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January 17, 2012

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Re: Cardiovascular Devices; Reclassification of External Pacemaker Pulse Generator Devices,
Docket No. FDA-2011-N-0650

Dear Dr. Hamburg,

Public Citizen, a consumer advocacy group representing more than 250,000 members and supporters nationwide, submits this comment strongly urging the Food and Drug Administration (FDA) to withdraw its proposed rule to arbitrarily reclassify the external pacemaker pulse generator preamendment Class III device to Class II (special controls) and to publish a new notice immediately that proposes a final regulation requiring the device to remain in Class III (premarket approval).

The external pacemaker pulse generator must remain categorized as Class III because it is a life-sustaining device for which clinical trials are necessary to provide reasonable assurance of

safety and effectiveness. In 1976, the Cardiovascular Devices Panel — the only independent expert panel to ever consider this issue — recommended that the external pacemaker pulse generator be categorized into Class III because the device provides temporary life support and certain kinds of failures can cause the device to emit inappropriate electric signals, which could cause cardiac irregularities and death, and because special controls would not be sufficient to provide reasonable assurance of safety and effectiveness.

Rather than follow the advice of the panel, the FDA sought advice from the device manufacturing industry, and based on the “new information” it received (which has not been made available to the public), it has now issued a notice that it plans to reclassify the external pacemaker pulse generator as a Class II device. The FDA’s proposed rule should be withdrawn because it was based on secret information and irrelevant evidence in violation of the Food, Drug, and Cosmetics Act (FDCA). Moreover, it is clear from the recommendations of the Cardiovascular Devices Panel and from the number of faulty external pacemakers cleared under the 510(k) process that a Class II categorization would not provide sufficient assurance of safety and effectiveness, and premarket approval is required for this device.

We therefore urge the FDA to immediately withdraw this notice and issue a final rule categorizing the external pacemaker pulse generator as a Class III device in accordance with the recommendation of the Cardiovascular Devices Panel. In the alternative, we urge the FDA to convene a new expert panel and seek a new recommendation regarding the external pacemaker pulse generator prior to issuing a final rule.

I. Description of the Device

The external pacemaker pulse generator (21 C.F.R. § 870.3600) is a device that has a power supply and electronic circuits that produce a periodic electrical pulse to stimulate the heart. The device itself is used outside the body but may be connected to a patient using leads inserted through the skin or veins and sometimes into the heart, or through electrode patches applied to the chest. The electrical pulse generated by the device serves as a temporary substitute for the heart’s intrinsic pacing system until a permanent pacemaker can be implanted. It also functions to control irregular heartbeats in patients following cardiac surgery or myocardial infarction (heart attack). In some situations, temporary pacing with this device can be lifesaving for patients.

II. Regulatory Background

The external pacemaker pulse generator is sometimes referred to as a “preamendment” device, because this type of device was on the market prior to the passage of the 1976 Medical Device Amendments to the FDCA.¹ This status means the device is subject to special regulatory requirements.

The Medical Device Amendments of 1976 established three classes of medical devices, referred to as Classes I, II, and III. Currently, Class I devices are defined as those for which compliance with general controls, such as good manufacturing practices specified in the FDA's quality system regulation, are sufficient to provide reasonable assurance of safety and effectiveness.^{2,3} Examples include tongue depressors, elastic bandages, reading glasses, and forceps.⁴

If general controls are insufficient to provide reasonable assurance of safety and effectiveness, but special controls may establish such assurance, the device may be categorized as Class II.⁵ Special controls may include performance standards, postmarket surveillance, patient registries, or specific FDA guidelines.^{6,7} Examples of Class II devices include electrocardiographs, powered bone drills, and mercury thermometers.⁸

Finally, if 1) general and special controls would be insufficient to provide a reasonable assurance of safety and effectiveness, and 2) the device supports or sustains human life, is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury, it must be categorized as Class III.⁹ Examples of this high-risk category include internal (implantable) pacemakers (21 C.F.R. § 870.3610) and replacement heart valves.¹⁰

When the FDA initially categorized all preamendment devices into one of the three classes,^a the agency was required by statute to obtain a recommendation from a panel of experts qualified by training or experience to evaluate the safety and effectiveness of devices referred to the panel.¹¹ Each panel had to include members with adequately diversified expertise in such fields as clinical and administrative medicine, engineering, biological and physical sciences, and other related professions.¹² Panelists were required, to the extent feasible, to possess skill in the use of the devices referred to that panel or have experience in the development, manufacture, or utilization of such devices.¹³ In addition, each panel had to include a representative of consumer interests and a representative of interests of the device manufacturing industry (as nonvoting members).¹⁴

Each class is generally subject to progressively more stringent regulatory requirements before a new device in that class may be cleared for marketing. The chief difference between Class II and Class III medical devices in terms of premarket clearance is that for Class III devices, the manufacturer generally must submit a premarket approval application (PMA) that includes evidence (typically with clinical data from at least one controlled clinical trial in humans) providing reasonable assurance that the new device is safe and effective.¹⁵ Class II devices generally may be cleared for marketing by submitting what is referred to as a 510(k) premarket

^a New devices are now automatically classified as Class III unless they fall within a Class I or II device category and can show substantial equivalence to another device within Class I or II, or unless the FDA takes steps to classify them as Class I or II in response to a reclassification petition. 21 U.S.C. § 360c(f)(1).

notification (because the notification requirement is described under section 510(k) of the FDCA).¹⁶ To qualify for the less stringent 510(k) notification process, the manufacturer need only demonstrate that a new device is “substantially equivalent” to a device already legally on the market.¹⁷ No PMA is required for such devices, and animal or bench testing is usually sufficient — the device need not be tested on human beings before being marketed on a wide scale.^b

While the structure of the FDCA suggests that all new devices categorized into Class III are generally required to submit a PMA, there are numerous exceptions that provide for approval without meeting this standard. One exception allows certain types of Class III devices that were in commercial distribution before the 1976 amendments (preamendment device types) to be cleared through the 510(k) process until the FDA publishes final regulations requiring them to go through the premarket approval process¹⁸ (or regulations reclassifying them as Class I or II¹⁹).

The process for publishing final regulations requiring premarket approval has been slow, and as a result, many categories of Class III devices have languished for years in this gray area between Class II and III, with new devices cleared for marketing using the lower standard of review simply because the agency has not had time and resources to publish a final regulation. In 1990, Congress issued the Safe Medical Devices Act (SMDA), requiring the FDA to reexamine the remaining preamendment Class III device types and establish a schedule to promulgate regulations requiring premarket approval for those that would remain in Class III.²⁰ SMDA established a hard deadline of Dec. 1, 1995, for the FDA to publish a regulation to determine whether to reclassify the device.²¹

While it has been more than 35 years since Congress first asked the FDA to require premarket approval for Class III devices, and more than 20 years since Congress ordered the FDA to hurry up and complete the process of issuing final regulations, a small number (22) of Class III device categories remain subject to the less rigorous 510(k) regulatory process due to this particular loophole, including the external pacemaker pulse generator.²² Of these, 17 categories include new devices cleared for market entry recently (between 2003 and 2007).²³

A 2009 report by the Government Accountability Office to Congress recommended that the FDA take steps to ensure that these remaining high-risk device types be approved through the

^b FDA review of 510(k) notifications also differs in other respects from premarket approval. For example, while FDA has some authority to request manufacturing information, conduct pre-approval inspections, review changes in manufacturing facilities, and order postmarket surveillance studies under either process, these regulatory tools are only routinely utilized for PMA application submissions. Department of Health and Human Services, Center for Devices and Radiological Health, Medical Devices Advisory Committee, Circulatory Systems Devices Panel. Testimony of Dr. Cara Krulewicz, Branch Chief, Division of Epidemiology, Food and Drug Administration. January 25, 2011, at 29-31.

more stringent premarket review process, by issuing final rules for these remaining devices.²⁴ In response, the FDA published a “515(i) order”^c in the *Federal Register* and sent letters to manufacturers of the remaining Class III preamendment devices for which no final rule had been published requiring the manufacturers to submit any information known or otherwise available to them respecting such devices.²⁵

III. Legal Standard for Reclassification

A device may be changed from Class III to Class II only upon a determination that special controls would provide reasonable assurance of the safety and effectiveness of the device (and that general controls would not provide such assurance).²⁶

The FDA’s decision to reclassify must be based on new information.²⁷ “New information,” for the purposes of the reclassification process, includes information developed as the result of reevaluation of the data before the agency when the device was originally classified, and may also be information not presented, not available, or not developed at that time.²⁸ Reevaluation of the data previously before the agency is an appropriate basis for subsequent regulatory action where the evaluation is made in light of newly available regulatory authority²⁹ or in light of changes in medical science.³⁰ To be considered, the “new information” supporting reclassification must be valid scientific evidence.^d Moreover, the valid scientific evidence upon which the FDA relies for reclassification must be publicly available. This means that the FDA may not rely on trade secrets and/or confidential commercial information, such as the confidential contents of a PMA.³¹

In promulgating a regulation reclassifying a device based on new information, the agency has the option of securing a new recommendation respecting the proposed change from the expert panel that covers the particular field for that device and that last reviewed that device.³²

IV. Specific Regulatory History for the External Pacemaker Pulse Generator

The external pacemaker pulse generator was reviewed by the Cardiovascular Devices Panel of experts, a panel convened by the FDA that complied with the requirements of the 1976 amendments. In 1979, the Cardiovascular Devices Panel recommended that the external pacemaker pulse generator be categorized as Class III because the device 1) provided

^c Section 515(i) of the FDCA, added as part of the SMDA, describes a process whereby manufacturers will be required to submit information relating to the product prior to issuing a regulation revising the Class III device into another category or requiring it to remain in Class III. Pub. L. No. 101-629, § 4(b), 104 Stat. 4511, 4515-17 (codified as 21 U.S.C. § 360e(i)).

^d As defined by section 513(a)(3) of the FDCA (21 U.S.C. 360c(a)(3) and 21 CFR § 860.7(c)(2). 76 FR 64224, October 17, 2011 (citing *General Medical Co. v. FDA*, 770 F.2d 214 (D.C. Cir. 1985); *Contact Lens Assoc. v. FDA*, 766 F.2d 592 (D.C. Cir.), cert. denied, 474 U.S. 1062 (1985)).

temporary life support and certain kinds of failures could cause the device to emit inappropriate signals, which could cause cardiac irregularities and death, and 2) general controls would not be sufficient to provide reasonable assurance of safety and effectiveness, and there was not enough information to establish a performance standard to provide such reasonable assurance.³³

In 1980, the FDA followed the panel's recommendation, classifying the external pacemaker pulse generator as a Class III device.³⁴ However, the FDA neglected to publish a final regulation requiring premarket approval, and as a result, new external pacemaker pulse generators could be approved through the 510(k) process, similar to Class II devices. In 1987, the FDA made this situation explicit by inserting language into the regulation explaining that no effective date had been established for the requirement of premarket approval.³⁵

In 2009, after the FDA had published its 515(i) order for submission of information from industry regarding all the remaining preamendment Class III device categories, the agency received reclassification petitions from three device manufacturers who all, unsurprisingly, recommended that the device be reclassified into Class II so that their products could remain subject to lower regulatory standards.³⁶ Following these petitions, the FDA declined to seek advice from the Cardiovascular Devices Panel and instead proceeded to publish a notice of proposed rulemaking reclassifying the device into Class II and identifying special controls in the draft guidance "Class II Special Controls Guidance Document: External Pacemaker Pulse Generator."³⁷

V. The FDA Should Immediately Withdraw Its Notice Proposing to Reclassify the External Pacemaker Pulse Generator Device as Class II Device

The FDA should withdraw its current notice proposing reclassification because it did not base its decision on publicly available valid scientific evidence. Instead, the FDA appears to have relied almost exclusively on secret documents submitted by device manufacturers in support of their petitions to reclassify. Issuing a final regulation under these circumstances would violate the FDCA and constitute an abuse of the public trust.

The only independent expert panel to consider the issue of classifying the external pacemaker pulse generator recommended that it be placed in Class III because 1) the device provided life support, and certain kinds of failures could cause the device to emit inappropriate electrical signals, resulting in cardiac irregularities and death, and 2) general controls were insufficient and there was not enough information to establish special controls.

The FDA acknowledged in its notice that risks associated with the external pacemaker pulse generator continue, including failure to pace, improper pacing leading to a high rate of pacing or unwanted stimulation (both of which can in turn lead to heart arrhythmias), and micro/macro electric shocks that can result in arrhythmia or cardiac tissue damage.^{38,39} Moreover, a search of the Manufacture and User Facility Device Experience (MAUDE) database for the last five years (Jan. 1, 2007, through Dec. 30, 2011), showed at least 13 deaths

associated with this device. There is no dispute that this device continues to support or sustain human life, is of substantial importance in preventing impairment of human health, and presents a potential unreasonable risk of illness or injury.

Yet the FDA has chosen to reclassify the device as Class II because it has somehow determined, contrary to the recommendation of the expert Cardiovascular Devices Panel, that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness.⁴¹ The agency has not identified appropriate “new information” in the form of publicly available valid scientific evidence upon which it could rationally base its decision to reclassify.

Instead, the FDA has simply stated that “special controls, in addition to general controls, can be established to provide reasonable assurance of the safety and effectiveness of the device.”⁴² This is not an explanation or new information, but rather it is an arbitrary, unsupported legal conclusion not based on any evidence presented by the FDA.

The agency also stated that “[i]n addition, there is now adequate effectiveness information sufficient to establish special controls to provide such [reasonable] assurance [of safety and effectiveness].”⁴³ Yet it fails to identify this effectiveness information. It merely states that

- 1) “The effectiveness and acceptability of pacing for the treatment of various cardiac arrhythmias has been demonstrated in extensive clinical studies and is summarized in the American College of Cardiology/American Heart Association Guidelines for implantable cardiac pulse generators.”
and
- 2) “Several key performance standards have been developed and used to support marketing applications over the years, which address various aspects of design and performance and have been determined to be sufficient in the establishment of requirements for market entry.”⁴⁴

Each of these statements fails to identify new information upon which the FDA could have based its reclassification decision. With regards to the first statement, the American College of Cardiology/American Heart Association guidelines contain no reference to external pacemakers. Instead the guidelines discuss *implantable* cardiac pulse generators. The implantable pacemaker pulse generator is a separate preamendment device covered under a different regulation (21 C.F.R. § 870.3610). In a separate notice issued this year, the FDA proposed a rule requiring a PMA for the implantable pacemaker pulse generator, which is to remain in Class III.⁴⁵ Therefore, to the extent that the external pacemaker pulse generator can be characterized by guidelines covering internal pacemaker pulse generators, such comparability indicates that the external pacemaker pulse generator should also remain in Class III and be approved only via a PMA. Moreover, the statement that pacing in general is an acceptable and effective form of treatment provides no information on whether special controls will be sufficient to ensure that an individual device will be safe and effective when used in patients.

Second, performance standards developed in support of PMAs are not public information, as these applications contain trade secrets and/or confidential commercial information and therefore cannot be made public except in heavily redacted form. To the best of Public Citizen's knowledge, no such performance standards have been made public in this case.

In addition, the FDA stated in its reclassification notice that its analysis of "Risks to Health" derived from:

- 1) Reports and recommendations from advisory committees (panels) for the classification of external pacemaker pulse generators;
- 2) Information submitted in response to the 515(i) order; and
- 3) Any additional information the FDA has encountered.⁴⁶

None of these sources of information constitute publicly available valid scientific evidence justifying the FDA's decision to reclassify. As previously stated, reports and recommendations from the Cardiovascular Devices Panel indicate that special controls are *not* sufficient. Information submitted by manufacturers in response to the 515(i) order is not publicly available: Public Citizen's attempts to identify these documents through the docket folder for the 515(i) order on regulations.gov revealed no matches, a finding that was confirmed in a personal communication with an FDA official who suggested that the submissions may not have been posted because they contained confidential commercial information or trade secrets.⁴⁷ The FDA has failed to identify other additional information it may have encountered that could have formed the basis of its decision to reclassify.

Finally, the FDA has not indicated that its decision to reclassify is based on reevaluation of the data previously before the agency in light of newly available regulatory authority, or in light of specific changes in medical science.

VI. Approval Under the 510(k) Process Is Not Sufficient to Provide Reasonable Assurance of Safety and Effectiveness, Even With Special Controls in Place

As previously noted, the only independent expert panel to have considered the issue recommended classifying external pacemakers as Class III devices because special controls are not sufficient to provide reasonable assurance of safety and effectiveness. Instead, premarket approval, with its accompanying clinical testing, is required to provide such assurance.

Evidence of the large number of adverse events related to external pacemakers indicates that these devices should remain in Class III, and the FDA should require PMA applications prior to market entry. The external pacemaker pulse generator has been approved for years under the 510(k) process due to the slow pace the agency has taken in finalizing the regulation for this Class III device. The FDA has indicated that it based its current proposed special controls on "several key performance standards [that] have been developed and used to support marketing applications over the years" with respect to this device.⁴⁸ While it is impossible to determine when these standards were developed or to review how they have been applied over the years

(as their source has not been made public), it is clear that a portion of the devices already on the market were reviewed under these standards. A search of the MAUDE database (also mentioned previously) revealed at least 13 deaths associated with these devices over the last five years. During that same period (Jan. 01, 2007, through Dec. 30, 2011), there were more than 1,800 additional MAUDE reports submitted to the FDA for external pacemaker pulse generators, a large number of which were device malfunctions that resulted in or could have resulted in patient injury. While some events resulted in more than one MAUDE report, the MAUDE reports on death and injury still probably grossly underrepresent the true number of incidents, due to significant underreporting to the MAUDE database.^e The reports are additional evidence that the “performance standards” used by the FDA that supposedly form the basis of the proposed draft guidance are not sufficient to ensure the safety and effectiveness of external pacemaker pulse generator devices.

VII. At a Minimum, the FDA Should Seek Advice From a New Expert Panel Prior to Reclassifying This Device

In 1976, Congress established a mechanism whereby the agency could obtain a report and recommendation from a well-balanced, independent committee of experienced experts. Now, after more than 35 years of agency delay, the FDA is approaching the point where it can fully implement Congress’ 1976 mandate and issue final regulations regarding the remaining preamendment Class III devices. Yet instead of utilizing the advisory panel process, the agency has chosen to implement only part of its statutory authority, gathering submissions from industry, but not other sources, prior to proposing a set of special controls.

This process is unacceptable. The FDA should exercise its statutory authority to seek advice from A New Expert Panel prior to reclassifying external pacemaker pulse generators into Class II. If it is no longer feasible to seek advice from the panel because of the agency’s own long delay, FDA should convene a new panel that meets the same statutory requirements.

VIII. Summary of the Arguments

The FDA should withdraw its current notice proposing reclassification into Class II because it did not base its decision on publicly available valid scientific evidence. Instead, the FDA appears

^e An October 2009 report by the Department of Health and Human Services Office of the Inspector General noted concerns about potential underreporting due to the low rate of reporting to the MAUDE database from most device user facilities: in 2007, only 350 facilities accounted for 78 percent of all user facility adverse event reports. This group of 350 “MedSun” user facilities represented a small fraction of the thousands of potential user facilities, and had received special training under FDA’s Medical Product Safety Network (MedSun) pilot project to increase user facility reporting rates. Department of Health and Human Services, Office of the Inspector General. Adverse Event Reporting for Medical Devices. October 2009. OEI-01-08-00110.

to have relied almost exclusively on secret documents submitted by device manufacturers in support of their petitions to reclassify. Issuing a final regulation under these circumstances would violate the FDCA and constitute an abuse of the public trust.

The FDA should issue a new regulation retaining the external pacemaker pulse generator in Class III and requiring premarket approval for new versions of this high-risk device. The only independent expert panel to consider the issue — the Cardiovascular Devices Panel — concluded that special controls are not sufficient to provide reasonable assurance of safety and effectiveness. The PMA process, with its accompanying clinical testing, should be required to provide such assurance.

At a minimum, the FDA should seek new advice from the Cardiovascular Devices Panel prior to reclassifying the external pacemaker pulse generator. In 1976 Congress directed the FDA to classify this device after considering the views of a well-balanced, independent committee of experienced experts. If the agency's decision to delay final action for more than 35 years has allowed the advice of the relevant panel to grow stale, the solution is not to override the independent expert panel based on secret information from industry, but rather to convene a new panel for reconsideration of the issue.

IX. Conclusion

For the foregoing reasons, we urge the FDA to withdraw this notice immediately and issue a final rule categorizing the external pacemaker pulse generator as a Class III device in accordance with the recommendation of the Cardiovascular Devices Panel. In the alternative, we urge the FDA to reconvene a new expert panel and seek a new recommendation regarding the external pacemaker pulse generator prior to issuing a final rule.

Thank you for taking our comments into consideration.

Sincerely,

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¹ Pub. L. No. 94-295, § 2, 90 Stat. 539-41.

² 21 U.S.C. § 360c(a)(1)(A).

³ 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. Government Accountability Office. January 2009. GAO-09-190 *at* 7. [hereinafter GAO Report]

⁴ GAO Report *at* 2.

⁵ 21 U.S.C. § 360c(a)(1)(B).

⁶ 21 U.S.C. § 360c(a)(1)(B).

⁷ GAO Report *at* 2.

⁸ GAO Report *at* 2.

⁹ 21 U.S.C. § 360c(a)(1)(C).

¹⁰ GAO Report *at* 2.

¹¹ 21 U.S.C. § 360c(b)(2).

¹² 21 U.S.C. § 360c(b)(2).

¹³ 21 U.S.C. § 360c(b)(2).

¹⁴ 21 U.S.C. § 360c(b)(2).

¹⁵ 21 U.S.C. § 360c (a)(3)(A).

¹⁶ *Codified as* 21 U.S.C. § 360 (k).

¹⁷ 21 U.S.C. § 360c (f)(1)(A)(ii).

¹⁸ 21 U.S.C. § 360e (b)(1)(B).

¹⁹ 21 U.S.C. § 360e (i)(2).

²⁰ Pub. L. No. 101-629, § 4(b)(3), 104 Stat. 4511, 4515-16 (*codified as* 21 U.S.C. § 360e(i)(3)).

²¹ The Agency had no more than 12 months from the effective date of the regulation requiring a device to remain in Class III to establish a schedule for issuing final regulations requiring premarket approval for that device. Pub. L. No. 101-629, § 4(b)(1), 104 Stat. 4511, 4515-16 (*codified as* 21 U.S.C. § 360e(i)(3)).

²² Westlaw Search of the Code of Federal Regulations for phrase "No effective date has been established of the requirement for premarket approval." Conducted January 17, 2011.

²³ GAO Report *at* 46-49.

²⁴ GAO Report.

²⁵ 74 FR 16214, April 9, 2009.

²⁶ 21 U.S.C. § 360c(e)(2)(A).

²⁷ 21 U.S.C. § 360c(e)(1)(A).

²⁸ 76 FR 64224, October 17 at 64224 (citing *Holland Rantos v. United States Department of Health, Education, and Welfare*, 587 F.2d 1173, 1174 n. 1 (D.C. Cir. 1978); *Upjohn v. Finch*, 422 F.2d 944 (6th Cir. 1970); *Bell v. Goddard*, 366 F.2d 177 (7th Cir. 1966)).

²⁹ *Id.* at 64224 (citing *Bell v. Goddard*, supra, 366 F.2d at 181; *Ethicon, Inc. v. FDA*, 762 F.Supp. 382, 389-91 (D.D.C. 1991)).

³⁰ *Id.* at 64224 (citing *Upjohn v. Finch*, supra, 422 F.2d at 951).

³¹ 76 FR 64224, October 17, 2011 at 64224 (citing 21 U.S.C. 360j(c)).

³² 21 U.S.C. § 360c(e)(1).

³³ 76 FR 64224, October 17, 2011 at 624225 (citing 44 FR 13284, March 9, 1979 and 44 FR 13372, March 9, 1979).

³⁴ 76 FR 64224, October 17, 2011 at 624225 (no citation offered).

³⁵ 76 FR 64224, October 17, 2011 at 64225 (citing 52 FR 17732, May 11, 1987).

³⁶ 76 FR 64224, October 17, 2011 at 64225.

³⁷ 76 FR 64224, October 17, 2011.

³⁸ 76 FR 64224, October 17, 2011 at 64225.

³⁹ Food and Drug Administration Center for Devices and Radiological Health, Draft Guidance for Industry and Food and Drug Administration Staff, Class II Special Controls Guidance Document: External Pacemaker Pulse Generator, Issued October 17, 2011 Available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm275701.htm>.

⁴¹ 76 FR 64224, October 17, 2011 at 64225.

⁴² 76 FR 64224, October 17, 2011 at 64225.

⁴³ 76 FR 64224, October 17, 2011 at 64225.

⁴⁴ 76 FR 64224, October 17, 2011 at 64225.

⁴⁵ 76 FR 44872, July 27, 2011.

⁴⁶ 76 FR 64224, October 17, 2011 at 64225.

⁴⁷ Personal Communication, Melissa Burns, Regulatory Advisor, Office of Device Evaluation, Center for Devices and Radiological Health. January 13, 2012.

⁴⁸ 76 FR 64224, October 17, 2011 at 64225.