Dear Claire,

Enclosed is the final report for the testing we coordinated for you. The information is retained by the testing laboratory.

NELSON NUMBER: 509500
TESTING LAB: WuXi AppTec, Inc.
TYPE OF TEST: Repeated Patch Dermal Sensitization Test (Buehler Method Modified for Medical Devices)

SAMPLE IDENTIFICATION:
SurgiPlus Surgical Drape- SMS fenestrated drape with Kraton; SurgiPlus Surgical Drape- SMS fenestrated drape with incise drape; SurgiPlus Surgical Drape- SMS fenestrated drape with absorbent reinforcement; Surgiplus Surgical Drape- SMS fenestrated drape with pouch.

If you have any questions, please feel free to call or email any of our Subcontracting personnel at 801-290-7500 or subcontracting@nelsonlabs.com. Thank you for testing with Nelson Laboratories, Inc.

Jennifer Shaw, B.S.
Subcontracting Coordinator

Sign Date
30 Mar 2010
FINAL STUDY REPORT

STUDY TITLE

Repeated Patch Dermal Sensitization Test
(Buehler Method Modified for Medical Devices)

TEST ARTICLE IDENTIFICATION

SurgiPlus Surgical Drape- SMS fenestrated drape with Kraton; SurgiPlus Surgical Drape- SMS fenestrated drape with incise drape; SurgiPlus Surgical Drape- SMS fenestrated drape with absorbent reinforcement; Surgiplus Surgical Drape- SMS fenestrated drape with pouch,

STUDY COMPLETION DATE

March 29, 2010

PERFORMING LABORATORY

WuXi AppTec, Inc.
2540 Executive Drive
St. Paul, MN 55120

SPONSOR

Nelson Laboratories, Inc.
6280 South Redwood Road
Salt Lake City, UT 84123

PROTOCOL

900899M

PROJECT NUMBER

132840

NLI#

509500

Reference PO # WUX-2010
QUALITY ASSURANCE UNIT SUMMARY

STUDY: Repeated Patch Dermal Sensitization Test

The objective of the Quality Assurance Unit is to monitor the conduct and reporting of nonclinical laboratory studies. This study has been performed under Good Laboratory Practices regulations (FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies) and in accordance to standard operating procedures and a standard protocol. The Quality Assurance Unit maintains copies of study protocols and standard operating procedures and has inspected this study on the dates listed below. Studies are inspected at time intervals to assure the quality and integrity of the study.

<table>
<thead>
<tr>
<th>Phase Inspected</th>
<th>Date</th>
<th>Study Director</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Challenge</td>
<td>03/19/10</td>
<td>03/19/10</td>
<td>03/29/10</td>
</tr>
<tr>
<td>Final Report</td>
<td>03/29/10</td>
<td>03/29/10</td>
<td>03/29/10</td>
</tr>
</tbody>
</table>

The findings of these inspections have been reported to management and the Study Director.

Quality Assurance Auditor: [Signature] Mark J. Peterson

Date: 3/29/10

GOOD LABORATORY PRACTICES STATEMENT

The study referenced in this report was conducted in compliance with U.S. Food and Drug Administration Good Laboratory Practice (GLP) regulations set forth in 21 CFR part 58.

The studies not performed by or under the direction of WuXi AppTec, Inc., are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test compound(s)/test article.

Study Director: [Signature] Nick Wolner

Date: 3/29/10

Professional Personnel Involved:

Teri Tanquist, BS  
Vice President of Process Improvement and Operations

Christine Olson, BS  
Study Operations Manager

Roxanne Miller, AA, CVT  
Associate Director, In-Life Studies

Nick Wolner, BA  
Study Director

Jean Mesarich, AA  
Client Relations Manager
PROJECT NUMBER: 132840

SPONSOR: Nelson Laboratories, Inc.
6280 South Redwood Road
Salt Lake City, UT 84123

DATA RETENTION: A certified copy of the original final report and all raw data pertinent to this study will be stored at WuXi AppTec, Inc., 2540 Executive Drive, St. Paul, MN 55120. It was the responsibility of the Sponsor to retain a sample of the test article.

SAMPLE STORAGE: Upon receipt by the Sample Receiving Department, the test samples were placed in a designated, controlled access storage area ensuring proper temperature conditions. Test and control article storage areas are designed to preclude the possibility of mix-ups, contamination, deterioration or damage. The samples remained in the storage area until retrieved by the technician for sample preparation and/or testing. Unused test samples remained in the storage area until the study was completed. Once completed, the remaining samples were discarded or returned as requested by the Sponsor.

CHARACTERIZATION: The Sponsor was responsible for all test article characterization data as specified in the GLP regulations. The identity, strength, stability, purity, and chemical composition of the test article were solely the responsibility of the Sponsor. The Sponsor was responsible for supplying to the testing laboratory results of these determinations and any others that may have directly impacted the testing performed by the testing laboratory, prior to initiation of testing. Furthermore, it was the responsibility of the Sponsor to ensure that the test article submitted for testing was representative of the final product that was subjected to materials characterization. Any special requirements for handling or storage were arranged in advance of receipt and the test article was received in good condition.

PURPOSE: This test was designed to evaluate the allergenic potential or sensitizing capacity of a test article. This test was used as a procedure for the screening of contact allergens in guinea pigs and extrapolating the results to humans, but does not establish the actual risk of sensitization in humans.

TEST FACILITY: WuXi AppTec, Inc.
2540 Executive Drive
St. Paul, MN 55120

DATE SAMPLE RECEIVED: 01/29/10
STUDY INITIATION DATE: 01/29/10
STUDY COMPLETION DATE: 03/29/10
IACUC APPROVAL NUMBER: 98-01D

METHOD: This study was based upon the procedures described in ISO 10993-10: 2002 Standard, "Biological Evaluation of Medical Devices", Part 10-Tests for Irritation and Delayed-Type Hypersensitivity" pp. 18-20. The repeated patch method of Buehler was used but modified to include a longer induction exposure period for solid test articles.

EXPERIMENTAL METHODS SUMMARY: In selecting a new material for human contact in medical applications, it is important to ensure that the material will not stimulate the immune system to produce an allergic response. The following method was used to determine the test articles potential to elicit a dermal sensitization reaction.
Ten test guinea pigs were patched with the test article and five guinea pigs were patched with the negative control blank. The bandages and patches were removed after at least 6 hours of exposure. After a 24 hour rest period, each site was observed on each animal for erythema and edema. This procedure was repeated three times per week for three weeks, for a total of nine (9) applications. Following a 2 week rest period, the animals were topically patched with the appropriate test article on the test animals and the control on the control animals. The patches were removed after at least 6 hours of exposure. The dermal patch sites were observed for erythema and edema 24 ± 2 and 48 ± 2 hours after patch removal. Each animal was assessed for a sensitization response based upon the dermal scores. The test results were based upon incidence and severity of the sensitization reaction.

DEVIANATIONS/AMENDMENTS: None.

TEST MATERIAL PREPARATION

Test Article Identification:

Test Article Name:
SurgiPlus Surgical Drape- SMS fenestrated drape with Kraton;
SurgiPlus Surgical Drape- SMS fenestrated drape with incise drape; SurgiPlus Surgical Drape- SMS fenestrated drape with absorbent reinforcement. Surgiplus Surgical Drape- SMS fenestrated drape with pouch

Lot #: Not Applicable
NLI#: 509500
Sterilization Method: None
Physical State: Insoluble Material
Stability (Expiration): Not Applicable
Storage Conditions: Room Temperature
Safety Precautions: Standard Precautions
Intended Use/Application: Unknown

Test Article Preparation: The test article appeared to consist of white Velcro with clear adhesive; white Velcro #2; blue fabric with clear adhesive; blue and green fabric (cold glue); clear film; blue film with clear backing; blue film; and blue and green fabric (hot glue). A representative sample of the test article was cut for extraction at a ratio of 120 cm² to 20 mL of extraction vehicle.

<table>
<thead>
<tr>
<th>EXTRACT VEHICLE</th>
<th>STUDY PHASE</th>
<th>TEST ARTICLE AMOUNT (cm²)</th>
<th>VEHICLE AMOUNT (mL)</th>
<th>NUMBER OF TEST ARTICLE DEVICES USED PER TEST</th>
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</thead>
<tbody>
<tr>
<td>0.9% Normal Saline (NS)</td>
<td>Buehler 1-9 and Challenge Phase</td>
<td>155.41</td>
<td>29.8*</td>
<td>1/100</td>
</tr>
</tbody>
</table>

*Due to the absorbent nature of the test article, an additional 3.9 mL of extract vehicle was added prior to extraction.

Test Article Extraction: The extraction mixtures and corresponding control blanks were incubated for 72 ± 2 hours at 37 ± 1 °C. The extracts were agitated during the course of the extraction period. At the end of the extraction period, the vessels were shaken well and the liquid aseptically decanted into a sterile glass vessel. The test article was observed after all extractions to be intact with no macroscopically observable degradation. The particles were allowed to settle prior to drawing the extract into the syringe for dosing. The extracts were not filtered prior to use. The extracts were maintained at room temperature and used within 24 hours of preparation. See Tables 1-3.
TABLE 2: EXTRACTION RECORD

<table>
<thead>
<tr>
<th>VEHICLE</th>
<th>CONDITION OF VEHICLE (PRE)</th>
<th>EXTRATION TEMPERATURE (IN)</th>
<th>DATE/TIME OF EXTRACTION START</th>
<th>EXTRATION TEMPERATURE (OUT)</th>
<th>DATE/TIME OF EXTRACTION END</th>
<th>CONDITION OF EXTRACT (POST)</th>
<th>DATE/TIME EXTRACT USED FOR TESTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS Induction 1</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>02/12/10 9:01 am</td>
<td>37.0 °C</td>
<td>02/15/10 7:37 am</td>
<td>Small amount of small white hair-like particulates</td>
<td>02/15/10 8:23 am</td>
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<tr>
<td>NS Induction 2</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>02/14/10 7:27 am</td>
<td>37.0 °C</td>
<td>02/17/10 6:05 am</td>
<td>Clear</td>
<td>02/17/10 8:06 am</td>
</tr>
<tr>
<td>NS Induction 3</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>02/16/10 7:02 am</td>
<td>37.0 °C</td>
<td>02/19/10 6:24 am</td>
<td>Small amount of small white hair-like particulates</td>
<td>02/19/10 8:05 am</td>
</tr>
<tr>
<td>NS Induction 4</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>02/19/10 8:07 am</td>
<td>37.0 °C</td>
<td>02/22/10 6:07 am</td>
<td>Small amount of small white flakes</td>
<td>02/22/10 7:49 am</td>
</tr>
<tr>
<td>NS Induction 5</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>02/21/10 7:51 am</td>
<td>37.0 °C</td>
<td>02/24/10 6:13 am</td>
<td>Small amount of small white flakes</td>
<td>02/24/10 8:30 am</td>
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<tr>
<td>NS Induction 6</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>02/23/10 7:52 am</td>
<td>37.0 °C</td>
<td>02/26/10 6:29 am</td>
<td>Small amount of small white hair-like particulates</td>
<td>02/26/10 7:50 am</td>
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<tr>
<td>NS Induction 7</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>02/26/10 7:37 am</td>
<td>37.0 °C</td>
<td>03/01/10 6:07 am</td>
<td>Small amount of small white hair-like particulates</td>
<td>03/01/10 8:18 am</td>
</tr>
<tr>
<td>NS Induction 8</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>02/28/10 7:50 am</td>
<td>37.0 °C</td>
<td>03/03/10 6:22 am</td>
<td>Clear</td>
<td>03/03/10 8:04 am</td>
</tr>
<tr>
<td>NS Induction 9</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>03/02/10 7:15 am</td>
<td>37.0 °C</td>
<td>03/05/10 6:12 am</td>
<td>Clear</td>
<td>03/05/10 7:40 am</td>
</tr>
<tr>
<td>NS Challenge</td>
<td>Clear</td>
<td>37.0 °C</td>
<td>03/16/10 7:00 am</td>
<td>37.0 °C</td>
<td>03/19/10 6:20 am</td>
<td>Small amount of medium white flakes</td>
<td>03/19/10 8:44 am</td>
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</table>

TABLE 3: VEHICLE RECORD

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<thead>
<tr>
<th>VEHICLE IDENTIFICATION:</th>
<th>LOT #</th>
<th>SUPPLIED BY:</th>
<th>EXPIRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS Induction 1 – 7</td>
<td>J9K640</td>
<td>Braun</td>
<td>2/2012</td>
</tr>
<tr>
<td>NS Induction 8, 9, &amp; Challenge</td>
<td>J9N719</td>
<td>Braun</td>
<td>4/2012</td>
</tr>
</tbody>
</table>

Negative Control Preparation: The NS control vehicle was applied (0.4 mL) to a blank Hill Top Chamber for each animal in the negative control group by removing the paper backing.

TEST SYSTEM

Species/Strain/Sex: Albino guinea pig, Hartley strain, (specific pathogen free), male.

Source: Charles River Laboratories, St. Constant, QUE

Animal Body Weight Range: All animals weighed between 300 and 500g upon assignment to the test and were within the required range for the test.

Age: Healthy young adults will be used.

Animal Identification: Individually numbered ear tags.
HUSBANDRY

Receipt: Animals were received on 02/03/10. Each animal was examined for signs of disease and injury.

Housing: Animals were housed in solid bottom plastic cages with contact bedding. The test and negative control animals were housed separately. Housing density complied with AAALAC International standards.

Environment: Animal rooms were maintained according to AAALAC International recommendations and the "Guide for Care and Use of Laboratory Animals". The laboratory and animal rooms were maintained as limited - access facilities.

Diet: Animals were supplied with certified commercial feed, ad libitum. No known contaminants present in the feed were expected to interfere with the test results.

Water: Animals were supplied potable water obtained from the St. Paul municipal water supply. No known contaminants present in the water were expected to interfere with the tests results.

Termination: Animals were euthanized by CO₂ asphyxiatiion following completion of this test.

Compliance: The care, housing and handling of the animals were in compliance with AAALAC International guidelines as reported in the "Guide for the Care and Use of Laboratory Animals", National Research Council - ILAR, Revised 1996; (OPRR), "Public Health Service Policy on Humane Care and Use of Laboratory Animals", and USDA, Department of Agriculture. Animal and Plant Health Inspection Service, 9 CFR, Parts 1, 2 and 3, Animal Welfare, Final Rule 1989.

Selection of Animals: Animals were randomly placed in cages upon receipt and were placed on study as available. Animals considered unsuitable due to poor health or outlying body weight were excluded from the study.

Animal Preparation: The application sites were prepared by removing a 5 x 7 cm area of fur with an electric clipper. The left flank of the animals was shaved before the induction dosing on Day 0, Day 1, Day 5, Day 8, Day 10, Day 12, Day 15, and Day 17. The right flank was shaved for the challenge on Day 31.

TEST ARTICLE ADMINISTRATION

Inductions / Topical Application: The normal saline (NS) extract (0.4mL) was applied to a blank Hill Top Chamber® and then attached to the left flank site of the test group animals. Similarly, NS control vehicle was applied (0.4 mL) to a blank Hill Top Chamber® and then attached to the negative control animals. The animals were wrapped with an elastic bandage (Petflex™) and secured with a hypoallergenic tape (Transpore™). The bandaging and patches were removed after at least 6 hours of exposure. At 24 ± 2 hours after topical application, the sites were assessed for erythema and edema using the grading scale given in Table 1. This procedure was repeated three (3) times per week for three (3) weeks for a total of nine (9) inductions.

Challenge Patch / Topical Application: The challenge procedure was initiated on the ten (10) test animals and the five (5) negative control animals 17 days after completion of the topical induction phases. The normal saline (NS) extract (0.4mL) was applied to a blank Hill Top Chamber® and then attached to the fur clipped right flank of the test animals. In addition, NS control vehicle was applied (0.4 mL) to a blank Hill Top Chamber® and then attached to the fur clipped right flank of each negative control animal. The bandaging and patches were removed after at least 6 hours of exposure.
OBSERVATIONS AND SCORING: The day following challenge exposure and prior to each scoring period, each site was wiped gently with a 70% isopropyl alcohol soaked gauze sponge. The challenge sites were observed for irritation and sensitization reaction, as indicated by erythema and edema. Daily challenge observation scores were recorded 24 ± 2 and 48 ± 2 hours after patch removal in accordance with the classification system for skin reactions in Table 4. Daily animal health observations were recorded throughout the study period.

<table>
<thead>
<tr>
<th>Patch Test Reaction</th>
<th>Grading Scale</th>
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<tbody>
<tr>
<td>No visible change</td>
<td>0</td>
</tr>
<tr>
<td>Discrete or patchy erythema</td>
<td>1</td>
</tr>
<tr>
<td>Moderate and confluent erythema</td>
<td>2</td>
</tr>
<tr>
<td>Intense erythema and swelling</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Erythema is defined as redness and edema is defined as a swelling at the challenge site. Any other adverse changes at the skin sites were recorded and reported.

EVALUATION CRITERIA

Main Test: Individual animal challenge scores of ‘1’ or greater in the test group generally indicate sensitization, provided scores of less than ‘1’ are observed on the negative control animals. If scores of ‘1’ or greater are noted on the negative control animals, then the reactions of the test animals which exceed the most severe negative control reaction are presumed to be due to sensitization. Background or artifactual reactions from fur clipping or patch edge were not considered as evidence of sensitization. An effect interpreted as "irritation" is generally observed at 24 hours, but diminishes thereafter. Closed patches typically show maximal sensitization response 48 hours after patch removal in test conditions.

The test results are interpreted based upon incidence and severity of the sensitization reaction. The incidence is defined as the percentage of animals exhibiting a sensitization reaction at each challenge time point (24 and 48 hours). The severity will be calculated as follows: The sum of the challenge scores will be divided by the total number of animals in a given group at each challenge time point (24 and 48 hours). In the final analysis of data, consideration will be given to the overall patterns, intensity, duration, and character of reactions of the test as compared with the control conditions.

RESULTS

Clinical Observations: None of the animals in the study showed abnormal clinical signs during the test period.

Main Test Dermal Observations

Induction Phase: The dermal responses to the repeated patching of the test article during the induction phase are indicated in Table 5. There was no irritation observed on the test article and control blank animals during the induction phase. None of the negative control animals were observed with a response at any time point, indicating a 0% incidence.

Challenge Phase: None of the test animals challenged with the test article were observed with a sensitization response at any time point, indicating a 0% incidence. The severity was calculated as ‘0’ at each time point. See Table 6 for individual animal scores.
**Positive Control:** A positive control was completed on 10/25/2009 (See Table 4 for individual animal scores). WuXi AppTec runs positive controls every 6 months as required per ISO. The methods for the positive control assay are identical to the methods described above in the “Experimental Methods Summary”. For the Induction phases, 0.3% Dinitrochlorobenzene (DNCB), a known sensitizer, in Ethanol is used. For the challenge phase, 0.15% DNCB in Acetone is used. The negative control animals are exposed to the appropriate vehicle (Acetone is used for the challenge and Ethanol is used for the inductions I and II) only.

Animals in the positive control test group exhibited confluent erythema to intense erythema and swelling reactions at the challenge sites treated with the 0.15% w/v mixture of DNCB in acetone. All reactions in the positive control test group scored of 2 - 3, had a 100% incidence and 21/10 severity (48 hour score) are considered to be sensitization reactions. Based on the results obtained, this test methodology demonstrated dermal sensitization in guinea pigs using DNCB, a known sensitizer.

**ANALYSIS AND CONCLUSION:** The potential sensitization of a biomaterial was based upon incidence and severity of the sensitization reaction. The negative control material had a 0% incidence and '0' severity. The test material had a 0% incidence sensitization response and '0' severity at each evaluated time point. Under the conditions of this protocol, SurgiPlus Surgical Drape- SMS fenestrated drape with Kraton; SurgiPlus Surgical Drape- SMS fenestrated drape with incise drape; SurgiPlus Surgical Drape- SMS fenestrated drape with absorbent reinforcement; Surgiplus Surgical Drape- SMS fenestrated drape with pouch, did not elicit a sensitization response.

**STATISTICAL METHODS:** None applied.

**TECHNICAL REFERENCES:**


US EPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS), Health Effects Test Guidelines, OPPTS 870.2600 Skin Sensitization.

WuXi AppTec Reference Library Contents, Form ALS-4650-1, (current revision).
TABLE 5: INDUCTION DERMAL OBSERVATIONS 24 HOURS AFTER UNWRAPPING

<table>
<thead>
<tr>
<th>ANIMAL #</th>
<th>PATCH 1 SCORE</th>
<th>PATCH 2 SCORE</th>
<th>PATCH 3 SCORE</th>
<th>PATCH 4 SCORE</th>
<th>PATCH 5 SCORE</th>
<th>PATCH 6 SCORE</th>
<th>PATCH 7 SCORE</th>
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### Table 6: Challenge Dermal Observations

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<th>Animal #</th>
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</tr>
<tr>
<td><strong>Total of Scores</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Severity (Total/10)</strong></td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td><strong>Incidence %</strong></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Negative Control Group</strong></td>
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<tr>
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<td>88601</td>
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<tr>
<td><strong>Total of Scores</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Severity (Total/5)</strong></td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td><strong>Incidence %</strong></td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
**TABLE 7: POSITIVE CONTROLS (COMPLETED ON 10/25/09)**

<table>
<thead>
<tr>
<th>ANIMAL #</th>
<th>24 HOURS SCORE</th>
<th>48 HOURS SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEST GROUP</strong></td>
<td></td>
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</tr>
<tr>
<td>79773</td>
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</tr>
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<td>79780</td>
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<td>79781</td>
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<tr>
<td>79782</td>
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<tr>
<td><strong>Total of Scores</strong></td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td><strong>Severity (Total/10)</strong></td>
<td>23/10</td>
<td>21/10</td>
</tr>
<tr>
<td><strong>Incidence %</strong></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>NEGATIVE CONTROL GROUP</strong></td>
<td></td>
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<td>79783</td>
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<td>79784</td>
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<td><strong>Total of Scores</strong></td>
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<tr>
<td><strong>Severity (Total/5)</strong></td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td><strong>Incidence %</strong></td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
PROTOCOL TITLE: REPEATED PATCH DERMAL SENSITIZATION TEST
(Buehler Method Modified for Medical Devices)

TEST CODE: 900899

PERFORMING LABORATORY: WuXi AppTec, Inc.
2540 Executive Drive
St. Paul, MN 55120

EFFECTIVE DATE: 26 February 2009

GLP PROTOCOL: 900899M

Quality Assurance has reviewed this protocol for compliance with applicable regulatory requirements and internal procedures.

Exact Copy
Initals: 80 Date: 3/9/10

PROPRIETARY INFORMATION
This document is provided with the understanding that the recipient shall recognize it contains WuXi AppTec proprietary information, that it shall be kept confidential by the person and/or company to whom it is addressed, and that it shall be used for no other purpose than assessing and approving the described services to be performed by WuXi AppTec or for the purpose of regulatory submission.
Repeated Patch Dermal Sensitization Test  
(Buehler Method Modified for Medical Devices)

1.0 PURPOSE  
This test is designed to evaluate the allergenic potential or sensitizing capacity of a test article. The test is used as a procedure for the screening of contact allergens in guinea pigs and extrapolating the results to humans, but it does not establish the actual risk of sensitization in humans.

In selecting materials for human contact it is important to ensure that the material will not stimulate the immune system to produce an allergic reaction. If applicable, the test material will be screened for irritation prior to conducting the main test by patching the test article in different concentrations to three (3) guinea pigs.

2.0 TEST FACILITY:  
WuXi AppTec, Inc.  
2540 Executive Drive  
St. Paul, MN 55120

3.0 SCHEDULING AND DISCLAIMER OF WARRANTY

3.1 Test protocol initiation is generally within 10 working days after receipt of the test article, a signed protocol/Client Protocol Approval form and a signed test request form. The Client Protocol Approval form and the test request form serve as addenda to this protocol. Written notification of the proposed initiation and completion dates will be provided at the time the test article and signed protocol is received by the laboratory. The estimated testing time is 35-38 days. Verbal results will be available from the Study Director upon completion of the study with the written quality assurance audited report to follow approximately 10 working days after completion of the study.

3.2 If a test, or a portion of it, must be repeated due to failure by WuXi AppTec to adhere to specified procedures, it will be repeated free of charge. If a test must be repeated, or a portion of it, due to failure of internal controls or failure to meet assay validity requirements, it will be repeated free of charge. “Methods Development” fees shall be assessed, however, if the test article and test system require modifications due to complexity and difficulty of testing.

3.3 If the Sponsor requests a repeat test, they will be charged for an additional test.

3.4 Neither the name of WuXi AppTec nor any of its employees are to be used in advertising or other promotion without written consent from WuXi AppTec.

3.5 The Sponsor is responsible for any rejection of the final report by the regulatory agency concerning report format, pagination, etc. To prevent rejection, the Sponsor should carefully review the WuXi AppTec final report and notify WuXi AppTec of any perceived deficiencies in these areas before submission of the report to the regulatory agency. WuXi AppTec will make reasonable changes deemed necessary by the Sponsor, without altering the technical data.
4.0 TEST ARTICLE CHARACTERIZATION
The Sponsor is responsible for all test article characterization data as specified in the Good Laboratory Practices (GLP) regulations. The identity, strength, stability, purity, and chemical composition of the test article is solely the responsibility of the Sponsor. The Sponsor is responsible for supplying to the testing laboratory results of these determinations and any others that may directly impact the testing performed by the testing laboratory, prior to initiation of testing. Furthermore, it is the responsibility of the Sponsor to ensure that the test article submitted for testing is representative of the final product that will be subjected to materials characterization. Any special requirements for handling or storage must be arranged in advance of receipt and the test article must be received in good condition.

5.0 JUSTIFICATION FOR SELECTION OF THE TEST SYSTEM
The albino guinea pig has historically been used in skin sensitization tests and is generally accepted as the most appropriate animal model for human allergic contact dermatitis. The guidelines have no alternative, non-animal methods.

6.0 PROCEDURE FOR IDENTIFICATION OF THE TEST SYSTEM

6.1 Species/Strain: Albino guinea pigs (Cavia porcellus), Hartley strain (specific pathogen free)

6.2 Source: A certified commercial vendor will be used as the animal source.

6.3 Weight Range: Animals for the main test will be between 300 - 500 g. The preliminary test animals, if needed, may be larger than 500 g, as larger animals are preferable for accommodating the number of applications required.

6.4 Age: Healthy, young adult guinea pigs will be used.

6.5 Number: This study uses a minimum of 15 and a maximum of 33 guinea pigs (for main and preliminary testing).

6.6 Sex: Either males or females can be used for the study. The specific gender will be recorded in the raw data. If females are used, they will be nulliparous, not pregnant and housed separately from the males for the duration of the study.

6.7 Animal Identification: Cage cards will be labeled and individual animals will be identified per WuXi AppTec SOP: ILS-0112, Animal Identification (current version).

6.8 IACUC Protocol / Approval Date
98-01D / May, 2007

6.9 Husbandry

6.9.1 Receipt And Acclimation
Receipt will be according to WuXi AppTec SOP: ILS-0092, Receiving Shipments of Animals (current version). The animals will be acclimated for a minimum of five days under the same conditions as the actual test.

6.9.2 Housing
Guinea pigs will be housed in solid bottom cages with contact bedding and up to five guinea pigs per cage. Housing density will comply with the NIH and AAALAC International guidelines for this species.
6.9.3 Environment
The environmental conditions in the animal rooms will be maintained according to WuXi AppTec SOP: ILS-0018, Environmental Conditions in the Animal Facility (current version). The temperature and photoperiod will meet the AAALAC International recommendations for this species. The laboratory and animal rooms will be maintained as limited-access facilities.

6.9.4 Diet
Animals will be supplied with certified commercial guinea pig feed, *ad libitum*. There are no known contaminants present in the feed expected to interfere with the test results.

6.9.5 Water
Potable water will be supplied from the St. Paul municipal water supply, *ad libitum*. There are no known contaminants present in the water expected to interfere with the test results.

6.9.6 USDA Animal Welfare Act
In order to satisfy the USDA Animal Welfare Act, the Sponsor agrees that testing of the submitted test article by this protocol is required in order to satisfy a state or federal regulatory requirement or is scientifically necessary. Further, such testing is not an unnecessary duplication of a previous test submission by the Sponsor. In addition, the duration of test is determined by the cited test references or by scientific justification and will not exceed the time limits contained therein. This procedure was reviewed and approved by WuXi AppTec’s Institutional Animal Care and Use Committee (IACUC) in compliance with the Animal Welfare Act.

It has been determined that no sedation, analgesia, or anesthesia is necessary in this procedure. In the event that an animal should become injured or moribund, euthanasia or veterinary care will be conducted according to WuXi AppTec SOP: ILS-0233, Proper Handling of Sick, Injured and/or Moribund Animals (current version), and current veterinary medical practices. The objectives of the study will be given full consideration in any decisions and the study Sponsor will be advised.

6.10 Testing is performed in strict adherence to WuXi AppTec standard operating procedures (SOPs) which have been constructed to cover all aspects of the work including, but not limited to, receipt, identification, log-in and tracking of test article(s). Additionally, each test is assigned a unique Project Number. This number is used for identification during the course of the test.

7.0 EXPERIMENTAL DESIGN
For the main test, ten guinea pigs will be occlusively patched with the Sponsor supplied test article three days each week for three (3) weeks. The contact duration will be at least six (6) hours. A negative control will be similarly patched to five (5) designated guinea pigs. Fourteen ± 1 day after the last induction patch, the animals will be shaved on the opposite flank and patched with the respective test or control article for at least six (6) hours. After removal of the patches, the sites will be scored for erythema and edema and assessed for incidence and severity of a sensitization reaction.
8.0 TEST METHOD

8.1 Selection Of Animals
The animals selected for the study have not been subjected to any previous experimental procedures. Animals are selected from a large pool of animals and will be examined to insure their skin is free from irritation, trauma and disease. Test animals are distributed into the following groups:

1) Test (10 animals / test material)
2) Negative Control (5 animals / control material)
3) Preliminary Test (if applicable) (3 animals)
4) Positive Control (10 positive control test / 5 vehicle control)

8.2 Test Article Preparation
The Sponsor will submit the material to be evaluated. All test articles will be tested neat (as is) unless otherwise specified by the Sponsor. If the material cannot be dosed 'as is', the use of material extracts is permissible. General guidelines for preparation are in Table 1 based on the physical state of the test article. Further instructions may be attached to the protocol.

<table>
<thead>
<tr>
<th>PHYSICAL STATE</th>
<th>HANDLING</th>
<th>PREPARATION INSTRUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid or Aerosol</td>
<td>neat or dilute</td>
<td>measure 0.4 mL for each dose aerosols will be collected in a container</td>
</tr>
<tr>
<td>Gel - Semi-solid</td>
<td>neat or dilute</td>
<td>measure 0.4 mL or 0.3 g for each dose as applicable</td>
</tr>
<tr>
<td>Powder</td>
<td>neat or dilute</td>
<td>measure 0.4 mL or 0.3 g for each dose as applicable</td>
</tr>
<tr>
<td>Moldable Solid</td>
<td>neat or extract</td>
<td>cut or form into 1x1 inch pieces or measure 0.4 mL or 0.3 g for each dose as applicable</td>
</tr>
<tr>
<td>Formed Solid</td>
<td>neat or extract</td>
<td>cut or form into 1x1 inch pieces or measure 0.4 mL or 0.3 g for each dose as applicable</td>
</tr>
<tr>
<td>Other</td>
<td>other</td>
<td>provide written instructions attached to this protocol</td>
</tr>
</tbody>
</table>

8.3 Negative Control Substance
For test substances dosed neat, Hill Top Chambers will serve as the negative control patch. If the material is extracted, a blank consisting of the vehicle alone will be subjected to identical conditions as the test material and used as the negative control substance.

8.4 Positive Controls
WuXi AppTec performs positive control testing no less than every 6 months per ISO regulations. The animals for the positive control assay will be patched with the positive control substance dinitrochlorobenzene (DNCB) for one day each week for three weeks for the induction phase and then patched 14 ± 1 day after the last induction patch for the challenge phase. Guinea pigs utilized for positive control studies will be of the Hartley strain and will be supplied by the same vendor as animals used for general testing.
For the induction phases, 0.3% DNBC in ethanol will be used. For the Challenge phase, 0.15% DNBC in acetone is used. The negative control animals will be exposed to only the appropriate vehicle (ethanol is used for Induction phase and acetone will be used for the Challenge phase). Results for the applicable positive control study will appear in the final report for this study.

8.5 Preliminary Tests
The preliminary tests are intended to determine the concentrations of the test material to be used in the main test. Medical devices intended for topical use and undiluted extracts using the usual solvents need not be subjected to preliminary testing per ISO regulations. For the typical medical device (or extract of a medical device), the preliminary test will not be conducted. The decision to run the preliminary test will be based on the discretion of the Study Director and the nature of the test article.

8.5.1 If applicable, the test material will be diluted with the liquid specified on the WuXi AppTec test request form attached to this protocol to the following concentrations: 90%, 75%, and 50%. If a diluent is not selected, 0.9% sodium chloride USP solution (NS) will be used.

8.5.2 Three (3) guinea pigs will be prepared by shaving the flanks with an electric clipper. The guinea pigs will be topically patched with 0.1 mL of each test article concentration (100%, 90%, 75%, and 50%). Each concentration will be applied to a 1 x 1 cm filter paper patch backed by an occlusive tape and will remain in place for a minimum of 6 hours.

If two (2) extracts are selected for this study, the three (3) guinea pigs will be patched with the polar extract concentrations on the right side and with the non-polar concentrations on the left side. At 24 ± 2 and 48 ± 2 hours after the topical application, the sites will be assessed for erythema and edema using the grading scale given in Table 2.

8.5.3 Induction Concentration Selection
For the topical induction phase, the highest concentration that causes slight erythema, but does not otherwise adversely affect the topically patched animals will be selected, if possible.

8.5.4 Challenge Concentration Selection
The highest concentration that produces no erythema on the topically patched animals will be selected for the challenge phase.

8.6 Test Article Administration

8.6.1 Preparation Of The Test Animals
Prior to the induction dose (if needed, but at least once per week), an approximate 5 x 7 cm area over the left flank will be prepared by clipping the skin of the test site free of fur with an electric clipper. Prior to the challenge phase, a similar area will be shaved on the right flank of each animal.
8.6.2 **Topical Induction Phase**
The test and negative control material will be dosed (as indicated in Table 1) to the same site of the shaved skin of the appropriate animals three (3) times each week for three (3) weeks for a total of nine (9) inductions. The applications will be left in place for at least six (6) hours. An assessment of irritation will be made 24 ± 2 hours after removal of the patches. A sample overview of the main test is listed in Table 3.

**Test Group:** The prepared test article patch will be secured to the animal and the trunk wrapped with an expandable wrapping material and secured with a hypoallergenic tape. This preparation will be left in place for at least six (6) hours.

**Negative Control Group:** The animals will be exposed to the diluent, extract vehicle or blank Hill Top Chamber® in the same manner as the experimental group.

8.6.3 **Challenge Phase**
At 14 ± 1 day after completion of the last topical induction dose, the challenge procedure will be initiated on the 10 experimental animals and the 5 negative control animals.

**Test Group:** A prepared patch will be applied to the fur clipped right flank or dorsum of each animal. The trunk of each animal will be wrapped for at least six (6) hours with an expandable wrapping material and secured with tape.

**Control Group:** The animals will be exposed to the diluent, extract vehicle or blank Hill Top Chamber® in the same manner as the experimental group.

8.7 **Observations**

8.7.1 **Dermal Observation Scoring**

**Inductions:** Each site on each animal will be observed for erythema and edema 24 ± 2 hour after patch removal. To assess for irritation, the reaction for each site will be gently wiped with 70% isopropyl alcohol on a gauze sponge and scored according to the scoring system in Table 2.

**Challenge:** The day after challenge exposure and prior to each scoring period, the site will be wiped gently with a 70% isopropyl alcohol soaked gauze sponge. The challenge sites will be observed for signs erythema and edema. Daily challenge observation scores will be recorded 24 ± 2 and 48 ± 2 hours after patch removal in accordance with the classification system listed in Table 2.

<table>
<thead>
<tr>
<th>PATCH TEST REACTION</th>
<th>GRADING SCALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No visible change</td>
<td>0</td>
</tr>
<tr>
<td>Discrete or patchy erythema</td>
<td>1</td>
</tr>
<tr>
<td>Moderate and confluent erythema</td>
<td>2</td>
</tr>
<tr>
<td>Intense erythema and swelling</td>
<td>3</td>
</tr>
</tbody>
</table>

**Note:** Erythema is defined as redness and edema is defined as a swelling at the challenge site. Any other adverse changes at the skin sites shall be recorded and reported.
Background or artifactual reactions from fur clipping, patch edge, or nonspecific tape adhesive effects will not be considered as evidence of sensitization.

8.7.2 Daily animal health observations will be recorded throughout the study period.

<table>
<thead>
<tr>
<th>DAY</th>
<th>SITE TESTED</th>
<th>ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>1</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>2</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>3</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>4</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>5</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>7</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>8</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>9</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>10</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>11</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>12</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>14</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>15</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>16</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>17</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>18</td>
<td>Left Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>19</td>
<td>Left Flank</td>
<td>Observe sites / Score Induction sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>31</td>
<td>Right Flank</td>
<td>Shave Challenge Sites</td>
</tr>
<tr>
<td>32</td>
<td>Right Flank</td>
<td>Dose animals / Remove Patches at least 6 hrs later</td>
</tr>
<tr>
<td>33</td>
<td>Right Flank</td>
<td>Score Challenge Sites (24 ± 2 hrs)</td>
</tr>
<tr>
<td>34</td>
<td>Right Flank</td>
<td>Score Challenge Sites (48 ± 2 hrs)</td>
</tr>
</tbody>
</table>

8.8 Termination
After the final observation period and after the study director's review of the data, the animals will be humanely euthanized by CO₂ gas asphyxiation.

9.0 METHOD FOR CONTROL OF BIAS: Not applicable.

10.0 DATA ANALYSIS
The severity will be calculated as follows: The sum of the challenge scores will be divided by the total number of animals in a given group at each challenge time point (24 and 48 hours).

The incidence is defined as the percentage of animals exhibiting a sensitization reaction at each challenge time point (24 and 48 hours).

11.0 STATISTICAL METHODS: None used.

12.0 ASSAY VALIDITY
Final evaluation of the validity of the assay and test article results will be based upon the criteria listed in Section 13.0 and scientific judgment.
13.0 EVALUATION OF RESULTS
The test results will be interpreted based upon incidence and severity of the sensitization reaction. The incidence is defined as the percentage of animals exhibiting a sensitization reaction at each challenge time point (24 and 48 hours). A test will be repeated in part or in total if a negative control failure occurs.

Grades of ‘1’ or greater in the test group generally indicate sensitization, provided grades of less than ‘1’ are observed on the negative control animals. If grades of ‘1’ or greater are noted on negative control animals, then the reactions of the test animals which exceed the most severe negative control reaction are presumed to be due to sensitization.

Occasionally, the test group has a greater number of animals showing a response than the negative controls, although the intensity of the reaction is not greater than that observed on the negative controls. In these instances, a rechallenge maybe necessary to define the response clearly. If necessary, a rechallenge shall be carried out approximately 1 - 2 weeks after the first challenge. The method used shall be as described for the first challenge, using the other flank of the animal.

14.0 PROTOCOL CHANGES
If it becomes necessary to make changes in the approved protocol, the revisions and reasons for changes will be documented, signed by the study director, dated, maintained with the protocol and reported to the sponsor. If an event occurs which may have an effect on the validity of the study, the sponsor will be notified as soon as is practical. If the Study Director is unable to complete the study, an alternate Study Director with full responsibility and authority regarding the study will be assigned.

15.0 FINAL REPORT
The final report will include but will not be limited to: the date of the study initiation and completion, the purpose as stated in the approved protocol, changes in the approved protocol, identification of the test system, applicable positive control results, a description of the methods used, and a conclusion as it relates to the test.

16.0 RECORD RETENTION
16.1 Study Specific Documents
All of the original raw data developed exclusively for this study shall be retained according to WuXi AppTec, Inc.'s standard operating procedures for archival. These original data include, but are not limited to the following:

16.1.1 All handwritten and equipment generated raw data for control(s) and test article(s).
16.1.2 Any protocol amendments/deviation notifications.
16.1.3 Memoranda, specifications, and other study specific correspondence relating to interpretation and evaluation of data, other than those documents contained in the final study report.
16.1.4 Original signed protocol.
16.1.5 Certified copy of final study report.
16.1.6 Study-specific SOP deviations made during the study.
16.1.7 QA reports for each QA inspection with comments.
16.2 **Facility Specific Documents**
The following records shall also be retained according to WuXi AppTec, Inc.'s standard operating procedures for archival. These documents include, but are not limited to, the following:

16.2.1 SOPs which pertain to the study conducted.
16.2.2 Non study-specific SOP deviations made during the course of this study which may affect the results obtained during this study.
16.2.3 Methods which were used or referenced in the study conducted.
16.2.4 Facility Records: Temperature Logs (ambient, incubator, etc.), Instrument Logs, Calibration and Maintenance Records.
16.2.5 Current job descriptions and summary of experience and training for all personnel involved in the study.

17.0 **REFERENCES**


17.5 US EPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS), Health Effects Test Guidelines, OPPTS 870.2600 Skin Sensitization.

17.6 WuXi AppTec Reference Library Contents, Form ALS-4650-1, (current revision).

18.0 **COMPLIANCE**

18.1 **Animal Husbandry**

18.2 **GLP Status**
If the Sponsor chooses to conduct the study under GLP compliance (FDA, 21 CFR, Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies), the study will be inspected during at least one phase and the final report will be audited by the WuXi AppTec Quality Assurance unit.
19.0 TEST ARTICLE IDENTIFICATION
Test article information to be included in the final report will be provided solely by the Sponsor on the WuXi AppTec test request form attached to this protocol.

20.0 TEST ARTICLE DISPOSITION
It is the responsibility of the Sponsor to retain a sample of the test material. All unused test material will be discarded following study completion unless otherwise requested by Sponsor.
CLIENT PROTOCOL APPROVAL FORM

PLEASE NOTE THAT TESTING CANNOT BE INITIATED UNTIL THIS FORM IS COMPLETED WITH AN AUTHORIZED SIGNATURE AND THE ORIGINAL IS RETURNED TO WUXI APPTEC.

SPONSOR:
Ms. Jennifer Shaw
Nelson Laboratories, Inc.
6280 South Redwood Road
Salt Lake City, UT 84123

NEL05
Phone #: 801-290-7540
Facsimile: 801-963-2630
E-mail: jshaw@nelsonlabs.com

Primary Approval Statement

I have read WuXi AppTec, Inc.’s client protocol, 900899M - Repeated Patch Dermal Sensitization Test (Buehler Method Modified for Medical Devices). I accept the test method described. I understand that my approval will be valid until one or both of the following occur:

1. The protocol is revised and a new version letter is issued.
2. The Primary Approver’s position with the Sponsor company is terminated or changes, whichever may occur first.

NAME: Jennifer Shaw
SIGNATURE: Jennifer Shaw
TITLE: Subcontracting
DATE: 05 Mar 2007

Associate(s) Approval Statement

The Primary Approver (above) has authorized the following Associate(s) to accept the responsibility for submitting samples for testing under this protocol. Each associate understands that their authorization for submission will be valid until one or more of the following has occurred:

1. The protocol has been revised and new version letter has been issued.
2. The primary Approver’s position with the Sponsor company is terminated or changes, whichever may occur first.
3. Any of the Associate’s positions with the Sponsor company are terminated or change, whichever may occur first.
4. The Primary Approver has removed any Associate’s authorization by sending a signed and dated letter to WuXi AppTec, ATTN: Client Services.

☐ I do not wish to have an Associate(s) authorized to initiate testing of samples under this protocol.
☒ I do wish to have the following Associate(s) authorized to initiate testing of samples under this protocol.

Name of Associate (please print)

Thor Rollins

Name of Associate (please print)

Tarika Onishi

WUXI APPTEC, INC.:  

NAME: Nick iJohn

SIGNATURE: Nick iJohn

Study Director

DATE: 1/2/13