TEST FACILITY

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SPONSOR

Geoff Daly
Analytica Ltd
85 Brandl Street Eight Mile Plains
Brisbane, Queensland, 4113
Australia

STUDY TITLE

ISO Maximization Sensitization Study - Extract

TEST ARTICLE NAME

Analytica AutoStart 150mL Burette

TEST ARTICLE IDENTIFICATION

Lot: 20080909

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Summary

A guinea pig maximization test of Analytica AutoStart 150mL Burette, Lot: 20080909, was conducted to evaluate the potential for delayed dermal contact sensitization. This study was conducted based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Delayed-Type Hypersensitivity.

The test article was extracted in 0.9% sodium chloride USP (SC). The extract was intradermally injected and occlusively patched to ten test guinea pigs in an attempt to induce sensitization. The vehicle was similarly injected and occlusively patched to five control guinea pigs. Following a recovery period, the test and control animals received a challenge patch of the test article extract and the reagent control. All sites were scored at 24 and 48 hours after patch removal.

Under the conditions of this study, the SC test article extract showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

Study and Supervisory Personnel:

Molly F. Corvo, B.S.
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Carrie A. Fetter
Jennifer M. Henry, B.S.
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Natasha N. Norris, B.S.
April A. Nietrzeba, B.S.
Michelle R. Horner, B.S.
Connie S. Setzler, B.S.
Anthony J. Campagna, B.S.
Lindsey E. Roberts, B.S.
Mark S. Werth
Don R. Pohl, B.S.
Colleen M. Stevenson, A.A.

Approved by:

Jolee Bartrom, B.S.
Study Director

11-11-08
Date Completed

Statement of GLP Compliance

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

There were no deviations from the protocol, standard operating procedures or the GLP Regulations which were judged to have had any significant impact on the validity or interpretation of the data.

All laboratory data has been accurately recorded and verified, as indicated by the signature below.

Study Director: Jolee Bartrom 11-11-08

Jolee Bartrom, B.S. Date

1. Introduction

Purpose
A guinea pig maximization test of the material identified below was conducted to evaluate the potential to cause delayed dermal contact sensitization. This study was conducted based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Delayed-Type Hypersensitivity.

Dates
The test article was received on September 15, 2008. Treatment began on October 2, 2008, and the observations were concluded October 28, 2008.

GLP Compliance
The study initiated by protocol signature on September 15, 2008, was conducted in accordance with the provisions of the FDA Good Laboratory Practice (GLP) Regulations, 21 CFR 58. A Statement of Quality Assurance Activities was issued with this report.

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

2. Materials

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

Test Article Name:	Analytica AutoStart 150mL Burette
Test Article Identification:	Lot: 20080909
Stability Testing:	In progress (per sponsor)
Expiration Date:	Stable for duration of intended testing (per sponsor)
Strength, Purity and Composition:	Strength: Not applicable as there are no active ingredients are used to formulate a concentration; Purity: Not applicable, because the test article is a multi-component device with no active ingredients; Composition: See Appendix 3.
Physical Description of the Test Article:	Single-use, sterile, medical device. Predominantly transparent PVC and white ABS.
Storage Conditions:	Room Temperature
Vehicle:	0.9% sodium chloride USP solution (SC)
Control Article Stability Testing:	Marketed product stability characterized by its labeling.
Control Article Strength, Purity and Composition:	SC: Strength: Not applicable, no active components in the formulation; Purity: Meets requirements of USP Sodium Chloride for Injection and is certified as USP Grade. 0.9% NaCl ± 5.0% of label claim, balance is water; Composition: CAS #: 7647-14-5 Sodium Chloride/Water CAS #: 7732-18-5.

Preparation: One device was filled to capacity with a total of 160 ml of the vehicle. The device was sealed as necessary to avoid loss of the vehicle during extraction. The test article was extracted with agitation in SC at 50°C for 72 hours. The vehicle (without test article) was similarly prepared to serve as the reagent control.

Condition of Extracts:

	SC Test	SC Control
Induction I:	clear with particulates	clear
Induction II:	clear with particulates	clear
Challenge:	clear	clear

Additional Materials: Freund's Complete Adjuvant (FCA) was mixed 50:50 (v/v) with the chosen vehicle and used at induction I. A 10% (w/w) sodium lauryl sulfate (SLS) suspension in petrolatum was used for induction II. These materials were provided by the test facility.

3. Test System

Test System

Species:	Guinea pig (*Cavia porcellus*)
Strain:	Crl:(HA) BR
Source:	Charles River Laboratories
Sex:	Female (nulliparous)
Body Weight Range:	305 grams to 391 grams at study initiation
Age:	Young adult
Acclimation Period:	Minimum 5 days
Number of Animals:	Fifteen
Identification Method:	Ear punch

Justification of Test System

The Hartley albino guinea pig has been used historically for sensitization studies (Magnusson and Kligman, 1970). The guinea pig is believed to be the most sensitive animal model for this type of study. The susceptibility of the Hartley guinea pig strain to a known sensitizing agent, 1-chloro-2,4-dinitrobenzene (DNCB), has been substantiated at NAMSA with this method under lab number 08T_28875_03 completed on July 11, 2008.

4. Animal Management

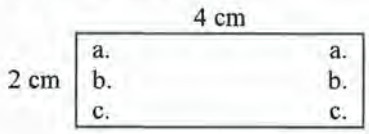
Husbandry:	Conditions conformed to Standard Operating Procedures that are based on the "*Guide for the Care and Use of Laboratory Animals.*"
Food:	A commercially available guinea pig feed was provided daily.
Water:	Potable water was provided *ad libitum* through species appropriate water containers or delivered through an automatic watering system.
Contaminants:	Reasonably expected contaminants in feed or water supplies did not have the potential to influence the outcome of this test.
Housing:	Animals were housed in groups in stainless steel suspended cages identified by a card indicating the lab number, animal numbers, test code, sex, animal code and first treatment date.
Environment:	The animal housing room temperature and relative humidity was monitored daily. The recommended temperature range for the room was 64-79°F and 30-70% for relative humidity. There were no significant temperature or relative humidity excursions that adversely affected the health of the animals. The light cycle was controlled using an automatic timer (12 hours light, 12 hours dark).
Accreditation:	NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare.
Personnel:	Associates involved were appropriately qualified and trained.
Selection:	Only healthy, previously unused animals were selected.

Sedation, Analgesia or Anesthesia:	Sedation, analgesia or anesthesia was not necessary during the routine course of this procedure.
Veterinary Care:	In the unlikely event that an animal became injured, ill, or moribund, care was conducted in accordance with current veterinary medical practice. If warranted for humane reasons, euthanasia was conducted in accordance with the current report of the American Veterinary Medical Association's Guidelines on Euthanasia. The objective of the study was given due consideration in any decision and the study sponsor was advised.
IACUC:	This procedure has been approved by NAMSA Institutional Animal Care and Use Committees (IACUC), and is reviewed at least annually by the same committees. Any significant changes to this procedure were approved by the IACUC prior to conduct.

5. Method

On the first day of treatment, fifteen guinea pigs (ten test, five control) were weighed and identified. The fur over the dorsoscapular region was removed with an electric clipper.

Induction I
The test animals were injected with the test article extract and the control animals were injected with the reagent control. Three rows of intradermal injections (two per row) were given to each animal within an approximate 2 cm x 4 cm boundary of the fur clipped area as illustrated below:



Control Animals:
a. 0.1 mL of 50:50 (v/v) mixture of FCA and the chosen vehicle
b. 0.1 mL of vehicle
c. 0.1 mL of a 1:1 mixture of the 50:50 (v/v) vehicle/FCA mixture and the vehicle

Test Animals:
a. 0.1 mL of 50:50 (v/v) mixture of FCA and the chosen vehicle
b. 0.1 mL of test extract
c. 0.1 mL of a 1:1 mixture of the 50:50 (v/v) vehicle/FCA mixture and the test extract

To minimize tissue sloughing the "a" and "c" injections were slightly deeper than "b". Site "c" was injected slightly more caudal than site "b".

Induction II
The day prior to conducting the Induction II patch, the fur over the dorsoscapular region (same area as used during induction I) was removed with an electric clipper and the area was treated with a 10% sodium lauryl sulfate (SLS) suspension in petrolatum sufficient to coat the skin. The SLS suspension, applied to provoke a mild acute inflammation, was massaged into the skin over the injection site. The area was left uncovered.

At 7 days (±1 day) after completion of the Induction I injection, any remaining SLS residue was gently removed with a gauze pad. A 2 cm x 4 cm section of filter paper, saturated with approximately 0.3 mL of freshly prepared test article extract, was then topically applied to the previously injected sites of the test animals. The control animals were similarly patched with the reagent control. Each patch was secured with a nonreactive tape and the trunk of each animal was wrapped with an elastic bandage. At 48 hours, the binders and patches were removed.

Challenge
At 14 days (±1 day) after unwrapping the Induction II wraps, the fur was removed from the sides and flank areas with an electric clipper. The nonwoven cotton disk contained in a Hill Top Chamber® was saturated with 0.3 mL of the test article extract or reagent control. The test extract was applied to the right flank of each animal and the control vehicle was applied to the left flank of each animal. Each patch was secured to the skin with semiocclusive hypoallergenic adhesive tape. The trunk of each animal was wrapped with an elastic bandage to maintain well-occluded sites. At 24 hours, the wraps and patches were removed and any residue remaining at the sites was removed.

Laboratory Observations
1. Animals were observed daily for general health.
2. Body weights were recorded at pretreatment.
3. Observations for dermal reactions were conducted at 24 and 48 hours after challenge patch removal. Prior to each scoring interval, the sites were wiped with 35% isopropyl alcohol. If necessary, the fur was clipped from each site to facilitate scoring. Scores were recorded in accordance with the criteria shown below:

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

6. Evaluation and Statistical Analysis

The responses from the challenge phase were compared within the test animal group and between test and control conditions. Control conditions were (1) the vehicle control solution on the test animals and (2) the test extract, control solution and biomaterial (if applied) on the control animals.

In the final analysis of data, consideration was given to the overall pattern, intensity, duration and character of reactions of the test as compared to the control conditions. Statistical manipulation of data was not applicable to this study. Grades of 1 or greater in the test group generally indicated sensitization, provided that grades of less than 1 were observed on the control animals. If grades of 1 or greater were noted on control animals, then the reactions of test animals that exceeded the most severe control reaction were considered to be due to sensitization.

7. Results

Body Weights and Clinical Observations
Individual body weights are presented in Appendix 1. All animals appeared clinically normal throughout the study.

Dermal Observations
Individual results of dermal scoring for the challenge phase appear in Appendix 2. No evidence of sensitization was observed.

8. Conclusion

Under the conditions of this study, the SC test article extract showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

Results and conclusions apply only to the test article tested. Any extrapolation of these data to other samples is the sponsor's responsibility. All procedures were conducted in conformance with good manufacturing practices, certified to ISO 13485:2003 and accredited to ISO 17025:2005.

9. Quality Assurance

Inspections were conducted at intervals adequate to assure the integrity of the study in conformance with 21 CFR 58.35(b)(3). The final report was reviewed for conformance to Section 58.185, Subpart J, of the GLP Regulations. A Statement of Quality Assurance Activities was issued with the report.

10. Proposed Dates

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

11. Records

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

12. References

21 CFR 58 (GLP Regulations).

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

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

International Organization for Standardization (ISO) 10993-10, Biological Evaluation of Medical Devices - Part 10: Tests for Irritation and Delayed-Type Hypersensitivity (2002).

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

Magnusson, B. and A. Kligman, *Allergic Contact Dermatitis in the Guinea Pig* (Springfield: C.H. Thomas, 1970).

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

13. Protocol Changes

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

Appendix 1 - Individual Body Weights and Clinical Observations

Group	Animal Number	Individual Observation	
		Pretreatment Body Weight (g)	Clinical Observations
Test	1	305	Animal appeared clinically normal throughout the study.
	2	366	Animal appeared clinically normal throughout the study.
	3	370	Animal appeared clinically normal throughout the study.
	4	315	Animal appeared clinically normal throughout the study.
	5	349	Animal appeared clinically normal throughout the study.
	6	388	Animal appeared clinically normal throughout the study.
	7	391	Animal appeared clinically normal throughout the study.
	8	324	Animal appeared clinically normal throughout the study.
	9	315	Animal appeared clinically normal throughout the study.
	10	350	Animal appeared clinically normal throughout the study.
Control	11	359	Animal appeared clinically normal throughout the study.
	12	314	Animal appeared clinically normal throughout the study.
	13	323	Animal appeared clinically normal throughout the study.
	14	363	Animal appeared clinically normal throughout the study.
	15	366	Animal appeared clinically normal throughout the study.

Appendix 2 - Dermal Reactions - Challenge

Group	Animal Number	Hours Following Patch Removal			
		24 Hour Score		48 Hour Score	
		Control	Test Extract	Control	Test Extract
Test	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	0	0	0	0
	7	0	0	0	0
	8	0	0	0	0
	9	0	0	0	0
	10	0	0	0	0
Control	11	0	0	0	0
	12	0	0	0	0
	13	0	0	0	0
	14	0	0	0	0
	15	0	0	0	0

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08T-48893

Materials List

This listing comprises 'wet' parts only, i.e. parts that come into contact with IV fluid during normal use.

Part Number and Name	*Material*
ALT002-0110 Dual-Outlet Spike	White ABS, Manufacturer: Chi Mei Corporation, Taiwan, Product Code: PA-757
ALT002-0113 Top Cap	
ALT002-0129 Alignment Piece	
ALT002-0118 Dropper Support	
ALT002-0117 Float Guide	
ALT002-0116 Float Body	
ALT002-0128 Float Bottom	
ALT002-0131 Bottom Cap	
ALT002-0120 Upper Dropper Tube	ASTM 304 S30400 Stainless steel tubing
ALT002-0119 Lower Dropper Tube	
ALT002-0166 Spike Cap	PVC – Taizhou Boren Plastic Products Co, Ltd. China – Grade MT-2 – Note: contains DEHP
ALT002-0114 Spike Port	
ALT002-0121 Inlet Tube	
ALT002-0122 Bypass Tube	
ALT002-0130 Central Tube	
ALT002-0115 Extruded Main Chamber	
ALT002-0041 Float Seal	Silicone Rubber - Wacker Elastosil R 401/20
ALT002-0096 Glue	99.5% Cyclohexanone ($C_6H_{10}O$) glue/solvent (cured/dry) - Jiangsu Tengxing chemical
ALT002-0159 Swabbable Needle-free injection Port	OEM – Halkey-Roberts part # 245204024 Polycarbonate: Clear polycarbonate Makrolon RX1805-451118 Silicone: Silicone 40 durometer, blue; Elastosil LR 3003140, OT color K-75238 Blue
ALT002-0105 Air Vent subassembly.	OEM – PVC + hydrophobic filter. Both materials with predicate use.

Geoff Daly, Operations Manager, Analytica Ltd
AUTHORIZED BY SPONSOR

9 SEPT 2008
DATE

NAMSA STUDY DIRECTOR

9-15-08
DATE

REV091107

Statement of Quality Assurance Activities

Phase Inspected	Auditor	Date
Extraction Pour	L. M. Byrd	October 6, 2008
Induction II Wrap	V. D. Gnepper	October 9, 2008
Study Data Inspection	S. M. Pellitieri	October 29, 2008
Final Report Review	D. S. Dunn	November 11, 2008

Reports to Management and Study Director(s)	Date
Periodic Status Report Periodic Status Report	October 10, 2008 November 10, 2008

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

Based on a review of this study, it has been concluded that this report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study. This study has been reviewed in accordance with the provisions of the FDA Good Laboratory Practice Regulations (21 CFR, Part 58).

QA Representative: Debra S Dunn — 11-11-08

Debra S. Dunn
Auditor, Quality Assurance

Date

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08T_48893
26068_001 26068

SPONSOR FINAL REPORT WILL BE ADDRESSED AND MAILED TO

ANALYTICA LTD — Geoff Daly
COMPANY NAME* — ATTN*
85 Brandl St, Eight Mile Plains
ADDRESS*
Brisbane — QLD — 4113
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COUNTRY*
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GDALY@ANALYTICAMEDICAL.COM
E-MAIL*

INVOICE INFORMATION
As Above
BILLING ADDRESS (include Company Name if different from mailed to)*

7233
PURCHASE ORDER NUMBER*

COST ESTIMATE AND PROPOSAL NUMBER

☐VISA ☐MasterCard ☐American Exp

CARD HOLDER NAME

CREDIT CARD NUMBER — EXPIRATION DATE
+61 (7) 3295-0507 — As Above
ACCOUNTS PAYABLE PHONE* — ACCOUNTS PAYABLE FAX*

Analytica AutoStart 150mL Burette
TEST ARTICLE NAME *USE EXACT WORDING DESIRED ON FINAL REPORT* *
As per GMDN code 12159 - Intravenous administration set, general-purpose

INTENDED CLINICAL USE OF TEST ARTICLE:*

☐ BATCH ☐ CODE ☑ LOT 20080909.
CHECK ONE — IDENTIFICATION NUMBER*

CONTROL ARTICLE NAME*

☐ BATCH ☐ CODE ☐ LOT
CHECK ONE — IDENTIFICATION NUMBER*
NAMSA recommends only one lot, batch, or code per test article submission.

QUANTITY SUBMITTED:* 25 units total (includes non-GLP test units)
(please specify quantities for each lot/batch/code provided)
Single-use, sterile, medical device. Predominantly transparent PVC and white ABS.
PHYSICAL DESCRIPTION OF TEST ARTICLE (Chemical/Material type/Color)*

TEST ARTICLE IS CATEGORIZED AS BEING A (check all that apply):* +
X MEDICAL DEVICE ☐ BIOLOGIC ☐ TISSUE
☐ PHARMACEUTICAL ☐ CHEMICAL ☐ OTHER

+ A detailed composition list and current MSDS sheet must accompany any chemical or biologic test article. A certificate of testing or reprocessing must be submitted for any human tissue derived sample or clinically used medical device

TEST ARTICLE BEING SUBMITTED IS:*
X STERILIZED ☐ NOT STERILIZED
☐ **NAMSA TO STERILIZE BY**: ☐ EO (additional charge) ☐ STEAM

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

STORAGE CONDITIONS*
X ROOM TEMPERATURE ☐ REFRIGERATION ☐ FREEZER
☐ OTHER:

① competed by JBloll on 9-15-08
JBloll 9-1508

TEST AND CONTROL ARTICLE CHARACTERIZATION: The sponsor assures the above test article has been characterized for identity, strength, purity, and composition as required by FDA Good Laboratory Practice Regulations of 21 CFR Part 58.105. Stability testing is the responsibility of the sponsor and is subject to FDA audit. Characterization and stability information are also required for control articles. Please check the statement(s) applicable to the test and control articles for both Stability and Characterization sections below.

Test Article	Control Article	Stability (Choose One)
X	☐	Stability testing is in progress; article is stable for duration of intended testing.
☐	☐	Stability testing is complete and on file with sponsor. Expiration date (test): Expiration date (control):
☐	☐	Marketed product stability characterized by its labeling.

Test Article	Control Article	Characterization (if not applicable state clearly the reason why)
① ☒	☐	Strength: N/A: No active ingredients are used to formulate a concentration
① ☒	☐	Purity: N/A because test article is a multi-component device with no active ingredients JBloll 9-15-08
X	☐	Composition: Refer attached materials list.

If requesting to return sample, please check the courier and include your:
☐ UPS ☐ Federal Express ☐ Other _____ Account Number _____

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UPS linhai univer start

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Materials List

08T-4809 3

This listing comprises 'wet' parts only, i.e. parts that come into contact with IV fluid during normal use.

Part Number and Name	*Material*
ALT002-0110 Dual-Outlet Spike	White ABS, Manufacturer: Chi Mei Corporation, Taiwan, Product Code: PA-757
ALT002-0113 Top Cap	
ALT002-0129 Alignment Piece	
ALT002-0118 Dropper Support	
ALT002-0117 Float Guide	
ALT002-0116 Float Body	
ALT002-0128 Float Bottom	
ALT002-0131 Bottom Cap	
ALT002-0120 Upper Dropper Tube	ASTM 304 S30400 Stainless steel tubing
ALT002-0119 Lower Dropper Tube	
ALT002-0166 Spike Cap	PVC – Taizhou Boren Plastic Products Co, Ltd. China – Grade MT-2 – Note: contains DEHP
ALT002-0114 Spike Port	
ALT002-0121 Inlet Tube	
ALT002-0122 Bypass Tube	
ALT002-0130 Central Tube	
ALT002-0115 Extruded Main Chamber	
ALT002-0041 Float Seal	Silicone Rubber - Wacker Elastosil R 401/20
ALT002-0096 Glue	99.5% Cyclohexanone ($C_6H_{10}O$) glue/solvent (cured/dry) - Jiangsu Tengxing chemical
ALT002-0159 Swabbable Needle-free injection Port	OEM – Halkey-Roberts part # 245204024 Polycarbonate: Clear polycarbonate Makrolon RX1805-451118 Silicone: Silicone 40 durometer, blue; Elastosil LR 3003140, OT color K-75238 Blue
ALT002-0105 Air Vent subassembly.	OEM – PVC + hydrophobic filter. Both materials with predicate use.

Geoff Daly, Operations Manager, Analytica Ltd
AUTHORIZED BY SPONSOR — DATE 9 SEPT 2008

NAMSA STUDY DIRECTOR — DATE 9-15-08

TEST FACILITY:

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6750 Wales Road
Northwood, OH 43619

SPONSOR:

Geoff Daly
Analytica Ltd
Eight Mile Plains
Brisbane, Quensland 4113
Australia

STUDY TITLE:

ISO Maximization Sensitization Study - Extract

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Approvals

Sponsor Representative (Sponsor):  Geoff Daly, Operations Manager Analytica Ltd.

Date Approved: Thursday, 4th September 2008

Study Director (NAMSA): 

Date Initiated: 9-15-08

1. Introduction

Purpose
The purpose of this study is to identify the potential for dermal sensitization. The Magnusson and Kligman method has been effective in identifying a variety of allergens. This study will be based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Delayed-Type Hypersensitivity.

GLP Compliance
Good Laboratory Practice – This nonclinical laboratory study will be conducted in accordance with the United States Food and Drug Administration Good Laboratory Practice Regulations, 21 CFR Part 58.

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

2. Materials

Test Article
The sponsor will submit the test article to be evaluated. Detailed information about the test article will be provided by the sponsor on the NAMSA Sample Submission Form or on a similar attachment to the protocol.

Preparation
The following is to be completed by the sponsor or study director. Further instructions may be attached to the protocol. The sample will be prepared as follows:

Ratio of test article to extraction vehicle (select one):

completed by sponsor dkm 9-15-08

___ Material thickness less than 0.5 mm - ratio of 120 cm^2:20 ml
___ Material thickness greater than or equal to 0.5 mm - ratio of 60 cm^2:20 ml
___ Irregularly shaped objects and/or sponsor option - ratio of 4 g:20 ml
X Other (explain): Wet internal surface area = approx 41127 mm^2, Fluid volume = 170mL total (tubes and chambers)

Test Article Preparation Instructions:
Refer to attached product labelling (file: ALT002-0082-200807232018.pdf). Open the air vent (item "E"). Open clamps C and D. Fill main chamber to approximately half way and close off clamps. With thumb and forefinger squeeze the pvc spike port (the small chamber to the right of label "G" in the diagram) until approximately almost full. Fluid will enter the chamber via the canula. Reopen the clamps and allow the fluid to flood the chamber. Close the vent(E). The item can now be exposed to the extraction conditions. To remove the extraction vehicle, open the air vent, and either puncture the diaphragm at the spike port (H), AND/OR the clamps opened and the device turned upside down, AND/OR the device may be punctured or otherwise destroyed or opened.

Extraction Vehicle (select all that apply):

X 0.9% sodium chloride USP solution (SC)
___ Vegetable oil
___ Other (specify):_____

Extraction Conditions (select one):

___ 37°C, 72 hours
X 50°C, 72 hours
___ 70°C, 24 hours
___ 121°C, 1 hour
___ Other (specify):_____

The test article itself is suitable for topical application at the challenge phase.

___ Yes
X No

completed by Sponsor dBloll 9-15-08

Disposition of Test/Control Article (select one):

X Discard ___ Return unused article ___ Return unused and used article

For studies >28 days in life, NAMSA will retain a representative portion of the test/control article.

Special Laboratory Instructions:

No special instructions from Sponsor

Control Article

The vehicle used to prepare the extract will be prepared in the same manner as the extract (but without test article) to serve as the control measure. Untreated skin will serve as an additional control reference for scoring dermal reactions during the challenge phase.

3. Test System

Test System

Species:	Guinea pig (*Cavia porcellus*)
Strain:	Hartley
Source:	NAMSA approved supplier
Sex:	No particular gender is prescribed for this test. If females are used, they will be nulliparous and not pregnant
Body Weight Range:	300-500 grams at study initiation
Age:	Young adults
Acclimation Period:	Minimum 5 days
Number of Animals:	Minimum of fifteen (per extract)
Identification Method:	Ear punch

Justification of Test System

The Hartley albino guinea pig has been used historically for sensitization studies (Magnusson and Kligman, 1970). The guinea pig is believed to be the most sensitive animal model for this type of study. The susceptibility of the Hartley strain to a known sensitizing agent, 1-chloro-2,4-dinitrobenzene (DNCB) has been substantiated at NAMSA with this method.

4. Animal Management

Husbandry:	Conditions will conform to Standard Operating Procedures that are based on the "Guide for the Care and Use of Laboratory Animals."
Food:	A commercially available guinea pig feed will be provided daily.
Water:	Potable water will be provided *ad libitum* through species appropriate water containers or delivered through an automatic watering system.
Contaminants:	Reasonably expected contaminants in feed or water supplies should not have the potential to influence the outcome of this test.
Housing:	Animals will be housed in groups in stainless steel suspended cages identified by a card indicating the lab number, animal numbers, test code, sex, animal code and first treatment date.
Environmental:	The room temperature will be monitored daily. The recommended temperature range for the room is 64-79°F. The room humidity will be monitored daily. The humidity range for the room is 30-70%. The light cycle will be controlled using an automatic timer (12 hours light, 12 hours dark).

Facility:	NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Laboratory Animal Welfare.
Personnel:	Associates involved will be appropriately qualified and trained.
Selection:	Only healthy animals will be selected.
Sedation, Analgesia or Anesthesia:	It has been determined that the use of sedation, analgesia or anesthesia will not be necessary during the routine course of this procedure.
Veterinary Care:	In the unlikely event that an animal should become injured, ill, or moribund, care will be conducted in accordance with current veterinary medical practice. If warranted for humane reasons, euthanasia will be conducted in accordance with the current report of the American Veterinary Medical Association's Panel on Euthanasia. The objective of the study will be given due consideration in any decision and the study sponsor will be advised.
IACUC:	This protocol has been approved by NAMSA Institutional Animal Care and Use Committees (IACUC), and is reviewed at least annually by the same committees. Any significant changes to this protocol must be approved by the IACUC prior to conduct.

5. Test and Control Article Preparation

Fresh extracts will be prepared at each phase of the study as previously indicated (see Test Article). If the test material is suitable for patching, a topical application of the test sample (2 cm x 2 cm patch) will be used at the challenge. The vehicle used to prepare the extract will be prepared in the same manner as the extract (but without test article) to serve as the control measure.

6. Method

On the first day of treatment, fifteen guinea pigs per extract (ten test, five control) will be weighed and identified. The fur from the dorsoscapular area of the animals will be removed with an electric clipper.

Induction I
Three pair of intradermal injections will be administered to the animals within an approximate 2 cm x 4 cm area over the dorsoscapular region as follows:

Control Animals
a. 0.1 ml of 50:50 (v/v) mixture of Freund's Complete Adjuvant (FCA) and the chosen vehicle
b. 0.1 ml of vehicle
c. 0.1 ml of a 1:1 mixture of the 50:50 (v/v) FCA and the vehicle

Test Animals
a. 0.1 ml of 50:50 (v/v) mixture of FCA and the chosen vehicle
b. 0.1 ml of test extract
c. 0.1 ml of a 1:1 mixture of the 50:50 (v/v) FCA and the test extract

To minimize tissue sloughing the "a" and "c" injections will be slightly deeper than "b". Site "c" will be injected slightly more caudal than site "b".

Induction II
The day prior to conducting the Induction II patch, the injection sites will be clipped free of fur again and treated with a 10% (w/w) sodium lauryl sulfate (SLS) suspension prepared by mixing the powdered SLS with petrolatum. The SLS suspension will be applied in an amount sufficient to coat the skin unless the animals exhibit excessive redness and/or swelling at site b. At 7 days (±1 day) after completion of the Induction I injection, any remaining SLS residue will be gently wiped from the area with gauze.

A 2 cm x 4 cm filter paper patch, saturated with approximately 0.3 ml of the extract preparation or vehicle, will be applied over the same injection area and secured with a nonreactive tape. The trunk of each animal will then be wrapped snugly with an elastic band for 48 hours (±2 hours).

Challenge

At 14 days (±1 day) after unwrapping induction II wraps, the fur will be clipped from the sides and flanks with an electric clipper. A nonwoven cotton disk backed by a flexible chamber (e.g. Hill Top Chamber®) and semiocclusive hypoallergenic tape, will be saturated with approximately 0.3 ml of freshly prepared test material extract and applied to the right flank or dorsum of each animal. In addition, the vehicle control will be patched to the left flank or dorsum of each animal. An approximate 2 cm x 2 cm section of test material itself (if appropriate) will be applied to the right flank.

The trunk of each animal will be wrapped to maintain well-occluded sites. At 24 hours (±2 hours) the wraps and patches will be removed and any residue remaining at the sites will be wiped with gauze.

Laboratory Observations

1. Animals will be observed daily for general health.
2. Body weights will be recorded at pretreatment.
3. Observations for dermal reactions will be conducted at 24 and 48 hours after patch removal. Prior to each scoring interval, the sites will be wiped with 35% isopropyl alcohol. If necessary, the fur will be clipped from each site to facilitate scoring. Dermal sensitization results will be compared between the test and control animals in accordance with the criteria shown below:

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

Rechallenge

Should the original challenge results prove to be equivocal, the animals may be rechallenged with a fresh test extract and vehicle control approximately 1 – 2 weeks after the first challenge patch application. The rechallenge will be conducted in the same manner as the challenge but at virgin sites on the opposite flank. After the test is completed, all animals will be handled in accordance with IACUC approved NAMSA procedures.

7. Evaluation and Statistical Analysis

In the final analysis of data, consideration will be given to the overall pattern, intensity, duration, and character of reactions of the test as compared to the control conditions. Statistical manipulation of data is not applicable to this study. Grades of 1 or greater in the test group generally indicate sensitization, provided that grades of less than 1 are observed on the control animals. If grades of 1 or greater are noted on control animals, then the reactions of test animals that exceeded the most severe control reaction will be considered to be due to sensitization.

For rechallenge results, the overall pattern, intensity, duration and character of reactions seen will be compared between the challenge and rechallenge. Recurring observations in at least one of the same animals will be considered as verification of earlier findings.

8. Report

A final report will be issued to include a description of the methods, the resulting data in tabular format and conclusions.

9. Quality Assurance

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

10. Proposed Dates

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

11. Records

Test article preparation, animal weights, treatment procedures, dermal reaction scores, and dates of relevant test activities from study initiation to completion will be recorded.

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

12. References

21 CFR 58 (GLP Regulations).

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

ISO 10993-10 (2002) Biological evaluation of medical devices - Part 10: Tests for irritation and delayed-type hypersensitivity.

Magnusson, B. and A. Kligman, *Allergic Contact Dermatitis in the Guinea Pig* (Springfield: C.H. Thomas, 1970).

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

United States Code of Federal Regulation (CFR) 9: The Animal Welfare Act.

13. Protocol Changes

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

OPEN

ANALYTICA

AutoStart®

STERILE SINGLE-USE 150 mL BURETTE

Setting Up

1. Close the WHITE On/Off clamp (D), and BLUE bypass clamp (C).

2. Open filtered vent (E). NOTE: This vent should be left open during normal use.

3. Remove the spike cap (A)

4. Puncture solution container with spike (B).

5. Open WHITE on/off clamp (D). Fluid will begin to fill the chamber and will be stopped by the float (G).

6. Open the spike port cap (H).

7. Connect an infusion line to the spike port (H).

8. Prime the system according to the infusion line instructions.

• The device is now ready for use.

Medication Delivery

1. Open and shut the BLUE bypass Clamp (C) to fill the Burette with infusion fluid.

2. Add medication via injection site (F) as per hospital protcol.

• The Autostart float (G) will automatically return the device to continuous infusion mode once the medication has been delivered.

⚠ **Important Notes**

• The float (G) shuts off flow once the fluid reservoir is empty. This shutoff is not for long-term use.

• Replace device every 24 hours or per hospital protocol.

• Sterile whilst packaging intact. Do not use if packaging is damaged or if protective caps are not in place.

• Gravity feed only.

• Use aseptic technique.

• WARNING: Air in infusion line may cause embolism

STERILE EO

NON-PYROGENIC
NON-TOXIC
LATEX FREE

CE 0123

Manufacturer: Zhejiang Lingyang Medical Apparatus Co. Ltd. Baishuiyang, Linhai City Province CHINA www.ly-medical.com LY

TGA Sponsor: Analytica Ltd. 85 Brandl St Eight Mile Plains, Brisbane, 4113 AUSTRALIA www.**AutoStartBurette**.com

ALT002-0082-v1

REF 0080

LOT

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08T-4803

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September 17, 2008

Geoff Daly
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PROTOCOL AMENDMENT I

Test Article: Analytica AutoStart 150mL Burette

Identification: Lot: 20080909

NAMSA Submission ID.: 08T_48893

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

NAMSA Code	NAMSA Lab Number	Study	Estimated Start Date:	Estimated Report Release Date:
V0014_130	08T_48893_02	Cytotoxicity Study Using the ISO Elution Method - 1X MEM Extract	October 1, 2008	October 9, 2008
TI261_300	08T_48893_03	ISO Maximization Sensitization Study - Extract - 0.9% SC Extract	September 27, 2008	November 19, 2008
TI251_800	08T_48893_04	ISO Intracutaneous Study - Extract - 0.9% SC Extract	September 21, 2008	October 15, 2008
T0625_500	08T_48893_05	ISO Systemic Toxicity Study - Extract - 0.9% SC Extract	September 22, 2008	October 15, 2008
V0607_100	08T_48893_06	ASTM Hemolysis - CMF-PBS Extract	October 16, 2008	October 20, 2008

Jolee Bartrom, B.S.
Study Director

9-17-08
Date

cc: QA (NAMSA)
Sponsor

NAMSA

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October 8, 2008

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REVISED*
PROTOCOL AMENDMENT I

Test Article: Analytica AutoStart 150mL Burette

Identification: Lot: 20080909

NAMSA Submission ID.: 08T_48893

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

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V0607_100	08T_48893_06	ASTM Hemolysis - CMF-PBS Extract	October 16, 2008	October 20, 2008

*This amendment has been revised to correct the sponsor's address.

Jolee Bartrom

Jolee Bartrom, B.S.
Study Director

10-8-08

Date

cc: QA (NAMSA)
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September 29, 2008

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PROTOCOL AMENDMENT II

Test Article: Analytica AutoStart 150mL Burette

Identification: Lot: 20080909

NAMSA Submission ID.: 08T_48893

NAMSA Code	NAMSA Lab Number	Study	Estimated Start Date:	Estimated Report Release Date:
TI261_300	08T_48893_03	ISO Maximization Sensitization Study - Extract - 0.9% SC Extract	September 27, 2008	November 19, 2008

This amendment was written to provide additional instructions regarding the Test Article Preparation section of the study protocol:

- The test article is unable to hold 170 mL of fluid. The test article should be filled to capacity and the volume utilized should be recorded.

Reason for Change: The test article preparation section was incorrect.

Jolee Bartrom, B.S.
Study Director

9-29-08
Date

cc: QA (NAMSA)
Sponsor