April 8, 2013

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WO 2200
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Re: Reclassification of Membrane Lung for Long-Term Pulmonary Support; Redesignation as Extracorporeal Circuit and Accessories for Long-Term Pulmonary/Cardiac Support [21 CFR Parts 868 and 870; Docket No. FDA-2012-N-1174]

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 the preamendment device known as “membrane lung for long-term pulmonary support” used in extracorporeal membrane oxygenation (ECMO) procedures from their current Class III designation 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.

ECMO devices must remain categorized as Class III devices for all indications because they are life-sustaining devices for which clinical trials are necessary to provide reasonable assurance of safety and effectiveness. If trials have already been conducted and deemed sufficient to provide such assurance, the FDA should formally review these data as part of PMAs, consistent with the devices’ current Class III designation.

Instead, on January 8, 2013, the FDA published a notice of proposed order (NPO) to reclassify ECMO devices as Class II devices, with special controls, “…when an acute (reversible)
condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in [the following] conditions:

1) where imminent death is threatened by cardiopulmonary failure in neonates and infants; or
2) where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery.¹

We urge the FDA to withdraw its proposal for Class II designation for ECMO devices for the indications above, and to issue a 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 Device²

As currently defined in 21 C.F.R. § 868.5610, a membrane lung for long-term pulmonary support is “...a device used to provide to a patient extracorporeal blood oxygenation for longer than 24 hours.” ECMO devices provide extracorporeal circulatory support and/or physiologic gas exchange of a patient’s blood when an acute, reversible condition prevents the patient’s own body from performing these functions needed to sustain life. According to the FDA, ECMO procedures are intended for “…patients with acute reversible respiratory or cardiac failure, unresponsive to optimal ventilation and/or pharmacologic management.”³

In its NPO of January 8, 2013, the FDA explains that the membrane lung for long-term pulmonary support refers specifically to the oxygenator component of an ECMO circuit used during long-term procedures. However, the FDA is considering all device components used in ECMO procedures in the scope of its NPO because it believes that the components can be appropriately regulated using the same set of regulatory controls as the oxygenator.

These component devices include, but are not limited to, an oxygenator, blood pump, cannulae, heat exchanger, tubing, filters, monitors/detectors, and other accessories. The circuit components and configuration of the circuit (e.g., arteriovenous, veno-venous, or veno-arterial) vary based on the needs of the individual patient or the condition being treated. (All device components, including the oxygenator employed in ECMO procedures are here referred to collectively as “ECMO devices.”)

II. Regulatory Background, Legal Standard for Reclassification, and Specific Regulatory History of the Device

A. General regulatory background

² Ibid.
³ Ibid.
ECMO devices are a type of Class III medical device that was on the U.S. market prior to the passage of the 1976 Medical Device Amendments to the Food, Drug and Cosmetics Act (FDCA) (“the 1976 Amendments”). As “Pre-amendment” Class III device types, ECMO devices are subject to a unique regulatory history that has permitted them to be marketed without evidence of safety and efficacy from well-controlled clinical trials.

The 1976 Amendments established the current framework for device regulation by the FDA. This law grouped devices by type and sorted each device type into one of three regulatory classes, referred to as Classes I, II, and III. Under this regulatory framework, device types are subject to an increasingly rigorous set of regulatory requirements depending on their class.

Devices in Class I are subject to the least rigorous regulatory requirements. These devices include low-risk devices, such as tongue depressors, elastic bandages, or reading glasses. Class I devices need not be cleared or approved by the FDA prior to being sold in the U.S., although they are still subject to other regulatory requirements called general controls.

Devices in Class II are subject to slightly more rigorous regulatory requirements. These devices include more complex or higher-risk items such as electrocardiographs, powered bone drills, and mercury thermometers. New Class II devices generally must be cleared by the FDA prior to being sold in the U.S. To obtain premarket clearance, the manufacturer of a Class II device must submit a notification to the FDA under section 510(k) of the FDCA and establish that the device is “substantially equivalent” to another Class II device already on the market in the U.S. (known as a “predicate device”). Such 510(k) clearances generally involve animal or bench testing to prove substantial equivalence, but they do not require that the company test the safety and effectiveness of the device in well-controlled clinical investigations. Thus, a new Class II device can be cleared based on a showing of substantial equivalence to a previously cleared predicate device that itself was not proven safe or effective in clinical trials.

The most stringent regulatory process is reserved for Class III devices, which include implantable, high-risk, or life-sustaining devices such as silicone breast implants, implantable pacemakers, certain types of fetal monitors used in labor, and replacement heart valves.

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4 21 C.F.R. § 880.6230.
5 21 C.F.R. § 880.5075.
6 21 C.F.R. § 886.5844.
7 21 U.S.C. § 360(l). However, Class I devices that are “of substantial importance in preventing impairment of human health,” or that present “potential unreasonable risk of illness or injury” are also subject to 510(k) notice requirements. Ibid.
8 21 C.F.R. § 870.2340.
9 21 C.F.R. § 872.4120.
10 21 C.F.R. § 880.2920.
14 21 C.F.R. § 870.3610.
In order to introduce a new device from a Class III device type into the U.S. market, a device manufacturer generally must submit a PMA that includes evidence from well-controlled investigations (typically with clinical data from at least one well controlled clinical trial in humans) providing reasonable assurance that the new device is safe and effective.\(^\text{18}\)

In addition to creating the three regulatory classes, the 1976 Amendments laid out a process by which the FDA would initially classify each device. Congress included in this process a requirement that the FDA consult with an advisory panel of qualified experts prior to making the final determination in classifying each device. The composition and procedures to be used by such panels were laid out in section 513, subsection (b) of the FDCA.\(^\text{19}\)

The 1976 Amendments did not require that manufacturers of device types in commercial distribution before the 1976 Amendments (the “Pre-amendment Device Types”) submit PMAs immediately. Instead, makers of these Pre-amendment Device Types could continue to use the 510(k) premarket notification process until such time as the FDA published final regulations requiring PMAs for that device type.\(^\text{20}\)

The process for publishing final regulations requiring premarket approval for the Pre-amendment Device Types has been slow, and as a result, many device types that were initially classified into Class III have languished in a regulatory gray area, undergoing 510(k) premarket clearance rather than the stricter requirements envisioned by Congress for Class III devices. In 1990, Congress passed the Safe Medical Devices Act (SMDA), amending Section 515(i) of the FDCA and requiring the FDA to order all manufacturers of Pre-amendment Device Types to submit safety and effectiveness information to facilitate finalizing rules for these devices or reclassifying them into Class I or II. SMDA also directed the FDA to establish a schedule to finalize PMA requirements for the remaining Pre-amendment Class III devices and established a hard deadline of December 1, 1995, for completing the process.\(^\text{21}\)

In April 1994, the FDA proposed a strategy for prioritizing actions on the remaining 117 Pre-amendment Class III Device Types for which final regulations had not yet been issued.\(^\text{22}\) Over the next decade, the FDA reclassified or issued final rules requiring PMAs for many of the remaining Pre-amendment Device Types. Nevertheless, by 2009, there remained 27 types of Class III devices that still had no final regulations requiring PMAs.\(^\text{23}\) On April 9, 2009, the FDA published the order required under Section 515(i) (“515(i) order”) requiring the manufacturers of

\(^{15}\) 21 C.F.R. § 870.3925.
\(^{16}\) 21 C.F.R. § 884.2620.
\(^{17}\) 21 C.F.R. § 878.3540.
\(^{18}\) 21 U.S.C. § 360c (a)(3)(A) (requiring evidence from well-controlled investigations, including 1 or more clinical investigations where appropriate, by qualified experts).
\(^{19}\) Codified as 21 U.S.C. § 360c(b).
\(^{21}\) 21 U.S.C. § 360e (b).
\(^{22}\) Pub. L. No. 101-629, § 4(b), 104 Stat. 4511, 4515-17 (codified as 21 U.S.C. §§ 360e(i)).
25 of the 27 remaining Class III Pre-amendment Device Types to submit “… 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.”

B. Legal standard for reclassification

The standard governing classification of a device into Class III is described in Section 513(a) of the Food, Drug and Cosmetics Act, codified as 21 U.S.C. § 360c(a). A device is to be classified as Class III and subject to premarket approval if:

(i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and

(ii) (I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (II) presents a potential unreasonable risk of illness or injury.

“General controls” are a set of regulatory standards promulgated under the FDA’s general authority to regulate adulterated drugs and devices, impose labeling and advertising requirements, register and inspect manufacturing facilities, impose good manufacturing practice requirements, and take other regulatory actions. “Special controls” are more specific requirements that can include performance standards, post-market surveillance, patient registries, or specific FDA guidelines.

Where a device has already been classified into Class III, it may be reclassified under Section 513(e) of the FDCA, codified as 21 U.S.C. §§ 360c(e). This section was recently amended under the Food and Drug Administration Safety and Innovation Act (“FDASIA”), enacted on July 9, 2012. The FDASIA authorized the FDA to reclassify a device through an administrative order, waiving the usual administrative rulemaking process and imposing a new set of administrative requirements:

Based on new information respecting a device, the Secretary may, upon the initiative of the Secretary or upon petition of an interested person, change the classification of such device, . . . by administrative order published in the Federal Register following

24 74 FR 16214 (April 9, 2009).
26 21 U.S.C. §§ 360c(a)(1), 351, 352, 360, 360f, 360h, 360i, and 360j.
29 The decision to reclassify may be delegated to the Director of the Center for Devices and Radiological Health (CDRH), acting in consultation with the FDA Commissioner, but may not be delegated to a lower official. Pub. L. 112-144, Codified as 21 U.S.C. § 360c(e)(1)(B).
publication of a proposed reclassification order in the Federal Register, a meeting of a
device classification panel described in subsection (b), and consideration of comments to
a public docket . . .

“New information” can include additional information not available at the time of the initial
classification, as well as evidence previously submitted to the agency when considered in light of
additional data or knowledge drawn from clinical experience. The new information must be
“valid scientific evidence” as defined in section 513(a) of the FDCA and 21 CFR § 860.7(c)(2).

The party seeking to reclassify the device bears the burden of proving that the device meets the
requirements for reclassification. The standard for reclassification is provided in Section 513(e)
which states that the Secretary or Center for Devices and Radiological Health (CDRH) director
and FDA commissioner may reclassify the device:

… to class II if the Secretary [or CDRH Director] determines that special controls would
provide reasonable assurance of the safety and effectiveness of the device and that
general controls would not provide reasonable assurance of the safety and effectiveness
of the device, or
… to class I if the Secretary determines that general controls would provide reasonable
assurance of the safety and effectiveness of the device.

C. Specific regulatory history of ECMO devices

In 1979, the FDA published a proposed rule for classification of ECMO devices as Class III
requiring premarket approval. The rule was made final in 1982. The FDA’s proposal
followed the recommendation of the Anesthesiology Device Classification Panel for a Class III
designation for the ECMO device due to its life-sustaining and life-supporting nature and the
panel’s finding that there was insufficient medical and scientific information necessary to ensure
the safety and efficacy of the device.

Despite the Class III designation, the FDA did not subsequently require PMAs for ECMO
devices, publishing a clarification in 1987 stating that no effective date had been established for
the requirement for premarket approval for such devices, which remains the case to this day.

32 21 U.S.C. § 360c(e).
34 21 U.S.C. § 360c(e).
36 Ibid (citing 47 FR 31130 (July 16, 1982)).
38 Ibid. (citing 52 FR 17732 at 17735; (May 11, 1987)).
Because the FDA neglected to issue a final order requiring premarket approval, ECMO devices have effectively been treated as Class II devices by default throughout their regulatory history.

As noted in the previous section, on April 9, 2009, the FDA issued its order under section 515(i) of the FDCA requiring the manufacturers of ECMO devices and other remaining preamendment Class III devices, to submit information to the FDA to assist the agency in determining whether to require PMAs or reclassify the devices into Class II.40

In response to this request, one manufacturer of ECMO devices submitted to the FDA data related to the use of ECMO devices and, on January 8, 2013, the FDA issued an NPO proposing recategorization of ECMO devices from Class III to Class II for “…conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery.”41

III. Efficacy of ECMO Therapy for the Proposed Class II Indications and Other Uses of ECMO Devices

A. Neonates with severe respiratory failure

The efficacy of ECMO therapy in neonates with severe respiratory failure has been established in four randomized, controlled trials (RCTs), conducted in the 1980s and 1990s, that were reviewed in a Cochrane meta-analysis published in 2008.42 The four studies were conducted in term or near-term (gestational age > 34 weeks) neonates with severe but potentially reversible respiratory failure, defined as PaO₂ < 40 mmHg or pH < 7.15 for two hours. All four employed venoarterial ECMO procedures, with one trial performing venoarterial ECMO for hemodynamically unstable patients and venovenous ECMO for other patients.

On the primary outcome of death before discharge (the only outcome reported across all four trials), there was a “…strong benefit of ECMO on mortality (typical RR 0.44; 95% CI: 0.31–0.61), especially for babies without congenital diaphragmatic hernia (typical RR 0.33, 95% CI: 0.21–0.53).”43 The authors of the meta-analysis noted the narrow confidence intervals as a measure of the relative certainty with which the trials had demonstrated this benefit. The absolute reduction in the rate of mortality at discharge with ECMO therapy was -0.32 (95% CI: 0.44 to -0.20), meaning that, for every three babies treated with ECMO rather than conventional ventilation, one death was prevented by the time of discharge.

40 74 FR 16214 (April 9, 2009).
43 Ibid.
By far the largest trial evaluated by the reviewers was the U.K. collaborative ECMO trial conducted between 1993 and 1995 in neonates with severe respiratory failure.\textsuperscript{44} Investigators allocated 185 neonates (gestational age ≥ 35 weeks) to consideration for treatment with ECMO at one of five specialist centers or continuation of intensive conventional management at the original hospital. The primary outcome was death or severe disability at one year of age.

Results showed that infants allocated to ECMO therapy died at significantly lower rates than infants allocated to conventional therapy on all measures: death before discharge (29% absolute reduction; RR 0.51 [95% CI: 0.36–0.73]), known death before age one year (26% absolute reduction; RR 0.55 [95% CI: 0.39–0.77]), and for infants reenrolled by December 1, 1994, lower rates of death or severe disability at one year (29% absolute reduction; RR 0.54 [95% CI: 0.36–0.80]). Follow-up evaluations demonstrated a persistence of the survival benefit at four years (RR 0.62; 95% CI: 0.45–0.86) and seven years (RR 0.64; 95% CI: 0.47–0.86).

Thus, it seems that ECMO devices, at least the versions dating from the 1980s-90s (the time period in which the four RCTs were conducted), have proven effective in increasing survival in term and near-term neonates with severe, reversible respiratory failure. We do not have sufficient knowledge of the design characteristics or functionality of devices that have come on the market since the 1990s to discern to what extent ECMO devices used in neonates today resemble the prior versions that demonstrated effectiveness in curbing neonate mortality.

B. Failure to wean from cardiopulmonary bypass due to cardiopulmonary failure

ECMO is used in patients who fail to wean from cardiopulmonary bypass following cardiac surgery due to either cardiopulmonary failure or cardiac failure alone (a condition known as postcardiotomy cardiogenic shock, or PCS, which can be related to failure to wean from bypass or can occur due to some other cause). In cases of cardiopulmonary failure, ECMO is cited as a preferred therapy because it temporarily replaces both cardiac and pulmonary functions.\textsuperscript{45}

There have been no RCTs assessing the efficacy and safety of ECMO therapy in patients who fail to wean from cardiopulmonary bypass. ECMO therapy is one of several pharmacologic and mechanical interventions commonly employed in such patients.\textsuperscript{46} The absence of RCTs evaluating the relative benefits and risks of these therapies precludes assessment of the benefit-to-risk profile of ECMO therapy compared with other therapies in these patients. Such studies are presumably challenging due to the unpredictability of when such therapies will be necessary and the acuity of the patients, for whom therapeutic decisions must be made within minutes. The high morbidity and mortality rates in this population, as well as the consequent need to often administer more than one intervention simultaneously, add to the difficulty of

\textsuperscript{44} UK Collaborative ECMO Trail Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. Lancet. 1996 Jul 13;348(9020):75-82.
\textsuperscript{46} Ibid.
conducting prospective trials. In some cases, ECMO is given only after inotropic agents and other mechanical agents have failed to resolve PCS.\(^47\)

To our knowledge, a report by Rastan et al. (2010) is the largest case series to date of ECMO therapy in adult patients with difficulty weaning from cardiopulmonary bypass. A total of 517 adult patients received ECMO therapy for PCS, though only 41.9% of the patients received ECMO during or immediately after weaning off cardiopulmonary bypass, while the rest received ECMO for complications following successful weaning from cardiopulmonary bypass.\(^48\) Patients had undergone isolated coronary artery bypass grafting (37.4%), isolated valve surgery (14.3%), coronary artery bypass grafting plus valve surgery (16.8%), thoracic organ transplantation (6.5%), or other cardiac surgeries (25.0%).

ECMO support was given for a mean of 3.28 days. Intra-aortic balloon pumps were implanted in 74.1% of patients. The majority (63.5%) of patients were successfully weaned from ECMO and most (56.4%) survived for longer than 24 hours following ECMO discontinuation. However, in-hospital mortality was high at 75.2%, mostly from cardiac causes, with a 6-month survival rate of only 17.6%. Complications possibly attributable to ECMO therapy included leg ischemia in 5.4% of all patients (19.9% of legs with femoral artery cannulation) and excessive bleeding, possibly due to systemic anticoagulation necessary for ECMO therapy, led to rethoracotomy in 58% of patients.

A smaller case series of 219 consecutive patients with PCS treated with ECMO reported similar results.\(^49\) Sixty percent of patients were successfully weaned from ECMO, 24% survived to hospital discharge, and 17% survived to five years. Complications included leg ischemia rates of 13% and rates of rethoracotomy due to excessive bleeding of 62%.

C. Uses of ECMO therapy not mentioned in FDA proposal

In its NPO, the FDA makes no mention of uses of ECMO devices other than those indications proposed for Class II designation.\(^50\) Commonly encountered uses in the literature include adults with acute respiratory distress syndrome (ARDS),\(^51\) children (non-neonates) with respiratory or...

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cardiac failure, adults with cardiac failure unrelated to cardiac surgery, and patients in cardiac arrest.\(^5\)

To our knowledge, adults with ARDS represent the only patient population outside of neonates in whom ECMO therapy has been studied in RCTs. A 2008 systematic review and meta-analysis of two small RCTs, in addition to three nonrandomized cohort studies, found that ECMO therapy was not associated with an improvement in survival rates compared with conventional therapy in adults with ARDS.\(^5\)

The subsequent publication of the larger (180 patients) Conventional Ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial in 2009 overturned these previous findings and found that ECMO therapy improved disability-free survival at six months when compared with conventional ventilation therapy.\(^5\) Some experts were cautious about CESAR’s findings of improved mortality with ECMO therapy, due primarily to the fact that 19% of patients assigned to the ECMO arm never received ECMO therapy but still survived at significantly higher rates than their counterparts assigned to conventional therapy.\(^5\) This suggested that the ECMO patients, simply by virtue of their referral to a tertiary care medical center, may have received superior care than patients assigned to conventional therapy, who were treated at smaller and possibly less-equipped hospitals. This was compounded by the fact that treatment for patients in the conventional therapy arm was not standardized.\(^5\) Given this and other potential limitations of the CESAR trial, more studies are needed to determine the true effect size of ECMO therapy in adults with ARDS.

Evidence from RCTs of the efficacy and safety of ECMO therapy in the other patient populations commonly treated with ECMO is still lacking.

### IV. Safety Concerns of ECMO Devices

#### A. Safety issues outlined by the FDA in its NPO

The following safety concerns were outlined by the FDA in its NPO (taken verbatim from the FDA’s NPO of January 8, 2013):\(^5\)


- Thrombocytopenia. Blood platelets important to the clotting cascade may be damaged by use of the device, resulting in a tendency toward increased bleeding.
- Hemolysis. Red blood cells may be damaged by mechanical, material, or surface features of the extracorporeal circuit.
- Thrombosis/thromboembolism. Blood clots may form within the extracorporeal circuit due to inadequate blood flow.
- Hemorrhage. To keep blood from clotting in the extracorporeal circuit, anticoagulants are generally used and may cause increased bleeding during the procedure.
- Hemodilution. Dilution of the patient's blood may be caused by the priming of the ECMO circuit.
- Inadequate gas exchange. Mechanical failure of the circuit components may result in inadequate gas exchange.
- Loss of mechanical integrity. Weakness in the connections or construction of the circuit components could lead to leaks in the extracorporeal circuit.
- Gas embolism. Air may be introduced into the extracorporeal circuit and result in a gas embolism.
- Adverse tissue reaction. The patient-contacting materials of the device may cause an adverse immunological or allergic reaction in a patient if the materials are not biocompatible.
- Infection. Defects in the design or construction of the device preventing adequate cleaning and/or sterilization may allow pathogenic organisms to be introduced and may result in infection.
- Mechanical injury to access vessels. Mechanical injury to vessels may be caused acutely during access, or over time due to the long-term duration of use.

In its discussion of these risks, the FDA cites a recent analysis of pediatric patients within the Extracorporeal Life Support Organization registry, which has tracked ECMO use in adults and children since the mid-1980s. Fleming et al. analyzed all 28,171 cases within the registry of ECMO use in neonates and children under 18 years of age from 1987 – 2006 to determine the prevalence of complications of devices used in ECMO procedures. The authors found that 4,187 ECMO runs (14.9% of all runs) performed in children during that time were associated with at least one mechanical failure, with rates in the most recent period, 1997 – 2006 (13.8%), only slightly improved than in the first decade studied, 1987 – 1996 (15.8%). However, any injuries or deaths resulting from these complications were not reported in this analysis.

B. Adverse events reported in the largest RCTs of ECMO therapy

The lack of controlled studies for many of the conditions for which ECMO therapy is used makes it difficult to ascribe significance to these risks in isolation without considering the devices’ potential efficacy and the known risks of alternative therapies, especially when considering the morbidity of the patient populations in whom the devices are used.

59 Ibid.
The CESAR trial reported a single adverse event attributable to ECMO therapy, a failed vessel cannulation resulting in perforation of the vessel, which investigators felt contributed to the patient’s death. The published report on the U.K. ECMO trial did not include complication or adverse event rates, mentioning only that one infant died after a failed vessel cannulation, but not whether this event contributed to the patient’s outcome.

C. Post-marketing adverse event and product malfunction reports to the MAUDE database

A search of the MAUDE database for adverse event reports submitted within the past 10 years (April 1, 2003 to April 2, 2013) returned a total of 26 reports of device malfunctions (e.g., circuit leaks) and adverse events. Four patient deaths were reported, three following the discovery of clotted blood in the ECMO circuit and one following an abrupt decrease in flow within the circuit, but it was not reported whether these events contributed to the patients’ deaths. One patient had to undergo surgery “sooner than desired” due to air found within the ECMO circuit.

It should be noted that our search considerably underestimated the number of adverse event reports for ECMO devices in the MAUDE database. Still, the paucity of reports is unusual for a device that comes with such a large number of risks and for which a rate of malfunction of approximately 15% has been reported in children and neonates. As is the case with all voluntary adverse event reports to the MAUDE database, these figures are likely underestimates of the true number of deaths and injuries associated with these devices. It also is possible that physicians may be less likely to recognize instances of device-induced morbidity and mortality in the very sick patient populations in whom ECMO devices are used and therefore under-report deaths and injuries associated with these devices. We could not find information as to how many ECMO devices are currently on the market.

62 Our search underestimates the number of reports. For one, the MAUDE database was searched (on April 2, 2013) for reports submitted to the FDA only during the most recent 10-year period (April 1, 2003 through April 2, 2013). In addition, we limited our search to two ECMO component devices (i.e. “product classes”): 1) “membrane lung (long-term) pulmonary support”, which yielded 14 reports of ECMO device malfunctions. One patient death was reported but the death was deemed unrelated to the device malfunction
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=845816; 2) “oxygenator, cardiopulmonary bypass”, which returned 1294 cases, only 500 of which were available for review. A word search of these 500 cases for the word “ECMO” under the “Brand Name” column was then performed. Only 7 cases were found, but as one case described 6 events in 3 patients at their facility, the total number of cases was 12. Four deaths were reported in association with ECMO use.
63 MAUDE database. MDR report keys: 2960619, 2960622, 2960626, and 2960640.
65 See footnote 62 supra.
V. Arguments for Maintaining Class III Designation, and Setting PMA Requirements, for All Indications

Regardless of the state of current knowledge regarding the use of ECMO therapy for the two indications proposed for Class II designation, Public Citizen argues that ECMO devices should remain as Class III devices for all indications, requiring PMAs to demonstrate safety and efficacy for the following reasons.

A. Prior to reclassifying the ECMO devices, the FDA must convene a subsection (b) device advisory panel to consider the question of reclassification.

Under the reclassification provision of the FDASIA, codified as 21 U.S.C. § 360c(e), the FDA may change the classification of a device based on “new information” only after carrying out the following three actions: (1) “publication of a proposed reclassification order in the Federal Register,” (2) “a meeting of a device classification panel described in subsection (b),” and (3) “consideration of comments to a public docket . . .”67 In construing these requirements, the courts will look to the plain meaning of the text, keeping in mind that “words of a statute must be read in their context. . .”68 It is obvious from reading the paragraph as a whole that the purpose of the device classification panel meeting is to allow the panelists an opportunity to consider the “new information” that forms the basis of the proposed reclassification decision and provide advice to the FDA that will inform the agency’s final order.

The FDA has not convened a subsection (b) device classification panel to consider the proposed reclassification of ECMO devices or advise the agency on that topic. In its 2013 NPO to reclassify the ECMO devices, the FDA states that it based its Nov. 2, 1979, proposed rule for Class III classification of ECMO devices on the recommendation of the Anesthesiology Device Classification Panel. This panel meeting, which from the wording in the NPO, was convened sometime before the 1979 proposed rule, obviously does not satisfy the requirement of § 360c(e), as the classification panel that met at that time did not have the opportunity to consider the device reclassification that the FDA first proposed in 2013, nor did the panels have the opportunity to consider the new information upon which the proposal was based.

For the FDA to rely on the advice from “a meeting of the device classification panel” that is more than 30 years old and directed toward another topic besides the proposed reclassification order is akin to suggesting that the FDA could meet its statutory obligation to consider “comments to a public docket” by responding to decades-old comments from a different rulemaking process. It is clear that the FDA must convene a new meeting of an appropriate device classification panel prior to issuing a final order to reclassify the device, and that the panel should have opportunity to consider the FDA’s proposal and view the new information on which the proposal is based.

The FDA also should move immediately to update the regulations governing reclassification in 21 C.F.R. § 860.130, so that the regulations reflect the procedural changes effected by the

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FDASIA. This change is necessary because the current regulations incorrectly suggest that a classification panel meeting is optional with respect to proposed reclassifications, rather than mandatory.\(^{69}\)

In addition, the FDA should update its website with the current language contained in the Food and Drug Administration Safety and Innovation Act, Pub. L. 112-144, revising 21 U.S.C. § 360c(e) subsection (1)(B). Although the statute was enacted on July 9, 2012, the website did not include the current language as of the date of these comments.\(^{70}\)

**B. 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**

Although some evidence may demonstrate efficacy and safety of ECMO devices for at least one of the indications for which Class II designation is being proposed (neonates with severe respiratory failure), it does not necessarily follow that this evidence should result in downgrading approval requirements for the device, even for this indication. If the FDA has deemed the evidence sufficient to determine efficacy and safety for the two indications proposed for Class II status, this evidence should be reviewed as part of a PMA submission, and the devices should remain designated as Class III.

Furthermore, even if the FDA has concluded that the existing evidence establishes reasonable assurance of the safety and efficacy of ECMO devices tested for the indications proposed for reclassification into Class II, that is beside the point. The question for the purposes of regulatory approval requirements 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 ECMO devices without requiring PMAs, including data from testing the new devices in well-controlled clinical trials.

Given that ECMO devices are intended for life-sustaining indications in patients in critical condition, even minor but therapeutically significant changes in the structure or functionality of the device could potentially mean the difference between life and death for a patient. It is precisely for this reason that ECMO and other similarly life-sustaining and life-supporting devices have traditionally been designated as Class III devices.

The history of the evidence for ECMO devices is a case in point. In the 1970s, a large RCT in adults with severe respiratory failure comparing ECMO devices with the conventional treatments of the time was terminated early due to futility.\(^ {71}\) More than 90% of patients died despite the treatments, with no significant difference in mortality between the arms. A subsequent 1994 trial also failed to demonstrate any benefit of ECMO therapy compared with conventional therapy in

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adults with ARDS.\textsuperscript{72} It was not until the publication of the CESAR trial in 2009 that efficacy was demonstrated. Thus, although the efficacy and safety profile of the device compared with conventional therapy tended to improve rather than worsen over time, there is no guarantee that future devices will be better than, or even as effective as, current models.

Therefore, rather than relying only on manufacturing controls 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. The proposed “special controls”\textsuperscript{73} are not sufficient to demonstrate that the newer versions of these devices will be safe and effective when used in clinical practice, even if current versions of the devices are safe and effective in some patients. 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.

\textbf{C. Possibility of approval through 510(k) pathway reduces the incentive to undertake future studies for untested indications}

With the possibility of clearance through the 510(k) pathway made possible by a Class II designation, which does not usually require submission of such evidence, few ECMO device manufacturers will pursue expensive clinical trials to support Class III approval for additional indications if the devices can readily be used “off-label” for these indications without clinical data. This will likely result in the continued, widespread use of the ECMO device for the remaining – and any future – Class III indications without evaluating safety and efficacy. This is a critical reason that life-supporting and life-sustaining devices, such as ECMO devices, should always remain as Class III devices requiring premarket clinical testing.

\textbf{D. PMA requirements for remaining uses of ECMO devices absent from the FDA’s proposal}

In its January 8, 2013, NPO, the FDA never mentions the regulatory approval status of the remainder of the indications for which ECMO devices are currently used (e.g., adults with ARDS).\textsuperscript{74} This is concerning, especially in light of the fact that the FDA has, since 1987, not set an effective date for the requirement for premarket approval for ECMO devices for any indication.\textsuperscript{75} These life-supporting devices have thus remained in regulatory limbo for more than 25 years now, remaining as Class III devices but with no date set to determine PMA requirements. In the absence of any language in the FDA’s NPO indicating otherwise, it is presumed that ECMO devices will remain in Class III for all indications other than those

\begin{footnotesize}
\begin{enumerate}
\item The FDA’s proposed special controls focus exclusively on ways to ensure device integrity and functionality and nonclinical performance evaluations to address safety concerns. 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. 21 CFR 868, 870. Docket No. FDA-2012-N-1174.
\item \textit{Ibid.} (citing 52 FR 17732 at 17735; May 11, 1987)).
\end{enumerate}
\end{footnotesize}
proposed for Class II status. The FDA needs to clarify whether this is the case and, if so, should immediately set a date by which sponsors must submit evidence in support of PMAs for these remaining Class III indications.

VI. Summary of Requests

In summary, Public Citizen urges the FDA to withdraw its proposal for Class II reclassification of ECMO devices for conditions in which imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery. The FDA should instead publish a proposed final rule maintaining the devices’ Class III classification for all indications and set an effective date requiring PMA submissions for these uses.

Thank you for taking our comments into consideration.

Sincerely,

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