLIS STAR-TRIBUNE (June 18, 2013), <http://strib.mn/1mgo2Xm>.

⁷² Rongwei Fu, et al., *Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis*. 158 ANNALS OF INTERNAL MEDICINE 890, 890 (2013), <http://bit.ly/1nwQAFD>.

⁷³ *Id.*, p. 899,

⁷⁴ See, e.g., Peggy Peck, *Wireless Device May Keep Heart Failure Patients Out of Hospital*, ABC NEWS (June 1, 2010), <http://abcn.ws/1OX2J3A>.

⁷⁵ Joshua P. Loh, Israel M. Barbash and Ron Waksman, *Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting on the CardioMEMS Champion Heart Failure Monitoring System*, 61 JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY 1571-1576, 1571 (April 16, 2013).

release issued by the developer of the CardioMEMS device, the study showed that use of CardioMEMS was associated “with a 30% reduction in heart failure hospitalization rates at 6 months.”⁷⁶

William Abraham, a co-principal investigator for the CHAMPION study,⁷⁷ “called the results of the CHAMPION study a “grand slam home run.”⁷⁸ ABC News paraphrased Abraham as saying that “there were no serious adverse events such as stroke or myocardial infarction” that occurred from the use of the device.⁷⁹

Abraham co-authored a peer-reviewed article published in the prestigious British medical journal *The Lancet* in February 2011, in which he and his co-authors reported the significant reduction in hospitalization rates for patients who had the CardioMEMS device implanted. The CardioMEMS “management strategy tested in the CHAMPION trial allowed further optimisation of standard treatments for heart failure,” Abraham *et al* wrote. “By contrast, non-implantable telemonitoring systems for heart failure do not seem to improve outcomes compared with standard of care.”⁸⁰

In the same issue of *The Lancet*, Henry Krum of Alfred Hospital in Melbourne, Australia, wrote in a commentary “The CardioMEMS device seems to be a simple but ingenious piece of bioengineering. Its simplicity lies in its smallness and ability to derive and transmit clinically useful data (continuous pulmonary artery pressures), via an implantation procedure that seems to add very little in terms of time or risk to that of standard right-heart catheterization.”⁸¹

Krum acknowledged that “no information was given about what drugs were changed in this trial, which is surprising because these treatment changes are the presumed reason for the achieved differences in clinical outcomes between the [intervention and control] groups.”⁸²

Despite his concerns about shortcoming in reporting, Krum concluded that “the risk versus benefit profile of the CardioMEMS device, as reported in CHAMPION, suggests that strong consideration should be given to its implantation in appropriate patients ... With increasing clinical use of these devices will come further technological advances. We are only at the beginning of this revolution in patient monitoring.”⁸³

⁷⁶ Press release, CardioMems, *Cardiomems Inc. Completes CHAMPION Clinical Trial Study: Study Results Indicate That the CHAMPION Implantable Hemodynamic Monitoring System Significantly Reduces the Leading Cause of Hospitalizations in the U.S.* (June 1, 2010), <http://prn.to/1JHcEbZ>.

⁷⁷ *Id.*

⁷⁸ Peggy Peck, *Wireless Device May Keep Heart Failure Patients Out of the Hospital*, ABC NEWS (June 1, 2010), <http://abcn.ws/1OX2J3A>.

⁷⁹ *Id.*

⁸⁰ William Abraham et al, *Wireless Pulmonary Artery Haemodynamic Monitoring in Chronic Heart Failure: A Randomised Controlled Trial*, 377 *The Lancet* 658-666, 664 (Feb. 19, 2011).

⁸¹ Henry Krum, *Telemonitoring of Fluid Status in Heart Failure: CHAMPION*, 377 *THE LANCET* 616-618, 617 (Feb. 19, 2011).

⁸² *Id.*

⁸³ *Id.*

Thus, the version of the CHAMPION study results presented in a conference and in a peer-reviewed journal study and commentary depicted the device as highly effective.

2011: FDA Rejects PMA for CardioMEMS

Yet, in 2011, the FDA's Circulatory System Devices Panel (an advisory committee) voted 6-4 against recommending approval of the CardioMEMS device. Although recipients of the device were hospitalized at a lower rate (20 percent) over a six-month span than those in the control group (29 percent), the FDA committee raised concerns that the results may have been skewed by the manner in which the trial was conducted.⁸⁴

In 2013, the *Journal of the American College of Cardiology* published an article that summarized the PMA review of CardioMEMS and the FDA's findings of flaws in the CHAMPION study.⁸⁵ Among the problems, the FDA's Division of Bioresearch Monitoring determined through an audit that the study's principal investigators – who were nationally recognized experts in the management of chronic heart failure – routinely contacted the physicians conducting the trial at investigational sites and made therapeutic recommendations via e-mail for the care of the study subjects in the experimental group. These recommendations were numerous and wide ranging. They included “titration of medication doses, addition or discontinuation of medications, recommendations for outpatient intravenous medication administration, addition of medications that were not in the protocol and sleep study evaluations that were not included in the protocol.”⁸⁶

Crucially, these recommendations were only made for the care of subjects in the experimental group, not for those in the control group.⁸⁷ This introduced bias into the study that may have caused patients in the experimental group to experience better results. This imbalance could have been avoided by ensuring that an equal number of such contacts occurred with physicians caring for subjects in the control group. Balancing these contacts would have distinguished the efficacy of the device from the impact of simply having the physicians caring for patients in the experimental group routinely consult with national heart failure experts.

In sum, the authors of the *Journal of the American College of Cardiology* article wrote, “according to the FDA, this mode of preferential communication introduces a significant bias to the study and

⁸⁴ Molly Peterson, *CardioMems Fails to Win FDA Panel Backing for Heart Sensor*, BLOOMBERG (Dec. 8, 2011), <http://bloom.bg/1m07gyQ>. Concerns raised by the FDA are summarized in a letter written by Public Citizen's Health Research Group. Michael A. Carome and Sidney M. Wolfe, Letter to Jeffrey E. Shuren, Director, FDA Center for Devices and Radiological Health (Dec. 2, 2013) <http://bit.ly/1njglea>.

⁸⁵ Josh P. Loh, Israel M. Barbash and Ron Waksman, *Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting on the CardioMEMS Champion Heart Failure Monitoring System*, 61 JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY 1571-1576 (2013).

⁸⁶ *Id.*, p. 1572.

⁸⁷ *Id.*

ultimately disallows objective assessment of the inherent effect of the CardioMEMS Champion HF monitoring device in the management of [heart failure] patients.”⁸⁸

The authors contrasted the resources of peer-reviewed journals with those associated with FDA analysis. “Auditing performed by the FDA uncovered certain conduct issues that challenged the validity of the published results. This type of auditing and availability of the FDA advisory panel are obviously beyond the scope and resources of any specific journal,” the authors wrote. “Although medical journals are focusing on publishing late-breaking trials expeditiously, the regulatory agencies are charged to conduct full investigations into the accuracy of the results and the integrity of its conduct.”⁸⁹

In this case, the authors of the *American College of Cardiology* article wrote, due diligence by the FDA “led to a disparity between praised study results published in a leading medical journal and contradictory interpretation by a respected panel of experts who advised the FDA that there is lack of reasonable assurance this technology is effective.”⁹⁰

2014: FDA Approves CardioMEMS

In 2013, the FDA’s Circulatory System devices panel discussed CardioMEMS following submission of additional data by its maker. Although only 4 of 11 voting committee members found that there was “reasonable assurance that the CardioMEMS HF Pressure Measurement System is effective” for the proposed use, the committee voted 6-4 (with one abstention) that the device’s benefits outweighed its risks.⁹¹

The FDA subsequently approved CardioMEMS in 2014,⁹² a decision opposed by Public Citizen.⁹³ However, the FDA’s detailed review process brought to light important flaws with the conduct of the CHAMPION trial that will influence adoption of the CardioMEMS device in the medical community. Otherwise, physicians would have had access only to peer-reviewed evidence that was carefully selected to present a biased picture of the device.

⁸⁸ *Id.*, p. 1572.

⁸⁹ *Id.*, p. 1575.

⁹⁰ *Id.*, p. 1575.

⁹¹ Brief summary of the circulatory system devices panel meeting – October 9, Food and Drug Administration (Oct. 9, 2013), <http://1.usa.gov/1n8eL3e>.

⁹² Press release, Food and Drug Administration, *FDA Approves First Implantable Wireless Device With Remote Monitoring to Measure Pulmonary Artery Pressure in Certain Heart Failure Patients* (May 28, 2014), <http://1.usa.gov/1UtRkwc>.

⁹³ Public Citizen’s Health Research Group testified against the approval of the device at an FDA advisory committee discussing CardioMEMS, pointing out that no new studies had been done to address the deficiencies cited by the FDA in its previous rejection of the device’s approval. See, Michael A. Carome and Sidney M. Wolfe, Letter to Jeffrey E. Shuren, Director, FDA Center for Devices and Radiological Health (Dec. 2, 2013) <http://bit.ly/1PuUtfO>.

Conclusion

The 21st Century Cures Act would dangerously undermine the quality of FDA review in numerous ways. One provision, which would serve to pressure the FDA to grant approvals for the highest-risk devices based primarily on evidence summarized in peer-reviewed journal articles, rather than independently reviewing the underlying data, could prevent important safety and efficacy concerns from coming to light. This will potentially lead to larger numbers of ineffective and unsafe medical devices reaching the market. The requirement for a class III high-risk device to gain PMA should include the submission of rigorous and comprehensive clinical data, and not depend on the brief and potentially biased summaries published in peer reviewed journals as the sole source of information about a high-risk device.

Public Citizen opposes the 21st Century Cures Act for the peer-reviewed journal provision, as well as numerous others. We strongly recommend that section 2222 be removed from the bill and that peer-reviewed journal articles not be considered sufficient for establishing the safety and effectiveness of new high-risk medical devices. We further recommend that that proposals like this be kept out of any future bills dealing with medical devices.