Lab No. 03C 03429 00

P.O. No. 225625
GLP-P3448-1A

**STUDY TITLE**:

USP AND ISO SYSTEMIC TOXICITY STUDY

EXTRACT

**TEST ARTICLE**:

Radel R5100/Plasti-Loc 8

**IDENTIFICATION NO.**:

Patient Contact Materials Subassembly (6C2 Nosepiece Case With Plasti-Loc 8)

**TEST FACILITY:**

NAMSA
9 Morgan
Irvine, CA 92618-2078

**SPONSOR**:

JOANNA DUNN
SIEMENS MEDICAL SOLUTIONS USA
1230 SHOREBIRD WAY
MOUNTAIN VIEW, CA 94043



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## SUMMARY

The test article, Radel R5100/Plasti-Loc 8, Identification No. Patient Contact Materials Subassembly (6C2 Nosepiece Case With Plasti-Loc 8), was extracted in 0.9% sodium chloride USP solution and cottonseed oil, NF. These extracts were evaluated for systemic toxicity in accordance with the guidelines of the current United States Pharmacopeia (USP) and the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity (ISO).

A single dose of the appropriate test article extract was injected into each of five mice per extract by either the intravenous or intraperitoneal route. Similarly, five mice were dosed with each corresponding blank vehicle. The animals were observed immediately and at 4, 24, 48, and 72 hours after systemic injection.

Under the conditions of this study, there was no mortality or evidence of systemic toxicity from the extracts. Each test article extract met the test requirements.

Study and Supervisory Personnel:

Marcia Mestre, B.S.
Emit Jatwani
David Vergil
Daliah Lambert
Tajinder Kaur Uppal, B.S.
America Salvador, B.S., ALAT

Study Director: Lubica Mikula 4-3-03

Lubica Mikula, B.S.
Study Director, Toxicology

Date Completed

/nee



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## INTRODUCTION

The test article identified below was extracted and the extracts were evaluated for biocompatibility in accordance with the guidelines of the current USP and ISO. The purpose of the study was to determine whether leachables extracted from the material would cause acute systemic toxicity following injection into mice. The test article was received on March 7, 2003. The animals were dosed on March 28, 2003, and the observations were concluded on March 31, 2003.

The study, initiated by protocol signature on March 18, 2003, was conducted in accordance with the provisions of the FDA Good Laboratory Practice (GLP) Regulations, 21 CFR 58. A Certificate of Quality Assurance Inspections was issued in conjunction with this report.

## MATERIALS

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

| | |
|---|---|
| Test Article: | Radel R5100/Plasti-Loc 8 |
| Identification No: | Patient Contact Materials Subassembly (6C2 Nosepiece Case With Plasti-Loc 8) |
| Stability Testing: | In Progress (per sponsor) |
| Expiration Date: | Stable for duration of intended testing (per sponsor) |
| Storage Conditions: | Room temperature |
| Vehicles: | 0.9% sodium chloride USP solution (SC)<br>cottonseed oil, NF (CSO) |
| Preparation: | Based on a ratio of 4 g:20 ml, a 6.2 gram portion of the test article was covered with 31 ml of the vehicle. The sample was cut in half horizontally, and only one half of the sample was prepared for the test. The test article was extracted in SC and CSO at 50°C for 72 hours. The extraction vehicles without test article were similarly prepared to serve as control blanks. |

| Condition of Extracts: | | Test | Control |
|---|---|---|---|
| | SC: | Clear | Clear |
| | CSO: | Clear | Clear |



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## METHODS

Test System:

| | |
|---|---|
| Species: | Mouse (*Mus musculus*) |
| Strain: | Crl:CF-1 BR |
| Source: | Charles River Laboratories |
| Sex: | Male |
| Body Weight Range: | 19 grams to 23 grams at injection |
| Age: | No particular age was prescribed for this test |
| Acclimation Period: | Minimum 1 day |
| Number of Animals: | Twenty |
| Identification Method: | Ear punch |

Justification of Test System:

Mice have historically been used to evaluate biomaterial extracts. The use of albino mice injected with a single intravenous (IV) or intraperitoneal (IP) dose of test article extract or control blank has been suggested by the current USP and ISO standards for evaluation of medical plastics.

Duplication of Experimental Work:

By signature on the protocol, the sponsor confirmed that the conduct of this study did not unnecessarily duplicate previous experiments.

Animal Management:

| | |
|---|---|
| Husbandry: | Conditions conformed to Standard Operating Procedures which are based on the "Guide for the Care and Use of Laboratory Animals." |
| Food: | PROLAB® R-M-H 1000 Rodent Diet was provided daily. |
| Water: | Freely available, municipal (Irvine, CA) water was delivered through an automatic watering system. |
| Contaminants: | Reasonably expected contaminants in feed or water supplies did not have the potential to influence the outcome of this test. |
| Housing: | Animals were housed in groups of five in stainless steel suspended cages identified by a card indicating the lab number, animal numbers, test code, sex, animal code and date dosed. |
| Environmental: | The room temperature was monitored daily. The temperature range for the room was within a range of 64-79°F.<br><br>The room humidity was monitored daily. The humidity range for the room was 30-70%.<br><br>The light cycle was controlled using an automatic timer (12 hours light, 12 hours dark). |
| Facility: | 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: | Only healthy, previously unused animals were selected. |



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Experimental Procedure:

Prior to dosing, the mice were identified and weighed. Five animals (per extract) were each injected with the test extract at a dose of 50 ml/kg. Five mice were similarly injected with the corresponding control. The SC was injected by the intravenous (IV) route while the CSO was injected by the intraperitoneal (IP) route. The animals were then returned to their cages.

Mice were observed for adverse reactions immediately after dosing, and at 4, 24, 48, and 72 hours. Following the 72 hour observation, the animals were weighed.

Evaluations and Statistics:

If during the observation period, none of the mice treated with the individual test extract exhibited a significantly greater reaction than the corresponding control mice, the test extract met the requirements. If two or more mice died, or if abnormal behavior such as convulsions or prostration occurred in two or more mice, or if body weight loss greater than 2 grams occurred in three or more mice, the test sample did not meet the test requirements.

## RESULTS

Individual observations appear in Appendix 1.

Body Weight: Body weight data were acceptable.

Mortality: There was no mortality during the study.

Clinical Observations: The test and control animals injected with CSO appeared ungroomed 4 hours after dosing; this was considered an expected effect due to the unctuous nature of the extract. All other animals appeared clinically normal throughout the study.

Results and conclusions apply only to the test article tested. No further evaluation of these results is made by NAMSA. Any extrapolation of these data to other samples is the responsibility of the sponsor. All procedures were conducted in conformance with good laboratory practice and ISO 17025.

## CONCLUSION

Under the conditions of this study, there was no mortality or evidence of systemic toxicity from the extracts. Each test article extract met the test requirements.

## RECORD STORAGE

All raw data pertaining to this study and a copy of the final report are to be retained in designated NAMSA archive files.



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APPENDIX 1

SYSTEMIC TOXICITY OBSERVATIONS

MORTALITY AND BODY WEIGHT DATA:

| | TEST EXTRACT | | | | CONTROL BLANK | | | |
|---|---|---|---|---|---|---|---|---|
| Extract, Route and Dose | Animal Number | Weight (g) Day 0 | Weight (g) Day 3 | #Dead/ #Tested | Animal Number | Weight (g) Day 0 | Weight (g) Day 3 | #Dead/ #Tested |
| 0.9% sodium chloride USP solution (SC) IV; 50 ml/kg | 1 | 20 | 27 | 0/5 | 1 | 19 | 23 | 0/5 |
| | 2 | 20 | 28 | | 2 | 22 | 27 | |
| | 3 | 21 | 29 | | 3 | 22 | 27 | |
| | 4 | 19 | 25 | | 4 | 20 | 25 | |
| | 5 | 21 | 28 | | 5 | 22 | 28 | |
| Cottonseed oil, NF (CSO) IP; 50 ml/kg | 1 | 23 | 31 | 0/5 | 1 | 21 | 28 | 0/5 |
| | 2 | 21 | 28 | | 2 | 20 | 26 | |
| | 3 | 22 | 29 | | 3 | 22 | 29 | |
| | 4 | 20 | 27 | | 4 | 20 | 26 | |
| | 5 | 19 | 24 | | 5 | 22 | 29 | |

CLINICAL OBSERVATIONS:

| | TEST EXTRACT | | CONTROL BLANK | |
|---|---|---|---|---|
| | SC | CSO | SC | CSO |
| Immediate | AN | AN | AN | AN |
| 4 Hours | AN | U-OAN | AN | U-OAN |
| 24 Hours | AN | AN | AN | AN |
| 48 Hours | AN | AN | AN | AN |
| 72 Hours | AN | AN | AN | AN |

AN = Appeared Normal
U-OAN = Ungroomed, otherwise AN



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## CERTIFICATE OF QUALITY ASSURANCE INSPECTIONS

| Phase Inspected | Date | Auditor | Reports to Management and Study Director(s) | Date |
|---|---|---|---|---|
| Term | 04-01-03 | W. Wooten | | |
| Final Report Review | 04-03-03 | W. Wooten | | |

This study will be included in the next periodic status report as completed.

This study has been conducted in accordance with the provisions of the FDA Good Laboratory Practice Regulations (21 CFR, Part 58).

QA Representative: _____ 4-3-03
William Wooten Date
Quality Assurance

pm/nee



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03C-03429-00

02197-29
SIEMENS MEDICAL SOLUTIONS USA

ABORATORIES:
toll free)
2261 Tracy Road
Northwood, OH 43619
419.662.2954 (fax)

# NAMSA™ GLP SAMPLE SUBMISSION FORM

**Sponsor (final report will be addressed and mailed to):**

Company Name: Siemens Medical Solutions USA Inc. Ultrasound Division
Street Address: 1230 Shorebird Way
City, State, Zip Mountain View, CA 94043.
Attn: Joanna Dunn M.S. 7-2
Phone: (650) 943-7568
Fax: (650) 903-9368
e-mail address: Joanna.Dunn@Siemens.com

**Send Invoice To:**

Company Name:
Address:
City, State, Zip
Attn: A/P. MS. 6-1
Phone:
Fax:
e-mail address:

**This form is used for non-clinical studies to be conducted according to the FDA Good Laboratory Practice Regulations of 21 CFR Part 58. Completion of this form identifies material that will be listed on a NAMSA Master Schedule Sheet available for FDA inspection. All information requested must be submitted to NAMSA before testing may begin.**

**Please include a signed protocol for each study as well as the signed Cost Estimate and Proposal with this submission form.**

Purchase Order: 225625 Cost Estimate and Proposal Number: P3448-1A
Credit Card: Mastercard/Visa Card #/Card Holder Name: _____ Exp. _____

**Test Article Name (use EXACT wording desired on final report)*:**
RADEL R5100 / Plasti-Loc 8

**Identification Number Batch/Code/Lot (circle one):** Patient Contact Materials Subassembly (6C2 Nosepiece Case with Plasti-Loc 8)

Storage Conditions: ☑ Room Temperature; ☐ Refrigeration; ☐ Freezer; ☐ Other _____

**Physical description of test article (chemical/material type/color):** A bead of gray epoxy on a Frost-gray injection molded poly-Phenylsolfone nosepiece case. (Picture attached)

**Control article Submitted By Sponsor*:** ☑ No ☐ Yes; Identification: _____

**Identification Batch/Code/Lot (circle one):** _____

Storage Conditions: ☐ Room Temperature; ☐ Refrigeration; ☐ Freezer; ☐ Other _____

Mixtures of test or control articles with carriers require analysis to demonstrate proper concentration, homogeneity and stability. Sponsor will provide analytical methods _____; or will perform analysis on representative aliquots provided by NAMSA _____.

***If your test or control article is a liquid, powder, or gel the sponsor must submit a detailed description of the composition of the material and whether or not the sample is biologic, human tissue derived, or hazardous in nature. Please check the appropriate box below.**

- ☐ The above test article is not biologic, human tissue derived or hazardous in nature.
- ☐ The above test article is hazardous in nature. An MSDS sheet is required before testing can be initiated. Please ensure an MSDS is submitted along with the test sample to expedite handling.
- ☐ The above test article is biologic in nature or human tissue derived. A certificate stating the sample is viral and pathogen free (e.g., hepatitis, HIV) must be submitted along with the test article to expedite handling.

**NOTE:** Biologic or hazardous test articles require additional fees for proper handling and disposal.

**Stability Data:** The sponsor assures the above test article has been characterized for identity, strength, purity and composition as required by FDA Good Laboratory Practice Regulations of 21 CFR Part 58.105. Stability testing is the responsibility of the sponsor and is subject to FDA audit. Characterization and stability information are also required for control articles. Please check the statements applicable to both the test and control articles.

| TEST ARTICLE | CONTROL ARTICLE | |
|---|---|---|
| ✓ | | Stability testing is in progress; article is stable for duration of intended testing. |
| | | Stability testing is complete and on file with sponsor.<br>Expiration Date:_____ (test) Expiration Date:_____ (control) |
| | | Marketed product stability characterized by its labeling. |

**Reporting Service:** NAMSA normally provides one original report. To obtain additional copies, originals, or electronic versions of reports, please check the appropriate box(es) below. Some of these options may incur additional fees.

- ☑ Fax Final Report
- ☐ Additional report copies. Number of copies requested:_____
- ☐ Duplicate original reports. Number of originals requested :_____ ($15.00 per report)
- ☐ Photocopies of raw data.
- ☐ Electronic report on CD Rom ($1.00 per page, minimum $15.00 per report)

**Disposition of Test/Control Article:** Remaining test/control articles are returned to the sponsor upon completion of testing unless otherwise indicated below.

☐ Ship test article dilutions outside of NAMSA for concentration analysis or other formulation stability

Courier:_____ Account:_____

Destination Requested:_____

**Raw Data and Report Storage:** All data including raw data, protocols, reports, and specimens will be archived for 5 years from completion of the final report. After the 5 year period has expired, these items will be destroyed unless specific instruction to return them to the sponsor is provided to NAMSA. Blocks, slides, test and control articles will be returned to the sponsor upon completion of the final report.

03C-03429-00

**Special Instructions:** 02197-29

SIEMENS MEDICAL SOLUTIONS USA

**Name of Principal Investigator (Sponsor):** Joanna Dunn **Title:** Reliability Engineer

**Signature:** Joanna Dunn **Date:** 3/5/03

To be completed at NAMSA Test Facility:

Study Director (GLP): _____ Date: _____

3-17-03

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Corp. Hdqtrs
3400 Cobb

03C-03429-00
02197-29
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# REVISED COST ESTIMATE AND PROPOSAL

TO: Peggy Bidwell
Siemens Medical Solutions, USA
1230 Shorebird Way
Mountain View, CA 94043

PHONE NO.: 650/943-7568
FAX NO.: 650/903-9368

NO.: P3448-1A

DATE: February 28, 2003

DATE OF INQUIRY: February 20, 2003

PAGE 1 OF 2

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TEST ARTICLE: Radel R5100 With Plasti-Loc 8

| NAMS CODE | STUDY Per Sponsor | $FEE PER TEST | $GLP FEE PER TEST |
|---|---|---|---|
| V0014-130 | Cytotoxicity Study using the ISO Elution Method (Extract) | 220.00 | 200.00 |
| TI251-800 | ISO Intracutaneous Study - Extract | | |
| | Saline Extract | 275.00 | 200.00 |
| | Cottonseed Oil Extract | 275.00 | |
| TU012-500 | USP and ISO Systemic Toxicity Study - Extract | | |
| | Saline Extract | 205.00 | 200.00 |
| | Cottonseed Oil Extract | 205.00 | |

/gd THIS ESTIMATE VALID FOR A PERIOD OF SIXTY (60) DAYS FROM DATE OF ISSUE 1/01

03C-03429-00

NAMSA

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Corp. Hdqtr 3400 Cob

02197-29
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# REVISED COST ESTIMATE AND PROPOSAL

**TO:** Peggy Bidwell
Siemens Medical Solutions, USA

**NO.: P3448-1A**
**PAGE 2 OF**

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**TEST ARTICLE: Radel R5100 With Plasti-Loc 8**

| NAMS CODE | STUDY Per Sponsor | $FEE PER TEST | $GLP FEE PER TEST |
|---|---|---|---|
| TI261-300 | ISO Sensitization Test in Fifteen Guinea Pigs, Per Extract, (Maximization Method) | | |
| | Saline Extract | 2990.00 | 300.00 |
| | Cottonseed Oil Extract | 2990.00 | 200.00 |
| | TOTAL: | $8,260.00 | |

3-18-03

**NEW REQUIREMENT: *A copy of your purchase order must accompany the signed cost estimate at the time of sample submission.**

GLP fees include protocol development, QA Inspections, GLP Certificate of Compliance.

Fees (U.S. Dollars) are subject to change in case of protocol modifications, extensive consultation, unanticipated specimen handling or client delays that affect study costs. For requested extra report copies or shipping, additional fees may apply.
To confirm your acceptance of this estimate, please return one signed copy to signatory below.

For North American Science Associates, Inc. (NAMSA):

By: _____
Aaron Skolmowski, B.S.

Date: 2-28-03

Accepted on behalf of: _____

By: _____

Date: _____

Lab No.: _____

*Purchase Order No.: _____

/gd THIS ESTIMATE VALID FOR A PERIOD OF SIXTY (60) DAYS FROM DATE OF ISSUE 1/01

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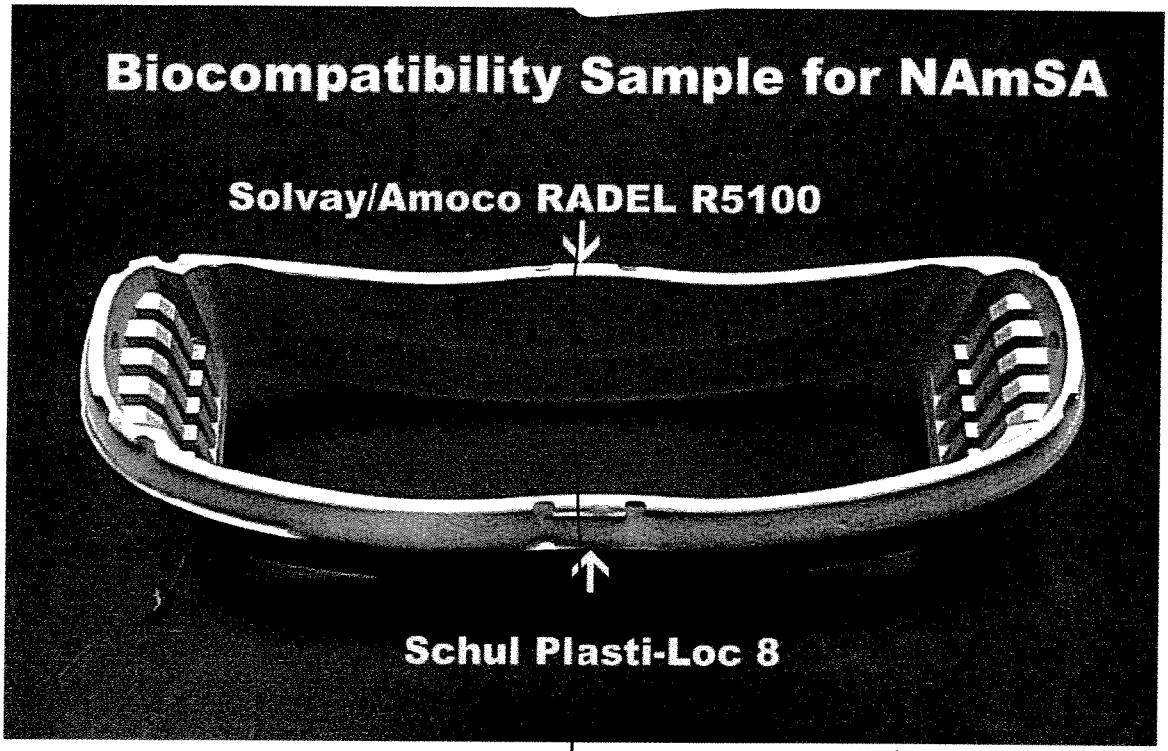


Horizontally
Cut this Way
3-24-03

SIEMENS

03C-03429-00

02197-29
SIEMENS MEDICAL SOLUTIONS USA

March 6, 2003

Marcia Mestre
NAmSA
9 Morgan
Irvine, Ca 92718

Dear Ms. Mestre,

I have been talking to Aaron Skolmowski regarding the biocompatibility test sample that I am sending you. He was able to provide me with a quote on the tests that we need to complete for the 510K filing. Please find the following items with this letter:

1. Purchase order.
2. Cost proposal from Aaron.
3. Signed GLP Sample Submission Form.
4. Signed test protocols.
5. Five patient contact subassemblies of 6C2 RADEL R5100 nosepiece case with Plastic-Loc 8 epoxy.

If you have any questions regarding this test request, please contact me at (650)943-7568 or via email at joanna.dunn@siemens.com. Your immediate support is most appreciated.

Sincerely,

Joanna Dunn
Reliability Engineer

**Siemens Medical Solutions USA, Inc.**

Ultrasound Division

1230 Shorebird Way
P.O. Box 7393
Mountain View, California 94039-7393

Tel: (650) 969-9112

TU012-500
R-07

# NAMSA™ GLP PROTOCOL T12

## USP AND ISO SYSTEMIC TOXICITY STUDY

## EXTRACT

---

Sponsor:

Siemens Medical Solutions, USA
1230 Shorebird Way
Mountain View, CA 94043

03C-03429-00

02197-29
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Peggy Bidwell

Test Facility:

North American Science Associates, Inc. (NAMSA)
9 Morgan
Irvine, CA 92618

NAMSA Use Only

Lab No. _____
CEP No. P3448-1A

Approvals:

Protocol Submitted By (NAMSA): _____
Aaron Skolmowski, B.S.
National Account Manager

Date Issued: 3-3-03

Principal Investigator:
(Sponsor) _____

Date Approved: 3/5/03

Study Director (NAMSA): _____

Date Initiated: 3/8/03

/gd



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TU012-500 Lab No. _____

# NAMSA™ GLP PROTOCOL T12

## USP AND ISO SYSTEMIC TOXICITY STUDY

## EXTRACT

Purpose of the Study:

The objective of this study is to evaluate acute systemic toxicity of leachables extracted from the test article following a single intravenous or intraperitoneal injection in mice. This study will be conducted in accordance with the methods recommended by the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity.

This study will be conducted in accordance with the requirements of the Good Laboratory Practice (GLP) Regulations, 21 CFR 58.

Test Article:

The sponsor will submit the material to be tested. Detailed information about the test article will be provided by the sponsor on the GLP Compliance Notification form furnished by NAMSA or a similar attachment to the protocol.

The following is to be completed (with initials and dates in the margin) by the sponsor or study director. Further instructions may be attached to the protocol. The sample will be prepared as follows:

1. Ratio of test article to extraction vehicle:
   - ___ Material thickness less than 0.5 mm - ratio of 120 $cm^2$:20 ml
   - ___ Material thickness greater than or equal to 0.5 mm - ratio of 60 $cm^2$:20 ml
   - JLE 3/5/03 ✓ Irregularly shaped objects and/or sponsor option - ratio of 4 g:20 ml
   - ___ Other (explain) for extraction cut into two equal portions (horizontally) 3-1 Rm

2. Extraction vehicles:
   - JLE 3/5/03 0.9% sodium chloride USP solution (SC)
   - ___ alcohol in saline 1:20 solution (AS)
   - ___ polyethylene glycol 400 (PEG)*
   - JLE 3/5/03 vegetable oil (CSO)
   - ___ Other (specify)_____

   Note: Due to the known pH of these vehicles, the pH of the test article extracts will not be determined.

   *If PEG is used, the PEG test extract and reagent control will be diluted with saline to obtain 200 mg of PEG/ml.

03C-03429-00

02197-29
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3. Extraction conditions:
   - ___ 121°C, 1 hour
   - 3/24 ___ 70°C, 24 hours
   - ✓ 50°C, 72 hours ←
   - ~~JLE 3/5/03 37°C, 72 hours~~ NA
   - ___ Other (specify)_____

Control Article:

Blank controls (extraction vehicle without test material) will be prepared in the same way and at the same time as the test extracts.



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TU012-500

Test System:

| | |
|---|---|
| Species: | Mouse (*Mus musculus*) |
| Strain: | Outbred albino |
| Source: | NAMSA approved supplier |
| Sex: | No particular gender is prescribed for this test |
| Body Weight Range: | 17-23 grams at injection |
| Age: | No particular age is prescribed for this test |
| Acclimation Period: | Minimum 1 day |
| Number of Animals: | Five per extract and control |
| Identification Method: | Ear punch |

Justification of Test System:

Mice have historically been used to evaluate biomaterial extracts. The use of albino mice injected with a single intravenous (IV) or intraperitoneal (IP) dose of test article extract or control blank have been suggested by the current USP and ISO for evaluation of medical plastics.

Duplication of Experimental Work:

By signature on this protocol, the sponsor confirms that the conduct of this study does not unnecessarily duplicate previous experiments.

Animal Management:

| | |
|---|---|
| Husbandry: | Conditions will conform to Standard Operating Procedures which are based on the "Guide for the Care and Use of Laboratory Animals." |
| Food: | A commercially available, rodent feed will be provided daily. |
| Water: | Freely available, municipal water will be delivered through an automatic watering system. |
| Contaminants: | Reasonably expected contaminants in feed or water supplies should not have the potential to influence the outcome of this test. |
| Housing: | Animals will be housed in groups of five in stainless steel suspended cages identified by a card indicating the lab number, animal numbers, test code, sex, animal code and date injected. |
| Environmental: | The room temperature will be monitored daily. The recommended temperature range for the room is 64-79°F.<br><br>The room humidity will be monitored daily. The humidity range for the room is 30-70%.<br><br>The light cycle will be controlled using an automatic timer (12 hours light, 12 hours dark). |
| Facility: | 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 will be appropriately qualified and trained. |
| Selection: | Only healthy, previously unused animals will be selected. |



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TU012-500 Lab No. 03C0342900

Sedation, Analgesia or Anesthesia: It has been determined that the use of these agents will not be necessary during the routine course of this procedure.

Veterinary Care: In the unlikely event that an animal should become injured, ill, or moribund, care will be conducted in accordance with current veterinary medical practice. If warranted for humane reasons, euthanasia will be conducted in accordance with the current report of the American Veterinary Medical Association's Panel on Euthanasia. The objective of the study will be given due consideration in any decision and the study sponsor will be advised.

IACUC: This protocol 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 protocol must be approved by the IACUC prior to conduct.

Methods and Route of Administration:

Prior to dosing, the mice will be identified and weighed. Five animals will each be injected with the appropriate test extract at a dose of 50 ml/kg (SC, AS, vegetable oil) or 10 g/kg (PEG). Five mice will be similarly injected with the corresponding extraction vehicles. The SC and AS will be injected intravenously via the lateral tail vein while the PEG and vegetable oil will be injected intraperitoneally.

Mice will be observed for adverse reactions immediately after dosing, and at 4, 24, 48 and 72 hours after injection. Following the 72 hour observation, the animals will be weighed. Any animal found dead will be subjected to a gross necropsy of the viscera. After the test is completed, all animals will be handled in accordance with IACUC approved NAMSA procedures.

Evaluations and Statistics:

No statistical analysis of the data will be performed. If during the observation period none of the mice treated with the test extract show a significantly greater reaction than the corresponding control mice, then the test sample meets the test requirements. If two or more mice die, or if abnormal behavior such as convulsions or prostration occurs in two or more mice, or if body weight loss greater than 2 grams occurs in three or more mice, the test sample does not meet the test requirements.

If any mice treated with the test extract show only slight signs of toxicity and not more than one mouse shows gross signs of toxicity or dies, a ten mouse retest may be required. If all ten mice treated with the test extract on the repeat test show no significant reaction greater than the control mice, then the test sample meets the current test requirements.

Report:

The final report will include a description of the methods employed, individual body weights, and any observations.

Quality Assurance:

Inspections will be conducted at intervals adequate to assure the integrity of the study in conformance with 21 CFR 58.35(b)(3). The final report will also be reviewed for conformance to Section 58.185, Subpart J, of the GLP Regulations. A Certificate of Quality Assurance Inspections will be provided with the final report.



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Records:

Test article preparation, dates of relevant activities (such as the study initiation and completion), initial and final body weights, and observations will be recorded.

All raw data pertaining to this study and a copy of the final report will be retained in designated NAMSA archive files.

Proposed Dates:

The study dates will be finalized by the study director following receipt of the sponsor-approved protocol and appropriate material for the study. Initiation of the study will be the date on which the study director signs the GLP protocol. Projected dates for starting the study (first treatment) and for the completion of the study (final report release) will be provided to the sponsor (or representative of the sponsor) and added to the protocol.

References:

21 CFR 58 (GLP Regulations).

*Guide for the Care and Use of Laboratory Animals*, Institute for Laboratory Animal Research, National Academy of Sciences (Washington: National Academy Press, 1996).

International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity.

OLAW, Public Health Service Policy on Humane Care and Use of Laboratory Animals (NIH Publication).

United States Pharmacopeia (USP), current edition.

Protocol Changes:

Any necessary changes to the protocol after sponsor approval or study initiation will be documented and approved by the study director as protocol amendments. Copies will be distributed to the sponsor, the raw data file, and the NAMSA Quality Assurance department.



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March 24, 2003

Joanna Dunn
Siemens Medical Solutions USA
1350 Shorebird Way
Mountain View, CA 94043

PROTOCOL AMENDMENT I

Test Article: Radel R5100/Plasti-Loc 8

Identification No.: Patient Contact Materials Subassembly (6C2 Nosepiece Case With Plasti-Loc 8)

NAMSA Lab No.: 03C-03429-00

We have received appropriate test article(s) and approved protocol(s) for the program to be conducted in accordance with the Good Laboratory Practice (GLP) Regulations on the material described above. Below is a projected schedule for the work to be performed.

| NAMSA Code | Study | Estimated Start Date | Estimated Report Release Date |
|---|---|---|---|
| V0014-130 | Cytotoxicity Study using the ISO Elution Method (Extract) | 3-25-03 | 3-28-03 |
| TI251-800 | ISO Intracutaneous Study in the Rabbit (Extracts) | 3-25-03 | 4-3-03 |
| TU012-500 | USP and ISO Systemic Toxicity Study in the Mouse (Extracts) | 3-25-03 | 4-3-03 |
| TI261-300 | ISO Sensitization Test in the Guinea Pig, Maximization Method (Extracts) | 3-25-03 | 5-5-03 |

Lubica Mikula, B.S.
Study Director, Toxicology

3-24-03
Date

cc: NAMSA QAU
GLP Study File
/gd