

REPORT

TEST FACILITY

NAMSA
6750 Wales Road
Northwood, OH 43619
419.666.9455

SPONSOR

Frank Fontan
Fiberguide Industries, Inc.
1 Bay Street
Stirling, NJ 07980

CONFIDENTIAL

STUDY TITLE

ISO Muscle Implantation Study - 1 Week

TEST ARTICLE NAME

HARD CLAD OPTICAL FIBER

TEST ARTICLE IDENTIFICATION

Lot: B042409A-1

NAMSA

TABLE OF CONTENTS

Page

Summary 3

1. Introduction..... 4

2. Materials 4

3. Test System 4

4. Animal Management 5

5. Method 5

6. Evaluation and Statistical Analysis..... 6

7. Results 6

8. Conclusion..... 6

9. Records 6

10. References 7

Appendix 1 - Body Weights and Macroscopic Observations..... 8

Appendix 2 - Microscopic Evaluation..... 9

Summary

The test article, HARD CLAD OPTICAL FIBER, Lot: B042409A-1, was implanted in muscle tissue of the rabbit. The muscle tissue was evaluated for evidence of irritation or toxicity in accordance with the International Organization for Standardization 10993-6, Biological Evaluation of Medical Devices – Part 6: Tests for Local Effects after Implantation.

Implant test articles and negative control articles were sterilized by ethylene oxide and then degassed for 7 days. The test article and negative control were implanted into rabbits and were then euthanized 1 week later. Muscle tissues were excised and the implant sites were examined macroscopically. A microscopic evaluation of representative implant sites from each rabbit was conducted to further define any tissue response.

Under the conditions of this study, the macroscopic reaction was not significant as compared to the negative control article. Microscopically, the test article was classified as a nonirritant as compared to the negative control article.

Study and Supervisory

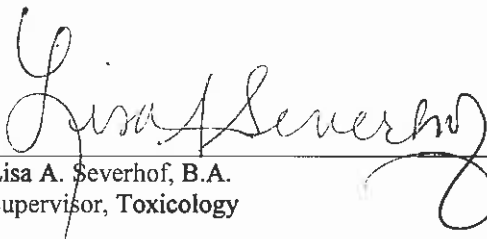
Personnel:

Lisa A. Severhof, B.A.

Contributing Scientist:

Robert F. Parker, D.V.M., Ph.D., D.A.C.V.P.
Study Pathologist

Approved by:



Lisa A. Severhof, B.A.
Supervisor, Toxicology

7-6-09
Date Completed

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1. Introduction

Purpose

The test article identified below was evaluated for the potential for a local irritant or toxic response to material implanted in direct contact with muscle tissue.

Testing Guidelines

The study was conducted based on the International Organization for Standardization 10993-6: Biological Evaluation of Medical Devices, Part 6: Tests for Local Effects after Implantation.

Dates

Test Article Receipt: May 26, 2009
Implant Date: June 4, 2009
Explant Date: June 11, 2009

2. Materials

The test article provided by the sponsor was identified and handled as follows:

Test Article Name: HARD CLAD OPTICAL FIBER

Test Article Identification: Lot: B042409A-1

Storage Conditions: Room Temperature

Negative Control Article: USP high density polyethylene reference standard was purchased from the US Pharmacopeial Convention.

Control Article

Stability Testing: Marketed product stability characterized by its labeling.

Control Article Strength, Purity and Composition:

Strength: Not applicable, no active components in the formulation; Purity: USP Certified Standard; Composition: Neat CAS #: 9002-88-4.

Preparation:

A minimum of four sections of the test article per rabbit, each approximately 1 mm x 1 mm x 10 mm were loaded into 16 gauge needles. For each rabbit, a minimum of four negative control articles were loaded into the same size needles as used for the test article. For each rabbit, a minimum of four negative control articles were prepared. Test and control articles were sterilized by ethylene oxide gas (EO) and then degassed for 7 days prior to implantation.

3. Test System

Test System

Species: Rabbit (*Oryctolagus cuniculus*)
Breed: New Zealand White
Source: Myrtle's Rabbitry, Inc.
Sex: Male
Body Weight Range: 2.8 kg to 3.2 kg at implantation
Age: Young adult
Acclimation Period: Minimum 5 days
Number of Animals: Three
Identification Method: Ear tag

Justification of Test System

The rabbit is the animal model identified for evaluating polymer materials. The muscle tissue is evaluated because the response to implanted material is easily graded and compared to a known negative control material.

4. Animal Management

| | |
|------------------|---|
| Husbandry: | Conditions conformed to NAMSA Standard Operating Procedures that are based on the " <i>Guide for the Care and Use of Laboratory Animals</i> ." |
| Food: | A commercially available rabbit feed, PROLAB Hi-Fiber Rabbit – 5P25, was provided daily. |
| Water: | Potable water was provided <i>ad libitum</i> through species appropriate water containers or delivered through an automatic watering system. |
| Contaminants: | Contaminants reasonably expected in feed or water supplies were not believed to have influenced the outcome of this test. |
| Housing: | Animals were individually housed in stainless steel suspended cages identified by a card indicating the lab number, animal number, test code, sex, and date implanted. |
| Environment: | The animal housing room temperature and relative humidity was monitored daily. The recommended temperature range for the room was 61-72°F and 30-70% for relative humidity. There were no significant temperature or relative humidity excursions that adversely affected the health of the animals. The light cycle was controlled using an automatic timer (12 hours light, 12 hours dark). |
| Accreditation: | NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare. |
| Personnel: | Associates involved were appropriately qualified and trained. |
| Selection: | Healthy animals were selected. To reduce the number of animals used for testing, and to comply with the directives of the NAMSA IACUC, rabbits on this study were used previously in an unrelated test model. Any previously evaluated test or control articles did not cause a response in the animals. Complete history of animal usage is traceable in laboratory records. Animals used for previous evaluations are identified in the report. |
| Veterinary Care: | Standard veterinary medical care was provided in this study. |
| IACUC: | This procedure has been approved by NAMSA Institutional Animal Care and Use Committees (IACUC), and is reviewed at least annually by the same committees. Any significant changes to this procedure were approved by the IACUC prior to conduct. |

5. Method

Rabbits were weighed and clipped free of fur over the paravertebral muscles. For general anesthesia, each rabbit was injected intramuscularly with a mixture of ketamine hydrochloride and xylazine (34 mg/kg + 5 mg/kg) at a dose volume of 0.6 mL/kg. For analgesia, each rabbit was then injected subcutaneously with 0.02 mg/kg buprenorphine. After the anesthetic had taken effect, the shaved area was cleaned with povidone iodine scrub, wiped with 70% isopropyl alcohol and painted with povidone iodine solution. A non-medicated ophthalmic ointment was applied to both eyes of each animal and reapplied at the discretion of the veterinarian.

One incision was made on each side of the back through the skin and parallel to the lumbar region of the vertebral column. A stylet was placed in the hub of a loaded needle. The skin was moved to the desired location and the needle was inserted through the incision into the muscle at a 45° angle. The needle was withdrawn over the stylet, leaving the article in the paravertebral muscle. Four test article sections were implanted in the right paravertebral muscle of each rabbit. Test article sections were placed at appropriately spaced intervals. In the opposite muscle, four negative control sections were similarly implanted. The skin incisions were closed with tissue glue.

Rabbits were returned to their respective cages following the procedure and monitored for recovery from the anesthetic. Another dose of buprenorphine was administered at the end of the day. On the day following implantation, a third buprenorphine injection was administered.

Laboratory Observations

1. Rabbits were observed daily for general health.
2. Body weights were recorded prior to implantation and at termination.

Terminal Procedures

At 1 week, the rabbits were weighed and then euthanized by an intravenous injection of a sodium pentobarbital based drug. The paravertebral muscles were dissected free and fixed in 10% neutral buffered formalin (NBF) to facilitate cutting. After fixation, the muscles were methodically cut to locate test and control article sites. All test and control sites were accounted for. Capsule formation or other signs of irritation were scored using low magnification and the scores were recorded as follows:

- 0 = No capsule, no adverse reaction (other than minimal hemorrhage)
- 1 = Up to 0.5 mm capsule or reaction area
- 2 = 0.6 to 1.0 mm capsule or reaction area
- 3 = 1.1 to 2.0 mm capsule or reaction area
- 4 = >2.0 mm capsule or reaction area

Representative tissue implant sites (test and control) from each rabbit were excised, allowing a sufficient area around the site for proper histological preparation. These sections were histologically processed (embedded, sectioned and stained in hematoxylin and eosin) for microscopic evaluation.

All times and temperatures reported herein are approximate and are within ranges established by the external standards described in the References section of this report and/or NAMSA standard operating procedures.

6. Evaluation and Statistical Analysis

The average macroscopic score for test sites was compared with the average score of the control sites. Calculations were rounded to the nearest 0.1. A difference of 0.0 to 0.5 in scores (test minus control) was regarded as "not significant," 0.6 to 1.0 as "trace," 1.1 to 2.0 as "slight," 2.1 to 3.0 as "moderate" and ≥ 3.1 as "marked."

A microscopic evaluation of representative implant sites from each rabbit was conducted to further define any tissue response. The evaluation was conducted by a pathologist. The microscopic irritant response was graded as nonirritant, slight, moderate, or severe.

7. Results

Clinical Observations

All animals appeared clinically normal throughout the duration of the study.

Body Weight Data

Body weight data for individual rabbits were considered acceptable. Individual body weights appear in Appendix 1.

Macroscopic Observations

There was no visible reaction at any test or control site.

This resulted in a macroscopic reaction classification of not significant tissue contact irritation.

The findings for the macroscopic evaluation are shown in Appendix 1.

Microscopic Observations

The test article was a nonirritant as microscopically compared to the negative control article. Individual results of the pathology findings appear in the microscopic evaluation report (Appendix 2).

8. Conclusion

Under the conditions of this study, the macroscopic reaction was not significant as compared to the negative control article. Microscopically, the test article was classified as a nonirritant as compared to the negative control article.

Results and conclusions apply only to the test article tested. Any extrapolation of these data to other samples is the sponsor's responsibility. All procedures were conducted in conformance with good manufacturing practices and certified to ISO 13485:2003.

9. Records

All raw data, wet tissues, paraffin blocks and tissue slides pertaining to this study and a copy of the final report are to be retained in designated NAMSA archive files.

10. References

Code of Federal Regulations (CFR), Title 9, Parts 1-199, Animal Welfare Act (2008).

National Research Council, *Guide for the Care and Use of Laboratory Animals*, Washington, DC: National Academy Press, 1996.

Office of Laboratory Animal Welfare (OLAW), Public Health Service Policy on Humane Care and Use of Laboratory Animals.

United States Pharmacopeia 31, National Formulary 26 (USP), General Chapter <88>, Biological Reactivity Tests, In Vivo, Implantation Test, Table 6: Evaluation of Encapsulation in the Implantation Test (2008).

International Organization for Standardization (ISO) 10993-6, Biological Evaluation of Medical Devices – Part 6: Tests for Local Effects after Implantation (2007).

International Organization for Standardization (ISO) 10993-2, Biological Evaluation of Medical Devices - Part 2: Animal Welfare Requirements (2006).

Appendix 1 - Body Weights and Macroscopic Observations

| Animal Number | Sex | Body Weight (kg) | | Test Article | Negative Control |
|---------------|------|------------------|-------|--------------|------------------|
| | | Day 0 | Day 7 | | |
| 62586* | Male | 3.1 | 3.1 | 0 | 0 |
| | | | | 0 | 0 |
| | | | | 0 | 0 |
| | | | | 0 | 0 |
| 62663* | Male | 3.2 | 3.2 | 0 | 0 |
| | | | | 0 | 0 |
| | | | | 0 | 0* |
| | | | | 0 | 0* |
| 62774* | Male | 2.8 | 3.0 | 0 | 0 |
| | | | | 0 | 0 |
| | | | | 0 | 0 |
| | | | | 0 | 0 |
| Average: | | | | 0.0 | 0.0 |

*Two sites were located in the same plane of muscle.

Appendix 2 - Microscopic Evaluation

Test Article: HARD CLAD OPTICAL FIBER

Interval Implanted: 1 Week

| Rabbit Number: | TEST | | | NEGATIVE CONTROL | | |
|--|---|-------|-------|------------------|-------|-------|
| | 62586 | 62663 | 62774 | 62586 | 62663 | 62774 |
| Inflammation | | | | | | |
| Polymorphonuclear | 2 | 0 | 0 | 2 | 0 | 0 |
| Lymphocytes | 1 | 1 | 1 | 1 | 1 | 1 |
| Plasma Cells | 0 | 0 | 0 | 0 | 0 | 0 |
| Macrophages | 2 | 1 | 1 | 2 | 1 | 2 |
| Giant Cells | 0 | 0 | 0 | 0 | 0 | 0 |
| Necrosis | 0 | 0 | 0 | 0 | 0 | 0 |
| SUB TOTAL (X2) | 10 | 4 | 4 | 10 | 4 | 6 |
| Neovascularisation | 0 | 0 | 0 | 0 | 0 | 0 |
| Fibrosis | 1 | 1 | 1 | 1 | 1 | 1 |
| Fatty Infiltrate | 0 | 0 | 0 | 0 | 0 | 0 |
| SUB TOTAL | 1 | 1 | 1 | 1 | 1 | 1 |
| TOTAL | 11 | 5 | 5 | 11 | 5 | 7 |
| GROUP TOTAL | 21 | | | 23 | | |
| AVERAGE* | TEST 7.0 (-) NEGATIVE CONTROL 7.7 = 0.0 | | | | | |
| *Used to determine Irritant Ranking Score shown below as the Conclusion. A negative difference was recorded as zero. | | | | | | |
| Traumatic Necrosis | 1 | 1 | 1 | 1 | 1 | 1 |
| Foreign Debris | 0 | 0 | 0 | 0 | 0 | 0 |
| No. Sites Examined | 4 | 4 | 4 | 4 | 4 | 4 |

Conclusion:

Under the conditions of this study, the test article was considered a X Nonirritant (0.0-2.9), ___ Slight Irritant (3.0-8.9), ___ Moderate Irritant (9.0-15.0), ___ Severe Irritant (≥15.1) to the tissue as compared to the control.

Comments: At 1 week post implantation, the observed tissue response to the test article was similar to that observed with the negative control article. Generally for the control and test articles, there was slight variability in the tissue response between implant sites in an individual animal and between animals.

Pathologist: Robert F. Parker Date 7-6-09
 Robert F. Parker, D.V.M., Ph.D.
 Diplomate, American College of Veterinary Pathologists
 Study Pathologist