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April 30, 1999

Janice Rullo
President and Chief Executive Officer
Rultract, Inc.
16 Morning Sun
Irvine, CA 92612

Re: Sterilization Verification Documentation

Dear Janice:

We are enclosing Biotest Laboratories, Inc.'s sterilization validation report for your currently recommended sterilization process as well as Gregg Mosley's additional reports verifying that Rultract's previously recommended steam sterilization processes were adequate. The reports are as follows:

1. Biotest's Core Report.

The main Biotest report is the binder entitled, "Verification of the 250°F Gravity, 270°F Gravity (Flash) and Prevacuum Steam Sterilization Cycles Recommended for Hospital Sterilization of the Rultract Surgical Retractors with the 'Skyhook' Spline Post/Clamp Systems Manufactured by Rultract, Inc." (also referred to as the "core report"). This report establishes your currently recommended cycle using conservative sterilization validation methods that are recognized in international standards and are accepted by FDA. These methods document the acceptability of the following recommended cycles:

- Prevacuum wrapped: 270°F at 5 minutes
- Flash unwrapped: 270°F at 5 minutes
- Gravity wrapped: 250°F at 40 minutes

The cycles are based on the hardest-to-sterilize area on the Rultract device, which was found to be the interior of the ball and socket joint. They provide Sterility Assurance Levels (SAL) of 10^{-20} or better, which are well in excess of the FDA's benchmark 10^{-6} SAL for implanted and blood-contact devices.

The recommended cycles were calculated using a conservative "overkill" approach known as the AAMI half cycle method. It uses the actual D_{121} value[1] of the organisms used in the sterilization test runs and an assumed bioburden of 10^6. It also requires complete destruction of all biological indicator organisms in the half cycle, as opposed to using a statistical approach. The organism used in the sterilization test runs, B. stearothermophilus, actually is a heat-loving spore-forming organism that would not be expected to be part of a room-temperature environment, such as a hospital, and is more heat resistant than organisms that would be expected to cause human infections. Accordingly, the use of this D-value and bioburden level constitutes a very conservative assumption about the number and heat resistance of the organisms the process is designed to kill.

Thus, the AAMI half-cycle method is an extremely conservative method of establishing a sterile process that is designed to be used by manufacturers of terminally sterilized medically devices that are then shipped sterile to the user location. Nevertheless, it is appropriate to use as Rultract's recommended process for hospitals, as it is the most commonly used way of evaluating prospectively the adequacy of a sterile process for a medical device, and it would be well understood by regulators.

2. Consultation Report Dated February 3, 1999.

This report describes Gregg Mosley's review of the adequacy of the original steam gravity cycle of 30 minutes at 250°F, using the data collected during the core validation study relating to the hardest-to-sterilize areas of the Rultract device. This review indicates that the original cycle was satisfactory to produce the required sterility assurance level (SAL) of 10^{-6} or better.

To analyze the actual processes that Rultract had been using, this report uses an overkill approach that assumes a D_{121} of 1.0 minute and a bioburden of 10^{-6}. This D-value reflects better both the types of organisms that would be expected to be found in normal temperature environments for

[1] The "D_{121}" value is the exposure time in saturated steam at 121°C required to cause a 1-logarithm, or 90%, reduction in the population of a particular organism.

human habitation and that are of concern in regard to human infection.[2] The analysis is based on ANSI/AAMI ST 34, which is an FDA-recognized consensus standard. The standard was developed for use with parenteral products, and cycles meeting the requirements of this approach are adequate to assure the safety of medical devices sterilized using them, assuming a normal temperature environment, good hospital practices in regard to handling instruments, and normal cleaning of the devices before sterilization. We note that presterilization cleaning instructions always have been part of Rultract's labeling.

3. Consultation Report of March 24, 1999.

This report adds the evaluation of Rultract's previous prevacuum and flash cycles to the written evaluation of the adequacy of Rultract's past cycles. It concludes that the flash cycle of three minutes at 270°F, unwrapped, and the pre-vacuum cycle of four minutes at 270°F, wrapped, both were adequate to produce an SAL of better than 10^{-6}. This evaluation of Rultract's previously used cycles was performed using the same method as was described in the February 3, 1999, consultation report discussed above.

* * * * *

Taken together, these reports mean that the cycles recommended in Biotest's core report should be used going forward, as they are the most conservatively designed cycles and the methodology is in common usage for devices that are shipped sterile. Nevertheless, an evaluation of the previously recommended cycles verifies that they delivered a sterility assurance level that met current safety standards, provided they were executed properly by the hospital.

You should maintain these studies in your files in case they are ever requested as validation of your currently or previously recommended cycles. If you redesign the device or make changes to it, you always should take into account, as part of the risk assessment that is incorporated into the change process, whether the change might affect the required sterility cycle. If a change could affect the cycle, it should be evaluated to determine whether a different cycle is appropriate.

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[2] By comparison, B. stearothermophilus has a D_{121} of 1.5-2.5 minutes and is "among the most heat-resistant of known living things." M. Frobisher, Fundamentals of Microbiology 273 (8th Ed. 1969). B. stearothermophilus grows at around 55°C (131°F) which is well above both ambient room temperature and human body temperature.

Please let us know if you have any questions.

Sincerely,

C. Stephen Lawrence
Hogan & Hartson L.L.P.

Gregg A. Mosley
Biotest Laboratories, Inc.

CSL:kmg

CONSULTATION REPORT
3/24/99

Review of Biotest Report RUL9812202FR 1/13/99 and Calculations of Sterility Assurance Levels for a 30 Minute, Gravity 250°F, 3 Minute Gravity "Flash" 270°F, and a 4 Minute 270°F Prevacuum Steam Sterilization Cycle.

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Consultation Report

I. BACKGROUND:

1.0 All calculations referenced are taken from data derived from the location proven to be the "most difficult to sterilize" in the study. (Biotest Laboratories Inc. report RUL981202FR) The calculations on pages 8 through 12 for the three different half cycles tested correctly indicate a minimum process log reduction value (LRV) of 13.09 logs at the "most difficult to sterilize" location.

Log Reduction Values at the "most difficult to sterilize" Location

Cycles Tested	Calculated LRV
20 Minute 250°F Gravity Cycle	>13.09 logs*
2.5Minute 270°F Prevacuum Cycle	>13.09 logs*
2.5Minute 270°F Gravity Cycle	>13.09 logs*

*B.stearothermophilus biological indicators D_{121}=1.9minutes

The report also identifies that the full cycles produced LRVs in excess of 26.18 (2 x 13.09) and SALs in excess of 10^{-20}. What the report does not show is that Rultract's originally recommended cycles would produce acceptable LRVs and SALs with respect to the "most difficult to sterilize" location.

2.0 Definitions

2.1 D_{121} -The exposure time of saturated steam at 121°C required to cause a 1-logarithm or 90% reduction in the population of a particular microorganism.

2.2 Log Reduction Value (LRV) -The number of logs a population (biological indicator) has been reduced during a specified process.

2.3 Sterility Assurance Level (SAL) -The expected probability that an item is sterile after exposure to a valid sterilization process, often expressed in terms of the probable maximum frequency of contamination.

II. CALCULATIONS:

1.0 Log Reduction Values (LRVs) for the cycles originally recommended by Rultract will be calculated by using the data obtained from (RUL981202FR). The relationship of LRV and exposure time is directly proportional when comparing one cycle time to another cycle time.

2.0 The LRVs and SALs are dependent on the D_{121}=1.0 minute value used as the reference value in ANSI/AAMI ST 34 (5.3.2 pg. 6) which is one of the FDA recognized consensus standards. On the pharmaceutical side the D_{121}=1.0 minute value is used almost exclusively and is based on Technical Monograph No. 1 - Validation of Steam Sterilization Cycles published by The Parenteral Drug Association, Inc. in 1978. The SAL calculations use the AAMI overkill approach and assume a bioburden of 10^6 with a resistance equivalent to D_{121} = 1.0 minute.

2.1 30 Minute 250°F Gravity, wrapped

LRV = (1.5 x 13.09) = 19.64 and a SAL in excess of 10^{-13}. This is in excess of the required 10^{-6} (1.5 is the multiplication factor used to compute the LRV based on the 20 minute fractional cycle data)

2.2 4 Minute 270°F Prevacuum, wrapped

LRV = (1.6 x 13.09) = 20.94 and a SAL in excess of 10^{-14}. This is in excess of the required 10^{-6} (1.6 is the multiplication factor used to compute the LRV based on the 2.5 minute fractional cycle data)

2.3 3 Minute 270°F "Flash" Gravity, unwrapped

LRV = (1.2 x 13.09) = 15.71 and a SAL of 10^{-9}. This is in excess of the required 10^{-6} (1.2 is the multiplication factor used to compute the LRV based on the 2.5 minute fractional cycle data)

Summary of Rultract's Originally Recommended Cycles
"most difficult to sterilize" location

Recommended Cycles	LRV		SAL Based on D_{121}=1.0 minute	
	Cycle Data Utilized For Calculations		Cycle Data Utilized For Calculations	
	2.5 Min.	20 Min.	2.5 Min.	20 min.
250°F 30 Minute Gravity	-	19.64	-	$>10^{-13}$
270°F 4 Minute Prevacuum	20.94	-	$>10^{-14}$	-
270°F 3 Minute "Flash" Gravity	15.71	-	$>10^{-9}$	-

III. REFERENCE CYCLES:

1.0 The originally recommended Rultract process cycles of 250°F 30 minutes gravity wrapped, 270°F 4 minute prevacuum wrapped and 270°F 3 minute "Flash" unwrapped is in keeping with ANSI/AAMI ST 46 section 5.8.2, which is also one of the FDA recognized consensus standards. The cycles are also in agreement with Annex B of AAMI TIR 12.

IV. CONCLUSIONS:

1.0 The following cycles have been shown to produce a SAL of 10^{-6} using FDA accepted references. These cycles are in keeping with referenced AAMI recommendations.

250°F 30 minutes, gravity, wrapped
270°F 4 minutes, prevacuum, wrapped
270°F 3 minutes, "Flash" gravity, unwrapped

V. REFERENCE DOCUMENTS:

1.0 FDA Recognized Consensus Standards, Appendix A. Supplemental Data Sheets. http:www.fda.gov/cdrh/modact/rccstand.html. Center for Devices and Radiological Health. 1/20/99 10:56 AM.

2.0 Association for the Advancement of Medical Instrumentation. Good hospital practice: Steam sterilization and sterility assurance, 3rd. edition (ANSI/AAMI ST46-1993). Arlington, VA: AAMI, 1993.

3.0 _____Good Hospital Practice: Flash sterilization steam sterilization of patient care items for immediate use, 3rd edition (ANSI/AAMI ST37-1996). Arlington, VA: AAMI, 1996.

4.0 _____American National Standard for Biological Indicators for Saturated Steam Sterilization Processes in Health Care Facilities (ANSI/AAMI ST19-1994). Arlington, VA: AAMI, 1994.

5.0 _____Steam sterilization and sterility assurance using table-top sterilizers in office-based, ambulatory-care medical, surgical, and dental facilities. (ANSI/AAMI ST-40 1992). Arlington, VA: AAMI, 1992.

6.0 _____Guideline for the use of ethylene oxide and steam biological indicators in industrial sterilization processes. (ANSI/AAMI ST-34 1991). Arlington, VA: AAMI, 1991

7.0 _____Designing, Testing and Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: A Guide for Device Manufacturers. (AAMI TIR-12 1994). Arlington, VA: AAMI, 1994

8.0 US FDA Guideline on General Principles of Process Validation. May 1986

9.0 US Pharmacopoeia (23rd ed.). (1211) Sterilization and Sterility Assurance of Compendia Articles. Taunton, MA: Rand McNally, 1994.

10.0 Parenteral Drug Association. Validation of Steam Sterilization Cycles. PDA Technical Monograph No. 1. Philadelphia, PA: PDA; 1978

11.0 ISO. Sterilization of Health Care Products – Biological Indicators – Part 3: Biological Indicators for Moist Heat Sterilization (ISO 11138-3). Geneve Switzerland. 1995.

VI. SIGNATURE

Gregg A. Mosley
Consultant

4/8/99
Date