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**Testimony before the FDA’s Circulatory System Devices Panel on the Proposed
Reclassification of the Membrane Lung for Long-term Pulmonary Support [ECMO]
Sammy Almashat, M.D., M.P.H.
Public Citizen’s Health Research Group
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My name is Sammy Almashat, a physician with Public Citizen’s Health Research Group, part of Public Citizen, a consumer advocacy group representing more than 300,000 members and supporters nationwide. I have no conflicts of interest.

Public Citizen 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 two 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 the trials conducted to-date are deemed sufficient to provide such assurance, why does the FDA not formally review these data as part of premarket approval applications (PMAs), consistent with the devices’ current Class III designation?

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

The two indications for which the FDA is proposing Class II designation are in situations: 1) where imminent death is threatened by cardiopulmonary failure in neonates and infants; and 2) where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery in pediatric patients.¹

There have been no randomized controlled trials supporting the efficacy and safety of ECMO therapy in patients who fail to wean from cardiopulmonary bypass in pediatric patients.² There is

¹ FDA Notice of Proposed Order: Anesthesiology Devices; Reclassification of Membrane Lung for Long-Term Pulmonary Support; Redesignation as Extracorporeal Circuit and Accessories for Long-Term Pulmonary/Cardiac Support (21 CFR 868 and 870). January 8, 2013. 78 FR 1158-1162.

<http://www.gpo.gov/fdsys/pkg/FR-2013-01-08/html/2013-00086.htm>. Accessed September 11, 2013.

² FDA Executive Summary. September 12, 2013 meeting of the Circulatory System Devices Panel. Classification of the Membrane Lung for Long-term Pulmonary Support [Extracorporeal Membrane Oxygenator –ECMO (21 CFR 868.5610)], p. 32.

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM367600.pdf>. Accessed on September 11, 2013.

sufficient evidence demonstrating safety and efficacy only for increasing survival in neonates with severe respiratory failure, based on randomized controlled trials conducted in the 1980s and 1990s.³

However, it does not follow that this evidence for effectiveness in neonates should necessarily result in downgrading approval requirements for the device. If the FDA has deemed the evidence sufficient to determine efficacy and safety for this indication, this evidence should be reviewed as part of a PMA submission.

Furthermore, the question is not whether any of the previously tested versions of the device were safe and effective, but whether moving forward, the FDA can reasonably be assured of the safety and efficacy of *new* ECMO devices without requiring data from 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.

In response to an earlier letter we sent the FDA urging Class III designation for all indications, the FDA responded that: "If different types of safety/effectiveness questions are raised based on the technological differences [between a new device and an older device], the newly designed device would be ineligible for the 510(k) process and be a Class III device, eligible for review through a PMA or the de novo process."⁴ This reasoning begs the question: how will the agency know whether technological differences raise clinically relevant safety questions if no clinical trials are required comparing newer to older versions of the device?⁵

The history of the evidence for ECMO devices in adults with acute respiratory distress syndrome (ARDS) is a case in point. In the 1970s, a large randomized controlled trial in adults with severe respiratory failure comparing ECMO devices with the conventional treatments of the time was terminated early due to futility.⁶ 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 adults with

Also, for a discussion of the current evidence, see Public Citizen. Comments Submitted to the FDA Regarding Extracorporeal Membrane Oxygenation (ECMO) Devices. April 8, 2013.

<http://www.citizen.org/documents/2110.pdf>. Accessed September 11, 2013.

³ Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. *Cochrane Database Syst Rev*. 2008 Jul 16;(3):CD001340.

⁴ FDA Executive Summary, p. 18.

⁵ The FDA's proposed special controls to demonstrate safety and efficacy of newer device versions require only "in vivo data", including observational studies, but not necessarily clinical trials. See Executive Summary, p. 50.

⁶ Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA*. 1979 Nov 16;242(20):2193-6.

ARDS.⁷ It was not until the publication of the CESAR trial in 2009 that efficacy was demonstrated⁸ (albeit with serious limitations precluding definitive conclusions⁹). It stands to reason that different design features of the ECMO versions tested in each trial were at least partly responsible for the markedly different trial results. Therefore, absent required clinical trials, how will the FDA provide reasonable assurance that future ECMO versions will be as safe and effective as current models?

The FDA points out correctly that, in some instances, such as cardiopulmonary failure where medical therapy has failed, controlled clinical trials would not be possible or ethical, given the inability to use failed medical therapy (or placebo) as a control.¹⁰ We agree that such studies would be patently unethical, but these are not the sort of trials that would be required under a PMA. A non-inferiority trial comparing a newer ECMO version to an existing version is precisely the sort of clinical data that would guarantee that the newer device is *substantially equivalent* to existing therapy. No ethical barrier of the sort identified by the FDA exists for such trials.

Possibility of approval through 510(k) pathway reduces the incentive to undertake future studies for untested indications

An unintended, but clearly foreseeable, consequence of the down-classification of ECMO devices to Class II for some indications is the potential for off-label use for other, Class III 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 for *all* indications.

It is for these reasons that 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.

Thank you for your time.

⁷ Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1994 Feb;149(2 Pt 1):295-305.

⁸ Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009 Oct 17;374(9698):1351-63.

⁹ Moran JL, Chalwin RP, Graham PL. Extracorporeal membrane oxygenation (ECMO) reconsidered. *Crit Care Resusc.* 2010 Jun;12(2):131-5

¹⁰ FDA Executive Summary, p. 47.