

ATTACHMENT 1

DESCRIPTION OF PROPOSED CHANGES TO THE GUIDANCE FOR CARDIOPULMONARY BYPASS ARTERIAL LINE BLOOD FILTER 510(k) SUBMISSIONS

**DESCRIPTION OF CHANGES TO THE GUIDANCE FOR
CARDIOPULMONARY BYPASS ARTERIAL LINE BLOOD FILTER
510(k) SUBMISSIONS**

1. Damage to formed blood elements, e.g., clotting, hemolysis

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 filter 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 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 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. Excessive pressure drop resulting in inadequate blood flow, damage to device, structural integrity, damage to the line

While 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 and 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. The Working Group also recommends that FDA change the test duration from "6 hours" to "over the labeled life of the device." 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 the intended use for 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 for test device. Use blood or a blood analog as the testing medium.

3. Connections pull apart

The Working Group recommends modifying the connections pull apart control to specify that the pull strength for the tubing attached to the connector port should be tested using a 15N pull force held for 15 second. These revisions would make the pull strength test similar to FDA's proposed control for oxygenators and to the oxygenator 7199 ISO/AAMI standard. The Working Group recommends that FDA revise the control as follows:

Test the pull strength of the tubing connections attached to the port using 15N pull force and hold for 15 seconds.

4. No blood flow

In the "Guidance for Extracorporeal Blood Circuit Defoamer 510(k) Submissions," FDA specified that problems with blood flow could result from an excessive pressure gradient. The Working Group recommends that FDA modify the title of this "Risk to Health" from "no blood flow" to "excessive pressure gradients; i.e., no blood flow" so that the filter guidance is consistent with FDA's defoamer guidance. As the control, 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:

4. *Excessive pressure gradients; i.e., no blood flow*

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

5. Does not provide efficient removal of solid and gaseous emboli

a. Filtration efficiency

Filtration efficiency testing should be conducted on the test article, but the results of this testing do not need to be compared to results from a predicate device because differences in pore sizes (openings in the filter mesh) that may exist between the two devices may cause differences in filtration efficiency. Where there are differences in pore size, one would expect differences in filtration efficiency; however, such differences would not necessarily be indicative of device performance. The Working Group believes that it is more appropriate to compare results for the test device to the indicated filter mesh openings. For example, if an arterial filter is indicated to have a 40 micron size filter, testing should be conducted to demonstrate the efficiency of the filter at the rated pore size. The Working Group also recommends that filtration efficiency testing should only be conducted at maximum flow rates, rather than over the range of labeled flow rates because determination of filtration efficiency at the maximum flow rate provides a "worst case" challenge for the device. At the highest flow rate, more pressure is exerted to push particulates through the filter material, whereas at lower flow rates, less pressure is exerted. Determination at

lower flow rates would not provide meaningful additional information about the device. The Working Group, therefore, recommends that FDA revise the filtration efficiency testing control as follows:

Determine filtration efficiency over the labeled range of particle size at maximum flow rate.

b. Air handling

The Working Group recommends that FDA remove the micro air handling evaluation because there is no standard test for micro air handling and there is no way that is currently known to present any meaningful information with regard to the size of bubbles. The counts that would be obtained from the test included in the filter guidance would have questionable significance. 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 (checklist attached).¹ This checklist is equally applicable to arterial filters. The 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. The Working Group, therefore, proposes that FDA add the following labeling control:

Labeling: Recommend use of Bypass Checklist.

6. User error

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:

THE USE OF A BUBBLE DETECTOR IS RECOMMENDED AS A CIRCUIT COMPONENT.

7. Not compatible with blood

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

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.

8. Infection/pyrogenicity complications

The Working Group recommends that FDA separate the "Infection/Pyrogenicity Complications" and related controls into two separate risks and controls so that the filter guidance is consistent with FDA's treatment of these risks and controls in the "Guidance for Extracorporeal Blood Circuit Defoamer 510(k) Submissions." The Working Group, therefore, recommends that risk number 8 be identified as "incompatibility of the product when exposed to circulating control and infection," with sterilization as the special control, and that risk number 9 be identified as "insufficient device performance, material compatibility, and lack of sterility over a period of time," with shelf-life as the special control.

For the sterilization special control, the Working Group recommends that FDA specify that testing should be conducted with biological indicators when indicated.

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. If real time studies are needed, these will be kept on file by the company. 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, an assessment will be made as to the 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 packaging-related testing. Finally, the Working Group agrees to include a statement in 510(k)s for filters 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 subject device meets its product specifications. The Working Group recommends that FDA revise the description of the risks and controls as follows:

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

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*

Shelf Life: Study and submit real or accelerated aging. If accelerated aging results are submitted in the 510(k), 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.