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Testimony before the FDA's Circulatory System Devices Panel on the Proposed Classification of the Membrane Lung for Long-Term Pulmonary Support [ECMO]
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My name is Sammy Almashat, and I am a physician and health researcher with Public Citizen, a consumer advocacy group representing more than 300,000 members and supporters nationwide. I have no financial conflicts of interest.

In September 2013, this panel convened to discuss the Food and Drug Administration's (FDA's) proposal to reclassify devices used in extracorporeal membrane oxygenation (ECMO) procedures to Class II for two pediatric indications: 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] The panel agreed with the FDA's proposed Class II reclassification for these two indications.

Public Citizen reiterates its opposition to the reclassification of ECMO devices to Class II for these two pediatric indications for the reasons detailed in our September 2013 testimony.[2] Today's testimony concerns our opposition to ECMO reclassification for acute catastrophic cardiogenic shock in adult patients, for which the FDA is now effectively recommending Class II designation.[3] We urge the panel to reject this reclassification for the following reasons.

The FDA states that a clear lack of equipoise precludes a clinical trial with anything other than a veno-arterial (VA)-ECMO comparator arm in patients with acute catastrophic cardiogenic shock, who would otherwise face imminent and certain death.[4] We agree that such studies would be patently unethical, but these are not the only type of trial that could be required under a premarket approval (PMA) application. A non-inferiority trial comparing a newer ECMO version to an existing version would yield precisely the sort of clinical data that would guarantee

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[1] FDA Executive Summary. May 7, 2014 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. 4 (**hereafter referred to as "FDA Executive Summary"**). http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM395652.pdf. Accessed May 5, 2014.

[2] Public Citizen. Testimony before the FDA's Circulatory System Devices Panel on the Proposed Reclassification of the Membrane Lung for Long-term Pulmonary Support [ECMO]. Sept. 12, 2013. http://www.citizen.org/documents/2159.pdf. Accessed May 5, 2014.

[3] FDA Executive Summary, at 44.

[4] FDA Executive Summary, at 44.

that the newer device is substantially equivalent to existing therapy. No ethical barrier of the sort identified by the FDA exists for such trials.

In fact, in the absence of a single randomized trial to date, it remains unknown whether all *currently marketed* VA-ECMO devices are equally safe and effective in the treatment of acute cardiogenic shock, a condition in which, for example, any slight malfunction resulting in a lapse in therapy can mean the difference between life and death. How can the FDA be confident that all existing ECMO device variants, all studied in uncontrolled case series in different clinical settings with different patient populations, are equally efficacious in reducing mortality in acute catastrophic cardiogenic shock? Are some devices inferior or more likely to malfunction than others? Are patients currently dying as a result of treatment with inferior ECMO devices?

Given the dire prognosis for these patients without the best available (and best-functioning) ECMO devices, such non-inferiority trials, required under a PMA application, would answer such critical questions. Grandfathering in all currently marketed ECMO devices under a Class II designation may effectively end the prospects for such expensive confirmatory trials.

Furthermore, the lack of sufficient information on the comparative efficacy and safety of existing ECMO devices raises serious concerns about future device approvals under the 510(k) process. With Class II designation for acute catastrophic cardiogenic shock, any currently marketed ECMO device would legally qualify as a predicate device for premarket clearance of a future device, without any strong evidence that it is as safe and effective as other variants, thus perpetuating the uncertainty as to the comparative effectiveness of the devices. (This has implications for the widespread off-label use of ECMO devices that will inevitably occur for other indications [e.g., respiratory failure] that even the FDA concedes should remain as Class III. 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 such trials.)

The FDA's reluctance to seek further clinical trials (e.g., under a PMA application) for acute catastrophic cardiogenic shock extends beyond the ethics of such trials, as it states that the "anecdotal reports available and their consistency over decades of use" render unnecessary any further clinical studies, considerations of equipoise aside.[5] We strongly disagree.

We do not believe that "anecdotal reports" in the form of case series (no matter how extensive) are an adequate substitute for trials with a control arm, without which it becomes exceedingly difficult, if not impossible, to evaluate the individual contribution of an intervention to the clinical outcome. This is especially true in critically ill patients, in whom myriad factors and complications inevitably confound determinations of cause and effect.

As it happens, the FDA agrees, at least in its assessment of the evidence for the broad indication of respiratory failure (for which the FDA, correctly, recommends maintaining Class III designation). In this case, the FDA notes that "the majority of the studies evaluating ECMO use for the [respiratory failure] indications for use assessed in this literature review were case series

[5] FDA Executive Summary, at 44.

and did not include control groups. **The lack of a control comparison limits the interpretability of the results as data on survival and complications related to ECMO use cannot be attributable to the actual use of the device vs. the patient population** [emphasis added], who already are at high risk for death due to other complications."[6]

Yet the FDA does not bring this reasoning to bear in its conclusions regarding the state of the evidence for acute catastrophic cardiogenic shock. Here, the FDA is content to rely on uncontrolled case series, with different patient populations, clinical settings, treatment thresholds, and of course ECMO device variants (with potentially numerous different combinations of individual circuit components[7]), in concluding that the evidence is strong enough that there is no need for further confirmatory controlled trials.

The FDA thus seems to employ strikingly different standards in its evaluation of the evidence for, and recommendations for regulatory classification of, the two broad adult indications reviewed in its Executive Summary.

It is for these reasons that we urge the panel to recommend that FDA maintain Class III designation, with a PMA requirement, for ECMO devices for all indications, including acute catastrophic cardiogenic shock in adult patients.

Thank you for your time.

[6] FDA Executive Summary, at 49.
[7] See e.g. regulatory history of different circuit components at FDA Executive Summary, p. 9-11.