GLP REPORT

TEST FACILITY

NAMSA
9 Morgan
Irvine, CA 92618
949.951.3110

SPONSOR

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

CONFIDENTIAL

STUDY TITLE

USP Pyrogen Study - Material Mediated

TEST ARTICLE NAME

Analytica AutoStart 150mL Burette

TEST ARTICLE IDENTIFICATION

Lot: 20080909

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Summary

The test article, Analytica AutoStart 150mL Burette, Lot: 20080909, was extracted in sterile, nonpyrogenic 0.9% sodium chloride solution. The extract was evaluated in the rabbit for material mediated pyrogenicity. The procedure is recommended in ISO 10993 - 11 (2006) Biological Evaluation of Medical Devices - Part 11: Tests for Systemic Toxicity.

A single dose of 10 mL/kg was intravenously injected via the marginal ear vein into each of three rabbits. Rectal temperatures were measured and recorded prior to injection and at 30 minute intervals between 1 and 3 hours after injection.

Under the conditions of this study, the total rise of rabbit temperatures during the 3 hour observation period was within acceptable USP limits. The test article was judged as nonpyrogenic.

Study and Supervisory Personnel:

John A. Muraski, Ph.D.
Robert Villani, AALAS Certified
David Vergil
Rafael Villegas
Carlos Ramos
Jolene Hernandez
Francisco Duran
Christopher Clements

Approved by:

Marcia Mestre, B.S.
Study Director

10-14-08
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: Marcia Mestre, B.S. 10-14-08 Date

1. Introduction

Purpose
The test article identified below was prepared and evaluated for material mediated pyrogenicity. The test was conducted based on USP General Chapter <151> PYROGEN TEST. The procedure is recommended in ISO 10993-11 (2006) Biological Evaluation of Medical Devices - Part 11: Tests for Systemic Toxicity. The purpose of this study was to determine whether an extract of the test article induced a pyrogenic response following intravenous injection in rabbits. *In vivo* biological reactivity was evaluated following a single injection of the extract.

Dates
The test article was received on September 19, 2008. The study was conducted on September 29, 2008.

GLP Compliance
The study initiated by protocol signature on September 23, 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)
Test Article Strength, Purity and Composition:	Strength: Not Applicable. There were no active ingredients used to formulate a concentration. Purity: Not Applicable. The test article is a multi-component device with no active ingredients. Composition: See Appendix 2.
Physical Description of the Test Article:	Single-use, sterile, medical device. Predominantly transparent PVC and white ABS
Storage Conditions:	Room Temperature
Sham Solution:	Sterile, nonpyrogenic 0.9% sodium chloride solution (SNPS), warmed to 37°C
Vehicle:	Sterile, nonpyrogenic 0.9% sodium chloride solution (SNPS)
SNPS Stability:	Marketed product stability characterized by its labeling
SNPS Strength, Purity and Composition:	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:	The test article air vent and clamps were opened. The fluid pathway of one device was then filled to capacity with 150 mL of SNPS and extracted with continuous agitation at 50°C for 72 hours. The device was decanted recovering approximately 150 mL of extraction volume. The test extract was warmed in a 37°C water bath for a minimum of 10 minutes prior to injection.
Condition of Extract:	Clear
Sample Disposition:	Any remaining sample was discarded.

3. Test System

Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Breed:	New Zealand White
Source:	Myrtle's Rabbitry, Inc.
Sex:	Male
Body Weight:	2.7 kg
Age:	No particular age was prescribed for this test
Acclimation Period:	Minimum 5 days
Number of Animals:	Three
Identification Method:	Ear tag

Justification of Test System

The pyrogen test is specified in the current USP and ISO 10993, Part 11 guidelines. No *in vitro* alternative exists for detecting material mediated pyrogens.

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:	Food was withheld from the animals used during the period of the test.
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 individually housed in stainless steel suspended cages identified by a card indicating the animal number, test code, and sex. Noise level will be maintained to avoid exciting the animals.
Environment:	The room temperature was monitored daily. The temperature range for the room was within a range of 20°C and 23°C (68.0°F and 73.4°F) and free from disturbances likely to excite the animals. The room humidity was monitored daily. The humidity range for the room was 30-70%. Any excursion from the recommended humidity range was minimal and was not considered to have adversely affected the health of the animals or the results of the study. 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 animals were selected. Rabbits used in this study were used previously for another pyrogen study. The establishment and maintenance of a pyrogen colony is defined in the current USP. Complete history of animal usage is traceable in laboratory records. The reuse criteria are described in NAMSA Standard Operating Procedures.

Sedation, Analgesia or Anesthesia:	Sedation, analgesia or anesthesia was not necessary during the routine course of this procedure.
Veterinary Care:	No animal became injured, ill, or moribund during the course of this study. The study was given due consideration in any decision and the study sponsor was advised. No veterinary care was necessary.
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

Preliminary Test - Sham

Animals were placed in a restrainer and a rectal probe was inserted in the rectum of each animal. The animals were allowed to acclimate to their restrainer position at least 1 hour prior to initiating temperature collection. Four temperature readings were conducted at 30 minute intervals beginning 90 minutes prior to injection. The mean temperature of the last two readings was considered the initial temperature.

Each of the rabbits was injected intravenously via the marginal ear vein with SNPS at a dose of 10 mL/kg. The solution was injected within a 4 minute period. For all rabbits, temperatures were recorded at 30 minute intervals for 3 hours after injection. Animals with a temperature rise of greater than 0.6°C, animals with temperatures outside of the 38.0°C to 39.8°C range or animals with a temperature variation greater than 0.2°C between the 0.5 and 0.0 hour pre-injection temperatures were excluded from the main test.

Main Test

Three animals were placed in a restrainer and a rectal probe was inserted in the rectum of each animal. The animals were allowed to acclimate to their restrainer position at least 15 minutes prior to initiating temperature collection. Two control temperatures were taken at least 30 minutes apart. The second temperature was recorded no more than 30 minutes prior to the injection; this temperature became the baseline temperature for the study.

Each of the rabbits was injected intravenously via the marginal ear vein with the test extract at 10 mL/kg of body weight. The test extract was injected within a 10 minute period. For all rabbits, temperatures were recorded at 30 minute intervals between 1 and 3 hours after injection.

6. Evaluation and Statistical Analysis

No statistical analysis of the data was performed. Once the temperature readings had been recorded, the maximum rise in temperature for each rabbit was determined. A decrease in temperature was recorded as a 0.0°C change. If no single animal showed an increase of 0.5°C or more above its baseline temperature, then the extract was judged nonpyrogenic. If the total maximum temperature of all three rabbits exceeded 3.3°C the extract was judged pyrogenic.

7. Results

Main Test

No single animal showed a temperature increase of 0.5°C or more above its baseline temperature. Individual temperatures are presented below.

Rabbit Number	Gender	Weight (kg)	Dose Volume (mL)	Temperature - °C							Maximum Rise
				Before Injection		Hours after Injection					
				Control 1	Baseline	1.0	1.5	2.0	2.5	3.0	
91184*	Male	2.7	27	39.1	39.0	39.2	39.1	39.0	39.2	39.1	0.2
91185*	Male	2.7	27	39.0	39.0	39.0	39.0	39.0	39.0	39.0	0.0
91186*	Male	2.7	27	39.2	39.1	39.1	39.2	39.2	39.0	39.1	0.1
										TOTAL RISE:	0.3

*Previous use history traceable in laboratory records.

8. Conclusion

Under the conditions of this study, the total rise of rabbit temperatures during the 3 hour observation period was within acceptable USP limits. The test article was judged as nonpyrogenic.

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 and certified to ISO 13485:2003.

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 to be 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.

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

International Organization for Standardization (ISO) 10993-11 Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (2006).

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

United States Pharmacopeia 31, National Formulary 26 (USP), General Chapter 151, Pyrogen Test (2008).

13. Protocol Changes

There were no changes to the protocol after sponsor approval or study initiation.

Appendix 1 - Test Article Composition

08C - 49544

NAMSA

SAMPLE SUBMISSION FORM

PEOPLE › SCIENCE › SOLUTIONS

*Annotates a required field

USA Corporate Headquarters
6750 Wales Rd
Northwood Ohio 43619
T 866 666 9455 (toll free)
F 419 662 4386

California
9 Morgan
Irvine California 92618
T 949 951 3110
F 949 951 3280

Georgia
900 Circle 75 Parkway
Suite 1240
Atlanta Georgia 30339
T 770 563 1660
F 770 563 1661

Ohio
6750 Wales Rd
Northwood Ohio 43619
T 866 666 9455
F 419 666 2954

Materials List

08T - 48893 01

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 09-220V

REV091107

Statement of Quality Assurance Activities

Phase Inspected	Auditor	Date
Temperature	A. Yi	September 29, 2008
Raw Data Review	J. Gil	October 13, 2008
Final Report Review	B. Admans	October 14, 2008

Reports to Management and Study Director(s)	Date
Periodic GLP report issued	October 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: B Admans 10-14-08

Barbara Admans
Quality Assurance

Date

NAMSA

PEOPLE

C091908_050

*Annot UPS NAMSA OH

orporate Headquarters
Wales Rd
wood Ohio 43619
666 9455 (toll free)
662 4366

California
9 Morgan
Irvine Califo
T 949 951 3
F 949 951 3280

08T_48893
26068_001 26068

Ohio
6750 Wales Rd
Northwood Ohio 43619
T 866 666 9455
F 419 666 2954

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
CITY* — STATE* — ZIP*
AUSTRALIA
COUNTRY*
+61 (7) 3278-1950
PHONE*
+61 (7) 3259-8313
FAX*
GDALY@ANALYTICAMEDICAL COM
E-MAIL*

INVOICE INFORMATION
As Above
BILLING ADDRESS (include Con

08C_49544
26068_001 26068

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

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

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.

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

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)*

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

①completed by JBOII on 9-15-08
JBOII 9-15-08

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 JBOII 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 _____

T091508_017
UPS linhai univer start

GLP PROTOCOL

TEST FACILITY:

NAMSA
9 Morgan
Irvine, CA 92618

SPONSOR:

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

STUDY TITLE:

USP Pyrogen Study, Material Mediated

NAMSA

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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: September 23, 2008

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1. Introduction

Purpose
The purpose of the study is to determine if a test solution (TS) induces a pyrogenic response following intravenous injection in rabbits. The test article will be extracted in sterile, nonpyrogenic 0.9% sodium chloride solution (SNPS). This study will be conducted based on the methods described in USP General Chapter <151> PYROGEN TEST. The USP method is recommended by ISO 10993-11 (2006) Biological Evaluation of Medical Devices - Part 11: Tests for Systemic Toxicity.

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. It is recommended that a minimum 150 mL extract of the material in SNPS be prepared as follows:

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

___ Material thickness less than 0.5 mm - 900 cm^2:150 mL (ratio of 120 cm^2:20 mL)
___ Material thickness greater than or equal to 0.5 mm - 450 cm^2:150 mL (ratio of 60 cm^2:20 mL)
___ Irregularly shaped objects and/or sponsor option - 30 g:150 mL (ratio of 4 g:20 mL)
① X Other (explain): Wet internal surface area = approx 41127 mm^2, Fluid volume = 170mL total (tubes and chambers)

⑤ **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 ② 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 Conditions (select one):
② Fill through port (B) on diagram. Fill with approximately 160 mL as 170 mL does not fit in device, per OH lab.
If 170 mL of extraction ~~volume~~ ③ vehicle fits then use 170 mL - If it does not, use approximately 160 mL of extraction vehicle
uuc9-2303

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

Does the test article contain a protein component?
___ Yes
① X No

③ Same as uuc9-2303

The test solution will be warmed in a 37°C water bath or incubator for a minimum of 10 minutes prior to dosing.

① Completed by sponsor uuc9-2207

Disposition of Test Article (select one):

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

Special Laboratory Instructions:

No special instructions from Sponsor

Control Article

No control article will be needed in the study.

3. Test System

Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Breed:	New Zealand White
Source:	USDA licensed supplier
Sex:	No particular gender is prescribed for this test
Body Weight Range:	Not less than 1.5 kg at injection
Age:	No particular age is prescribed for this test
Acclimation Period:	Minimum 5 days
Number of Animals:	Three
Identification Method:	Ear tag

Justification of Test System

The pyrogen test is specified in USP General Chapter <151> PYROGEN TEST and ISO 10993-11 (2006) Biological Evaluation of Medical Devices - Part 11: Tests for Systemic Toxicity. No *in vitro* alternative exists for detecting material mediated pyrogens. Three healthy albino rabbits, previously sham tested will be used for the study. Five additional rabbits may be required for retest in the event of a high temperature rise in the three rabbit test.

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:	Food will be withheld from the animals used during the period of the test.
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 individually housed in stainless steel suspended cages identified by a card indicating the animal number, test code and sex. Noise level will be maintained to avoid exciting the animals.
Environment:	The room temperature will be monitored daily. The temperature range for the room is 20°C and 23°C (68.0°F and 73.4°F) and free from disturbances likely to excite the animals. The room humidity will be monitored daily. The humidity range for the room is 30-70%. 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 will be appropriately qualified and trained.

080-49544 02

Completed by Sponsor 11/04/2304

Selection:	Rabbits used in this study may have been used previously for another pyrogen study. The establishment and maintenance of a pyrogen colony is defined in the current USP. Complete history of animal usage will be traceable in laboratory records. The reuse criteria are described in NAMSA Standard Operating Procedures.
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. Method

Three animals will be placed in a restrainer and a rectal probe will be inserted in the rectum of each animal. The animals will be allowed to acclimate to their restrainer position at least 15 minutes prior to initiating temperature collection. Two control temperatures will be taken at least 30 minutes apart. The second temperature will be recorded no more than 30 minutes prior to the injection; this will become the baseline temperature for the study.

Each of the rabbits will be injected intravenously via the marginal ear vein with the test extract at 10 mL/kg of body weight. The TS will be injected within a 10 minute period. For all rabbits, temperatures will be recorded at 30 minute intervals between 1 and 3 hours after injection. After the test is completed, all animals will be handled in accordance with IACUC approved NAMSA procedures.

6. Evaluation and Statistical Analysis

No statistical analysis of the data will be performed. Once the temperature readings have been recorded, the maximum rise in temperature for each rabbit will be determined. If no single animal shows an increase of 0.5°C or more above its baseline temperature, then the extract will be judged nonpyrogenic. If the total maximum temperature of all three rabbits exceeds 3.3°C, the extract will be judged pyrogenic. If one or more rabbits show an increase of 0.5°C or more above its baseline temperature then the extract will be injected in five additional rabbits. In this case, if the total temperature increase of the eight rabbits does not exceed 3.3°C and if no more than three of the eight rabbits attain an individual temperature increase of 0.5°C or more, the extract will be judged nonpyrogenic. A decrease in temperature will be recorded as a 0.0°C change. In the case of a retest a fresh extract will be prepared or the refrigerated extract can be used, provided it does not exceed 24 hours after decanting.

If the test solution is judged pyrogenic, an *in vitro* endotoxin specific assay may be conducted to confirm that the response is due to a non-endotoxin (chemical). Approval by the sponsor will be obtained prior to the conduct of the *in vitro* assay.

7. Report

The final report will include a description of the methods employed, baseline and temperature recordings at 30 minute intervals and maximum temperature rises for the test animals.

8. 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.

08C-49544 02

9. 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).

10. Records

Test article preparation, body weights, rabbit temperatures and maximum rises 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.

11. References

Code of Federal Regulations (CFR), Title 21, Part 58, Good Laboratory Practice for Nonclinical Studies (2007).

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

International Organization for Standardization (ISO) 10993-11 Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (2006).

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

Code of Federal Regulations (CFR), Title 9, Parts 1-199, Animal Welfare Act (2007).

United States Pharmacopeia 31, National Formulary 26 (USP), General Chapter 151, Pyrogen Test (2008).

12. 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.

NAMSA

PEOPLE › SCIENCE › SOLUTIONS

USA Corporate Headquarters
6750 Wales Rd
Northwood, Ohio 43619
T 866.666.9455 (toll free)
F 419.662.4386

California
9 Morgan
Irvine, California 92618
T 949.951.3110
F 949.951.3280

Georgia
900 Circle 75 Parkway
Suite 1240
Atlanta, Georgia 30339
T 770.563.1660
F 770.563.1661

Ohio
6750 Wales Rd
Northwood, Ohio 43619
T 419.666.9455
F 419.666.2954

September 24, 2008

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

PROTOCOL AMENDMENT I

Test Article: Analytica AutoStart 150mL Burette

Identification: Lot: 20080909

NAMSA Submission ID.: 08C_49544

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:
TU010_807	08C_49544_02	Pyrogen Study - Material Mediated - 0.9% SC Extract	September 24, 2008	October 14, 2008

Marcia Mestre, B.S.
Study Director

09-24-08
Date

cc: QA (NAMSA)
Sponsor