

regulations designed to help ensure the safety, purity, and potency of the licensed product, and that the product is not misbranded.

In addition, FDA continues to help ensure the safety and effectiveness of licensed biological products through the development and application of additional standards and mechanisms. These mechanisms assist FDA in evaluating and monitoring the safety and effectiveness of biological products.

### C. Summary of Comments to the Proposed Rule

FDA did not receive any comments on the proposed rule.

### D. General Overview of the Final Rule

The final rule removes §§ 601.25 and 601.26 of the regulations, which prescribe procedures for FDA's review and classification of biological products licensed before July 1, 1972. FDA is taking this action because these regulations are obsolete and no longer necessary in light of other statutory and regulatory authorities established since 1972, which allow FDA to evaluate and monitor the safety and effectiveness of all biological products.

## III. Legal Authority

FDA is issuing this regulation under the biological products provisions of the PHS Act (42 U.S.C. 262 and 264) and the drugs and general administrative provisions of the FD&C Act (sections 201, 301, 501, 502, 503, 505, 510, 701, and 704 (21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 371, and 374)). Under these provisions of the PHS Act and the FD&C Act, we have the authority to issue and enforce regulations designed to ensure that biological products are safe, pure, and potent; and to prevent the introduction, transmission, and spread of communicable disease.

## IV. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule removes regulations that are obsolete and no longer necessary in light of other current statutory and regulatory authorities, FDA certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$144 million, using the most current (2014) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in any 1-year expenditure that would meet or exceed this amount.

## V. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant adverse effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VI. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

## VII. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## List of Subjects in 21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 601 is amended as follows:

## PART 601—LICENSING

■ 1. The authority citation for 21 CFR part 601 continues to read as follows:

**Authority:** 15 U.S.C. 1451–1561; 21 U.S.C. 321, 351, 352, 353, 355, 356b, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263, 264; sec 122, Pub. L. 105–115, 111 Stat. 2322 (21 U.S.C. 355 note).

### § 601.25 [Removed]

■ 2. Remove § 601.25.

### § 601.26 [Removed]

■ 3. Remove § 601.26.

Dated: February 5, 2016.

**Leslie Kux,**

*Associate Commissioner for Policy.*

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Parts 868 and 870

[Docket No. FDA–2012–N–1174]

#### Anesthesiology Devices; Reclassification of Membrane Lung for Long-Term Pulmonary Support; Redesignation as Extracorporeal Circuit and Accessories for Long-Term Respiratory/Cardiopulmonary Failure

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final order.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final order to redesignate membrane lung devices for long-term pulmonary support, a preamendments class III device, as extracorporeal circuit and accessories for long-term respiratory/cardiopulmonary failure, and to reclassify the device to class II (special controls) in patients with acute respiratory failure or acute cardiopulmonary failure where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent. A membrane lung device for long-term pulmonary support (>6 hours) refers to the oxygenator in an extracorporeal circuit used during long-term procedures, commonly referred to

as extracorporeal membrane oxygenation (ECMO). Because a number of other devices and accessories are used with the oxygenator in the circuit, the title and identification of the regulation are revised to include extracorporeal circuit and accessories for long-term respiratory/ cardiopulmonary failure. Although an individual device or accessory used in an ECMO circuit may already have its own classification regulation when the device or accessory is intended for short-term use ( $\leq 6$  hours), such device or accessory will be subject to the same regulatory controls applied to the oxygenator (*i.e.*, class II, special controls) when evaluated as part of the ECMO circuit for long-term use ( $> 6$  hours). On its own initiative, based on new information, FDA is revising the classification of the membrane lung device for long-term pulmonary support.

**DATES:** This order is effective February 12, 2016.

**FOR FURTHER INFORMATION CONTACT:** Fernando Aguel, Center for Devices and Radiological Health, 10903 New Hampshire Ave., Bldg. 66, Rm. 1234, Silver Spring, MD 20993, 301-796-6326, [fernando.aguel@fda.hhs.gov](mailto:fernando.aguel@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

**I. Background—Regulatory Authorities**

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (Pub. L. 101-629), the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107-250), the Medical Devices Technical Corrections Act (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), among other amendments, established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d) of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976

(generally referred to as preamendments devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices) are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification procedures (510(k)) to such a preamendments device or to a device within that type (both the preamendments and substantially equivalent devices are referred to as preamendments class III devices) may be marketed without submission of a premarket approval application (PMA) until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval or until the device is subsequently reclassified into class I or class II.

On July 9, 2012, FDASIA was enacted. Section 608(a) of FDASIA (126 Stat. 1056) amended section 513(e) of the FD&C Act, changing the mechanism for reclassifying a device from rulemaking to an administrative order.

Section 513(e) of the FD&C Act provides that FDA may, by administrative order, reclassify a device based upon "new information." FDA can initiate a reclassification under section 513(e) of the FD&C Act or an interested person may petition FDA to reclassify a preamendments device. The term "new information," as used in section 513(e) of the FD&C Act, includes information developed as a result of a reevaluation of the data before the

Agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, *e.g.*, *Holland-Rantos Co. v. United States Department of Health, Education, and Welfare*, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); *Upjohn v. Finch*, 422 F.2d 944 (6th Cir. 1970); *Bell v. Goddard*, 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent action where the reevaluation is made in light of newly available authority (see *Bell*, 366 F.2d at 181; *Ethicon, Inc. v. FDA*, 762 F.Supp. 382, 388-391 (D.D.C. 1991)), or in light of changes in "medical science" (*Upjohn*, 422 F.2d at 951). Whether data before the Agency are old or new data, the "new information" to support reclassification under section 513(e) of the FD&C Act must be "valid scientific evidence," as defined in section 513(a)(3) of the FD&C Act and 21 CFR 860.7(c)(2). (See, *e.g.*, *General Medical Co. v. FDA*, 770 F.2d 214 (D.C. Cir. 1985); *Contact Lens Manufacturers Assoc. v. FDA*, 766 F.2d 592 (D.C. Cir. 1985), cert. denied, 474 U.S. 1062 (1986).)

FDA relies upon "valid scientific evidence" in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the "valid scientific evidence" upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, *e.g.*, the contents of a pending PMA (see section 520(c) of the FD&C Act (21 U.S.C. 360j(c)).)

Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final reclassification order. Specifically, prior to the issuance of a final order reclassifying a device, the following must occur: (1) Publication of a proposed order in the **Federal Register**; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments to a public docket.

**II. Regulatory History of the Device**

FDA published a proposed order to reclassify this device in the **Federal Register** of January 8, 2013 (78 FR 1158) (the "proposed order"). As noted in the proposed order, on July 16, 1982, the Agency issued a final rule classifying all membrane lungs for long-term pulmonary support into class III (47 FR 31130). On May 11, 1987, FDA published a final rule amending the codified language for this device to clarify that no effective date had been

established for the requirement for premarket approval for membrane lungs for long-term pulmonary support devices (52 FR 17732 at 17735). This device is currently under product code BY5.

As discussed in the proposed order, FDA considered the available information on these devices and concluded that these devices could be reclassified to class II, subject to the identified special controls. As required by section 513(e)(1) of the FD&C Act, FDA convened a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to the membrane lung devices for long-term pulmonary support on September 12, 2013, followed by a meeting on May 7, 2014. The deliberations of the device classification panels are discussed in section IV of this order. FDA received and has considered two comments on the January 8, 2013, proposed order, as discussed in section III. Therefore, FDA has met the requirements for issuing a final order under section 513(e)(1) of the FD&C Act.

### III. Public Comments in Response to the Proposed Order

FDA received two comments in response to the January 8, 2013, proposed order to reclassify membrane lung devices for long-term pulmonary support 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.

One comment supported FDA's reclassification proposal but requested that the Agency clarify the population covered and the conditions included in the reclassification. According to the commenter, it seemed that the membrane lung device could be used for long-term support in neonates and infants only when imminent death is threatened by cardiopulmonary failure, but for the remaining population (*e.g.*, pediatric and adult patients), the membrane lung could be used for long-term support only when cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery. With respect to the conditions covered, the commenter sought clarification as to whether the reclassification was limited only to cardiopulmonary conditions or to cardiac failure as well. FDA is clarifying the intended uses covered by the reclassification in this final order. Specifically, after considering the input from the September 12, 2013, and May

7, 2014, classification panel meetings, comments on the proposed order and all other available information, FDA has determined that the reclassification applies to ECMO as a system of devices and accessories that provide extracorporeal circulation and physiologic gas exchange of blood in patients with acute respiratory failure or acute cardiopulmonary failure where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent. This revised scope better reflects use of ECMO as a tool that provides extracorporeal circulation and physiologic gas exchange of blood and more accurately reflects the function of the device. FDA has not cleared any ECMO devices that are indicated for specific patient populations or conditions. As such, FDA believes that the intended uses included in this final order should remain broad, rather than specify patient populations or conditions to be treated, to reflect use of ECMO as a tool.

Another comment disagreed with FDA's intent to reclassify membrane lung devices for long-term pulmonary support, stating that "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." FDA disagrees with this comment. According to section 513(a)(1)(C) of the FD&C Act, a class III device is defined as a device which: (1) 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 (2) cannot be classified as a class II device because insufficient information exists to determine that the special controls would provide reasonable assurance of its safety and effectiveness; and (3) 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 (4) presents a potential unreasonable risk of illness or injury.

Although FDA considers membrane lung devices for long-term pulmonary support to be life-supporting, a viewpoint that was supported by the panel members at the September 12, 2013 (2013 Panel), and May 7, 2014 (2014 Panel), device classification panel meetings, FDA believes that the available information supports FDA's determination that special controls, in addition to general controls, would be sufficient to provide a reasonable

assurance of safety and effectiveness. Further, the 2013 and 2014 Panels largely supported reclassification of ECMO for use in patients with acute respiratory failure or acute cardiopulmonary failure as noted in section IV of this order. As mentioned previously and discussed further in section IV, ECMO is a tool which provides extracorporeal circulation and physiologic gas exchange of blood. The special controls identified in this final order, including clinical performance data, ensure that the device can function as intended to provide extracorporeal circulation and physiologic gas exchange of blood for the intended duration of device use. The Agency believes that the risks of ECMO devices are sufficiently understood based on valid scientific evidence and that the risks of ECMO devices can be mitigated with the special controls identified in this final order. The special controls mitigate the risks to health identified for the device as outlined in section IV, table 1. Therefore, FDA does not agree that membrane lung devices for long-term pulmonary support for use in patients with acute respiratory failure or acute cardiopulmonary failure should remain a class III device.

The commenter also expressed concern that the reclassification of these devices would mean that companies manufacturing new versions of the device would not be required to show that their products are safe and effective. The commenter suggests that classification to class II (special controls) precludes FDA from requesting clinical data for these devices. FDA disagrees with this comment. FDA believes that the identified special controls provide a reasonable assurance of safety and effectiveness for membrane lung devices for long-term pulmonary support for use in patients with acute respiratory failure or acute cardiopulmonary failure, where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent. FDA has determined that by complying with the identified special controls, the currently legally marketed devices within this classification regulation will be reasonably safe and effective when used for acute respiratory failure or acute cardiopulmonary failure. Future devices claiming substantial equivalence to an available predicate(s) must demonstrate that they are substantially equivalent, as defined under section 513(i) of the FD&C Act, to the predicate device and comply with all applicable FDA regulations and with the special

controls in order to be classified into class II. Classification to class II (special controls) does not preclude FDA from requesting clinical data for these devices. In some cases, clinical data may be needed to comply with the special controls and demonstrate substantial equivalence to an available predicate. For example, special control § 870.4100(b)(v) regarding *in vivo* evaluation of the device could include clinical trial data, clinical information from the literature, and/or animal study data.

The commenter further expressed concern that reclassification for some indications will reduce the incentive to undertake future studies for untested indications due to the availability of the devices for “off-label” use. FDA notes in response to this comment that, generally, FDA regulates the use of a device as indicated by the party offering the device for interstate commerce.

The commenter also sought assurance from FDA that membrane lung devices for long-term pulmonary support for indications not identified in the proposed order would remain in class III and therefore require the submission of a PMA. FDA notes that by identifying the intended uses covered by the revised classification regulation, uses that fall outside the definition would not be subject to the order but rather would be classified under section 513 of the FD&C Act.

#### **IV. Deliberations of the Panels and FDA Consideration of Panel Input**

As required by section 513(e)(1) of the FD&C Act, FDA convened a meeting of the Circulatory System Devices Panel to consider the existing valid scientific evidence to support reclassification to class II of membrane lung devices for long-term pulmonary support. One meeting was held on September 12, 2013 (2013 Panel), regarding pediatric uses for ECMO and another meeting was held on May 7, 2014 (2014 Panel), regarding adult uses for ECMO (Refs. 1 and 2).

On September 12, 2013, FDA presented the risks associated with use of the membrane lung device for long-term pulmonary support. The 2013 Panel mostly agreed that the risks to health were adequately captured as presented by FDA. Several 2013 Panel members discussed whether the list of risks to health should also include information on renal dysfunction, neurologic injury, disseminated intravascular coagulation, transfusion issues, and inflammatory responses. FDA explained that such effects are more appropriately characterized not as risks to health but rather as adverse

events that may result from the risks to health. The 2013 Panel understood this distinction but requested that FDA consider expanding the definition of adverse tissue reaction to include inflammatory response. FDA considered the 2013 Panel’s input when updating the risks to health for the 2014 Panel and this final order.

The 2013 Panel agreed that the available scientific evidence supported the safety and effectiveness for ECMO and its accessories for conditions where the subject is at threat of imminent death caused by acute reversible respiratory failure (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or where acute cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery in all pediatric patients.

The 2013 Panel also agreed that the probable benefits to health from use of the extracorporeal circuit and its accessories for long-term pulmonary and cardiopulmonary support for these uses outweigh the probable risks. As noted previously, FDA has further considered all available information and has determined that the risks to health identified for ECMO are the same across neonatal, infant, pediatric, and adult populations. This is consistent with input from the 2013 and 2014 Panels, which found that the risks to health for the pediatric and adult populations do not differ. Further, FDA believes that the available safety and effectiveness information supports use of ECMO as a tool to provide extracorporeal circulation and physiologic gas exchange of blood in patients with acute respiratory failure or acute cardiopulmonary failure, where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent. FDA is providing greater clarity in this final order by simplifying the identification of ECMO devices in the classification regulation to better reflect what an ECMO circuit performs, not specify patient populations or conditions to be treated. Specific indications for use for ECMO, including specific patient populations and/or conditions, are further discussed in this document.

In general, the 2013 Panel believed the special controls in the proposed order would mitigate the identified risks to health and provide reasonable assurance of safety and effectiveness of the extracorporeal circuit and its accessories. However, some 2013 Panel members recommended that compatibility of the various circuit

accessories be evaluated to ensure that the circuit accessories can function together as intended. FDA believes that the special controls will be able to address the issue of circuit accessories’ compatibility. Specifically, the following special controls from the classification regulation address this concern: (1) The design characteristics of the device must ensure that the geometry and design parameters are consistent with the intended use; (2) non-clinical performance evaluation of the device must demonstrate substantial equivalence for performance characteristics on the bench, mechanical integrity, electromagnetic compatibility (where applicable), software, durability, and reliability; and (3) labeling must include a detailed summary of the non-clinical and clinical evaluations pertinent to use of the device and adequate instructions with respect to anticoagulation, circuit setup, performance characteristics with respect to compatibility with other circuit accessories, and maintenance during a procedure.

The 2013 Panel unanimously agreed that the membrane lung device for long-term pulmonary support is life-supporting. The 2013 Panel further stated that the available scientific evidence and the proposed special controls, in conjunction with general controls, supported the reclassification to class II of membrane lung devices for long-term pulmonary/cardiopulmonary support in pediatric patients. The 2013 Panel expressed concern about not having had the opportunity to review data regarding use of the device in adults, given that use of ECMO in adults had increased significantly over the years. The 2013 Panel recommended that FDA convene another meeting to review the available literature regarding use of the membrane lung device for long-term pulmonary support in adults before finalizing the proposed reclassification.

On May 7, 2014, FDA convened the 2014 Panel to discuss the classification of the membrane lung for long-term support, specifically for adult pulmonary and cardiopulmonary indications. For both pulmonary and cardiopulmonary intended uses, the 2014 Panel believed that the list of risks to health presented by FDA were comprehensive and adequately captured. Of note, in response to the 2013 Panel’s recommendation regarding risks to health, FDA expanded the definition of adverse tissue reaction to include inflammatory response.

The majority of the 2014 Panel believed that the available scientific evidence is adequate to support a

reasonable assurance of safety and effectiveness of the extracorporeal circuit and its accessories for long-term pulmonary support in adults, but recommended that FDA modify the intended use from “pulmonary support” to “acute, hypoxic, reversible respiratory failure.” FDA agrees with the 2014 Panel that “respiratory failure” is a more accurate reflection of the use of ECMO as a tool to provide extracorporeal circulation and physiologic gas exchange of blood in patients rather than “pulmonary support.” FDA has considered this input from the panel and has determined that acute respiratory failure is the appropriate intended use from a clinical and regulatory perspective to reflect such use. This change is reflected in the classification regulation. The Panel also agreed that the available scientific evidence is adequate to support a reasonable assurance of safety and effectiveness of the device for long-term cardiopulmonary support in adults

suffering from “cardiopulmonary failure due to acute catastrophic cardiogenic shock.” FDA agrees with the 2014 Panel that “acute cardiopulmonary failure” is a more accurate reflection of the use of ECMO as a tool to provide extracorporeal circulation and physiologic gas exchange of blood in patients rather than “cardiopulmonary support.” FDA has considered this input from the panel and has determined that acute cardiopulmonary failure is the appropriate intended use from a clinical and regulatory perspective to reflect such use. This change is reflected in the classification regulation. For both pulmonary and cardiopulmonary support in adults, the 2014 Panel agreed that the probable benefits to health from use of the device outweigh the probable risks to health where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent.

The 2014 Panel agreed that FDA’s list of special controls were appropriate and

comprehensive. The 2014 Panel further agreed that the special controls would mitigate the identified risks to health and provide reasonable assurance of safety and effectiveness for the device when used to provide long-term support in adults with acute respiratory failure or cardiopulmonary failure.

For both acute respiratory and acute cardiopulmonary indications in adults, the 2014 Panel unanimously agreed that the membrane lung device for long-term support is life-supporting. The 2014 Panel further believes that the available scientific evidence and the proposed special controls support the reclassification to class II of membrane lung devices for long-term support in adults with acute respiratory failure or acute cardiopulmonary failure.

After considering input from both the 2013 and 2014 Panels, FDA believes that the risks to health identified can be mitigated by the special controls as outlined in Table 1.

TABLE 1—HEALTH RISKS AND MITIGATION MEASURES FOR ECMO DEVICES

Identified risk	Mitigation measures
Thrombocytopenia .....	Technological characteristics; Non-clinical performance evaluation; In vivo evaluation; Labeling.
Hemolysis .....	Technological characteristics; Biocompatibility testing; Non-clinical performance evaluation; Labeling.
Adverse tissue reaction (including inflammatory response) .....	Biocompatibility testing; Labeling.
Inadequate gas exchange .....	Non-clinical performance evaluation; In vivo evaluation; Labeling.
Gas embolism .....	Non-clinical performance evaluation; In vivo evaluation; Labeling.
Mechanical failure .....	Technological characteristics; Non-clinical performance evaluation; Labeling.
Hemorrhage .....	In vivo evaluation; Labeling.
Hemodilution .....	Non-clinical performance evaluation; In vivo evaluation; Labeling.
Thrombosis/thromboembolism .....	Non-clinical performance evaluation; In vivo evaluation; Labeling.
Infection .....	Sterility; Shelf life testing.
Mechanical injury to access vessels .....	Non-clinical performance evaluation; In vivo evaluation; Labeling.

At both the 2013 Panel and 2014 Panel meetings, FDA provided a summary of information from the clinical literature regarding specific patient populations and conditions to be treated using ECMO (Refs.1 and 2). Of note, FDA has not cleared any ECMO devices that are indicated for specific patient populations or conditions. As such, FDA believes that the intended uses included in this final order should remain broad to reflect use of ECMO as a tool to provide extracorporeal circulation and physiologic gas exchange of blood in patients with acute respiratory failure or acute cardiopulmonary failure, where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent. However, FDA believes that there are specific indications (patient

populations and/or conditions) that would fall within this broader intended use and therefore be within the scope of this regulation as outlined in this document.

Specifically, FDA has reviewed the clinical literature and has determined that there are sufficient data available to support labeling ECMO devices for the following specific indications (patient populations and/or conditions) at this time: Meconium aspiration in neonates and infants; congenital diaphragmatic hernia in neonates and infants; pulmonary hypertension in neonates and infants; failure to wean from cardiopulmonary bypass following cardiac surgery in pediatric and adult patients; and ECMO-assisted cardiopulmonary resuscitation in adults.

FDA has further evaluated data from the clinical literature and determined that the data available do not support labeling ECMO devices for certain specific indications (patient populations and/or conditions) at this time without additional clinical data from sponsors to support such uses, consistent with the identified special controls, including but not limited to: High risk percutaneous coronary intervention; trauma resuscitation; failed heart or lung transplant; acute respiratory distress syndrome; and/or acute decompensation of chronic obstructive pulmonary disease.

For ECMO devices that have not been legally marketed prior to the effective date of the final order, or models (if any) that have been legally marketed but are required to submit a new 510(k) under § 807.81(a)(3) because the device is

about to be significantly changed or modified, manufacturers must obtain 510(k) clearance, among other relevant requirements, and demonstrate compliance with the special controls included in the final order, before marketing the new or changed device.

#### V. The Final Order

Under section 513(e) of the FD&C Act, FDA is adopting its findings as published in the preamble to the proposed order (78 FR 1158) with modifications as discussed in section IV of this final order. FDA is issuing this final order to reclassify the membrane lung devices for long-term pulmonary support from class III to class II for use in patients with acute respiratory failure or acute cardiopulmonary failure, where other available treatment options have failed and continued clinical deterioration is expected or the risk of death is imminent, and to establish special controls. FDA is removing the regulation from 21 CFR part 868 (Anesthesiology Devices) and adding it to 21 CFR part 870 (Cardiovascular Devices) to better align this device type (and the review thereof) with other similar types of cardiovascular devices. The title and identification of § 870.4100 (21 CFR 870.4100) reflects the Agency's intent to regulate ECMO and the accessories used in ECMO under the same set of regulatory controls. However, an individual device or accessory in an ECMO circuit may already have its own classification regulation when intended for short-term use (≤6 hours) and, in those instances, such device or accessory is subject to the preexisting regulation(s).

Following the effective date of this final order, firms marketing membrane lung devices for long-term pulmonary support for use in patients with acute respiratory failure or acute cardiopulmonary failure, where other available treatment options have failed and continued clinical deterioration is expected or the risk of death is imminent, must comply with the particular mitigation measures set forth in the special controls.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the devices. FDA has determined that premarket notification is necessary to provide reasonable assurance of safety and effectiveness of membrane lung devices for long-term pulmonary support for use in patients with acute respiratory failure

or acute cardiopulmonary failure, where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent, and, therefore, this device type is not exempt from premarket notification requirements.

#### VI. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### VII. Paperwork Reduction Act of 1995

This final order refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The collections of information in 21 CFR part 812 have been approved under OMB control number 0910–0078; the collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910–0120; the collections of information in 21 CFR part 814, subpart B, have been approved under OMB control number 0910–0231; and the collections of information under 21 CFR part 801 have been approved under OMB control number 0910–0485.

#### VIII. Codification of Orders

Prior to the amendments by FDASIA, section 513(e) of the FD&C Act provided for FDA to issue regulations to reclassify devices. Although section 513(e) of the FD&C Act as amended requires FDA to issue final orders rather than regulations, FDASIA also provides for FDA to revoke previously issued regulations by order. FDA will continue to codify classifications and reclassifications in the Code of Federal Regulations (CFR). Changes resulting from final orders will appear in the CFR as changes to codified classification determinations or as newly codified orders. Therefore, under section 513(e)(1)(A)(i) of the FD&C Act, as amended by FDASIA, in this final order, we are revoking the requirements in 21 CFR 868.5610 related to the classification of membrane lung for long-term pulmonary support as class III devices and codifying under § 870.4100 the reclassification of membrane lung for long-term pulmonary support for use in patients with acute respiratory failure or acute cardiopulmonary failure, where other available treatment options have failed, and continued clinical

deterioration is expected or the risk of death is imminent into class II (special controls).

#### IX. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

1. The panel transcript and other meeting materials for the September 12, 2013, Circulatory System Devices Panel are available on FDA's Web site at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm342357.htm>.
2. The panel transcript and other meeting materials for the May 7, 2014, Circulatory System Devices Panel are available on FDA's Web site at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm395638.htm>

#### List of Subjects in 21 CFR Parts 868 and 870

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 868 and 870 are amended as follows:

#### PART 868—ANESTHESIOLOGY DEVICES

- 1. The authority citation for 21 CFR part 868 continues to read as follows:

**Authority:** 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

#### § 868.5610 [Removed]

- 2. Remove § 868.5610.

#### PART 870—CARDIOVASCULAR DEVICES

- 1. The authority citation for 21 CFR part 870 continues to read as follows:

**Authority:** 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

- 2. Add § 870.4100 to subpart E to read as follows:

**§ 870.4100 Extracorporeal circuit and accessories for long-term respiratory/cardiopulmonary failure.**

(a) *Identification.* An extracorporeal circuit and accessories for long-term respiratory/cardiopulmonary support (>6 hours) is a system of devices and accessories that provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood in patients with acute respiratory failure or acute cardiopulmonary failure, where other available treatment options have failed, and continued clinical deterioration is expected or the risk of death is imminent. The main devices and accessories of the system include, but are not limited to, the console (hardware), software, and disposables, including, but not limited to, an oxygenator, blood pump, heat exchanger, cannulae, tubing, filters, and other accessories (e.g., monitors, detectors, sensors, connectors).

(b) *Classification*—Class II (special controls). The special controls for this device are:

(1) The technological characteristics of the device must ensure that the geometry and design parameters are consistent with the intended use, and that the devices and accessories in the circuit are compatible;

(2) The devices and accessories in the circuit must be demonstrated to be biocompatible;

(3) Sterility and shelf-life testing must demonstrate the sterility of any patient-contacting devices and accessories in the circuit and the shelf life of these devices and accessories;

(4) Non-clinical performance evaluation of the devices and accessories in the circuit must demonstrate substantial equivalence of the performance characteristics on the bench, mechanical integrity, electromagnetic compatibility (where applicable), software, durability, and reliability;

(5) In vivo evaluation of the devices and accessories in the circuit must demonstrate their performance over the intended duration of use, including a detailed summary of the clinical evaluation pertinent to the use of the devices and accessories to demonstrate their effectiveness if a specific indication (patient population and/or condition) is identified; and

(6) Labeling must include a detailed summary of the non-clinical and in vivo evaluations pertinent to use of the devices and accessories in the circuit and adequate instructions with respect to anticoagulation, circuit setup, performance characteristics with respect to compatibility among different devices

and accessories in the circuit, and maintenance during a procedure.

Dated: February 8, 2016.

**Leslie Kux,**

*Associate Commissioner for Policy.*

[FR Doc. 2016-02876 Filed 2-11-16; 8:45 am]

**BILLING CODE 4164-01-P**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 878**

[Docket No. FDA-2016-N-0237]

**Medical Devices; General and Plastic Surgery Devices; Classification of the Scalp Cooling System To Reduce the Likelihood of Chemotherapy-Induced Alopecia**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final order.

**SUMMARY:** The Food and Drug Administration (FDA) is classifying the scalp cooling system to reduce the likelihood of chemotherapy-induced alopecia into class II (special controls). The special controls that will apply to the device are identified in this order and will be part of the codified language for the scalp cooling system to reduce the likelihood of chemotherapy-induced alopecia's classification. The Agency is classifying the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device.

**DATES:** This order is effective February 12, 2016. The classification was applicable on December 8, 2015.

**FOR FURTHER INFORMATION CONTACT:** Neil Ogden, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. G414, Silver Spring, MD 20993-0002, 301-796-6397.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until the device is classified or reclassified

into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1) of the FD&C Act. Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, within 30 days of receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a classification under section 513(f)(2) of the FD&C Act. If the person submits a request to classify the device under this second procedure, FDA may decline to undertake the classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device submitted is not of "low-moderate risk" or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA will classify the device by written order within 120 days. This classification will be the initial classification of the device.

On March 6, 2015, Target Health, Inc. (on behalf of Dignitana AB) submitted a request for classification of the DigniCap™ Scalp Cooling System under section 513(f)(2) of the FD&C Act. The manufacturer recommended that the device be classified into class II (Ref. 1).

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the