Guidance for Cardiopulmonary Bypass Oxygenators 510(k) Submissions; Final Guidance for Industry and FDA Staff

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Food and Drug Administration
Center for Devices and Radiological Health

Circulatory Support and Prosthetic Devices Branch
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation

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Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Cardiopulmonary Bypass Oxygenator 510(k) Submissions

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both

This guidance document describes a means by which cardiopulmonary bypass oxygenator devices may comply with the requirement of special controls for class II devices. Designation of this guidance document as a special control means that manufacturers attempting to establish that their device is substantially equivalent to a predicate cardiopulmonary bypass oxygenator device should demonstrate that the proposed device complies with either the specific recommendations of this guidance or some alternate control that provides equivalent assurances of safety and effectiveness.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be approved/cleared for marketing. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that information is being requested that is not relevant to the regulatory decision for your pending application or that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

1. Device Identification

"Cardiopulmonary bypass oxygenator (21 CFR §870.4350) - A cardiopulmonary bypass oxygenator is a device used to exchange gases between blood and a gaseous environment to satisfy the gas exchange needs of a patient during open-heart surgery." The device is intended for use up to six hours in duration.

2. Purpose and Scope

This guidance document is intended to identify the minimum information to submit in support of a substantial equivalence finding for a cardiopulmonary bypass oxygenator. It identifies testing protocols that may be followed in providing the necessary data. Since these protocols may not be applicable to all devices, manufacturers should verify that testing is conducted which provides appropriate data to determine the substantial equivalence of their oxygenator. Manufacturers should be aware that the national and international standards available on oxygenators provide details on characterization and performance testing of these devices, but they do not serve as comprehensive guides for the submission of data necessary for a regulatory review. (ISO 7199:1996(E) and CAN/CSA-Z364.3-M90 (1990))

3. Definitions

Test oxygenator	the oxygenator submitted for 510(k) regulatory clearance.
Aged test oxygenator	the test oxygenator after it has undergone appropriate accelerated or real time aging.
Predicate oxygenator	a similar oxygenator to the test oxygenator that has previously been cleared by FDA and is currently in commercial distribution in the United States.
Control blank circuit	a recirculation circuit that does not include an oxygenator but is otherwise identical to those circuits used to test oxygenators for blood damage.
Static control blood	a small volume of blood that is not circulated in a circuit and used to monitor autohemolysis.
Index of Hemolysis	the mass of hemoglobin released from the red blood cells per 100L of blood pumped through the device.
Modified Index of Hemolysis	the ratio of the amount of hemoglobin released into the plasma normalized by the total amount of hemoglobin pumped through the device.

4. Oxygenator Testing

To evaluate substantial equivalence of a cardiopulmonary bypass oxygenator, provide data addressing the biological, material, physical, and performance characteristics over the expected storage (shelf life) and use lifetime of the oxygenator. The potential failure modes for oxygenators, which should be investigated thoroughly, include leaks, toxicity, loss of gas transfer efficiency, gas embolism, thromboembolism, and blood damage. The oxygenator should be tested over its entire performance specification range under expected use conditions for six hours in duration. Integrity testing should be conducted for 6 hours. *In vitro* testing should be conducted according to an established protocol using at least five devices for each test. Submit the testing protocols along with the results of the tests reported in a statistically meaningful manner. Include the range of values, mean, standard deviation and standard error of the mean for each data set. For any comparative test, provide the p-value or similar measure indicating statistical significance of the comparison. Calibrate all instruments and equipment used in conducting these tests, to minimize the limit of testing error. Accuracy of the test apparatus should conform to that in section 11.1.2 of standard CAN/CSA-Z 364.3M90 (1990) or equivalent.

4.1 Comparative Data

You should compare the test oxygenator to a similar legally marketable oxygenator, the predicate. If the predicate oxygenator is not currently on the market it must not have been removed for either safety or regulatory issues. Additionally, for tests where there are pass/fail criteria (e.g., biocompatibility, blood pathway integrity, fluid integrity, etc.) there is no need to perform comparison testing with the predicate.

4.2 Preparation of the Test Oxygenator

Parallel testing should also be performed on the oxygenators only after they have undergone appropriate accelerated or real time aging and sterilization. The purpose of the testing is to determine adverse effects that may not be apparent in recently manufactured devices.

Before testing the test oxygenator subject it to shock/vibration and temperature/humidity conditioning to simulate the expected use environment and anticipated transport, and storage conditions. The oxygenator can be tested in accordance with tests that best simulate the device's exposure, including the shocks,

vibrations, temperatures and humidity expected prior to and during intended use. Following environmental testing, the device should be visually inspected and functionally tested. Any evidence of damage or inability to perform within specification will constitute a failure of the test. Some recommended standards for environmental testing are IEC 68-2 Basic Environmental Test Procedures, MIL-STD-810E, UL-2601.

4.3 Biological Compatibility

The materials of the finished oxygenator should be tested for biocompatibility, e.g., cytotoxity, irritation or intracutaneous reactivity, systemic toxicity, and hemocompatibility, in accordance with ISO 10993 (Biological Evaluation of Medical Devices) and sensitivity and genotoxicity in accordance with FDA Blue Book Memo G95-1: Use of International Standard ISO 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" dated May 1, 1995. The materials of the finished oxygenator should be compatible with any compounds expected to be introduced into the blood circuit and exposed to the oxygenator (e.g., anesthetic agents, other gases, liquids, and medications).

4.4 Physical Characterization/Integrity

You should perform physical characterization/integrity testing on oxygenators only after they have undergone appropriate accelerated or real-time aging and sterilization. The mechanical integrity of the finished, sterilized, and aged oxygenator should be demonstrated by subjecting the blood and water (within integral heat exchangers) pathways to pressures of at least 1.5 times the recommended maximum operating limit for 6 hours.

4.4.1 Blood Pathway Integrity

Using water as the test liquid, subject the blood path of the device to 1.5 times the maximum recommended pressure for 6 hours to determine whether leakage occurs, i.e., blood side to gas side, blood side to atmosphere. The pressure should be increased gradually to avoid water hammer or shock waves.

4.4.2 Heat Exchanger Fluid Pathway Integrity

Using water as the test liquid, subject the heat exchanger fluid path of the device to 1.5 times the maximum recommended pressure for 6 hours to determine whether water leakage occurs, i.e., water side to blood side, water side to atmosphere.

4.4.3 Gas Pathway Integrity

Subject the gas pathway of the device to 1.5 times the maximum recommended pressure limit for 10 minutes to determine whether there is loss of mechanical integrity of the connectors, housing, or integral structures.

4.4.4 Blood Volume Capacity of Oxygenator

Determine the static volume of blood within the device over the entire range of operating conditions. The static priming volume is the minimum volume of fluid residing in the oxygenator after priming at zero flow.

4.5 Performance Characterization

You should conduct performance testing on oxygenators only after they have undergone appropriate accelerated or real-time aging and sterilization. The performance characterization of the aged and sterilized test, and predicate oxygenators should be based on dynamic testing over the entire range of operating variables for the aged, sterilized test and predicate oxygenator for six hours in duration using whole blood. Submit testing protocols with detailed descriptions and figures of the testing circuit components. Submit data in tabular and graphical forms. Both testing protocols and data should be submitted on oxygen and carbon dioxide transfer rates, blood side pressure drop, heat exchanger performance, and blood cell damage. Atmospheric pressure during testing should be noted in the submission.

4.5.1 Blood Used for Evaluations

Use fresh whole animal blood collected and refrigerated for less than 24 hours for performance testing. Bovine blood is most commonly used in this type of testing. To minimize the effects of interanimal variation, it is

advised that the common blood pool be composed of blood from more than one animal. To simulate clinical usage, FDA and ISO 7199 recommend anticoagulation of the blood with heparin (e.g. 4500 units of heparin per liter of blood).

4.5.2 Oxygen and Carbon Dioxide Transfer Rates/Blood Side Pressure Drop

The oxygenator's gas transfer characteristics, and blood side pressure drop are evaluated using operational variable settings that span the manufacturer's recommended operating range of six hours.

4.5.2.1 General Testing

Identify the components of the testing circuit (described in the text and in figures) and include the following components as a minimum:

- Test oxygenator
- Conduit tubing
- Connectors
- Blood pump
- Blood reservoir
- Deoxygenator
- Heater/cooler unit
- Monitors and, or transducers

For determining gas transfer rates, a device is used in the loop to deoxygenate the blood and maintain the same venous inlet blood conditions to the oxygenator under evaluation. Blood sampling ports directly before the inlets and directly after the outlets of each of the oxygenators are used to measure blood gases and pressure drops across the oxygenator as a function of the operating variable.

4.5.2.2 Inlet Blood Conditions to Each Oxygenator for Gas Transfer

The testing circuit for evaluating gas transfer should provide an identical blood condition at the inlet of each oxygenator as

described. This should be checked at baseline, 90, 180, 270, and 360 minutes.

- Hemoglobin concentration: 12 ± 1 g/dl
- Oxyhemoglobin saturation: 65 ± 5%
- pCO2: 45 ± 5 mm Hg
- Base excess: 0 ± 5 mmol/L
- Temperature: 37 ± 2°C
- pH:7.4 ± 0.1

Since the characteristics of blood may degrade over time outside the body, the gas exchange capability of the oxygenator may be compromised. Therefore, to effectively assess the gas exchange capability of the oxygenator, circulating blood may be replaced with fresh blood after three hours of recirculation. Obtain a blood sample immediately after the blood exchange to verify that inlet blood conditions specified above are met.

4.5.2.3 Gas Transfer and Blood Pressure Drop Data Over the Operational Range of the Oxygenator

For gas exchange and blood side pressure drop measurements, cover the manufacturer's range of specified blood flow (i.e., minimum, nominal, and maximum recommended blood flows) for 6 hours duration. At each blood flow rate, record the gas transfer (refer to Tables 1, 2, and 3) for various gas flow rates within the manufacturer's recommended range. Data should be included for gas to blood flow rate ratios of 0.5:1, 1:1, and 2:1. The composition of the sweep gas and the gas pressures should also be provided at the gas inlet and outlet ports for each setting. The sweep gas and the gas pressures need to be met and corrected throughout the testing period.

TABLE 1. Oxygen Gas Transfer Data Set *

*Provide a table of data for each of the three different blood flow rates (minimum, nominal, and maximum) per the manufacturer's recommendation, and according to the labeling. FDA suggests the table format given below.

Gas: Blood Flow Rates (L/min)

Minimum Blood Flow Rate = (L/min)	F/Q = 0.5:1 Minimum	F/Q=1:1 Nominal	F/Q=2:1 Maximum
Inlet PO_2, % Sat, pCO_2, pH			
Outlet PO_2, % Sat, pCO_2, pH			
Calculate Oxygen Transfer Rate+			

+ Oxygen Transfer Rate [ml O_2 (STPD)/min] = Q x (CaO_2 outlet - CvO_2 inlet

Q = blood flow rate in L/min.

F = gas flow rate in L/min.

CaO_2 outlet = blood O_2 content (ml O_2/L blood) calculated at the outlet

CvO_2 inlet = blood O_2 content (ml O_2/L blood) calculated at the inlet

Since CaO_2 or CvO_2)= CaO_2 (or CvO_2) bound to hemoglobin + CaO_2 or CvO_2 dissolved in the plasma, CaO_2 outlet and CaO_2 inlet can be calculated from the following formula (assuming that the total hemoglobin concentration of the blood is 12 g/dl):

CvO_2 (or CaO_2) [ml O_2/L blood] = 12 g Hb/ 100 ml blood x 1.34 ml O_2/ 1 Gm Hb x 1000 ml blood/ 1 L blood x (% O_2 saturation) + (PO_2 mmHg x 0.00314 ml O_2/ (100 ml blood) (mmHg) x 1000 ml blood/ 1 L blood)

STPD = standard temperature and pressure, dry

TABLE 2. Carbon Dioxide Gas Transfer Data Set *

***** Provide a table with data for each of the three different blood flow rates (min, max, and nominal). FDA suggests the table format given below.

	Gas Flow Rates (L/min)		
Blood Flow Rate = (L/min)	F/Q = 0.5:1 Minimum	F/Q = 1:1 Nominal	F/Q = 2:1 Maximum
Inlet gas composition			
Outlet gas composition			
$\%\Delta CO_2$ [ml CO_2 (STPD)/L gas]			
Calculate CO_2 Transfer Rate+			

The gas flow entering and leaving the oxygenator should be analyzed for CO_2. The CO_2 transfer rate is calculated as follows:

+ CO_2 Transfer Rate [ml CO_2 (STPD)/min] = F x $\%\Delta$ CO_2

F = gas flow rate, exiting the blood-gas exchange device, L/min.
$\%\Delta CO_2$= the change in carbon dioxide concentration between the inlet and outlet flow [ml CO_2 (STPD)/L gas].

TABLE 3. Blood Pressure Drop Data Set *

*****Provide a table of data for each of the three different blood flow rates (minimum, nominal, and maximum). Hydrostatic differences between the locations of the inlet and outlet pressure transducers should be accounted for in the table. FDA suggests the table format given below.

Blood Flow Rate = (L/min)	Minimum	Nominal	Maximum
Inlet Blood Pressure (mmHg)			
Outlet Blood Pressure (mmHg)			
Blood Pressure Drop (mmHg)			

Provide graphs along with the above tables showing gas transfer rate (O_2 and CO_2) as a function of blood flow rate and gas flow rate. Determine the blood flow rate at which the gas exchange is sufficient to cause the outlet O_2 saturation to be 95% O_2 saturation.

Provide a graph along with the above data tables showing the blood side pressure drop as a function of blood flow rate.

To better simulate the clinical use of the device, submit data that shows the effects on gas transfer and pressure drop when the blood side outlet of the oxygenator experiences a mean minimum backpressure of 150 mmHg.

4.5.2.4 Gas Transfer and Pressure Drop Data

Record pressure drops and gas exchange parameters as stated above over a six-hour period. During the testing, blood should be circulated at the maximum recommended flow rate. The specified time intervals for tabular and graphical data are at baseline, 90, 180, 270, and 360 minutes.

5. Heat Exchanger Performance Evaluation

The performance of the oxygenator's heat exchanger is evaluated using fixed temperature differences between the inlet blood and water, fixed water flow rates, and blood flow rates spanning the recommended operating range specified by the manufacturer.

5.1 General Testing

Identify the components of the testing circuit (described in the text and in figures) and include the following components as a minimum:

- Test oxygenator
- Conduit tubing
- Connectors
- Blood pump
- Blood reservoir
- Heat exchange device acting to chill the blood
- Monitors and, or transducers

For determining the performance factor of the oxygenator's heat exchanger, a heat-exchanging device is used in the loop to maintain the same venous inlet blood temperature conditions to each of the oxygenators under evaluation. Blood sampling ports directly before the inlets and directly after the outlets of each of the heat exchangers are used to measure the blood temperature as a function of the operating variables.

Monitor the heat exchange and waterside pressure drop over a six-hour period, in addition to recording blood and water parameters as stated above. During the testing, blood should be circulated at the maximum recommended flow rate. The specified time intervals for tabular and graphical data are at 10 min, 1 hr, 2 hr, 4 hr, and 6 hr.

5.1.1 Inlet Blood Conditions to Each Oxygenator

The blood should have total hemoglobin content of 12 ± 1 g/dl. The inlet blood temperature to each oxygenator should be maintained at 30 ± 1°C

using a water bath. The inlet water temperature to each oxygenator should be maintained at 40 ± 1°C.

5.1.2 Heat Transfer and Water Pressure Drop Data over the Operational Range of the Oxygenator

For heat exchange measurements, cover the manufacturer's range of specified blood flow rates (i.e., minimum, nominal, and maximum recommended blood flows). At each blood flow rate, record the temperature needed to determine heat transfer (refer to Tables 4 and 5) for various water flow rates within the manufacturer's recommended range.

TABLE 4. Heat Exchanger Data Set *

***Provide a table of data for each of the three different blood flow rates (minimum, nominal, and maximum). FDA suggests the table format given below.

	Water Flow Rates (L/min)		
Blood Flow Rate = (L/min)	Minimum	Nominal	Maximum
Inlet Blood Temperature (°C)			
Outlet Blood Temperature (°C)			
Inlet Water Temperature (°C)			
Outlet Water Temperature (°C)			
Calculate Performance Factor+			

+ The efficiency of the heat exchanger can be expressed as a heat exchanger performance factor (R) defined as the difference between the outlet and inlet oxygenator blood temperatures divided by the difference in temperatures in °C between the water and blood at their respective inlets to the oxygenator.

$$R = (B_o - B_i)/ (W_i - B_i)$$

Where B_o = blood temperature at the oxygenator outlet

B_i = blood temperature at the oxygenator inlet

W_i = water temperature at the oxygenator inlet

TABLE 5. Water Pressure Drop Data Set *

***Provide a table of data for each of the three different blood flow rates (minimum, nominal, and maximum). Hydrostatic differences between the locations of the inlet and outlet pressure transducers should be accounted for in the table. FDA suggests the table format given below.

	Water Flow Rates (L/min)		
Blood Flow Rate = (L/min)	Minimum	Nominal	Maximum
Inlet Water Pressure (mmHg)			
Outlet Water Pressure (mmHg)			
Water Pressure Drop (mmHg)			

Provide a graph along with the above data tables showing the heat exchanger performance factor as a function of both blood flow rate and water flow rate. Provide a graph along with the data tables showing the waterside pressure drop as a function of blood flow rate and water flow rate.

To better simulate the clinical use of the device, data should also be submitted showing the effects on heat transfer and water pressure drop when the blood side outlet of the oxygenator experiences a mean minimum backpressure of 150 mmHg during use.

6 Blood Damage Performance Evaluation

The oxygenator will be evaluated for in vitro blood damage by monitoring the plasma hemoglobin concentration, WBC and platelets for six hours in duration.

6.1 General Testing

Identify the components of the testing circuit (described in the text and in figures) and include the following components as a minimum:

- Test oxygenator
- Conduit tubing
- Connectors
- Blood pump

- Blood reservoir
- Heater/cooler unit
- Monitors and, or transducers

The aged, test oxygenators and the predicate oxygenators should be tested in paired fashion using identical circuits with the same pool of blood. The total volume of blood in the test circuits should be identical and minimized so that the sensitivity of the testing for the blood damage is increased. In general, the total circuit blood volume should be 500 mL - 2500 mL depending on the maximum recommended blood flow rate.

Investigators should also consider running a "control blank circuit" concurrently with the test and predicate device circuits to determine the baseline blood damage caused by the components of the recirculation circuit when an oxygenator is not present (using a long tubing compressive clamp to create the back pressure on the pump and diffuse external heating of the blood tubing or reservoir to maintain proper temperature). Besides creating baseline blood damage data, running a "control blank circuit" with each blood pool also creates a means to evaluate variations in blood fragility between tests and to make comparisons to published values.

6.1.1 Condition of Blood for Damage Testing

- Hemoglobin concentration: 12 ± 1 g/dL
- pCO_2 : 40 ± 5 mmHg
- pH: 7.4 ± 0.1
- minimum Activated Clotting Time (ACT): 300s
- blood glucose 100-300 mg/dL
- temperature: 37 ± 2°C

6.1.2 Blood Damage Testing Protocol

A detailed protocol with figures for performing the blood damage testing should be provided. The gas flow rate should be set to match the blood flow rate according to the manufacturer's specifications. The mean backpressure on each oxygenator should be maintained at a minimum of 150 mmHg to simulate clinical use conditions. Important procedures to control include:

- precise occlusivity setting of the roller pumps prior to blood introduction in every test loop (if a roller pump is used)

- priming and wetting of all surfaces of the circuits by recirculating saline through the circuits for 5 minutes prior to the introduction of blood

- minimizing any air/ blood interfaces, minimizing the total circuit blood volume, and

- purging each blood sampling port by withdrawing (for disposal) approximately 1 mL of blood prior to taking the actual blood sample using a separate syringe

Inherent in this type of testing is the assumption that the blood damage caused by the other (non-oxygenator) components of the testing circuits is identical in each circuit. Experience has shown that this is not necessarily true and that precise occlusivity setting of the roller pumps (if used) using saline prior to the introduction of blood is an important step in the testing. Due to uncontrollable variations in blood, it is preferable to perform the blood damage testing on the aged, sterilized test oxygenator circuit, the predicate oxygenator circuit, and the control blank circuit at the same time using the same blood pool. However, this may not always be possible. The day, time, and blood pool that were used in the testing of each circuit should be apparent in the final report. The total volume of blood in the test circuits should be identical and minimized so that the sensitivity of the testing for blood damage is increased. In general, the total circuit blood volume should be 500 - 2500 mL depending on the maximum recommended blood flow rate.

6.1.3 Blood Damage Data Reporting

For *in vitro* blood damage testing, provide data according to the sampling schedule in Table 6. Raw data and corrected data (with respect to "baseline" values) for each of the individual testing circuits should be provided in both

tabular and graphical form. The plasma hemoglobin is reported as a concentration (mg/dL) that increases over time. Mean (± SD) results should also be tabulated and graphed for the aged, sterilized test oxygenator circuit and the predicate oxygenator circuit. The day, time, and blood pool that were used in the testing of each circuit should be apparent in the final report. Appropriate statistical testing should be performed to account for testing using different blood source pools at different times.

TABLE 6. Parameter Sampling Schedule

		Sampling Schedule (minutes)				
Parameter	Main Blood Pool	Baseline*	90	180	270	360
Plasma Hemoglobin Concentration	X	X	X	X	X	X
Activated Clotting Time (ACT)	X	X		X		X
Hematocrit	X	X		X		X
Platelets and WBC	X	X	X	X	X	X
Total Blood Hemoglobin	X	X				X
Temperature		X	X	X	X	X
Blood Gas Values (pO_2, pCO_2, pH,)		X	X	X	X	X
Blood and Gas Flow Rates		X	X	X	X	X

* "Baseline" refers to the time (at "zero minutes" on the sampling schedule) after all of the blood has been introduced into the circuit, all bubbles have been removed from the circuit, the recirculation pump has been run at the proper blood flow rate for at least 5 minutes to insure complete mixing throughout the circuit, and the blood gas values, gas flow rate, and gas composition conditions have been established.

A traditional normalized "index of hemolysis" (IH), interpreted as the mg of hemoglobin released from the red blood cells per 100L of blood pumped through the device, should be calculated using the following formula (be sure to check the units of each entity in the equation):

$$IH\ [mg/\ 100L] = [(\Delta plHgb/\Delta t) \times ((100 - Hct)/100) \times Vol. \times 1000] / Q$$

$\Delta plHgb/\Delta t$ (mg/dl min) = the slope of the plasma hemoglobin concentration (mg/dl) versus time (min.) plot obtained from a linear best-fit to this data
Hct (%) = average hematocrit of the blood circuit
Vol (L) = average blood volume of the circuit
Q (L/min) = blood flow rate during testing

Traditionally, only the plasma hemoglobin concentration at time zero and time 360 min were used to calculate the IH. However, using the slope of the plasma hemoglobin concentration versus time plot allows all of the data to be equally weighted in the determination of the IH. Although the IH has been used by several groups to "normalize" their blood damage data, it actually varies directly with the amount of cellular hemoglobin being pumped through the circuit. For this reason, the "modified index of hemolysis" (MIH), which is the ratio of the amount of hemoglobin released into the plasma normalized by the total amount of hemoglobin pumped through the device, should also be calculated in the submission as follows:

$$MIH\ [mg/\ mg] = [(\Delta plHgb/\Delta t) \times ((100 - Hct)/100) \times Vol \times 10^{6}] / (Q \times Hb)$$

Where Hb (mg/dl) = average total hemoglobin concentration in the circuit

Although a standardized testing protocol has not been established, supplemental testing for up to six hours in duration at the manufacturer's specified minimum blood flow rate (with blood with an ACT of 300-450 seconds and a normal to high platelet count) is also recommended. In-line monitoring for microparticle formation and post-test oxygenator evaluation for evidence of areas of blood stasis, thrombus deposition, and maldistribution of flow are encouraged.

6.2 Acceptable Endpoints

The oxygenator should not fail any of the testing after undergoing shock, vibration, temperature, and humidity conditioning.

6.3 Biological/ Material Compatibility

The test oxygenator should demonstrate acceptable biological compatibility.

6.4 Physical Characterization/Integrity

The test oxygenator should withstand 1.5 times maximum recommended flow rates (blood and water pathways) and pressures for six hours.

6.5 Performance Characterization

Mean oxygenator outlet saturation, oxygen and carbon dioxide transfer rates, and blood side pressure drop should be comparable to the predicate.

7. Packaging

7.1 Performance Evaluation

- Perform a sterilization validation to ensure that the sterilization process is capable of providing the Sterility Assurance Limit (SAL) of 10^{-6}, in accordance with suitable guidance (e.g., ANSI/AAMI VP20-1994, Section 4.5 (Sterility), ANSI/AAMI/ISO 11134-1993, ANSI, AAMI/ISO 11135-1994, and ANSI/AAMI/ISO 11137-1994). Alternate sterilization methods should be validated to an appropriate SAL.

- Describe the sterilization method that will be used; the method that used to validate the sterilization cycle, and the SAL.

- Describe how the packaging serves to maintain the device sterility. For ETO sterilization, state the maximum levels of residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol. State whether the product is non-pyrogenic, and describe the method used to make that determination. For radiation sterilization; state the radiation dose used. See also, Sterility Review Guidance #K90-1.

- Conduct preclinical and/or clinical (in vivo) evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for In Vivo

Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through in vitro testing.

7.2 Labeling -- Instructions For Use

- Provide a statement that biological testing (including pyrogen and bioburden testing) will be or has been performed to assess acceptable limits of biological contaminants.

- Provide a statement that package shelf life validation (including package integrity/distribution testing, accelerated aging, microbial challenge testing, and real time follow-up) will be or has been performed, in accordance with ANSI/AAMI VP20-1994, Section 4.5.1 (Shelf life), to determine that the device and package will maintain their integrity for the period of time specified on the device label, or provide a justification as to why such validation is not necessary.

- Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).

- State that the product is supplied sterile on the product package label and in the Instructions for Use.

- Provide instructions for opening the sterile package.

- Instruct the user that sterility cannot be assured if the packaging has been opened or damaged.

- State that the health care provider must observe aseptic technique in preparation and use of the device.