Final Report

Study Title:	**Repeated Patch Dermal Sensitization Test (GLP - Buehler Method Modified for Medical Devices)**
Sponsor:	**Klarity Medical Products, LLC** **1987 Coffman Road** **Newark, OH 43055** **US**
Sponsor Account Number:	**4003497**
Performing Laboratory:	WuXi AppTec 2540 Executive Drive St. Paul, MN 55120 US
Folder Number:	D00009282
Test Code:	900899.1
Report Number:	17015
Sample Number:	D00009282001
Test Article Name:	Klarity AccuCushion R550-M
Test Article Lot#:	50506Z

QUALITY ASSURANCE UNIT SUMMARY

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
Dosing	06/23/15	06/23/15	07/28/15
Final Report	07/28/15	07/28/15	07/28/15

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

Quality Assurance Auditor: Stefanie Johnson Date: 7-29-15

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 are exempt from this Good Laboratory Practice Statement and include characterization and stability of the test compound(s)/test article.

Study Director: Kelly Hire Date: 7/29/15

Professional Personnel Involved:

Teri Tanquist, BS	Vice President of Operations
Roxanne Miller, AA, CVT	Sr. Director of Operations
Sarah Steinmetz, BA	Director of Study Operations
Lynn Devine-McDonald, BA	Director of In-Life Operations
Kelly Hire, MS	Study Director

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
2540 Executive Drive
St. Paul, MN 55120

DATE SAMPLE RECEIVED: 06/08/15
STUDY INITIATION DATE: 06/10/15
STUDY COMPLETION DATE: 07/29/15

TEST ARTICLE IDENTIFICATION

Test Article Name:	Klarity AccuCushion R550-M
Lot/Batch #:	50506Z
Sterilization Method:	Non-Sterile
Physical State:	Insoluble Material
Expiration Date:	05/06/18
Storage Conditions:	Room Temperature
Intended Use/Application:	Patient stabilization for Radiation therapy treatments.
Physical Description:	According to the Sponsor, the test article consisted of a moldable pillow with nylon fabric surface.

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.

SAFETY

Appropriate routine safety procedures were followed in handling the test article, unless more cautious procedures were specified by the Sponsor. All applicable WuXi AppTec safety policies and procedures were observed during the performance of the test.

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.

EXPERIMENTAL DESIGN

Experimental Summary

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 was screened for irritation prior to conducting the main test by patching the test article in different concentrations to three guinea pigs. This study is based upon the procedures described in ISO 10993-10: 2010 Biological Evaluation of Medical Devices, Part 10-Tests for Irritation and Skin Sensitization. pp. 23-25. U.S. EPA – Office of Prevention, Pesticides and Toxic Substances, (OPPTS), Health Effects Test Guidelines, OPPTS 870.2600 Skin Sensitization.

Eleven test guinea pigs were patched with the test article and six guinea pigs were patched with the negative control blank. The bandages and patches were removed after 6 hours ± 30 minutes 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 applications. Following a two-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 6 hours ± 30 minutes 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.

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.

Institutional Animal Care and Use Committee (IACUC)
The protocol and any amendments or procedures involving the care or use of animals on this study were reviewed and approved by WuXi AppTec's IACUC prior to the initiation of such procedures.

IACUC Protocol / Effective Date: 98-01F / May, 2013.

PROTOCOL AMENDMENTS/DEVIATIONS
There were no amendments or deviations that occurred during the course of this study.

IDENTIFICATION OF THE TEST SYSTEM

Species/Strain: All of the animals used in this study were albino guinea pig (*Cavia porcellus*), Hartley strain, specific pathogen free (SPF).

Source: Animals were obtained from Charles River Laboratories, a previously approved vendor of commercial laboratory animals.

Sex: Animals used were male.

Body Weight Range: All animals weighed from 363.4 to 444.2 grams upon assignment to the test and were within the required range for the test.

Age: All animals were approximately 6 weeks old at the start of the study.

Number: This test used 17 guinea pigs.

Animal Identification: Cage cards were labeled and individual animals were identified per WuXi AppTec SOP: ILS-0112.

HUSBANDRY

Receipt: Animals were received on 06/03/15 according to WuXi AppTec SOP: ILS-0092. Each animal was examined for signs of disease and injury. The animals were acclimated for a minimum of five days under the same conditions as the actual test.

Housing: Animals were housed in solid bottom plastic cages with contact bedding and up to two guinea pigs per cage. Housing density complied with NIH and AAALAC International standards. The test and negative control animals were housed separately.

Environment: The environmental conditions in the animal rooms were maintained according to WuXi AppTec SOP: ILS-0018. The temperature and photoperiod met the AAALAC International recommendations for this species. The laboratory and animal rooms were maintained as limited-access facilities.

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

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

Termination: Animals were euthanized by CO_2 asphyxiation following completion of this test.

TEST MATERIAL PREPARATION

A representative sample of the test article was cut into approximately 1 inch x 1 inch patches. The plastic packaging (bag) was removed and only the nylon fabric was tested.

Negative Control Preparation

One blank Hill Top Chamber® was prepared for each animal in the negative control group by removing the paper backing.

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 cm x 7 cm area of fur with an electric clipper. The left flank of the animals was shaved on Days 0, 1, 3, 5, 8, 10, 12, 15, and 17. The right flank was shaved for the challenge on Day 31.

TEST ARTICLE ADMINISTRATION

Inductions / Topical Application: A 1 inch x 1 inch section of the test article was applied to the left flank site of the test group animals. Similarly, Blank Hill Top Chamber® control patches were applied to the negative control animals. The animals were wrapped with an elastic bandage and secured with a hypoallergenic tape (Transpore®). The bandaging and patches were removed after 6 hours ± 30 minutes of exposure. At 24 ± 2 hours after removal of the topical application, the sites were assessed for erythema and edema using the grading scale given in Table 1. This procedure was repeated three times per week for three weeks for a total of nine inductions.

Challenge Patch / Topical Application: The challenge procedure was initiated on the eleven test animals and the six negative control animals 14 days after completion of the topical induction phases. The test article was prepared and applied to the fur clipped right flank of the test animals. In addition, one blank Hill Top Chamber® was applied to the fur clipped right flank of each negative control animal. The bandaging and patches were removed after 6 hours ± 30 minutes of exposure. At 24 ± 2 and 48 ± 2 hours after removal of the topical application the sites were assessed for erythema and edema using the grading scale given in Table 1.

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.

ASSAY VALIDITY
Final evaluation of the validity of the assay and test article results was based upon the evaluation criteria listed above and scientific judgment.

METHOD FOR CONTROL OF BIAS: Not applicable.

DATA ANALYSIS
The severity was calculated as follows: The sum of the challenge scores was divided by the total number of animals in a given group at each challenge time point (24 and 48 hours). The incidence was defined as the percentage of animals exhibiting a sensitization reaction at each challenge time point (24 and 48 hours).

STATISTICAL METHODS: None used.

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

OBSERVATIONS AND SCORING
During the inductions, each site on each animal was observed for erythema and edema 24 ± 2 hours after patch removal. To assess for irritation, each site was gently wiped with 70% isopropyl alcohol on a gauze sponge and scored according to the scoring system in Table 1.

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 1. Daily animal health observations were recorded throughout the study period.

TABLE 1: DERMAL OBSERVATION SCORING (AS PER MAGNUSSON AND KLIGMAN SCALE)

Patch test reaction	Grading scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

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.

COMPLIANCE

Animal Welfare

WuXi AppTec maintains the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International accreditation. All applicable portions of this study conformed to the following regulations and guidelines regarding animal care and welfare:

- NIH guidelines as reported in the "Guide for the Care and Use of Laboratory Animals," National Research Council of the National Academies, eighth edition, 2011;
- (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; and
- WuXi AppTec Policy on Humane Care.

International Standards

This study was also in compliance with the following international standard:

ISO 10993-10:2010. Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitization. pp. 23-25.

TEST ARTICLE DISPOSITION: Unused test samples remain in the storage area until all testing is completed. Once completed, the remaining samples were discarded or returned as requested by the Sponsor.

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 2. 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.

TABLE 2: INDUCTION DERMAL OBSERVATIONS 24 HOURS AFTER UNWRAPPING

Animal #	Patch 1 Score	Patch 2 Score	Patch 3 Score	Patch 4 Score	Patch 5 Score	Patch 6 Score	Patch 7 Score	Patch 8 Score	Patch 9 Score
TEST GROUP									
5865	0	0	0	0	0	0	0	0	0
5866	0	0	0	0	0	0	0	0	0
5867	0	0	0	0	0	0	0	0	0
5868	0	0	0	0	0	0	0	0	0
5869	0	0	0	0	0	0	0	0	0
5870	0	0	0	0	0	0	0	0	0
5871	0	0	0	0	0	0	0	0	0
5872	0	0	0	0	0	0	0	0	0
5873	0	0	0	0	0	0	0	0	0
5874	0	0	0	0	0	0	0	0	0
5875	0	0	0	0	0	0	0	0	0
NEGATIVE CONTROL GROUP									
5859	0	0	0	0	0	0	0	0	0
5860	0	0	0	0	0	0	0	0	0
5861	0	0	0	0	0	0	0	0	0
5862	0	0	0	0	0	0	0	0	0
5863	0	0	0	0	0	0	0	0	0
5864	0	0	0	0	0	0	0	0	0

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 3 for individual animal scores.

TABLE 3: CHALLENGE DERMAL OBSERVATIONS

Animal #	24 Hours Score	48 Hours Score
TEST GROUP		
5865	0	0
5866	0	0
5867	0	0
5868	0	0
5869	0	0
5870	0	0
5871	0	0
5872	0	0
5873	0	0
5874	0	0
5875	0	0
Total of Scores	0	0
Severity (Total/11)	0/11	0/11
Incidence %	0%	0%
NEGATIVE CONTROL GROUP		
5859	0	0
5860	0	0
5861	0	0
5862	0	0
5863	0	0
5864	0	0
Total of Scores	0	0
Severity (Total/6)	0/6	0/6
Incidence %	0%	0%

Positive Control: A positive control was completed on 04/10/15 (See Table 4 for individual animal scores). WuXi AppTec completes positive controls at least every 6 months as required per ISO guidelines. The methods for the positive control assay are performed similar to the Experimental Summary above, except that for the induction phases, the animals were patched once a week for three weeks instead of three times per week for three weeks. 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, II and III) only.

At the 24-hour scoring period, all of the animals in the test group were observed with erythema ranging from moderate and confluent (scores of '2' for eight animals) to intense erythema and swelling (scores of '3' for three animals) when challenged with 0.15% w/v mixture of DNCB in acetone. At the 48-hour scoring period, all of the animals in the test group were observed with erythema ranging from discrete or patchy (scores of '1' for six animals) to moderate and confluent (scores of '2' for five animals) when challenged with 0.15% w/v mixture of DNCB in acetone. This represented an incidence of 100% at both scoring periods and a severity of 2.3 and 1.5 at the 24-hour and 48-hour scoring periods, respectively (Table 4).

By contrast, none of the animals in the negative control group were observed with erythema at either the 24-hour or 48-hour scoring periods, representing 0% incidence and 0.0 severity. Therefore, all reactions in the positive control test group 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.

TABLE 4: CHALLENGE DERMAL OBSERVATIONS

ANIMAL #	24 HOURS	48 HOURS
	POSITIVE CONTROL TEST GROUP	
0113	2	1
0114	2	1
0115	2	1
0116	3	2
0117	2	1
0118	2	2
0119	3	2
0120	3	1
0121	2	2
0122	2	2
0123	2	1
Total of Scores	25	16
Severity (Total/11)	25/11	16/11
Incidence %	100%	100%
ANIMAL #	**NEGATIVE CONTROL GROUP**	
0107	0	0
0108	0	0
0109	0	0
0110	0	0
0111	0	0
0112	0	0
Total of Scores	0	0
Severity (Total/6)	0/6	0/6
Incidence %	0%	0%

ANALYSIS AND CONCLUSION

The potential sensitization of the 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, the test article **did not** elicit a sensitization response.

REFERENCES

Dermatotoxicology, Zhai, H. and Maibach, H.I., editors, 6th edition, 2004, pp. 739-741, CRC Press.

Principles and Methods of Toxicology, Wallace Hayes, A., editor, 3rd edition, 1994. Dermatotoxicology Chapter 21, pp. 777, Ravin Press, New York.

Ritz H.L. and Buehler E.V. (1980). "Procedure for Conducting the Guinea Pig Assay." Current Concepts in Dermatology, Drill V.A. and Lazar P. (eds), Academic Press, New York, NY, pp 25-40.

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

WuXi AppTec SOP: ILS-0018, Environmental Conditions in the Animal Facility

WuXi AppTec SOP: ILS-0092, Placing Animal Orders and Receiving Shipments of Animals

WuXi AppTec SOP: ILS-0112, Animal Identification

WuXi AppTec SOP: ILS-0233, Proper Handling of Sick, Injured, and/or Moribund Animals

WuXi AppTec SOP: ILS-0455, Positive Control for the Buehler Sensitization Test

WuXi AppTec SOP: ILS-0460, Buehler Sensitization Test

Test Request Form and Protocol

药明康德 WuXi AppTec

Biocompatibility TEST REQUEST FORM

FOR WUXI APPTEC USE ONLY: D9282-1

P.O. NUMBER: ICP520424

QUOTE NUMBER (QUO - #####- ######- #): QUO- 15997 - SIL8W6 - 0

Complete this form and include it with your test article shipment. Ship to:
WuXi AppTec • 2540 Executive Drive • St. Paul, MN 55120
(1) 651.675.2000 TOLL FREE 888.794.0077

CLIENT INFORMATION

ACCOUNT NUMBER (Required): 4003497

COMPANY NAME • STREET ADDRESS • CITY / STATE / ZIP • COUNTRY	CONTACT NAME	
Klarity Medical Products, LLC 1987 Coffman Road Newark Ohio 43055	Peter Larson BBJ 6-8-15	
	PHONE	EMAIL
	740-788-8107 ex111	peter@klaritymedica.com

REQUESTED TESTING

TEST CODE	TEST NAME
140150.1	ISO Agarose Overlay Using L-929 Mouse Fibroblast Cells (GLP)
Protocol Version #: 18 • Effective Date: 12/17/2013	
900899.1	Buehler Dermal Sensitization - Repeated Patch (GLP)
Protocol Version #: 17 • Effective Date: 05/29/2013	
910699.1	ISO Primary Skin Irritation (GLP) – 4 hours Ø
Protocol Version #: 18 • Effective Date: 07/15/2013	

☐ *Check here if more space is needed to list requested testing. An additional page – with space for continued test listings – will be added.*

Form ALS-8000-1.15 WuXi-3177003995 • Page 1 of 4 Effective Date: 06.01.15

① Per Sponsor JN 6/10/15

EXACT COPY
INITIAL/DATE JN 6/10/15
PAGES 4

TEST ARTICLE INFORMATION	QUANTITY OF TEST ARTICLES SUBMITTED:	CLICK HERE for Sample Requirements Guide

TEST ARTICLE NAME (As to be described on the final report)
Klarity AccuCushion R550-M

LOT NUMBER: 50506Z
☐ Various (LIST ATTACHED) ☐ N.A.
Limit of 25 characters for lot number. To provide unique identifiers or other information that needs to be specified in test article information for the final report, enter in "Test Article Name" space above.

EXPIRATION DATE:
5/6/18

PHYSICAL DESCRIPTION (As to be described on the final report)
Moldable pillow with nylon fabric surface

INTENDED USE / APPLICATION
Patient stabilization for Radiation therapy treatments

PHYSICAL STATE	SAFETY PRECAUTIONS	CONTROLLED STORAGE CONDITIONS
Insoluble	None/Unknown	Room Temperature

STERILITY			
Select one of the three options shown.	☐ Test article submitted sterile. Indicate sterilization method: Not Applicable	☐ Test article is not sterile. WuXi AppTec to expose to: Not Applicable *Additional fees apply.*	☑ Test article is not sterile. To be tested non-sterile.

For GLP studies (required by US FDA)
TEST ARTICLE CHARACTERIZATION
① ☒ Sponsor affirms test article has been characterized or that characterization testing is planned.

Sponsor is solely responsible for all test article characterization data as required in Good Laboratory Practices (GLP) regulations (21CFR58) – identity, strength, stability, purity, and chemical composition. Sponsor is also responsible for ensuring that test article here submitted is representative of the final product that will be subjected to materials characterization.

TEST ARTICLE DISPOSITION (NOTE: Additional fee may apply for returns.)	Courier and account # for shipping: (Required for returns)

Form ALS-6000-1.15 WUXI-3177003385 • Page 2 of 4 Effective Date: 04.01.15

① per sponsor SN 6/10/15

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

TEST ARTICLE HANDLING & PREPARATION

Preparation Requirements / Instructions ☐ N.A.	☐ Do NOT cut test article.	Is test article absorbent?
NOTE: Entire article will be tested unless information is provided here as to materials/components to be included/excluded for testing.	Unless box is checked, test article may be cut into sizes needed for testing.	Unknown
remove plastic packaging (bag) before testing. Surface to be tested is the nylon fabric which will come into contact with patients skin during use.	NOTE: Hemocompatibility testing typically requires the test article to be cut.	

EXTRACTION PARAMETERS ☐ N.A.

If requested tests require extraction, this entire section must be completed by Sponsor. For assistance, contact your Project Manager.

NS = Normal Saline SO = Sesame Oil AS = Alcohol Saline PEG = Polyethylene Glycol PBS = Phosphate Buffered Saline DMSO = Dimethyl Sulfoxide

TYPE OF EXTRACT	EXTRACTION RATIO	EXTRACTION CONDITIONS
Cytotoxicity: Culture Media Sensitization • Irritation • Acute Systemic Toxicity • Mouse Micronucleus: Not Applicable LLNA • Ames • Mouse Lymphoma • Chromosomal Aberration: Not Applicable *Select "NS & PEG" for materials incompatible with DMSO. Select "NS & DMSO or NS & PEG" if DMSO compatibility unknown. WuXi AppTec to determine extract.* Subacute/Subchronic Toxicity: Not Applicable	*Per ISO 10993-12, a surface area ratio should be used whenever possible rather than a weight ratio. The "surface area" includes the combined areas of all sides of the test article and excludes indeterminate surface irregularities.*	*Cytotoxicity: 37°C / 24 hrs* *All other extraction testing:* *Conditions recommended for most devices: 50°C / 72 hrs* Not Applicable *Extraction conditions are based on an exaggeration of product use. For insoluble materials, use highest temperature possible without causing degradation of material.*

FOR HEMOCOMPATIBILITY TESTS *(Incl. Hemolysis, PTT, P&L Counts, IVT Hemo, PT and Complement Activation)* ☐ N.A.

☐ Test blood-contacting portions ONLY (per ISO 10993-4) *NOTE: Entire article will be tested unless box is checked.* Specify blood-contacting components/materials to be tested:	PTT (Partial Thromboplastin Time): RATIO: 4cm² / 1mL Platelet & Leukocyte Count and IVT Hemocompatibility: RATIO: 12cm² / 1mL Complement Activation and PT (Prothrombin Time): RATIO: Not Applicable	ASTM Hemolysis TYPE OF EXTRACT: PBS RATIO: Not Applicable CONDITIONS Direct Contact: 37°C / 3 hrs Extract Method: Not Applicable

FOR MHLW (Japan) TESTS ☐ N.A.

Extraction parameters for MHLW tests are the same as for ISO/ASTM except for the specific tests described here.

MHLW Genotoxicity and Sensitization	MHLW Cytotoxicity	MHLW Hemolysis
These tests are performed using exhaustive extraction method in methanol/acetone with terminal evaporation.	RATIO: Not Applicable	CONDITIONS: Not Applicable

☐ Check here if comparison/control article is being submitted. *(If checked, you will see an additional section that must be completed.)*

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COMMENTS

May be disposed of with normal household waste.

Sponsor signature is required before testing will be initiated.
Services requested in this form will be governed in accordance with WuXi AppTec's "Standard Terms and Conditions." To the extent WuXi AppTec's Standard Terms and Conditions are in conflict with an applicable agreement (Agreement) between Customer listed in this form and WuXi AppTec, such Agreement will govern.

TESTING AUTHORIZATION & PROTOCOL APPROVAL

SIGNATURE	PRINT NAME	DATE
2015.06.02 09:40:08 -05'00'	Peter M. Larson	6/1/15

Print / Save as PDF

To save an electronic copy of this completed form, select Adobe PDF Writer or Microsoft XPS Document Writer in your print dialog.

Always print a hard copy to ship with your samples.

For any test being conducted GLP:
By signing above, you acknowledge that you have reviewed the most current version of the protocol(s) listed on this form and your signature constitutes approval of the protocol(s). If you would like to review any or all of the protocols, click here to email WuXi AppTec and indicate the protocol(s) you want to review.

initiated electronically by KMH on 6/1/15
KMH 6/1/15

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(For Laboratory Use Only)

WuXi AppTec Study # DR282-1

WuXi AppTec

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:	29 May 2013
GLP PROTOCOL:	900899-17

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

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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.

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

3.0 SCHEDULING AND DISCLAIMER

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 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.

3.3 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.

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.

4.0 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.

5.0 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.

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6.0 SAFETY

Appropriate routine safety procedures will be followed in handling the test article, unless more cautious procedures are specified by the Sponsor. All applicable WuXi AppTec safety policies and procedures will be observed during the performance of the test.

7.0 EXPERIMENTAL DESIGN

7.1 Experimental Overview

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 guinea pigs.

For the main test, 11 guinea pigs will be occlusively patched with the Sponsor supplied test article three days each week for three weeks. The contact duration will be at least six hours. A negative control will be similarly patched to six 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 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.

7.2 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.

7.3 Institutional Animal Care and Use Committee (IACUC)

The protocol and any amendments or procedures involving the care or use of animals on this study will be reviewed and approved by WuXi AppTec's IACUC prior to the initiation of such procedures.

IACUC Protocol / Effective Date: 98-01F / May, 2013

It has been determined that no sedation, analgesia, or anesthesia is necessary in this procedure. In the unlikely event that an animal should become sick or injured, euthanasia or veterinary care will be conducted according to WuXi AppTec SOP: ILS-0233 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.

7.4 Amendments / Deviations

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.

8.0 IDENTIFICATION OF THE TEST SYSTEM

8.1 Species/Strain: All of the animals to be used in this testing will be albino guinea pigs (*Cavia porcellus*), Hartley strain (specific pathogen free).

8.2 Source: Animals will be obtained from a previously approved vendor of commercial laboratory animals.

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8.3 **Sex:** Either males or females may 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.

8.4 **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.

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

8.6 **Number:** This study uses a minimum of 17 and a maximum of 37 animals (for preliminary and main testing).

8.7 **Animal Identification:** Cage cards will be labeled and individual animals will be identified per WuXi AppTec SOP: ILS-0112.

8.8 **Husbandry**

8.8.1 **Receipt And Acclimation**
Receipt will be according to WuXi AppTec SOP: ILS-0092. The animals will be acclimated for a minimum of five days under the same conditions as the actual test.

8.8.2 **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.

8.8.3 **Environment**
The environmental conditions in the animal rooms will be maintained according to WuXi AppTec SOP: ILS-0018. 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.

8.8.4 **Feed**
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. Feed analysis results are available and archived at WuXI AppTec.

8.8.5 **Water**
Potable water will be supplied from the local 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.

9.0 TEST METHOD

9.1 **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.

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Table 1: Test Article Preparation Instructions

Physical State	Handling	Preparation Instruction
Liquid or Aerosol	neat or dilute	measure 0.4 mL for each dose aerosols will be collected in a container
Gel - Semi-solid	neat or dilute	measure 0.4 mL or 0.3 g for each dose as applicable
Powder	neat or dilute	measure 0.4 mL or 0.3 g for each dose as applicable
Moldable Solid	neat or extract	cut or form into 1 x 1 inch pieces or measure 0.4 mL or 0.3 g for each dose as applicable
Formed Solid	neat or extract	cut or form into 1 x 1 inch pieces or measure 0.4 mL or 0.3 g for each dose as applicable
Other	other	provide written instructions attached to this protocol

9.2 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.

9.3 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% DNCB in ethanol will be used. For the challenge phase, 0.15% DNCB 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.

9.4 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	(11 animals / test material)
2)	Negative Control	(6 animals / control material)
3)	Preliminary Test (if applicable)	(3 animals)
4)	Positive Control	(11 positive control test / 6 vehicle control)

9.5 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.

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9.5.1 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.

9.5.2 Three 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 6 hours (± 0.5 hour).

If two extracts are selected for this study, the three 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.

9.5.3 **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.

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

9.6 **Test Article Administration**

9.6.1 **Preparation Of The Test Animals**
Prior to the induction dose (if needed, but at least once per week), 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.

9.6.2 **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 days each week for three weeks for a total of nine inductions. The applications will be left in place for six hours (± 0.5 hour). 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 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.

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

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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 six hours (± 0.5 hour) 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.

9.7 Observations

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

9.7.2 **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 2: Dermal Observations and Scoring (as per Magnusson and Kligman scale)

Patch Test Reaction	Grading Scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

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.

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Table 3: Sample Overview of the Main Test Study Design

Day	Site Tested	Activity
0	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
1	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
2	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
3	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
4	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
5	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
7	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
8	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
9	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
10	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
11	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
12	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
14	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
15	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
16	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
17	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
18	Left Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
19	Left Flank	Observe sites / Score Induction sites (24 ± 2 hrs)
31	Right Flank	Shave Challenge Sites
32 (Challenge)	Right Flank	Dose animals / Remove Patches 6 hrs later (± 0.5 hour)
33	Right Flank	Score Challenge Sites (24 ± 2 hrs)
34	Right Flank	Score Challenge Sites (48 ± 2 hrs)

9.8 Termination

After the final observation period, the animals will be humanely euthanized by CO_2 gas asphyxiation.

10.0 EVALUATION CRITERIA

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.

11.0 ASSAY VALIDITY

Final evaluation of the validity of the assay and test article results will be based upon the criteria listed in Section 10.0 and scientific judgment.

12.0 METHOD FOR CONTROL OF BIAS: Not applicable.

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13.0 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).

14.0 STATISTICAL METHODS: None used.

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.
16.2.6 Water and feed analysis reports.

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17.0 COMPLIANCE

17.1 Animal Welfare
WuXi AppTec, Inc. maintains the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International accreditation. All applicable portions of the study will also conform to the following regulations and guidelines regarding animal care and welfare:

17.1.1 NIH guidelines as reported in the "Guide for the Care and Use of Laboratory Animals," National Research Council of the National Academies, eighth edition, 2011;

17.1.2 (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;

17.1.3 USDA, Department of Agriculture, Animal and Plant Health Inspection Service, 9 CFR, Parts 1, 2, and 3, *Animal Welfare*, Final Rule 1989; and

17.1.4 WuXi AppTec Policy on Humane Care.

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

17.3 GLP Status
The study will be conducted 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.

17.4 International Standard
ISO 10993-10: 2010 Biological Evaluation of Medical Devices, Part 10-Tests for Irritation and Skin Sensitization. pp. 23-25.

18.0 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 the Sponsor.

19.0 REFERENCES

19.1 Dermatotoxicology, Zhai, H. and Maibach, H.I., editors, 6th edition, 2004, pp. 739-741, CRC Press.

19.2 Principles and Methods of Toxicology, Wallace Hayes, A., editor, 3rd edition, 1994. Dermatotoxicology Chapter 21, pp. 777, Ravin Press, New York.

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19.3 Ritz H.L. and Buehler E.V. (1980). "Procedure for Conducting the Guinea Pig Assay." Current Concepts in Dermatology, Drill V.A. and Lazar P. (eds), Academic Press, New York, NY, pp 25-40.

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

19.5 WuXi AppTec Reference Library Contents, Form ALS-4650-1

19.6 WuXi AppTec SOP: ILS-0018, Environmental Conditions in the Animal Facility

19.7 WuXi AppTec SOP: ILS-0092, Placing Animal Orders and Receiving Shipments of Animals

19.8 WuXi AppTec SOP: ILS-0112, Animal Identification

19.9 WuXi AppTec SOP: ILS-0233, Proper Handling of Sick, Injured, and/or Moribund Animals

19.10 WuXi AppTec SOP: ILS-0455, Positive Control for the Buehler Sensitization Test

19.11 WuXi AppTec SOP: ILS-0460, Buehler Sensitization Test

20.0 VERSION CHANGE SUMMARY – from Version 900899-16 to 900899-17

20.1 Sections 3.3 and 3.4 were removed from the protocol.

20.2 The IACUC protocol version and effective date were updated.

20.3 The number of animals used per test was updated per the IACUC protocol.

20.4 Section 9.7.2 and Table 2 were updated per ISO guidelines.

20.5 In Reference 19.7 the title of ILS-0092 was updated.

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