NELSON
LABORATORIES

14 Apr 2009

Jodie Alexander
Oerlikon Balzers Coating USA, Inc.
1181 Jansen Farm Court
Elgin, IL 60123

Dear Jodie,

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

NELSON NUMBER: 465457

TESTING LAB: WuXi AppTec, Inc.

TYPE OF TEST: ISO Intracutaneous Reactivity Test

SAMPLE IDENTIFICATION:
#4 BaLinit – A – Medical TIN

If you have any questions, please feel free to call any of our Subcontracting personnel at 801-963-2600 or 800-826-2088. Thank you for testing with Nelson Laboratories, Inc.

Thor Rollins, B.S. RM(NRM)
Subcontracting Section Leader

14 APR 2009
Sign Date

FRM0641 Rev.1

St. Paul

Report

WuXi AppTec

FINAL STUDY REPORT

STUDY TITLE

ISO Intracutaneous Reactivity Test

TEST ARTICLE IDENTIFICATION

#4 BaLinit - A - Medical TIN

STUDY COMPLETION DATE

April 13, 2009

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

910700R

PROJECT NUMBER

118180

NLI#

465457

Reference PO # WUX-2009

NEL05

118180

jshaw@nelsonlabs.com

QUALITY ASSURANCE UNIT SUMMARY

STUDY: ISO Intracutaneous Reactivity 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.

Phase Inspected	Date	Study Director	Management
Scoring	03/25/09	03/25/09	04/13/09
Final Report	04/10/09	04/13/09	04/13/09

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

Quality Assurance Auditor: Yunhua Wu Date: 4/13/09
Yunhua Wu

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: Michelle Dietzel Date: 4/13/09
Michelle Dietzel

Professional Personnel Involved:

Lisa Olson, BS	Vice President St. Paul Operations
Don Palme, Ph.D.	Vice President of Toxicology and In-Life Testing
Roxanne Miller, AA, CVT	Associate Director, In-Life Studies
Michelle Dietzel, BS	Senior Study Director
Jean Mesarich, AA	Client Relations Manager

PROJECT NUMBER: 118180

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

RECORD RETENTION: An exact 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 is 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: The purpose of this test was to determine if any chemicals that may leach or be extracted from the test article were capable of causing local irritation in the dermal tissues of rabbits.

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

DATE SAMPLE RECEIVED:	03/12/09
STUDY INITIATION DATE:	03/12/09
STUDY COMPLETION DATE:	04/13/09
IACUC APPROVAL:	07-122A

METHOD: This study was conducted in accordance with the International Organization for Standardization 10993-10: 2002, Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Delayed-type Hypersensitivity, pages 23-25.

EXPERIMENTAL SUMMARY: Each rabbit received five sequential 0.2 mL intracutaneous injections along either side of the dorsal mid-line with the test article extract on one side and the concurrent vehicle control on the other. The vehicles used were 0.9% normal saline and cottonseed oil. The irritation reaction of the test extracts were compared to vehicle controls and recorded over a 72-hour period according to the standard ISO Irritation Scoring System. According to ISO 10993:10 test criteria, if the difference between the average scores for the extract of the test article and the vehicle control is less than or equal to 1.0, the test article is considered non-irritating. The differences in the mean test and control scores of the 0.9% normal saline and cottonseed oil extract dermal observations were less than 1.0, indicating that the requirements of the ISO Intracutaneous Reactivity Test have been met by Nelson Laboratories, Inc., #4 BaLinit - A - Medical TIN.

DEVIATIONS/AMENDMENTS: None.

TEST MATERIAL PREPARATION

Test Article Identification :

Test Article Name:	#4 BaLinit - A - Medical TIN
Lot/Batch #:	Not Applicable
NLI#:	465457
Sterilization Method:	Non-Sterile
Physical State:	Insoluble Material
Stability (Expiration):	Not Applicable
Storage Conditions:	Room Temperature
Safety Precautions:	Standard Precautions
Intended Use/Application:	Unknown

Test Sample Preparation: The test article appeared to consist of gold-colored metal. The test article was extracted intact, placed into test tubes and prepared at a ratio of 60 cm^2 to 20 mL of extraction vehicle.

TABLE 1: TEST ARTICLE RECORD

EXTRACT VEHICLE	TEST ARTICLE AREA (CM^2)	VEHICLE AMOUNT (mL)	NUMBER OF TEST ARTICLE DEVICES USED PER EXTRACT
0.9% Normal Saline (NS)	228.0	76.0	1
Cottonseed Oil (CSO)	228.0	76.0	1

Test Article Extraction: The extraction mixtures and corresponding control blanks were incubated for 24 ± 2 hours at 70 ± 2 °C. 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 extraction in CSO to be intact with no macroscopically observable degradation. The NS extraction caused the test article to appear moderately rusted. The NS test extract was cloudy brown with a large amount of small brown flakes. 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

VEHICLE	CONDITION OF VEHICLE (PRE)	EXTRACTION TEMPERATURE (IN)	DATE/TIME OF EXTRACTION START	EXTRACTION TEMPERATURE (OUT)	DATE/TIME OF EXTRACTION END	CONDITION OF EXTRACT (POST)	DATE/TIME EXTRACT USED FOR TESTING
NS	Clear	70 °C	03/23/09 0725	70 °C	03/24/09 0618	Cloudy brown with large amount of small brown flakes	03/24/09 1223
CSO	Clear	70 °C	03/23/09 0725	70 °C	03/24/09 0618	Clear	03/24/09 1223

TABLE 3: VEHICLE RECORD

VEHICLE IDENTIFICATION:	LOT #	SUPPLIED BY:	EXPIRATION
NS	J9B563	Braun	08/11
CSO	YA0319	Spectrum	01/31/10

TEST SYSTEM

Species/Strain/Sex: Albino rabbits, New Zealand White strain, male

Age: No specific age required.

Source: Bakkom Rabbitry, Viroqua, WI

Animal Body Weight Range: All animals weighed in excess of the 2.0 kg minimum ISO weight limit.

Animal Identification: Individually numbered ear tags

HUSBANDRY

Receipt: Animals were received on 03/17/09. Each animal was examined for signs of disease and injury prior to entry into the research area. The animals were acclimated for a minimum of 5 days under the same conditions as the actual test.

Housing: One rabbit was housed per suspended stainless steel cage. Cage dimensions were in compliance with NIH and AAALAC International guidelines.

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 rabbit chow. No known contaminants present in the feed were expected to interfere with the test results.

Water: Potable water was obtained from the St. Paul municipal water supply. No known contaminants present in the water were expected to interfere with the test results.

Termination: Animals were euthanized by lethal injection with a sodium pentobarbital based solution.

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", Health Research Extension Act of 1985 (Public Law 99-158), Revised 1986, 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. Any animals considered unsuitable due to poor health, abraded skin or outlying body weight were excluded from the study.

ANIMAL PREPARATION: Each animal was weighed and the weight recorded prior to test injection. The fur of the animals was clipped on both sides of the spinal column to expose a sufficient sized area for injection.

TEST ARTICLE ADMINISTRATION: The two test article extracts and the two vehicle controls were each injected into two rabbits. Each rabbit received five sequential 0.2 mL intracutaneous injections of the test article extract on the right side of the vertebral column and similarly the control vehicle on the left side. The second test and control extract injections were parallel and distal to the first injection sites. (Figure 1)

FIGURE 1: INJECTION SITES ON RABBITS

CONTROL		HEAD	TEST		
	Control Vehicle #2	Control Vehicle #1	Test Extract #1	Test Extract #2	
	1	1	1	1	0.2 mL Test Article Extract Injected
0.2 mL Control Vehicle Injected	2	2	2	2	
	3	3	3	3	
	4	4	4	4	
	5	5	5	5	
		TAIL			

OBSERVATIONS AND SCORING: The animals were observed daily for abnormal clinical signs. The appearance of each injection site was noted at 24 ± 2, 48 ± 2 and 72 ± 2 hours post injection. The tissue reactions were rated for gross evidence of erythema and edema. The skin was lightly swabbed with dilute alcohol to enhance the appearance of any erythema or edema. The intradermal injection of CSO frequently elicits an inflammatory response. CSO erythema scores ≤ 2 are considered normal. Table 4 was used to score the reactions.

TABLE 4: DERMAL OBSERVATION SCORING

ERYTHEMA	EDEMA
0 = No erythema	0 = No edema
1 = Very slight erythema (barely perceptible)	1 = Very slight edema (barely perceptible)
2 = Well defined erythema	2 = Slight edema (raised edges)
3 = Moderate to severe erythema	3 = Moderate edema (raised ~1 mm)
4 = Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4 = Severe edema (raised > 1 mm and extending beyond area)

RESULTS

Clinical Observations: None of the animals on study showed abnormal clinical signs during the 72 hour test period.

TABLE 5: DERMAL OBSERVATIONS – 0.9% NORMAL SALINE

RABBIT # 10175	CONTROL SCORES						TEST SCORES					
	24 HOUR		48 HOUR		72 HOUR		24 HOUR		48 HOUR		72 HOUR	
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
Site 1	0	0	0	0	0	0	0	0	0	0	0	0
Site 2	0	0	0	0	0	0	0	0	0	0	0	0
Site 3	0	0	0	0	0	0	0	0	0	0	0	0
Site 4	0	0	0	0	0	0	0	0	0	0	0	0
Site 5	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0	0	0
RABBIT # 10176	**CONTROL SCORES**						**TEST SCORES**					
	24 HOUR		48 HOUR		72 HOUR		24 HOUR		48 HOUR		72 HOUR	
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
Site 1	0	0	0	0	0	0	0	0	0	0	0	0
Site 2	0	0	0	0	0	0	0	0	0	0	0	0
Site 3	0	0	0	0	0	0	0	0	0	0	0	0
Site 4	0	0	0	0	0	0	0	0	0	0	0	0
Site 5	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0	0	0

ER=Erythema
ED=Edema

RABBIT	CONTROL SCORES			TEST SCORES		
10175	0	0	0	0	0	0
10176	0	0	0	0	0	0
Total	0			0		
Average (Total/12)	0/12 = 0			0/12 = 0		
Comparative Results	0					

TABLE 6: DERMAL OBSERVATIONS – COTTONSEED OIL

RABBIT # 10175	CONTROL SCORES						TEST SCORES					
	24 HOUR		48 HOUR		72 HOUR		24 HOUR		48 HOUR		72 HOUR	
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
Site 1	1	0	1	0	1	0	1	0	1	0	1	0
Site 2	1	0	1	0	1	0	1	0	1	0	1	0
Site 3	1	0	1	0	1	0	1	0	1	0	1	0
Site 4	1	0	1	0	1	0	1	0	1	0	1	0
Site 5	1	0	1	0	1	0	1	0	1	0	1	0
Total	5	0	5	0	5	0	5	0	5	0	5	0
RABBIT # 10176	**CONTROL SCORES**						**TEST SCORES**					
	24 HOUR		48 HOUR		72 HOUR		24 HOUR		48 HOUR		72 HOUR	
	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
Site 1	0	0	1	0	1	0	0	0	1	0	1	0
Site 2	0	0	1	0	1	0	1	0	1	0	1	0
Site 3	0	0	1	0	1	0	1	0	1	0	1	0
Site 4	0	0	1	0	1	0	0	0	1	0	1	0
Site 5	1	0	1	0	1	0	0	0	1	0	1	0
Total	1	0	5	0	5	0	2	0	5	0	5	0

ER=Erythema
ED=Edema

RABBIT	CONTROL SCORES			TEST SCORES		
10175	5	5	5	5	5	5
10176	1	5	5	2	5	5
Total	26			27		
Average (Total/12)	26/12 = 2.2			27/12 = 2.3		
Comparative Results	2.3 – 2.2 = 0.1					

CALCULATIONS: The erythema and edema scores were determined for each test sample and control vehicle. Each total score was divided by 12 (2 animals *x* 3 observation periods *x* 2 scoring categories) to determine the overall mean score for each test extract versus each corresponding control. The results are presented in Tables 5 and 6.

EVALUATION CRITERIA: According to ISO 10993-10, the requirements of the test are met if the difference between the test article and the control mean score is 1.0 or less.

ANALYSIS AND CONCLUSION: The test was considered valid as the vehicle control injection sites were within acceptable parameters. The differences in the mean test and control scores of the 0.9% normal saline and cottonseed oil extract dermal observations were less than 1.0, indicating that the requirements of the ISO Intracutaneous Reactivity Test have been met by the test article. Under the test conditions of this protocol, #4 BaLinit - A - Medical TIN, would be considered a **non-irritant.**

STATISTICAL METHODS: None.

TECHNICAL REFERENCES:

ISO 10993-10: 2002 Standard, Amendment 1, 2006, Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Delayed-type Hypersensitivity, Pages 23 – 25.

ISO 10993-12:2007 Biological Evaluation of Medical Devices, Part 12: Sample Preparation and Reference Materials.

U.S. Pharmacopeia, Section 88, current revision.

WuXi AppTec SOP: ALS-0260, Sample Extraction Procedures, (current revision).

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

WuXi AppTec SOP: ILS-0018, Environmental Conditions in the Animal Facility (current revision).

WuXi AppTec SOP: ILS-0092, Receiving Shipments of Animals, (current revision).

WuXi AppTec SOP: ILS-0112, Animal Identification, (current revision).

WuXi AppTec SOP: ILS-0230, Euthanasia Procedures, (current revision).

WuXi AppTec SOP: ILS-0233, Proper Handling of Sick and Moribund Animals (current revision).

WuXi AppTec SOP: TRG-0300, Preparation of Biomaterials for Extraction, (current revision).

(For Laboratory Use Only)

WuXi AppTec Study # 118180

WuXi AppTec

PROTOCOL TITLE: **ISO INTRACUTANEOUS REACTIVITY TEST**

TEST CODE: **910700**

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

EFFECTIVE DATE: 13 February 2009

GLP PROTOCOL: **910700R**

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

Exact Copy
Initals: SO Date: 4/13/09

2540 Executive Drive • St. Paul, MN 55120 • 888.794.0077 • 651.675.2000 • Fax: 651.675.2005

ISO Intracutaneous Reactivity Test

1.0 PURPOSE

The purpose of this test is to determine if chemicals that may leach or be extracted from the test material are capable of causing local irritation in the dermal tissues of the rabbit.

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 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 3 - 7 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

This test method and species have historically been used to assess the potential of the material under test to produce intradermal irritation to help determine biocompatibility of materials used in medical devices. The animal species, number and route of test article administration will be as recommended in ISO 10993-10.

6.0 PROCEDURE FOR IDENTIFICATION OF THE TEST SYSTEM

6.1 **Species/Strain:** Albino rabbits (*Oryctolagus cuniculus*) / New Zealand White strain

6.2 **Source:** Rabbits will be obtained from certified commercial vendors.

6.3 **Weight Range:** Each rabbit will weigh at least 2.0 kg.

6.4 **Age:** The rabbits will be young adults, but no particular age is required, however vendor practice assures consistency in the age of the animals.

6.5 **Number:** A total of two (2) animals per extract or pair of extracts will be used for this study. If a retest is indicated, three (3) additional rabbits will be used.

6.6 **Sex:** Either males or females will be used for this study. Females will be nulliparous and non-pregnant.

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**
07-122A / May, 2007

6.9 **Husbandry**

6.9.1 **Receipt And Acclimation**
Animal 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 5 days under the same conditions as the actual test.

6.9.2 **Housing**
One rabbit will be housed per suspended stainless steel cage. Housing dimensions will comply with 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). A twelve hour light/dark cycle will be used. The temperature and photoperiod will meet the AAALAC International recommendations for these species. The laboratory and animal rooms will be maintained as limited-access facilities.

6.9.4 **Diet**
Animals will be supplied with certified commercial feed, *ad libitum*. There are no known contaminants present in the feed expected to interfere with the test results. Analytical results of the feed are archived at WuXi AppTec.

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6.9.5 Water

Animals will be supplied with potable water 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. Periodic analysis of the water is conducted and the results are archived at WuXi AppTec.

6.9.6 USDA Animal Welfare Act

In order to satisfy the USDA Animal Welfare Act, the Sponsor agrees that this testing 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 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 unlikely 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 and Moribund Animals (current version), and current veterinary medical practices. The objectives of the study will be given full consideration prior to 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 safety evaluation of a biomaterial sample, rabbits will be injected intracutaneously (Dose = 0.2 mL x 5 sites) with extracts of the test article and associated vehicle controls. Injection sites will be examined and scored at 24 ± 2, 48 ± 2, and 72 ± 2 hours after treatment for signs of skin reactions. If the difference between the average scores for the extract of a test article and the control is less than or equal to 1.0, the test article passes the test.

8.0 TEST METHOD

8.1 Selection Of Animals

Animals will be selected at random from a larger pool of animals. Selection criteria will be based on the required weight range of this study and the condition and suitability of the animal skin, as observed after shaving. Each animal is observed for any signs of clinical disease prior to introduction into the study.

8.2 Test Article Preparation

The Sponsor submitted test article will be prepared and extracted as indicated on the WuXi AppTec test request form attached to this protocol per ISO 10993:12, Sample Preparation and Reference Materials, and according to WuXi AppTec SOPs: TRG-0300, Preparation of Biomaterials for Extraction and ALS-0260, Sample Extraction Procedures (current versions). The extractions will be stored at room temperature and used within 24 hours of preparation.

8.3 Test Article Administration

8.3.1 The fur on the animal's back will be closely clipped 4 - 18 hours before the test to expose a sufficient area on either side of the spinal column to allow for injections and observations to be made. Mechanical irritation and trauma to the skin will be avoided during clipping.

8.3.2 At five (5) sites on the right side of the spinal column on two rabbits, 0.2 mL of the test article extract will be injected intracutaneously. At five (5) sites on the left side of the spinal column on two (2) rabbits, 0.2 mL of the corresponding vehicle control will be injected intracutaneously. If a second extract is used, it will be injected as the first extract on sites parallel and distal to the test and control injections. (see Figure 1).

FIGURE 1: INJECTION SITES ON RABBITS

HEAD

CONTROL		TEST	
Vehicle #2	Vehicle #1	Extract #1	Extract #2
1	1	1	1
2	2	2	2
3	3	3	3
4	4	4	4
5	5	5	5

TAIL

8.4 Observations

8.4.1 The appearance of each site will be observed at 24 ± 2, 48 ± 2, and 72 ± 2 hours post injection.

8.4.2 The tissue reactions will be evaluated according to Table 1 for gross evidence of erythema, edema, and necrosis. The animals' skin will be lightly swabbed with diluted alcohol to facilitate scoring.

TABLE 1: DERMAL OBSERVATION SCORING

ERYTHEMA	EDEMA
0 = No erythema	0 = No edema
1 = Very slight erythema (barely perceptible)	1 = Very slight edema (barely perceptible)
2 = Well defined erythema	2 = Slight edema (raised edges)
3 = Moderate to severe erythema	3 = Moderate edema (raised ~1 mm)
4 = Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4 = Severe edema (raised > 1 mm and extending beyond area)

Note: Other adverse changes at the injections sites shall be noted and reported.

8.5 Termination

All animals will be euthanized according to WuXi AppTec SOP: ILS-0230, Euthanasia Procedures (current version) by lethal injection with a sodium pentobarbital based solution after the 72-hour observations are recorded.

9.0 METHOD FOR CONTROL OF BIAS: Not applicable.

10.0 DATA ANALYSIS

The erythema and edema scores will be determined for each test sample and control vehicle. The total score is calculated by summation of the Dermal Observation Scores (Table 1) at the dosed injection sites from each observation period on both rabbits. The observation scores for the test sample and control vehicle are totaled separately. Each total score will be divided by 12 (2 animals x 3 observation periods x 2 scoring categories) to determine the overall mean score for each test sample versus each corresponding control vehicle.

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 below and scientific judgment.

The study will be considered valid if there are no normal saline (NS) control scores of '1' or greater and no cottonseed oil (CSO) control scores of '3' or greater.

13.0 TEST EVALUATION

13.1 Positive Response

If the difference between the test and control mean scores is greater than 1.0, the requirements of the test are not met.

13.2 Negative Response

The test is considered negative if the difference between the test and control mean score is 1.0 or less.

13.3 Repeat Assays

Using the above method of computation, if at any observation period the average reaction to the test sample is questionably greater than the average reaction to the control vehicle, the test should be repeated using three (3) additional rabbits. On the repeat of the test, the requirements of the test are met if the difference between the test sample and the control vehicle mean score is 1.0 or less.

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, a description of the methods used, results, and 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

17.1 ISO 10993-10: 2002 Standard, Amendment 1, 2006, Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Delayed-type Hypersensitivity, Pages 23 – 25.

17.2 ISO 10993-12:2007 Biological Evaluation of Medical Devices, Part 12: Sample Preparation and Reference Materials.

17.3 U.S. Pharmacopeia, Section 88, current revision.

17.4 WuXi AppTec SOP: ALS-0260, Sample Extraction Procedures, (current revision).

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

17.6 WuXi AppTec SOP: ILS-0018, Environmental Conditions in the Animal Facility (current revision)

17.7 WuXi AppTec SOP: ILS-0092, Receiving Shipments of Animals, (current revision).

17.8 WuXi AppTec SOP: ILS-0112, Animal Identification, (current revision).

17.9 WuXi AppTec SOP: ILS-0230, Euthanasia Procedures, (current revision).

17.10 WuXi AppTec SOP: ILS-0233, Proper Handling of Sick and Moribund Animals (current revision)

17.11 WuXi AppTec SOP: TRG-0300, Preparation of Biomaterials for Extraction, (current revision).

18.0 COMPLIANCE

18.1 Animal Husbandry

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", Health Research Extension Act of 1985 (Public Law 99-158), Revised 1986; USDA, Department of Agriculture, Animal and Plant Health Inspection Service, 9 CFR, Parts 1, 2, and 3, Animal Welfare, Final Rule 1989.

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.

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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, 910700R - ISO Intracutaneous Reactivity Test. 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 TITLE: Subcontracting

SIGNATURE: Jennifer Shaw DATE: 16 Feb 2009

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.

Thor Rollins
Name of Associate (please print)

\-
Name of Associate (please print)

Tarika Onishi
Name of Associate (please print)

\-
Name of Associate (please print)

WUXI APPTEC, INC.:

NAME: Michelle L. Dietzel
Study Director

SIGNATURE: Michelle Dietzel DATE: 3/12/09
Study Director