ATTACHMENT 1

DESCRIPTION OF PROPOSED CHANGES TO THE GUIDANCE FOR CARDIOPULMONARY BYPASS OXYGENATOR 510(k) SUBMISSIONS

AdvaMed/Blood Oxygenator Guidance Group Comments on the "Guidance for Cardiopulmonary Bypass Oxygenators 510(k) Submissions" (issued on January 17, 2000)

Introductory Paragraph

The Working Group recommends that the following sentence be added to the introductory paragraph of the guidance document (after the first sentence) in order to identify the potential risks associated with cardiopulmonary oxygenators and that the special controls provide a reasonable assurance of safety and effectiveness:

> *The special controls discussed in this guidance document address the potential risks associated with cardiopulmonary bypass oxygenators (biocompatibility of materials; blood damage; gas embolism; particulate embolism; thromboembolism; leaks and mechanical integrity; and inadequate gas exchange) and provide a reasonable assurance of the safety and effectiveness of the device.*

1. **Device Identification** (Guidance Document, page 1)

The Working Group has no comments on this section.

2. **Purpose and Scope** (Guidance Document, page 1)

Currently, the Guidance document specifies that it will only apply to "oxygenators with integral heat exchangers." (Guidance, page 1) The Working Group suggests that the guidance apply to all oxygenators: those with heat exchangers and without heat exchangers. Testing that will be conducted on each test oxygenator will be the same whether the device has a heat exchanger or not (with the exception of heat exchanger efficiency testing). Furthermore, the testing on the heat exchangers will be consistent with that for currently marketable heat exchangers. The Working Group, therefore, recommends that FDA delete the following sentence:

> *This guidance includes only oxygenators with integral heat exchangers.*

3. **Definitions** (Guidance Document, page 2)

The Working Group has no comments on this section.

4. **Oxygenator Testing** (Guidance Document, page 2)

FDA's Guidance states that each test oxygenator should be tested over its entire performance specification range under expected-use conditions for six hours in duration. It may not always be practical, or necessary, to conduct a specific test for a 6-hour duration. For example, pressure/integrity testing of a device for a 6 hour duration is not an expected clinical

condition under which the device could normally be used. Therefore, the Working Group recommends that the oxygenator should only be tested over its entire specification range under expected use conditions over the labeled life of the device. The Group recommends that FDA modify the following sentence as follows:

> *The oxygenator should be tested over its entire performance specification range under expected use conditions for the labeled life of the oxygenator.*

In the last sentence of this section, FDA indicates that the test apparatus' accuracy should conform to section 11.1.2 of standard CAN/CSA-Z 364.3M90 (1990). The Working Group believes that FDA is being too restrictive in prescribing conformance to a single standard. Therefore, the text describing the test apparatus' accuracy should be revised to allow a manufacturer to use requirements that are comparable to those in section 11.1.2 of standard CAN/CSA-Z 364.3M90 (1990). The Group recommends that FDA add the words "or equivalent" as follows:

> *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 (Guidance Document, page 3)

FDA's current proposal for comparative data suggests that "all testing" conducted with the "test oxygenator should be compared to a similar currently legally marketed oxygenator, the predicate." The Working Group questions the need to do comparative evaluations when the manufacturer is only evaluating a specific attribute of a particular test. For example, there is little value or significance in conducting a comparison test on the predicate when a structural integrity test performed on the test oxygenator demonstrates that the device meets the required specification of 1.5 times the maximum labeled value.

In recently cleared 510(k) submissions, predicate device testing has not been submitted for mechanical integrity or static priming volume testing because these tests are considered to be for physical attribute evaluations. These submissions have included a rationale for not performing comparative evaluations for these tests. Additionally, for tests where there are pass/fail criteria, the Group does not believe that there is any need to perform comparison testing with the predicate (e.g., biocompatibility, blood pathway integrity, fluid integrity, etc.). Moreover, the statute does not require that a device be substantially equivalent to a currently legally marketed oxygenator, but only a legally marketable oxygenator, which, for reasons wholly unrelated to safety or regulatory issues, may have been removed from the market. The Working Group suggests that FDA accept testing that demonstrates that the device meets the manufacturer's specifications for the test oxygenator. The Group recommends that Section 4.1 be modified as follows:

> *For all testing, the test oxygenator should be compared to a similar legally marketable oxygenator, the predicate, or to the manufacturer's specifications for the test oxygenator.*

4.2 **Preparation of the Oxygenator** (Guidance Document, page 3)

The Working Group suggests that the scope of this section be clarified to specify that the preparation of the oxygenator applies to the Physical Characterization/Integrity and Performance Characterization sections of the Guidance. The Group recommends that the first sentence of this section be revised as follows:

> *For Physical Characterization/Integrity, section 4.4, and Performance Characteristics, section 4.5, testing should be performed on the oxygenators only after they have undergone appropriate accelerated or real-time aging and sterilization.*

The Working Group questions the value of having to subject all test articles to shock/vibration and temperature/humidity testing prior to testing. The Group recommends that FDA delete the following text because the testing should be part of the device's verification/qualification:

> *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 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 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** (Guidance Document, page 3)

The Working Group recommends that FDA clearly and distinctly identify the processing of the devices that will be subjected to biocompatibility evaluations. Manufacturers need certainty as to the nature of the biocompatibility testing that will be acceptable. To that end, the Working Group proposes that biological testing can be performed on unaged test oxygenators unless the material has not been previously used in blood contacting applications. Additionally, the Group recommends that FDA clarify the materials that should be subjected to such testing by adding "blood pathway" to the first sentence as follows:

> *The blood pathway materials of the oxygenator should be tested sterile and unaged unless the material has not been previously used in a blood contacting application, for biocompatibility, e.g., cytotoxicity, 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 Working Group recommends that FDA delete the following sentence:

> *The materials of the 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).*

Removal of this statement is recommended because it is impossible for the device manufacturer to have full knowledge of all gases, liquids, and medications that could potentially be introduced into the cardiopulmonary bypass circuit and subsequently contact the oxygenator; thus, it is impossible to verify the validity of this statement. There is historical evidence that materials used in currently marketable cardiopulmonary bypass circuits can withstand exposure to the gases, liquids, and medications used. One exception to this is liquid volatile anesthetics. During cardiopulmonary bypass surgery, it is common for the anesthesiologist to utilize an anesthetic vaporizer in the cardiopulmonary bypass gas supply line which permits the anesthetic to be delivered via the gas flow through the oxygenator. Materials used in currently marketable oxygenators can withstand exposure to anesthetic agents in their vaporized state; however, contact between liquid volatile anesthetics such as isoflurane and the plastics of the oxygenator can cause cracks and potential leakage. To address this issue, an appropriate special control would be for device labeling to contain a caution to the user regarding contact of the oxygenator with liquid volatile anesthetics. Toward this end, a labeling requirement has been added to Section 7.3 of this guidance.

4.4 **Physical Characterization/Integrity** (Guidance Document, page 4)

FDA's proposal for physical characterization/integrity indicates that all three pathways (water/blood/gas) should be subjected to pressures and flow rates of at least 1.5 times the maximum limit for six hours. The Working Group recommends that FDA focus the physical characterization/integrity evaluation on the effect of pressure on the blood and water pathways by removing the evaluation of its effect on the gas pathway. Additionally, the Group recommends that some tests do not necessarily need to be conducted for six hours when a shorter duration will effectively demonstrate a particular test's objective. Furthermore, the Group recommends that FDA eliminate the evaluation of flow rate on the oxygenator's blood, water, and gas pathways because it is not practical to subject the blood pathway to 1.5 times the maximum flow limit.

Certain oxygenators have, for example, a maximum flow rate of 7.0 LPM. It is not practical to test the blood pathway at a flow rate of 10.5 LPM for six (6) hours. Some roller-pumps cannot operate at 10.5 LPM. Moreover, testing a device for six (6) hours at 10.5 LPM is not likely during clinical use of the device when the device is used as intended. Similarly, it is not practical to subject the other pathways to 1.5 times maximum flow or pressure limits for a 6-hour duration. In a clinical setting, these pathways would not be subject to excessive pressures for such a lengthy period of time. In recently cleared 510(k) submissions, manufacturers have

typically performed and submitted pressure tests that were conducted for a period of up to 10 minutes. FDA has cleared such oxygenators, thereby, demonstrating that these tests were sufficient to establish the substantial equivalence of previously-cleared oxygenators. The Working Group, therefore, recommends that FDA revise the paragraph in section 4.4 as follows:

> *The mechanical integrity of the sterilized, aged oxygenator should be demonstrated by subjecting the blood and water pathways (integral heat exchangers) to pressures of at least 1.5 times the recommended maximum operating limit for ten minutes.*

4.4.1 Blood Pathway Integrity (Guidance Document, page 4)

The Working Group recommends that the evaluation period for the blood pathway integrity test be changed from 6 hours to 10 minutes as follows:

> *Using water as the test liquid, subject the blood path of the device to 1.5 times the maximum recommended pressure for 10 minutes to determine whether leakage occurs, i.e., blood side to gas side, blood side to atmosphere.*

The Working Group recommends that FDA delete the following sentence because the sentence doesn't have anything to do with the requirements for blood pathway integrity testing:

> *The pressure should be increased gradually to avoid water hammer or shock waves.*

4.4.2 Heat Exchanger Fluid Pathway Integrity (Guidance Document, page 4)

The Working Group recommends that the evaluation period for the heat exchanger fluid pathway integrity test be changed from 6 hours to 10 minutes as follows:

> *Using water as the test liquid, subject the heat exchanger fluid path of the device to 1.5 times the maximum recommended pressure for 10 minutes to determine whether water leakage occurs, i.e., water side to blood side, water side to atmosphere.*

4.4.3 Gas Pathway Integrity (Guidance Document, page 4)

The Working Group recommends that FDA delete Section 4.4.3 describing the requirements related to the device's gas pathway integrity for several reasons. The gas pathways of oxygenators are vented/low pressure pathways. Since they are vented to atmosphere it is not possible to perform pathway integrity analysis provided the device is maintained as it would be used clinically. The vented areas can be mechanically obstructed; however this is not representative of clinical use. The blood and water pathway integrity tests are the most realistic means to challenge the oxygenator. The Group recommends that FDA delete the following sentence:

Subject the gas pathway of the device to 1.5 times the maximum recommended pressure limit for 6 hours to determine whether there is loss of mechanical integrity of the connectors, housing, or integral structures.

4.4.4 **Blood Volume Capacity of Oxygenator** (Guidance Document, page 5)

The Working Group recommends that FDA focus the determination for the oxygenator's blood volume capacity on the static volume of blood within the device. The Group, therefore, recommends that FDA delete the phrases "and dynamic (volume)" and "over the entire range of operating conditions" from the first sentence because these phrases are relevant for bubble oxygenators and reservoirs but are not relevant to the devices that are within the scope of this guidance. The revised sentence would read as follows:

Determine the static volume of blood within the device.

This section should be renumbered from 4.4.4 to 4.4.3 if the previous section is removed from the guidance.

4.5 **Performance Characterization** (Guidance Document, page 5)

The Working Group recognizes that manufacturers will be providing two different types of data in oxygenator 510(k)s. Some testing will be performed over the labeled life of the device to demonstrate that the device can meet the test requirements over the labeled duration. Other testing will be performed to characterize the performance of the device. Typically, the latter testing is conducted for a length of time that is appropriate to the characteristic tested. Characterization testing, therefore, need not necessarily be conducted for 6 hours. The Working Group recommends that FDA modify the specified duration for the various performance characterization tests as appropriate. Specific recommendations are provided below.

The Working Group recommends that FDA add a reference to tables 1-3 where the operating variables are described. The revised sentence would read as follows:

The performance characterization of the aged test, and predicate oxygenators should be based on dynamic testing over the entire range of operating variables, as described in tables 1-3, for the aged, sterilized test and predicate oxygenator for the maximum labeled life of the device using whole blood.

4.5.1 **Blood Used for Evaluations** (Guidance Document, page 5)

FDA's proposal suggests that testing should be performed with blood collected and stored at 5° C for less than 24 hours. The last sentence of this section suggests that antibiotics should be used when blood is stored for more than 24 hours. The Working Group recommends that FDA clarify the blood storage conditions by combining the first and last sentences since both pertain to blood processing. Furthermore, the Group recommends that FDA revise the

Guidance to indicate that the blood may be "refrigerated" rather than the current requirement for storage at 5° C because the Group feels that FDA's storage temperature will not allow for any temperature variations. The first sentence would be revised as follows:

> *Use fresh whole animal blood collected and refrigerated for less than 24 hours for performance testing, unless blood is stored for more than 24 hours in which case antibiotics should be used.*

The Working Group recommends that FDA allow use of appropriate anticoagulation protocols by deleting use of an "anticoagulant concentration of 4500 units of heparin per liter of blood" by revising the text as follows:

> *To minimize the effects of interanimal variation, it is advised that the common blood pool be composed of blood from more than one animal. FDA recommends an adequate anticoagulant protocol be used as appropriate.*

Currently, different anticoagulation protocols are required and used. As long as controls are used and tests are conducted in a similar fashion, use of different anticoagulation protocols should be appropriate.

4.5.2 Oxygen and Carbon Dioxide Transfer Rates/ Blood Side Pressure Drop (Guidance Document, page 6)

Gas transfer rate testing is conducted to demonstrate that a particular oxygenator meets its labeled ratings at certain gas flow rates. Testing of the oxygenator is, therefore, conducted over the manufacturer's specified range of operating variables. Data characterizing the oxygenator can be conducted for a time period that is relevant to the characteristic being evaluated. This type of testing does not necessarily need to be conducted for the 6 hours specified in FDA's Guidance. The Working Group recommends that FDA remove the 6 hour test duration requirement revising the gas transfer section as follows:

> *Gas transfer and blood side pressure drop characteristics are determined by circulating blood and gas through the test oxygenator over the manufacturer's specified range of operating variables. Changes in gas transfer and blood side pressure drop over time is determined by evaluating these characteristics over the labeled life of the test oxygenator as recommended by the manufacturer.*

4.5.2.1 General Testing (Guidance Document, page 6)

The general testing section includes eight different components for the testing circuit. The Working Group recommends that FDA delete "separate oxygenator acting as a" as a qualifier for the deoxygenator because in some test situations the manufacturer can use the test oxygenator to reequilibrate or deoxygenate. The revised bullet would simply read:

> *6. "Deoxygenator"*

The Working Group recommends that FDA add two components to the test circuit. The Group recommends that a blood gas analyzer and CO_2 analyzer should be added because these components are used to measure blood gases and are included for completeness. Bullets 9 and 10 would read:

9. *Blood Gas Analyzer*

10. *CO_2 analyzer*

The Working Group recommends that FDA modify the first sentence in the text following the bullets to change "separate oxygenator" to "device." The revised sentence would read:

> *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.*

4.5.2.2 Inlet Blood Conditions to Each Oxygenator for Gas Transfer (Guidance Document, page 7)

The Working Group is recommending that FDA revise the gas transfer evaluation characteristics as follows:

> *Use the following venous inlet blood conditions during gas transfer testing over the labeled life of the test oxygenator:*
>
> *$PvCO_2 = 45 \pm 5$ mmHg*
> *$pH = 7.4 \pm 0.1$*
> *Venous Base Excess $= 0 \pm 5$ meq/l*
> *Temperature $= 37 \pm 2°$ C*
> *Hemoglobin concentration $= 12 \pm 1$ g/dl*
> *Oxyhemoglobin saturation $= 65 \pm 5\%$*
>
> *Oxygenator outlet backpressure should be set at a minimum of 100 mmHg during gas transfer characterization and duration testing.*

The Working Group also recommends that FDA revise the test evaluation times from evaluation at baseline, 90, 180, 270, and 360 minutes to evaluation at "a minimum of baseline, 60, 180, and 360 minutes."

4.5.2.3 Gas Transfer and Blood Pressure Drop Data over the Operational Range of the Oxygenator (Guidance Document, page 7)

The Working Group believes that several different gas transfer protocols will provide data that will meet FDA's objectives. For example, some manufacturers perform two separate tests - one test that demonstrates short term gas transfer at three different gas flow rate ratios ("F/Qs") and another 6-hour test conducted at a F/Q at 1:1. The Working Group suggests that alternative testing may better simulate actual clinical conditions and evaluate the device's performance given a steady state of conditions over a longer period of time than that identified in FDA's Draft Guidance. The Group recommends that FDA adopt the following language:

> *The test oxygenator should be characterized for oxygen and carbon dioxide transfer rates, blood and gas side pressure drop measurements over the manufacturer's recommended range of operation (i.e., minimum, nominal, and maximum blood flow rates). Short term testing should include gas to blood flow rate ratios of 0.5:1, 1:1, and 2:1. Testing over the labeled life of the device should be performed at a 1:1 F/Q at the maximum flow rate.*

The Working Group recommends that FDA delete the phrase about "sweep gas and the gas pressures" because current testing provided in submissions presents data on the maximum performance of the device - the maximum flow blood flow rate and the maximum sweep rate (100%).

For the Carbon Dioxide Gas Transfer Data Set, the Working Group recommends that FDA change gas streams to gas flow because gas flow is the more common terminology. See Table 2. The revised sentence is as follows:

> *The gas flow entering and leaving the oxygenator should be analyzed for CO_2.*

Similarly, the Working Group recommends that FDA change inlet and outlet streams to inlet and outlet flow because "flow" is the more common terminology. The revised sentence is as follows:

> *%Change ΔCO_2 = the change in carbon dioxide concentration between the inlet and outlet flow [ml CO_2 (STPD)/L gas].*

For the Blood Pressure Drop Data Set in Table 3, the Group recommends that FDA change "a graph" to "graphs" because more than one table will be required to adequately depict the data in tables 1-3. The revised sentence will read:

> *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.*

Additionally, the Working Group recommends that FDA delete the following sentences from the Blood Pressure Drop description because manufacturers are stating and testing the labeled flow rate rather than at the blood flow rate where O_2 saturation is 95%:

> *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.*

In describing the backpressure experienced by the oxygenator's blood side outlet, the Group recommends that FDA change "approximately" to "a minimum of" 100 mmHg in the following sentence:

> *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 backpressure of a minimum of 100 mmHg during use.*

The Working Group also recommends that FDA move this sentence to the conditions described in paragraph 1 of this section, placing it immediately before Table 1.

4.5.2.4 Gas Transfer and Pressure Drop Data (Guidance Document, page 10)

In the draft Guidance, FDA indicated that plasma leakage should be performed during the 6-hour trial (in parallel with gas transfer testing). Additionally, FDA is suggesting that plasma leakage testing should be performed with blood flow rates at maximum flow. The Working Group does not believe that it is possible to perform plasma leakage where the blood flow has been maintained at a maximum flow rate for 6 hours when this testing is done in conjunction with gas-transfer testing because the F/Q is being changed periodically throughout the test period. Furthermore, plasma leakage testing is not relevant to short term use of oxygenators and is not routinely submitted in 510(k)s for these products. The Working Group recommends that all references to plasma leakage testing be deleted from this guidance. The Group recommends that the text in this section be revised as follows:

> *Change in oxygen and carbon dioxide transfer rates and blood and gas side pressure drop over time is measured at the maximum blood flow rate and at 1:1 gas flow rate. Samples are drawn at time 0 and one hour, and every three hours thereafter for the labeled life of the oxygenator.*

FDA has indicated that data shall be collected at 10 minute, 1 hour, 2, hour, 4 hour, and 6 hour time points. These data are collected at different times versus the gas transfer data. In order to make the times consistent, the Working Group recommends that FDA change the time periods for the tabular and graphical data from "10 mm, 1 hr, 2 hr, 4 hr, and 6 hr" to "baseline, 1 hr, 3 hr, and 6 hr" as follows:

The specified time intervals for tabular and graphical data are at baseline, 1 hr, 3 hr, and 6 hr.

The Working Group recommends that FDA add the following sections to the Guidance:

4.5.2.5 Data Collection and Calculations (new)

Calculated oxygen and carbon dioxide transfer rates should be provided in tabular and graphical form as a function of blood flow rate and gas flow rate.

To Calculate Oxygen Transfer:

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

To Calculate Carbon Dioxide Transfer:

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 streams [ml CO_2 (STPD)/L gas].

Blood side pressure drop should be provided in tabular and graphical form as a function of blood flow rate.

Gas side pressure drop should be provided in tabular and graphical form as a function of gas flow rate.

4.5.2.6 Raw Data and Calculated Data Tables (new)

For change in gas transfer over time and gas transfer characterization, provide a table containing raw data. Include blood flow (Q), gas flow (F), CO_2 concentration, arterial and venous blood gases, and arterial and venous saturation.

Table 4

			ARTERIAL SAMPLE				VENOUS SAMPLE			
Q	F	CCO_2	pH	PCO_2	PO_2	SAT	pH	PCO_2	PO_2	SAT

For gas transfer characterization, provide a table containing oxygen transfer rate for each of the different F/Qs and a table containing carbon dioxide transfer rate for each of the blood flow rates.

For change in gas transfer over time, provide a table containing oxygen transfer rate over the minimum and maximum rated blood and gas flow rates and a table containing carbon dioxide transfer rate over the minimum and maximum rated blood and gas flow rates.

For blood side pressure drop characterization and change over time, provide a table containing the pressure drop for each flow rate.

For gas side pressure drop characterization and change over time, provide a table containing the pressure drop for each gas flow rate.

5. Heat Exchanger Performance Evaluation (Guidance Document, page 11)

5.1 General Testing (Guidance Document, page 11)

The Working Group recommends that the component in the testing circuit described in item 6 that acts to "chill the blood" be revised from "separate heat exchanger" to "heat exchange device." This change is being made because the heat exchanger may be part of the device. As revised, bullet number 6 will read:

Heat exchange device acting to chill the blood

The word "separate" should also be removed from the description of the heat exchanger in the paragraph immediately following item 7 as follows:

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.

5.1.1 **Inlet Blood Conditions to Each Oxygenator** (Guidance Document, page 11)

The Working Group suggests that FDA delete the use of a water bath in the following sentence because a water bath is not necessarily needed during this evaluation:

> *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**

The Working Group has no comments.

5.1.3 **Heat Transfer and Water Pressure Drop Data (Six hour duration)** (Guidance Document, page 12)

In the Draft Guidance at 5.1.3, FDA indicated that blood should be circulated at the maximum recommended flow rate. Table 4 indicates that data are to be provided at three different blood flow rates which is not consistent with the requirement in Section 5.1.3. The Working Group believes that the maximum flow rate should be sufficient because this rate would represent worst case testing for effective heat transfer. Additionally, this testing should be adequate because heat exchangers do not change over time. The Group, therefore, recommends that FDA delete section 5.1.3 which reads as follows:

> *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.*

The Working Group recommends that FDA delete the Water Pressure Drop Data Set in Table 5 because it is not relevant. The sentence immediately following Table 5 should be moved to the end of Table 4. After Table 4, the paragraph should read:

> *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.*

The Working Group recommends that FDA delete the following sentence because waterside pressure drop has little clinical relevance and manufacturers have not been including waterside pressure drop in their oxygenator 510(k)s:

> *Provide a graph along with the data tables showing the waterside pressure drop as a function of blood flow rate and water flow rate.*

Furthermore, the Working Group recommends that FDA move the last paragraph in section 5.1.3 to section 5.1 before the beginning of section 5.1.1 because the paragraph describes criteria that are generally applicable to the evaluation of the heat exchanger's performance. Furthermore, the Group recommends that FDA change "approximately" to "a minimum of" 100 mmHg in the following sentence:

> *To better simulate the clinical use of the device, data may also be submitted showing the effects on heat transfer and water pressure drop when the blood side outlet of the oxygenator experiences a backpressure of a minimum of 100 mmHg during use.*

5.2 Blood Damage Performance Evaluation (new section would be 6.) (Guidance Document, page 14)

The Working Group recommends that FDA change the numbering of the Blood Damage Performance Evaluation section from Section 5.2 to Section 6.0.

The Group recommends that FDA change the evaluation period from "six hours in duration" to the "labeled life as recommended by the manufacturer." As revised, the new section 6.0 reads:

> *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 the labeled life as recommended by the manufacturer.*

5.2.1 General Testing (new section would be 6.1) (Guidance Document, page 14)

The Working Group recommends that FDA remove the evaluation of the control blank circuit due to the number of variables that can influence the test results by eliminating the paragraph following the test circuit components and replacing with the following:

> *The test oxygenator and the predicate oxygenator should be tested using identical circuits with the same pool of blood.*

5.2.1.1 Condition of Blood for Blood Damage Testing (new section would be 6.1.1) (Guidance Document, page 14)

The Working Group recommends that FDA not specify the conditions of the blood for blood damage testing because the 7199 standard dictates the conditions that are appropriate for blood damage testing. The paragraph should be deleted and replaced with the following:

> *Conditions of the blood for blood damage testing should be consistent with 7199.*

5.2.1.2 Blood Damage Testing Protocol (new section would be 6.1.2) (Guidance Document, page 15)

The Working Group recommends that FDA revise the text in the first paragraph to delete reference to "gas flow rate" because gas flow rate is not necessary to maintain physiological parameters at the maximum flow because, with this kind of circuit, the parameters tested will reflect the gas flow rate tested. The sentence, as revised, reads:

> *The blood flow rate to the oxygenator will be the maximum specified by the manufacturer.*

The Working Group recommends that FDA change "approximately" to "a minimum of" 100 mmHg in the following sentence:

> *The back pressure on each oxygenator should be maintained at a minimum of 100 mmHg during use to simulate clinical use.*

The Working Group recommends that the first procedure that needs to be controlled should be qualified to indicate that this procedure is only required if a roller pump is used. This change should be made because a manufacturer may not use a roller pump. As revised, the first procedure should read:

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

The Working Group recommends that the fourth procedure be revised to change "clearing" to "purging" and to delete "(for disposal)." Furthermore, the sentence should be revised to more accurately reflect the current purging practice. As revised, the fourth procedure should read:

- *purging each blood sampling port by withdrawing blood in a syringe prior to taking the actual blood sample using a second syringe*

Similarly, the Group recommends that the following sentence be revised to apply only when a roller pump is used:

> *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.*

The Working Group recommends that FDA revise the following sentence to read:

> *Due to uncontrollable variations in blood, it is preferable to perform the blood damage testing on the test oxygenator circuit and the predicate oxygenator circuit at the same time using the same blood pool.*

The Working Group recommends that the total circuit blood volume should be dependent on the maximum blood flow rate rather than on a specific blood volume. The Group, therefore, recommends that FDA revise the text as follows:

> *In general, the total circuit blood volume should be dependent on the maximum recommended blood flow rate.*

5.2.1.3 Blood Damage Data Reporting (new section would be 6.1.3) (Guidance Document, page 16)

The Working Group recommends that FDA change the blood damage raw and calculated data from "each of the individual testing circuits" to "each device." Additionally, the Group believes that calculated data should be provided in both tabular and graphical form, but that it is appropriate to only provide raw data in tabular form. The revised sentences should read:

> *Raw data and calculated data (with respect to "baseline" values) for each device should be provided in tabular form. Calculated data should also be provided in graphical form.*

The Working Group recommends that the blood damage data reporting section be clarified as follows:

> *Mean (± SD) results should also be tabulated and graphed for the aged, sterilized test oxygenator circuit and the predicate oxygenator circuit at the same time using the same blood pool.*

The Working Group recommends that the final report describe the correlation between data from the various circuits rather than the day, time and blood pool that were used because the results will be dependent on the maximum recommended blood flow rate. The Group, therefore, suggests that FDA delete "The day, time, and blood pool that were used in the testing of each circuit" and revise the following sentence as follows:

> *Correlation between the blood used with the control and test circuits run for each set of data should be apparent in the final report.*

TABLE 6. Parameter Sampling Schedule

It is not necessary, nor is it beneficial to perform hemolysis at the minimum labeled blood flow rate. The indicated areas of concern can be determined in other testing. Furthermore, it is very difficult to maintain the suggested activated clotting time ("ACT") of 300 seconds during *in vitro* testing; simply specifying a minimum time period provides the manufacturer with much greater flexibility in performing this evaluation. Table 6 has been revised to reflect the Group's recommended sampling schedule as follows:

TABLE 6. Parameter Sampling Schedule

Parameter	Main Blood Pool	Sampling Schedule (minutes) Baseline*	30	90	180	360
Plasma Hemoglobin Concentration	X	X	X	X	X	X
Activated Clotting Time (ACT)	X	X	X		X	X
Hematocrit	X	X	X		X	X
Platelet and White Blood Cell Count		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

The Working Group recommends that FDA delete all of the text describing the normalized "index of hemolysis" and modified index of hemolysis following Table 6 because the index of hemolysis does not provide meaningful information. The gas flow rates are set to maintain physiological blood/gas values. Thus the Working Group recommends that the following paragraph below Table 6 be deleted:

> *Traditionally, only the plasma hemoglobin concentration at time zero and time 360 min were used to calculate the index of hemolysis . . . where tHb (mg/dl) = average total hemoglobin concentration in the circuit.*

In the next paragraph, FDA recommends that manufacturers perform "supplemental testing for up to six hours in duration." For reasons stated previously, the Working Group recommends that this language be changed from "up to six hours in duration" to "for the labeled life of the oxygenator."

> *Although a standardized testing protocol has not been established, supplemental testing for the labeled life of the oxygenator 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 recommended.*

5.3 Acceptable Endpoints (new section would be 6.2) (Guidance Document, page 19)

The Working Group recommends that FDA modify the endpoints to focus on the statutory requirement of demonstrating that the oxygenator is substantially equivalent to a predicate device. Furthermore, the oxygenator should meet device specifications. The Group recommends Section 5.3 be revised to read:

> *The oxygenator should meet product specifications and be substantially equivalent to the predicate or other legally marketable oxygenators.*

5.4 Biological/Material Compatibility (new section would be 6.3) (Guidance Document, page 19)

FDA has indicated that the test oxygenator should "not be significantly different than the predicate oxygenator in terms of its biological or material compatibility." The compatibility testing should only be performed on the test article to determine its biocompatibility. No comparison testing should be required. The Working Group recommends that FDA revise the sentence to read:

> *The test oxygenator will demonstrate acceptable biological/material compatibility.*

5.5 Physical Characterization/Integrity (new section would be 6.4) (Guidance Document, page 19)

It is not entirely clear how FDA determined what the appropriate physical characterization/integrity specifications should be for test oxygenators. The Working Group is not aware that these specifications have been published in the literature. Furthermore, as previously indicated, the blood flow rate cannot be tested at 10.5 LPM due to possible limitations of the equipment. Finally, the Group does not, in its collective experience, feel that such testing is representative of clinical expectations. Therefore, the Group recommends that FDA revise Section 5.5 to read:

> *The test oxygenator should withstand 1.5 times maximum recommended blood and water pathway pressures.*

5.6 Performance Characterization (new section would be 6.5) (Guidance Document, page 19)

In the Draft Guidance, FDA suggests that the oxygenator's performance characterization should be based on four criteria. The Working Group believes that the performance of the test oxygenator should be compared to the predicate device without delineating specific thresholds for such evaluation. The manufacturer need only demonstrate that the test oxygenator is substantially equivalent to a legally marketable predicate. The Group is justifiably concerned

that these criteria were not based on published literature. The Working Group recommends that FDA revise section 5.6 to delete the four criteria and revise the section as follows:

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

6. Packaging (new section would be 7.) (Guidance Document, page 19)

6.1 Performance Evaluation (new section would be 7.1) (Guidance Document, page 19)

FDA suggested that the packaging performance evaluation should be based on four criteria. While the Working Group agrees with the first three criteria, the Group strongly recommends that the fourth criteria be deleted. As written, the fourth criteria instructs the manufacturer to:

> *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.*

Currently, FDA has the option to require clinical data when appropriate. Therefore, criteria 4 is redundant and should be removed.

6.2 Labeling 510(k) Certifications (new section would be 7.2) (Guidance Document, page 20)

The Working Group recommends that "Instructions for Use" be removed from the header for Section 6.2 because some of this section applies to required statements in the 510(k), while other parts of this section applies only to labeling requirements. The Group recommends that the section be broken into two sections: the (1) 510(k) certifications section will contain 510(k)-required labeling statements and (2) labeling requirements that will contain statements required on the package label or in the instructions for use.

Labeling is required as a component of every 510(k) submission. *See* 21 C.F.R. § 807.87(e). FDA included seven (7) criteria in its requirements for oxygenator labeling. The Working Group will address each of FDA's proposed criteria.

Criteria 1

The Group recommends that "bioburden" be changed to "nonpyrogenic or fluid path non-pyrogenic" because bioburden is only used to monitor cleanroom environment and to determine sterility assurance levels (SALs). Criteria 1 as revised should read:

1. *The 510(k) will contain a statement that biological testing (including pyrogen and nonpyrogenic or fluid path nonpyrogenic testing) will be or has been performed to assess acceptable limits of biological contaminants.*

Criteria 2

The Group recommends that the labeling contain a statement that package shelf life validation testing has been or will be performed. The labeling does not need to contain the extensive information FDA has proposed in criteria 2 because the information is already provided in the product's device history file.

2. *The 510(k) will include a statement that package shelf life validation will be or has been performed.*

Criteria 3

The Group strongly recommends that Criteria 3 be deleted because Section 4 of the ANSI/AAMI VP20-1994 standard does not provide a safer, more effective product.

Criteria 4-7

The Group recommends that FDA create a separate section for criteria 4-7 entitled "Labeling Requirements." While the Group agrees with the content of criteria 4, 6, and 7, the Group would suggest that FDA delete criteria 5 because the instructions for opening the sterile package would be covered by criteria 7 indicating that the health care provider must observe aseptic technique. Furthermore, the Group would recommend that FDA add a required warning as described in 4.3 above. The revised section would read as follows:

6.2.1 Labeling Requirements (new) (new section would be 7.3)

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

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

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

4. *The labeling should contain a statement cautioning the user against use of the oxygenator with liquid volatile anesthetics.*