

ATTACHMENT 1

DESCRIPTION OF PROPOSED CHANGES TO THE GUIDANCE FOR EXTRACORPOREAL BLOOD CIRCUIT DEFOAMER 510(k) SUBMISSIONS

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EXTRACORPOREAL BLOOD CIRCUIT DEFOAMER
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i. Scope

FDA defines extracorporeal circuit blood defoamers as a filter device. The word “filter” should be removed so that the definition of a defoamer in FDA’s Guidance comports with the definition of a defoamer in the Code of Federal Regulations. See 21 C.F.R. §870.4230. Additionally, the Working Group recommends that FDA modify the evaluation period from “6 hours” to “over the labeled life of the device” because it is a business decision to label the device for 6 hours or for some other duration (e.g., 4 hours). Companies should be expected to provide data to support the claim of the device’s labeled life, whether it is 6 hours or for some other duration. Therefore, the Working Group recommends that FDA revise the scope as follows:

An extracorporeal circuit blood defoamer (21 CFR 870.4230) is a device used to remove gas bubbles from the blood over the labeled life of the device.

1. Thromboembolism, Embolism Complications, Blood Damage

The Working Group recommends comparing white blood cell and platelet depletion for the test device to the predicate device at the maximum flow rate because testing at the maximum flow rate represents a worst case scenario in that maximum cellular damage will be produced under these conditions. The Working Group recommends eliminating blood component functionality testing because there are no known blood component function tests that are reproducible and that provide results that can be directly correlated to clinical outcomes. Additionally, while FDA’s Guidance states that each device should be tested for 6 hours, the Working Group recommends that FDA change the test duration to specify that testing should be conducted “over the labeled life of the device” because it may not always be practical, or necessary, to conduct testing for 6 hours. The Working Group recommends that FDA revise the blood study control as follows:

Evaluate hemolysis, white blood cells, and platelet depletion over the labeled life of the device. Compare the subject device with the predicate device at the maximum rated flow rate.

2. Inadequate Blood Flow, Excessive Pressure Gradients, Structural Integrity

FDA’s Guidance combines pressure and leak testing. The Working Group recommends that two different tests be performed as the control, namely, pressure integrity and pressure drop testing. The pressure integrity testing would be conducted using water or saline as the test medium while the pressure drop testing would be conducted using blood or a blood analog. Additionally, the Working Group recommends that pressure drop testing be conducted at the device’s highest rated flow rate because at the highest flow rate, one would see the highest pressure drop and the highest internal pressure on the device. Additionally, the Working Group

recommends that FDA change the test duration from 6 hours to “over the labeled life of the device” because it may not always be practical, or necessary, to conduct testing for 6 hours. The Working Group recommends that FDA revise the pressure integrity and pressure drop control as follows:

Pressure Integrity Testing: Perform burst pressure for test device using sustained static pressure at 1.5 times the maximum anticipated pressure for intended use over the labeled life of the device. Observe for leaks, tears, and structural integrity. Use water or saline as the test medium.

Pressure Drop: Perform pressure drop testing to steady state at highest rated flow rate. Use blood or a blood analog as the testing medium.

3. Structural Damage under Intended Use Conditions

The Working Group recommends modifying the leak testing to delete the pull strength evaluation for the connections because these defoamers are an integral part of a larger device, and the larger device will be tested for pull strength. The Working Group recommends that FDA delete the last sentence of this control as follows:

Leak Testing: Assess mechanical integrity by testing under static conditions as noted in pressure testing above.

4. Gaseous emboli

For the defoaming testing, FDA’s Guidance states that a bubble detector must be included as a circuit component. Sometimes bubble detectors are not necessary in the circuit and are not necessarily reflective of current perfusion practice. The Working Group, therefore, recommends that FDA revise the language to recommend use of a bubble detector rather than to mandate such use. Dictating all of the devices that must be included in a cardiopulmonary bypass circuit unnecessarily constrains the practice of medicine and is not in the best interest of public health. The Working Group recommends that FDA revise the control as follows:

RECOMMEND USE OF A BUBBLE DETECTOR AS A CIRCUIT COMPONENT.

The Working Group continues to believe that the Centrifugal Pump Bypass Checklist (“Bypass Checklist”), which was submitted by HIMA at the request of FDA to address human factors issues and developed and validated by independent engineering consultants, Human Factors Industrial Design, presents the most appropriate method for minimizing the risks associated with gaseous microemboli.¹ This Checklist is equally applicable to defoamers. The

1 The Bypass Checklist was developed during the course of the Centrifugal Pump reclassification process. When the Circulatory System Devices Panel discussed classification of the centrifugal pump, the Panel unanimously endorsed the Bypass Checklist as a special control in its vote to reclassify the centrifugal pump.

Checklist instructs the perfusionist to prime and debubble the pumphead, as well as to continue to monitor the operations of the pump, to ensure that air does not enter the circuit. Additionally, the Working Group recommends that FDA add a labeling control for use of an appropriate filter. The Working Group, therefore, proposes that FDA add the following labeling controls:

Labeling: Recommend use of Bypass Checklist. Recommend use of an appropriate filter.

5. Excessive pressure gradients; i.e., blood damage, inadequate flow

To address the risk of excessive pressure gradients, FDA indicated that manufacturers should “determine the flow rate limitation(s) to assure safe and effective use.” The Working Group proposes that recommending use of a bypass loop or change-out procedure in the product’s labeling would be a more effective control to address this risk. The Working Group, therefore, recommends that FDA replace flow rate capacity with the following control:

Labeling: Recommend use of bypass loop or change-out procedure.

6. User Error

While filtration efficiency evaluations are appropriate for filters, there is no control or other requirement specifying that filtration efficiency should be evaluated for defoamers. The Working Group does not feel that filtration efficiency evaluations are appropriate or pertinent to defoamers and, therefore, recommends that FDA remove the requirement that manufacturers provide “rated filtration efficiency” information. Additionally, FDA’s Guidance states that “a bubble detector must be included as a circuit component.” As previously stated, sometimes bubble detectors are not necessary in the circuit and are not necessarily reflective of current perfusion practice. The Working Group, therefore, recommends that FDA revise the language to recommend use of a bubble detector rather than to mandate such use. Dictating all of the devices that must be included in a cardiopulmonary bypass circuit unnecessarily constrains the practice of medicine and is not in the best interest of public health. The Working Group recommends that FDA revise the control as follows:

Provide flow rate and duration of use (e.g., 6 hours), and other pertinent information obtained through performance testing. THE USE OF A BUBBLE DETECTOR IS RECOMMENDED AS A CIRCUIT COMPONENT.

7. Blood incompatibility

The Working Group concurs with the biocompatibility testing control and does not have any comment on this risk or control.

8. Incompatibility of the product when exposed to circulating blood; and infection

For the sterilization control, the Working Group recommends that FDA specify that testing should be conducted with biological indicators when indicated. The Working Group recommends that FDA revise this control as follows:

Sterilization: Perform sterilization validation to ensure that the sterilization process is capable of providing a Sterility Assurance Level (SAL) of 10⁻⁶. Perform biological indicator (as applicable), pyrogen, and bioburden testing to ensure acceptable limits of biological contaminants.

9. Insufficient device performance, material incompatibility, and lack of sterility over a period of time

For shelf-life and related evaluations, the Working Group recommends that FDA reorder the information listed in the special control to specify first that manufacturers may conduct real or accelerated aging evaluations. The Working Group agrees that either real or accelerated aging should be evaluated and either may be turned in at the time of the 510(k) submission. However, if accelerated aging studies are conducted, the company will make an assessment as to the need to conduct parallel studies on real time aged products. Rather than requiring real-time follow up for accelerated aging testing, it is therefore proposed that if accelerated aging is utilized to confirm shelf life, the 510(k) sponsor will assess whether there is a need to follow-up with real time aging.

The Working Group further recommends that the evaluation of package shelf-life be followed by the package integrity and barrier property assessment, because package integrity describes package-related testing. Finally, the Working Group agrees to include a statement in 510(k)s for defoamers indicating that shipping evaluations will be conducted prior to commercial release of the product to provide flexibility to the manufacturers in their product development process. This certification is an appropriate special control in lieu of providing actual shipment and functionality testing in the 510(k) which is a routine part of qualification for these devices. In terms of the shipping studies, the Working Group recommends that FDA delete the evaluation of atmospheric conditions because this type of device is not affected by extremes in atmospheric pressures. Furthermore, the Working Group suggests that FDA delete the qualifier indicating that these tests should be performed under "extreme" conditions because manufacturers will conduct testing that demonstrates that the test device meets its product specifications. The Working Group recommends that FDA revise this control as follows:

Shelf Life: Study and submit real or accelerated aging. If accelerated aging results are submitted in the 510(k), the sponsor will make an assessment as to the need to follow-up with real-time results.

Validate the package shelf-life to ensure that the device will remain sterile for the period of time specified on the label.

Include package integrity and barrier property assessment: using validated physical or microbial-based methods.

Include a statement in the 510(k) indicating that that simulated or real shipment and handling condition (dropping, vibration, stacking, temperature, and humidity) evaluations followed by device functionality testing) will be completed before commercial release.