February 13, 2013

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Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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WO 66, Room 5442
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Re: Classification of Intra-Aortic Balloon Pump (IABP) Devices (21 C.F.R. § 870.3553)

Dear Dr. Hamburg and Dr. Shuren:

Public Citizen, a consumer advocacy group representing more than 300,000 members and supporters nationwide, strongly urges the Food and Drug Administration (FDA) to withdraw its dangerous proposal to reclassify intra-aortic balloon pump (IABP) preamendment Class III devices to Class II (special controls) for certain indications and instead publish a proposed rule that would maintain such devices in the more-regulated Class III and require submission of premarket approval applications (PMAs) for all indications.

The IABP devices must remain categorized as Class III because they are life-sustaining devices for which clinical trials are necessary to provide reasonable assurance of safety and effectiveness. In 1976, the Cardiovascular Devices Panel recommended that IABP devices be categorized as Class III because the devices are life-supporting and because there was insufficient medical and scientific information at the time to establish a standard to assure their safety and effectiveness.

Since 1979, although IABP devices have remained categorized as Class III, they have been provisionally treated from a regulatory standpoint as Class II devices and cleared for marketing under the 510(k) premarket notification process.
On December 5, 2012, during a meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee, the FDA presented a proposal to reclassify IABPs as Class II devices, with special controls, for the following indications:

1) Acute coronary syndrome (ACS)
2) Cardiac and noncardiac surgery
3) Congestive heart failure (CHF)

The FDA proposed maintaining Class III designation, requiring premarket clinical studies, for the following two (and all other) indications:

1) Septic shock
2) Intraoperative pulsatile flow generation

The Circulatory System Devices Panel agreed with the FDA’s proposal on all counts.

We urge the FDA to withdraw its proposal for Class II designation for IABP devices for the three indications above, and to issue a proposed final rule maintaining the Class III designation for these devices and requiring PMA submissions for all indications, based on the arguments presented below.

I. Description of the Device

As currently defined in 21 C.F.R. § 870.3535, an “intra-aortic balloon and control system” (i.e., an IABP) is a device consisting of: (1) an inflatable balloon, placed in the aorta to improve cardiovascular function during certain life-threatening emergencies, and (2) a control system for regulating the inflation and deflation of the balloon with the cardiac cycle, through synchronization with an electrocardiogram.

The IABP is inserted through the femoral artery and is situated in the descending aorta (the main artery leading from the heart). Conventional timing inflates the balloon at the onset of diastole (similar to the aortic valve closure time point), thereby increasing blood flow to the coronary arteries and oxygen delivery to the heart muscle. The balloon remains inflated throughout the diastolic phase, maintaining the increased pressure in the aorta.

The balloon deflates at the onset of systole during isovolumetric contraction or very early in the systolic ejection phase. This deflation causes a decrease in aortic pressure, reducing the pressure that needs to be generated by the left ventricle to achieve ejection of blood through the aortic valve. This decrease in afterload, therefore, decreases the oxygen demand of the myocardium (heart muscle) while increasing blood flow to the systemic circulation (the rest of the body).

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II. General Regulatory Background for Medical Device Classification

The IABP 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 Federal Food, Drug, and Cosmetic Act (FDCA). Preamendment 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. Examples include tongue depressors, elastic bandages, reading glasses and forceps.

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

A device must be categorized as Class III 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. Examples of this high-risk category include internal (implantable) pacemakers and replacement heart valves.

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

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5 GAO Report at 2.
7 Ibid.
8 Ibid.
9 Ibid.
11 21 C.F.R. § 870.3610.
12 21 C.F.R. § 870.3925.
13 21 U.S.C. § 360c (a)(3)(A) (requiring evidence from well-controlled investigations, including one or more clinical investigations where appropriate, by qualified experts).
premarket notification (because the notification requirement is described under section 510(k) of the FDCA).\textsuperscript{14} 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.\textsuperscript{15} No PMA is required for such devices, and animal or bench testing is usually sufficient. In other words, the device need not be tested on human beings before being marketed on a wide scale.\textsuperscript{16}

Although the structure of the FDCA suggests that all new devices that have been categorized as Class III are generally required to submit a PMA, there are numerous exceptions that allow approval without having met 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 either final regulations requiring them to go through the premarket approval process\textsuperscript{17} or, conversely, regulations reclassifying them as Class I or II.\textsuperscript{18}

The process for publishing final regulations requiring premarket approval for these preamendment devices 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. Twenty-three years ago, in 1990, 14 years after the 1976 amendments were passed, 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.\textsuperscript{19} SMDA established a hard deadline of Dec. 1, 1995, for the FDA to publish a regulation to determine whether to reclassify all such devices.\textsuperscript{20}

In 2009, the Government Accountability Office (GAO) published a report reviewing the FDA’s progress in issuing final regulations on the remaining preamendment Class III devices types, finding that in the fiscal years 2003 through 2007, the FDA had cleared 24 types of Class III devices through the 510(k) process.\textsuperscript{21} The GAO recommended that the FDA take steps to issue final rules for the remaining preamendment device types.\textsuperscript{22} In response, on April 9, 2009, the

\textsuperscript{14} Codified as 21 U.S.C. § 360 (k).
\textsuperscript{16} FDA review of 510(k) notifications also differs in other respects from premarket approval. For example, while the 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 Krulewitch, Branch Chief, Division of Epidemiology, Food and Drug Administration. January 25, 2011, at 29-31.
\textsuperscript{17} 21 U.S.C. § 360e (b)(1)(B).
\textsuperscript{18} 21 U.S.C. § 360e (i)(2).
\textsuperscript{20} 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)).
\textsuperscript{21} GAO Report.
\textsuperscript{22} Ibid.
FDA published a “515(i) order” 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 with respect to such devices.

While it has been more than 36 years since Congress first asked the FDA to require premarket approval for Class III devices, and 23 years since Congress ordered the FDA to promptly complete the process of issuing final regulations, as of December 2012, a small but worrisome number (18) of Class III devices, including IABP devices, remained subject to the less-rigorous 510(k) regulatory process due to this particular loophole. Of these, 15 categories include new devices identified by the GAO as having been cleared for market entry recently (between 2003 and 2007).

III. Specific Regulatory History of the IABP

The regulatory classification of IABP devices was initially discussed, along with other devices in use at the time, at the Cardiovascular Device Classification Panel meeting in 1976. The panel recommended a Class III designation for the IABP device due to its life-supporting nature and the panel’s finding that there was insufficient medical and scientific information necessary to assure the safety and efficacy of the device for its indications at that time. Three years later, in 1979, the FDA published a proposed rule following the panel’s recommendations and proposed classification of IABP devices as Class III requiring premarket approval. The rule was made final in 1980.

Despite the Class III designation, the FDA did not subsequently require premarket evidence supporting safety and efficacy of the device, publishing a clarification in 1987 stating that no effective date had been established for the requirement for premarket approval for IABP devices, which remains the case to this day. Therefore, IABP devices have effectively been treated as Class II devices since the 1980 FDA decision.

At the time of the FDA’s initial 1980 Class III classification of IABP devices, the device was only used for acute myocardial infarction leading to early signs of left heart failure and early signs of cardiogenic shock and interim left ventricular support to permit the performance of emergency coronary artery bypass grafting (CABG). In the 32 years since the 1980 FDA classification, the device has been used extensively in clinical practice, with numerous clinical trials and registries demonstrating its efficacy and safety.

23 Section 515(i) of the FDCA, added as part of the SMDA, describes a process requiring manufacturers 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)).
24 74 FR 16214, April 9, 2009.
25 Westlaw Search of the Code of Federal Regulations for phrase “No effective date has been established of the requirement for premarket approval.” Conducted December 17, 2012.
26 GAO Report at 46-49.
27 FDA Executive Summary, page 5. (citing 41 FR 39818 (Sep 16, 1976)).
28 FDA Executive Summary, page 6. (citing 44 FR 13369 (March 9, 1979)).
29 FDA Executive Summary, page 6. (citing 45 FR 7939 (February 5, 1980)).
31 21 C.F.R. § 870.3535.
decision, IABP devices have been cleared through the 510(k) process to treat a multitude of cardiovascular conditions, including the following:\(^{32}\)

- 1980–1989: Refractory ventricular failure, cardiogenic shock, unstable refractory angina, impending infarction, mechanical complications due to acute myocardial infarction (i.e., ventricular septal defect, mitral regurgitation, or papillary muscle rupture), ischemia related intractable ventricular arrhythmias, cardiac support for high-risk general surgical patients, and septic shock.


- 2000–2012: Prophylactic support in preparation for cardiac surgery, postsurgical myocardial dysfunction, cardiac contusion, mechanical bridge to other assist devices, cardiac support following correction of anatomical defects, and support for failed angioplasty and valvuloplasty.

IABP devices for one or more of these additional indications were cleared by the FDA through the 510(k) process, therefore avoiding the requirement for data from well-controlled investigations demonstrating reasonable assurance of safety and effectiveness. Not only were IABP devices cleared for these additional indications without the requirement of new clinical data, but the IABP devices were themselves modified repeatedly over time, with no trials typically necessary to demonstrate “substantial equivalency” with pre-1976 versions of the device.

As noted in the previous section, on April 9, 2009, the FDA issued an order under section 515(i) of the FDCA requiring the manufacturers of 25 of the remaining 27 preamendment Class III devices, including IABP devices, for which regulations requiring submission of PMAs had not yet been issued to submit to the FDA a summary of “… information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices … in order to determine … whether the classification of the device should be revised to require the submission of a PMA [under Class III] … or whether the device should be reclassified into Class I or II.”\(^{33}\)

In response to this request, four of the five manufacturers of IABP devices submitted to the FDA data related to the use of IABP devices. Three of the four manufacturers recommended reclassification of IABP devices to Class II for all indications, with the fourth manufacturer stating that it was “not aware of adequate and valid scientific information that would support reclassification of the device to Class I or II.”\(^{34}\)

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\(^{32}\)FDA Executive Summary, page 5.

\(^{33}\)FDA Executive Summary, page 7. (citing 74 FR 16214 (April 9, 2009)).

\(^{34}\)FDA Executive Summary, page 7. Names of the four IABP manufacturers were not included within the FDA presentation and a search (on Jan. 9, 2013) of the relevant Docket folder for the April 2009 FDA order (74 FR 16214; Docket Folder FDA-2009-M-0101) did not yield any publicly available comments from IABP manufacturers.
The agency reviewed the information submitted by the manufacturers and performed its own systematic review of the medical literature for all clinical studies of IABP devices. Following this review, the FDA proposed the reclassification of IABP as a Class II device, with special controls, for the following indications:\(^{35}\)

1) ACS  
2) Cardiac and noncardiac surgery  
3) CHF

The FDA proposed maintaining Class III designation, requiring premarket clinical studies, for the following two (and all other) indications:

1) Septic shock  
2) Intraoperative pulsatile flow generation

On October 31, 2012, the FDA issued a notice announcing a meeting of the Circulatory System Devices Panel of the FDA’s Medical Devices Advisory Committee to discuss its proposals and make recommendations regarding the classification of IABP devices for various intended uses.\(^{36}\) As noted above, the panel met on December 5, 2012, and agreed with the FDA’s proposals on all counts.

**IV. Legal Standard for Reclassification of Medical Devices**

A device may be changed from Class III to Class II only upon a determination that general controls and special controls together “are sufficient to provide reasonable assurance of safety and effectiveness for such devices”.\(^{37}\) In considering reasonable assurance of safety, the FDA employs a risk/benefit assessment based on valid scientific evidence, as follows:

> [t]here is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.\(^{38}\)

In determining whether a device is effective, the agency looks to whether a “significant portion” of the population targeted for the device will obtain clinically significant results, as follows:

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\(^{35}\) FDA Executive Summary, page 26.  
\(^{38}\) 21 C.F.R. § 860.7(d)(1).
[t]here is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

“Valid scientific evidence” is defined by FDA regulations as “evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device.”

By contrast, the regulations make clear that “[i]solated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.”

V. Efficacy Data for Proposed Class II Reclassification for Certain Indications

Acute coronary syndrome, with and without cardiogenic shock

The treatment of cardiogenic shock with IABP devices in the setting of ACS has become the standard of care, with the American College of Cardiology (ACC) and American Heart Association (AHA) recommending IABP therapy to treat both ST-segment elevation myocardial infarction (STEMI; Class I recommendation for STEMI-related hypotension and shock) and non-ST elevation myocardial infarction (NSTEMI) or unstable angina (Class IIa recommendation for NSTEMI or unstable angina-related persistent ischemia, hemodynamic instability, or mechanical complications).

These recommendations have primarily been based on data from large registries of patients treated with IABP devices. As discussed below, data from randomized trials failed to show a clinical benefit for IABP devices for ACS.

The IABP Benchmark registry enrolled 5,495 patients with acute myocardial infarction (AMI) who had received IABP therapy. IABP devices were most commonly used for AMI with cardiogenic shock (27.3%), hemodynamic support during diagnostic catheterization or

39 21 C.F.R. § 860.7(e)(1).
40 21 C.F.R. § 860.7(c)(2).
41 Ibid.
percutaneous coronary intervention (PCI) (27.2%) for AMI, patients with mechanical complications of AMI (11.7%), and prophylactically before high-risk cardiac surgical intervention in AMI (11.2%). The in-hospital mortality rate for all patients in the registry was 20% (38.7% for patients with cardiogenic shock in the setting of AMI).

A second registry, the National Registry of Myocardial Infarction 2 (NRMI-2), was studied by Chen et al. (2003) for hospital-level correlations between IABP use and AMI mortality in 12,730 patients. Multivariate analysis demonstrated that hospitals with high IABP volume reported lower mortality in patients with AMI and cardiogenic shock compared with intermediate- and low-volume hospitals (OR = 0.71, 95% CI = 0.56 to 0.90). Another analysis of the same registry by Barron et al. (2001) demonstrated an adjusted 18% reduction in hospital mortality (OR = 0.82; 95% CI = 0.72 to 0.93) associated with IABP treatment and thrombolytic therapy in patients with infarct-related cardiogenic shock.

A number of small, randomized controlled trials (RCTs) of IABP therapy have been conducted in subjects with ACS, with two meta-analyses of these RCTs published over the past three years.

Sjauw et al. (2009) analyzed seven RCTs (n = 1,009) of IABP use in STEMI subjects treated with fibrinolysis (two trials), PCI (three trials), or no reperfusion therapy (two trials). IABP did not alter 30-day mortality nor left ventricular ejection fraction but was associated with significantly higher stroke and bleeding rates. Unverzagt et al. (2011) performed a Cochrane meta-analysis of six RCTs (n=190 subjects) on IABP in the setting of AMI with cardiogenic shock. Three studied IABP as an adjunct to standard therapy (fibrinolysis, PCI, or CABG) and three compared IABP to percutaneous left ventricular assist devices (LVADs) in the setting of standard therapy. As with the Sjauw meta-analysis, IABP conferred no benefit on in-hospital, 30-day, 6-month, or 1-year mortality, when compared to either LVAD or standard medical therapy only, although substantially fewer patients in the IABP group had re-occlusion and subsequent revascularization than those in the control groups. Hemodynamic indices showed mixed results with IABP therapy, with some trials demonstrating a worse cardiac index and mean arterial pressure following IABP placement.

The change in the standard of care for AMI from fibrinolysis to PCI led to RCTs investigating the efficacy of IABP primarily in the setting of PCI.

The Intraaortic Balloon Pump in Cardiogenic Shock (IABP SHOCK) trial (analyzed in the Unverzagt et al. meta-analysis) randomized 45 subjects with AMI and cardiogenic shock

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undergoing PCI to IABP or no IABP.\textsuperscript{49} IABP did not significantly improve either the primary morbidity endpoint (serial APACHE-II scoring in the first 4 days) nor hospital mortality (IABP: 36.8\%, no IABP: 28.6\%). IABP also did not improve hemodynamic markers, such as cardiac index or reduction of inflammatory state but significantly improved levels of another biomarker, brain natriuretic peptide. IABP SHOCK had an exceedingly small sample size, however, that precluded any definitive assessment of the clinical or hemodynamic effects of IABP therapy.

The subsequent IABP-SHOCK II trial, published in the October 4, 2012 issue of the \textit{New England Journal of Medicine}, is, to our knowledge, the largest adequately powered RCT to-date of IABP therapy in subjects with ACS and cardiogenic shock.\textsuperscript{50} The IABP-SHOCK II trial randomized 600 subjects with AMI complicated by cardiogenic shock to receive IABP (n = 301) or standard medical therapy (n = 299). All subjects were expected to undergo early revascularization with either PCI or bypass surgery. IABP therapy did not significantly improve mortality at 30 days (39.7\% with IABP vs. 41.3\% without IABP; p = 0.69), nor did it confer any benefit on secondary endpoints, including time to hemodynamic stabilization, length of intensive care unit stay, serum lactate levels, the dose and duration of catecholamine therapy, or renal function. IABP did not seem to confer any additional harm, with rates of major bleeding (3.3\% and 4.4\%; p = 0.51), peripheral ischemic complications (4.3\% and 3.4\%, p = 0.53), sepsis (15.7\% and 20.5\%, p = 0.15), and stroke (0.7\% and 1.7\%, p = 0.28) all statistically similar in IABP and standard therapy subjects, respectively.

\textit{Cardiac and noncardiac surgery}

There is limited evidence from a number of small RCTs that prophylactic IABP therapy is effective in patients undergoing cardiac surgery. A 2011 Cochrane meta-analysis of all RCTs assessing prophylactic IABP therapy in subjects undergoing CABG found that IABP therapy improved in-hospital mortality and cardiac index.\textsuperscript{51} However, the authors noted that there were “many problems with the quality, validity and generalisability of the trials,”\textsuperscript{52} including the fact that all the RCTs were small, five were conducted at a single institution, and all included many patients with emergent, rather than elective, indications for CABG (e.g., AMI with cardiogenic shock) in whom IABP therapy was therapeutic (as in IABP-SHOCK II) rather than prophylactic.\textsuperscript{53} Because of this, the authors cautioned that the “… available evidence is not robust enough to extend the use of [prophylactic] IABP to truly elective, high risk patients [undergoing CABG].”\textsuperscript{54} The use of prophylactic IABP for noncardiac surgery has not been


\textsuperscript{52} \textit{Ibid.} Page 2.

\textsuperscript{53} \textit{Ibid.} Page 7.

\textsuperscript{54} \textit{Ibid.} Page 2.
studied in RCTs. The FDA presented only two case series at the meeting of the Circulatory System Devices Panel, consisting of 11 patients in total in which IABP therapy resulted in favorable cardiac outcomes. The FDA concluded that the evidence on the efficacy of IABP use in cardiac and noncardiac surgery was “conflicting.”

**Congestive heart failure**

The FDA presented four case series at the meeting of the Circulatory System Devices Panel, ranging from two to 43 subjects, of patients with both advanced CHF and acute cardiogenic shock administered IABP therapy. In the largest such case series, Rosenbaum et al. (1994) studied the hemodynamic and end-organ (renal and hepatic) effects of IABP in 43 patients with end-stage CHF who received IABP as a bridge to heart transplant. Most patients (27) had nonischemic CHF, and 16 had ischemic CHF. Hemodynamic parameters, such as cardiac index, filling pressures, and markers of end-organ function improved in the patients following the IABP insertion. However, without a control group, it is impossible to assess the clinical significance of these improvements. The FDA did not present any RCTs assessing the use of IABP devices in subjects with advanced CHF; therefore, it is presumed that no such data were considered in making the determination to reclassify the device to Class II for this indication.

**VI. Safety Concerns with IABP Use**

**MAUDE database review**

According to the FDA’s review of the MAUDE database, there have been a total of 189 deaths and 1,797 injuries reported in relation to IABP use since 2002. Although the number of injury reports has decreased markedly in recent years, the number of annual death reports has increased markedly over the past three years: from a range of five to 18 from 2002 through 2009 to 31 in 2010, 30 in 2011, and 22 through the first ten months of 2012.

As is the case with all voluntary adverse event reports, these figures are likely underestimates of the true number of deaths and injuries associated with these devices. While it is certainly plausible that these figures may overestimate the true number of cases attributable to IABP due to the sicker patient population in whom the devices are generally used, physicians may also be less likely to recognize instances of device-induced morbidity and mortality in such a sick patient population and therefore under-report deaths and injuries associated with these devices.

Moreover, reports of IABP malfunctions, which do not suffer from as much causal uncertainty as clinical outcomes, have increased more sharply, with 536 malfunctions per year reported on

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56 FDA Executive Summary, pages 20-21.
57 FDA Executive Summary, pages 19, 21.
58 FDA Executive Summary, page 22.
60 FDA Executive Summary, page 25.
average since 2008, compared with 129 malfunctions per year reported on average from 2002 to 2007. A total of 3,449 malfunctions of IABP devices have been reported since 2002.

**Literature safety review**

Adverse events reported in association with IABP use were compiled by the FDA from studies published after 2000 into the following table.\(^{62}\)

<table>
<thead>
<tr>
<th>Adverse Event (range of sample sizes)</th>
<th>No time specified</th>
<th>&lt;6 months</th>
<th>6 - &lt;12 months</th>
<th>≥12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-related mortality (16.990 - 22.663)</td>
<td>NR</td>
<td>0.05%</td>
<td>NR</td>
<td>0.05 - 0.07%</td>
</tr>
<tr>
<td>Major limb ischemia/circulatory problem in leg (11 - 22.663)</td>
<td>0 - 5%</td>
<td>0 - 4.3%</td>
<td>0%</td>
<td>0.8 - 2.5%</td>
</tr>
<tr>
<td>Bleeding (11 - 22.663)</td>
<td>1.8 - 9%</td>
<td>0 - 20.6%</td>
<td>1 - 15%</td>
<td>7%</td>
</tr>
<tr>
<td>Bleeding at access site (9.7 - 16.909)</td>
<td>0.6 - 25%</td>
<td>0 - 4.30%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rupture aortic/aortic injury (114)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Femoral artery occlusion (135-181.559)</td>
<td>0.1 - 5.0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Groin hematoma (85)</td>
<td>2.4%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Infection (22 - 19.543)</td>
<td>0.1 - 3.0%</td>
<td>0 - 2.6%</td>
<td>0.10%</td>
<td>0.5 - 9.6%</td>
</tr>
<tr>
<td>Residual failures (38 - 478)</td>
<td>10.14%</td>
<td>1.2 - 17.6%</td>
<td>NR</td>
<td>2.9%</td>
</tr>
<tr>
<td>Hemorrhagic stroke (58 - 549)</td>
<td>0%</td>
<td>0 - 2.6%</td>
<td>NR</td>
<td>7-9%</td>
</tr>
<tr>
<td>Vascular complications (51 - 114)</td>
<td>NR</td>
<td>5.9 - 13.7%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pseudoaneurysm (85 - 181.599)</td>
<td>4 - 12%</td>
<td>4.0%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Visceral thrombus (5.495)</td>
<td>NR</td>
<td>NR</td>
<td>0.1%</td>
<td>NR</td>
</tr>
<tr>
<td>Amputation (5,495)</td>
<td>NR</td>
<td>NR</td>
<td>0.1%</td>
<td>NR</td>
</tr>
<tr>
<td>Phlebitis (11-60)</td>
<td>0%</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

| NR – Not reported |

In the absence of a consistent control group, it is difficult to ascribe causality of any of these adverse events to the IABP device (with the exception of “device-related mortality,” which ranged from 0.05 to 0.07%). However, in IABP-SHOCK II, the largest randomized trial to date of IABP therapy, the insertion of an IABP did not significantly increase the rate of a number of adverse events, including major bleeding (3.3% with IABP and 4.4% without IABP; p = 0.51), peripheral ischemic complications (4.3% and 3.4%, p = 0.53), sepsis (15.7% and 20.5%, p = 0.15), and stroke (0.7% and 1.7%, p = 0.28) relative to patients on standard medical therapy.\(^{63}\)

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\(^{61}\) Ibid.

\(^{62}\) FDA Executive Summary, pages 10, 13.

VII. Discussion of, and Arguments Against, FDA Rationale for Class II Classification for Certain Indications

The FDA’s rationale for reclassifying IABP devices into Class II for ACS, cardiac and noncardiac surgery, and CHF is discussed below as well as countered for each indication.

ACS

The FDA’s recommendation for Class II designation for ACS, just two months after the publication of the IABP-SHOCK II trial, is inexplicable, considering that the “valid scientific evidence” in this case definitively shows no “probable benefit to health” from the use of IABP devices. (Although the trial seemed to show no “unreasonable risk” to patients, the safety profile of the device becomes irrelevant in the absence of benefit.) Despite these unequivocal findings, as well as those of earlier RCTs, the FDA concluded in its review of the evidence that:

In early data from trials of AMI complicated by cardiogenic shock treated with fibrinolysis, IABP treatment demonstrated improvement in mortality. In more recent trials of this patient population [AMI with cardiogenic shock] treated by early revascularization using PCI, as opposed to fibrinolysis, IABP treatment may have a reduced benefit. Trials performed to investigate the benefit of IABP using the modern standard of care have been underpowered to demonstrate improvement, or have had other limitations, such as variability in the timing of IABP usage.

IABP did not demonstrate a “reduced benefit,” but rather no benefit at all in patients undergoing PCI in the IABP-SHOCK II trial. Furthermore, there could not be a “reduced” benefit in this patient population in the first instance, as IABP therapy did not significantly improve mortality in patients treated with fibrinolysis in earlier RCTs.

Given that the standard of care for AMI has shifted from fibrinolysis to PCI, the IABP-SHOCK II trial provides the best possible evidence of the current “target population” and “intended uses and conditions of use” for this indication. It is clear from the results of that trial that the device shows no benefit under these conditions and will therefore not “provide clinically significant results” for its intended uses and conditions of use, and cannot be considered effective for the AMI with cardiogenic shock indication.

The FDA’s attempt to downplay the importance of the more recent RCTs that used the “modern standard of care” (i.e., PCI) by asserting that they were “underpowered” is patently misleading, as it ignores the fact that the IABP-SHOCK II trial was, in fact, adequately powered to detect a 12% difference in 30-day mortality. Moreover, the variability in the timing of IABP insertion (before or after revascularization) cannot be used to explain away the lack of benefit in the

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64 FDA Executive Summary, page 19.
IABP-SHOCK II trial, as timing of insertion was not associated with different 30-day mortality rates in that trial.\(^{67}\)

Finally, and most importantly, if the FDA believes that further studies are needed to demonstrate benefits by varying the timing of IABP usage or adjusting other features, the FDA should elicit such studies by designating the device as Class III and requiring PMA submissions that will include data from well-designed RCTs that can demonstrate reasonable assurance of efficacy prior to granting further approvals for this indication.

It is precisely because more granularity is needed regarding which patient populations could benefit from IABP therapy that more, not fewer, trials are necessary to provide reasonable assurance of effectiveness prior to marketing IABP devices for use in patients with AMI. Class II designation for this indication will expose patients to this device on a wide scale, without adequate evidence of safety or effectiveness, and will make it far less likely that such studies will be undertaken in the future.

**Cardiac and noncardiac surgery**

The FDA summarizes the clinical evidence on the safety and efficacy of IABP devices in cardiac and noncardiac surgery and justifies its Class II designation as follows:\(^{68}\)

> In summary, the literature regarding the effectiveness of IABP in cardiac and non-cardiac surgery is conflicting, with some studies demonstrating utility and others which are equivocal or fail to demonstrate effectiveness. Demonstrating utility represents a challenge of clinical trial design, with well executed trials, free of crossover and bias, with carefully chosen patient selection criteria and endpoints.

Thus, the agency acknowledges that the evidence of IABP use for this indication is “conflicting” and that more rigorous trials, although “challeng[ing],” are necessary to demonstrate its effectiveness. The FDA’s assertion that such trials are uniquely “challenging” does not accord with the fact that trials of prophylactic IABP insertion, in presumably stable patients prior to surgery, would, in all likelihood, be less “challenging” than trials, such as IABP-SHOCK II, of therapeutic IABP use in patients with emergent conditions, such as cardiogenic shock. Nevertheless, if trials of IABP insertion in surgical patients are indeed more “challenging” according to the FDA, then an incentive, in the form of premarket clearance under Class III, for companies to undertake such difficult trials becomes even more imperative.

Finally, the wide-ranging scope of the proposed Class II designation, covering all patients undergoing any type of surgery, is clearly out of line with the FDA’s own assertion that only certain (unspecified) surgical patient populations might benefit from the therapy:\(^{69}\)

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\(^{67}\) See *Ibid*, page 1293.

\(^{68}\) FDA Executive Summary, page 21.

\(^{69}\) FDA Executive Summary, page 21.
Given the benefit demonstrated in some such trials, it is clear that certain groups of patients with specific clinical indicators and features of surgical risk may benefit from IABP use for this group of indications.

The FDA’s finding that “certain groups of patients… may benefit” does not meet the applicable regulatory standard requiring the device to provide “clinically significant results” in a “significant portion of the target population.” The FDA’s rationale for Class II designation for this indication is therefore not only unwise but highly speculative.

**CHF**

Since the FDA did not present any RCTs assessing the use of IABP devices in patients with advanced CHF, it is therefore presumed that the agency did not rely on any such data in making its proposed determination to reclassify the device into Class II. The FDA instead appears comfortable relying on case series and “expert consensus” for the CHF indication as a substitute for rigorous clinical trials:

Clinical practice and expert consensus has followed from this evolution of the device use, and it is accepted as effective based on this background and the prolonged history of use.

It is astonishing that the FDA should place such faith in “expert consensus” a mere two months following the publication of the IABP-SHOCK II trial that overturned decades of such consensus regarding routine IABP use for AMI and cardiogenic shock based on registry data, small observation studies, and case series. (In fact, the purported evidence base for AMI with cardiogenic shock, ultimately overturned by several RCTs, including the IABP-SHOCK II trial, was much more robust than that which exists for CHF.)

A New England Journal of Medicine editorial, published in response to IABP-SHOCK II’s findings, alluded to the danger of relying on such expert consensus in formulating clinical guidelines:

Despite a lack of robust data from outcomes trials and meta-analyses that have shown limited efficacy, international guidelines endorse the use of IABP for treating post-myocardial infarction shock, with a class I [highest level] recommendation…Members of guideline committees and clinicians should take note of another example of a recommendation that is based on insufficient data.

Because consensus has an unfortunate way of validating certain medical practices prematurely and without justification, more — not fewer — trials are needed for each IABP indication proposed by the FDA. As with the cardiac and noncardiac surgical indication, removing the requirement for clinical data through a Class II designation makes it far less likely that trials on the scale of IABP-SHOCK II (or even smaller RCTs) will be undertaken to definitively determine the efficacy and safety of IABP for CHF.

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70 FDA Executive Summary, page 22.
Evidence on the safety and efficacy of one or more prior versions of this life-sustaining device does not obviate the need for FDA review under Class III for future versions of the device

There is clearly a lack of sufficient evidence to conclude that any of the IABP devices tested for any of the indications the FDA has proposed for reclassification into Class II have demonstrated reasonable assurance of safety and effectiveness for their intended use. This includes the IABP devices tested in the IABP-SHOCK II trial for AMI with cardiogenic shock. However, even if the existing evidence were to establish reasonable assurance of safety and efficacy on any of the devices tested for indications proposed for reclassification into Class II, that information is beside the point. The question is not whether any of the previously tested versions of the device were safe and effective. Instead, the question is whether moving forward, the FDA can reasonably be assured of the safety and efficacy of new IABP devices without requiring a PMA, including data from testing the new device in a well-controlled clinical trial.

Given the fact that IABP devices are intended for life-sustaining indications, are used in technically complex surgery, and have rates of reported malfunctions that have increased rapidly in recent years, lab testing and the proposed “special controls”72 are not sufficient to demonstrate that the newer versions of these devices will be safe and effective when used in clinical practice, even if prior versions of the devices were safe and effective (a fact that has not been established). Rather than relying on bench testing and analogies to prior devices, the FDA should require that each new version of the device be tested in well-controlled clinical trials prior to being approved for mass marketing. Only by testing each new version of the device can the FDA ensure that newer versions are as safe and effective as previously approved counterparts.

In addition, placing different regulatory thresholds on the various indications for IABP use makes it more likely, if not certain, that off-label use of IABP therapy for the remaining (and future) Class III indications will become widespread. Few manufacturers will pursue expensive clinical trials to support Class III approval for relatively rare indications if the devices can readily be used off-label for the Class III indications, without clinical data, and because most of the revenue from IABP devices will undoubtedly come from the much more common, and untested, Class II indications of ACS, CHF, and cardiac and noncardiac surgery.

VIII. Summary of Arguments and Requests

Public Citizen agrees with the FDA’s proposed decision to maintain a Class III designation and require PMAs for IABP devices indicated for septic shock and intraoperative pulsatile flow generation. Based on the absence of safety and efficacy data for these indications in the medical literature, the FDA reasonably concluded that submission of evidence from well-controlled

72 The FDA’s proposed special controls focus exclusively on ways to ensure device integrity and functionality and nonclinical performance evaluations to address safety concerns, while ignoring efficacy considerations by failing to include a requirement for post-marketing clinical data of any IABP device (current or future). In addition, the labeling specifications do not require companies to distinguish between Class III and Class II indications for the device within the label, making off-label use for Class III indications even more likely. See FDA Executive Summary, pages 28-30.
investigations was therefore necessary prior to approving the marketing of these devices for such indications.

Unfortunately, the FDA did not employ the same logic in proposing reclassification of IABP devices to Class II for the ACS, cardiac and noncardiac surgery, and CHF indications. The FDA’s recommendations on reclassification of IABP therapy to Class II for these indications ignore and contradict existing evidence. Given the absence of adequate evidence confirming the safety and efficacy of IABP devices for CHF and surgery, and the strong evidence of a lack of efficacy for ACS, in addition to the troubling safety risks of IABP therapy, the special controls proposed by the FDA will not be sufficient to provide adequate assurance of safety and efficacy for these devices.

Therefore, the FDA should withdraw the proposal for Class II designation for these indications and should instead publish a proposed final rule maintaining the Class III designation for these devices and requiring PMA submissions for all IABP indications.

Thank you for taking our comments into consideration.

Sincerely,

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