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FINAL GLP REPORT: 15-03990-G4

CLASS VI TEST – USP

Test Article
THERMOLAST ® M TM9LFT

21 CFR Part 58 Compliance
Good Laboratory Practice for Nonclinical Laboratory Studies

Report Date
1/12/2016

Study Director
Christopher Parker, M.S., M.B.A.

Sponsor
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Germany

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STUDY SUMMARY

The USP 0.9% Sodium Chloride for Injection (NaCl), Cottonseed Oil (CSO), 1 in 20 Ethanol in NaCl (EtOH), and Polyethylene Glycol 400 (PEG) extracts of the test article, following Intracutaneous Injection in rabbits and Systemic Injection in mice, and the test article, following implantation in rabbits, did not produce a biological response.

Based on the criteria of the protocol and the USP guidelines for Class VI Plastics – 70 °C, the test article, THERMOLAST ® M TM9LFT, meets the requirements of the test.

QUALITY ASSURANCE STATEMENT

The Quality Assurance Unit conducted inspections on the following dates. The findings were reported to the Study Director and to Toxikon's Management.

The final report was reviewed to assure that the report accurately describes the methods and standard operating procedures. The reported results accurately reflect the raw data of the nonclinical study conducted per the protocol.

Phase	Inspection Date	Date Reported to Study Director	Date Reported to Management
BODY WEIGHT	11/20/2015	11/20/2015	11/20/2015
DATA	1/11/2016	1/11/2016	1/11/2016
FINAL REPORT	1/12/2016	1/12/2016	1/12/2016

Katherine Atkinson, B.A.
Quality Assurance Signature

01/12/2016
Date

GLP COMPLIANCE STATEMENT

This study meets the technical requirements of the protocol.

This study was conducted in compliance with the current U.S. Food and Drug Administration 21 CFR, Part 58 Good Laboratory Practices for Nonclinical Laboratory Studies.

The sections of the regulations not performed by or under the direction of Toxikon Corporation, exempt from this Good Laboratory Practice Statement, included characterization and stability of the test article, 21 CFR, Part 58.105, and its mixture with carriers, 21 CFR, Part 58.113.

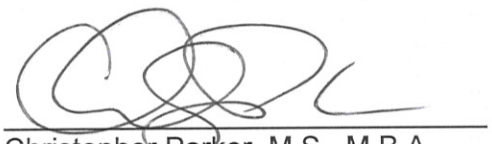
SIGNATURES

Signature Information	
Protocol Number	P15-0384-00A
Study Director	Christopher Parker, M.S., M.B.A.
Study Supervisor	Allan Sleger, A.S., LAT
Company	Toxikon Corporation

VERIFICATION DATES

The study initiation day is the date the protocol is signed by the Study Director.

Verification Dates	
Test Article Receipt	11/11/2015
Project Log	11/11/2015
Study Initiation	11/13/2015
Study Completion	1/12/2016



Christopher Parker, M.S., M.B.A.
Study Director Signature

1/12/16
Date

1.0 PURPOSE

The purpose of the study was to determine the biological response of animals to direct and indirect contact with the test article or injection of the test article extract.

2.0 REFERENCES

The study was based upon the following references:

2.1 United States Pharmacopeia 38, National Formulary 33, 2015. <88> Biological Reactivity Tests, *In Vivo*.

2.2 ISO/IEC 17025, 2005, General Requirements for the Competence of Testing and Calibration Laboratories.

3.0 COMPLIANCE

The study conformed to the current FDA 21 CFR, Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies.

4.0 IDENTIFICATION OF TEST AND CONTROL ARTICLES

The Sponsor supplied the following information on a GLP Test Requisition Form or other correspondence, wherever applicable (excluding confidential or trade secret information). The Sponsor was responsible for all test article characterization data as specified in the GLP regulations.

4.1 Test Article:

Name	THERMOLAST ® M TM9LFT
CAS/Code Number	Not Supplied by Sponsor (N/S)
Lot/Batch Number	Not Supplied by Sponsor (N/S)
Storage Condition	Room Temperature
Physical State	Solid
Color	natural
Density	1,10

4.2 Negative Control Articles (Toxikon Supplied):

4.2.1

Name	USP 0.9% Sodium Chloride for Injection (NaCl)
Toxikon QC Number	CSC–15–08–00085

4.2.2

Name	Cottonseed Oil (CSO)
Toxikon QC Number	CSC–15–10–00165

4.2.3

Name	1 in 20 Ethanol in NaCl (EtOH)
Toxikon QC Number	LPR–15–11–0005

4.2.4

Name	Polyethylene Glycol 400 (PEG)
Toxikon QC Number	CSC–14–08–00136

4.2.5

Name	Negative Control High Density Polyethylene Equivalent to Negative Control USP High Density Polyethylene Reference Standard (Negative Control Plastic)
Toxikon QC Number	CSC–04–05–009–CC

4.3 Reagent (Toxikon Supplied):

Name	Sterile Water for Injection (SWFI)
Toxikon QC Number	CSC–15–09–00078

5.0 IDENTIFICATION OF TEST SYSTEM

5.1 Animals Used in the Study:

5.1.1 Systemic Injection Test:

Number and Species: 40 Albino Swiss Mice (*Mus musculus*)

Sex: female (females were non–pregnant and nulliparous)

Weight/Age Range: 18.0 – 23.0 grams / at least 34 days old (adult)
weighed to the nearest 0.1 g

Health Status: healthy, not previously used in other experimental procedures

Animal Purchase: Envigo, Indianapolis, IN

Animal Identification: ear punch

Acclimation: minimum 5 days, under same conditions as for the actual test

Animal Selection: selected from larger pool and examined to ensure lack of adverse clinical signs

5.1.2 Intracutaneous Injection and Implant Tests:

Number and Species: 6 New Zealand White rabbits (*Oryctolagus cuniculus*)

Sex: 4 males and 2 females (females were non–pregnant and nulliparous)

Weight/Age Range: 2.75 – 3.38 kilograms for Intracutaneous
3.28 – 3.56 kilograms for Implant Test
at least 10 weeks old (young adult)
weighed to nearest 10 g

Health Status: healthy, Intracutaneous animals were previously used in other experimental procedures. Implant animals were not previously used in other experimental procedures.

Animal Purchase: Covance Laboratories, Denver, PA

Animal Identification: ear marker for intracutaneous injection rabbits

ear tattoo for implant rabbits

Acclimation: minimum 5 days, under same conditions as for the actual test

Animal Selection: selected from larger pool and examined to ensure lack of adverse clinical signs

5.2 Animal Care and Maintenance:

5.2.1 Systemic Injection Test:

Animal Room Target Temperature: 68 ± 5 °F

Animal Room Target Relative Humidity: 30–70%

Air Exchanges per Hour: a minimum of 10 changes per hour

Lights: 12–hour light/dark cycle, full spectrum fluorescent lights

Housing: group housed (5 per cage of same sex)

Cages: polycarbonate

Bedding: hardwood chips, PJ Murphy, Montville, NJ (contact)

Animal Rations: Teklad 2020X Rodent Diet, Envigo, Madison, WI, *ad libitum*

Water: tap water, *ad libitum*

There were no known contaminants present in the feed, water, or bedding expected to interfere with the test data.

The laboratory and animal rooms were maintained as limited–access facilities.

5.2.2 Intracutaneous Injection and Implant Tests:

Animal Room Target Temperature: 68 ± 5 °F

Animal Room Target Relative Humidity: 30–70%

Air Exchanges per Hour: a minimum of 10 changes per hour

Lights: 12–hour light/dark cycle, full spectrum fluorescent lights

Housing: individually housed

Cages: suspended stainless steel

Bedding: Alfa Cobs, Scotts Distributing Inc., Hudson, NH (non–contact)

Cages: suspended stainless steel

Bedding: Alfa Cobs, Scotts Distributing Inc., Hudson, NH (non–contact)

Animal Rations: Teklad Global High Fiber Rabbit Diet 2031, Envigo, Madison, WI, *ad libitum*

Water: tap water, *ad libitum*

There were no known contaminants present in the feed, water, or bedding expected to interfere with the test data.

The laboratory and animal rooms were maintained as limited–access facilities.

6.0 JUSTIFICATION OF TEST SYSTEM AND ROUTE OF ADMINISTRATION

6.1 Justification of Test System:

6.1.1 Systemic Injection Test:

Historically, mice have been used in systemic safety evaluation studies because the guidelines have no alternative (non–animal) methods.

6.1.2 Intramuscular Implant and Intracutaneous Injection Tests:

Historically, New Zealand White rabbits have been used in intracutaneous injection and intramuscular implantation safety evaluation studies because the guidelines have no alternative (non–animal) methods.

6.2 Route of Administration:

Animals were treated by intravenous and intraperitoneal routes for the Systemic Injection Test. Animals were treated by intracutaneous injections and intramuscular implantation. The animal species, number, and route of test article administration were recommended by both the USP guidelines. The test article was extracted and administered *in vivo* through a medium compatible with the test system, as indicated on the GLP Test Requisition Form.

7.0 EXPERIMENTAL DESIGN AND DOSAGE

7.1 Preparation of Test and Control Articles:

7.1.1 The test article (60 cm^2) was combined with 20 mL of vehicle following a USP ratio of 60 cm^2 per 20 mL. The test article was extracted in NaCl, CSO, EtOH, and PEG at 70 ± 2 °C for 24 ± 2 hours for the Systemic Injection and Intracutaneous Injection tests.

7.1.2 Prior to extraction, the test article was washed two times with 70 mL of SWFI. The test article sample prepared for extraction with CSO was dried at 50 ± 2 °C for 1 ± 0.1 hour.

7.1.3 Properly prepared test articles were placed in separate extraction vessels and to each vessel the appropriate medium was added. The extraction medium completely covered the test article.

7.1.4 An untreated control (blank) was prepared for parallel treatment and comparison. The untreated control was the extraction medium that was subjected to the same temperature and for the same duration as the test article.

7.1.5 Following extraction, the vessel containing each test or control article was cooled to room temperature.

7.1.6 Each extract was agitated vigorously prior to administration.

7.1.7 After the completion of the extraction, the extracts were kept at room temperature and were used the same day the extraction was completed. The Systemic Injection and Intracutaneous tests were performed using the same extracts. The test article appeared unchanged by the extraction procedure. The extracts were clear and free from particulates. No storage of the extracts occurred. The extracts were not filtered, centrifuged or pH adjusted.

7.1.8 Implant Testing Preparation:

The test and control articles were cut into strips measuring 1 mm × 1 mm × 10 mm. The test and control article strips were sterilized by dipping in 70% ethanol prior to implantation.

7.2 Pre–Dose Procedure:

7.2.1 Systemic Injection Test:

7.2.1.1 Acclimated animals were weighed prior to dosing.

7.2.1.2 For the Systemic Injection Test, the PEG test article extract and the corresponding control were diluted with NaCl to obtain a PEG concentration of approximately 200 mg/mL.

7.2.2 Intracutaneous Injection Test:

7.2.2.1 On the day of the test, the animals were weighed and clipped free of fur on the dorsal side.

7.2.2.2 For the Intracutaneous Test, the PEG test article extract and the corresponding control were diluted with NaCl to obtain a PEG concentration of approximately 120 mg/mL.

7.2.3 Implant Test:

Two rabbits were used for the Implantation Test. On the day of the test, the animals were weighed and the skin on both sides of the spinal column was clipped free of fur. Each animal was anesthetized to prevent muscular movement.

7.3 Dose Administration:

7.3.1 Systemic Injection Test:

Groups of 5 animals were injected with either the test article extract or the corresponding control article extract in the same amounts and by the same routes set forth below:

Extract	Route	Dose/kg	Injection Rate
NaCl	Intravenous	50 mL	0.1 mL/second
CSO	Intraperitoneal	50 mL	—
EtOH	Intravenous	50 mL	0.1 mL/second
*PEG	Intraperitoneal	10 g	—

* Prior to injection, the PEG extract (test and control) was diluted with NaCl to an approximate concentration of 200 mg per mL.

7.3.2 Intracutaneous Injection Test:

7.3.2.1 A volume of 0.2 mL of each test article extract was injected intracutaneously at five sites on one side of each of two rabbits. More than one test article extract was used per rabbit.

7.3.2.2 At five sites on the other side of each rabbit, 0.2 mL of the corresponding control article was injected.

7.3.3 Implant Test:

Four samples of the test article were implanted into the paravertebral muscle on one side of the spine of each of two rabbits (2.5 to 5.0 cm from the midline, parallel to the spinal column and about 2.5 cm from each other). In a similar fashion, two strips of the Negative Control Plastic were implanted in the contralateral muscle of each animal.

7.4 Post–Dose Procedure:

7.4.1 Systemic Injection Test:

7.4.1.1 The animals were observed for clinical signs immediately after injection, 4 hours after injection, and at least 24, 48, and 72 hours after injection. Observations conducted included all clinical and toxicologic signs.

7.4.1.2 The animals were weighed at the end of the observation period.

7.4.1.3 Animals were sacrificed by carbon dioxide (CO_2) inhalation.

7.4.2 Intracutaneous Injection Test:

7.4.2.1 The injection sites on each animal were observed for signs of erythema and edema 24, 48, and 72 hours after injection of the test article. Observations were scored according to the Evaluation of Skin Reactions (Appendix I). Observations conducted also included all clinical signs.

7.4.2.2 Animals were weighed at the end of the observation period.

7.4.2.3 The animals were returned to the general colony.

7.4.3 Implant Test:

7.4.3.1 The animals were maintained for a period of 6 days.

7.4.3.2 The animals were observed daily for this period to ensure proper healing of the implant sites and for clinical signs of toxicity. Observations included all clinical manifestations.

7.4.3.3 At the end of the observation period, the animals were weighed. Each animal was sacrificed by an injectable barbiturate.

7.4.3.4 Sufficient time was allowed to elapse for the tissue to be cut without bleeding.

7.4.3.5 The area of the tissue surrounding the center portion of each implant strip was examined macroscopically using a magnifying lens. Hemorrhaging, necrosis, discolorations, and infections were scored using the following scale:

0 = Normal
1 = Mild
2 = Moderate
3 = Severe

Encapsulation, if present, was scored by first measuring the width of the capsule (the distance from the periphery of the implant to the periphery of the capsule) rounded to the nearest 0.1 mm. The encapsulation was scored as follows:

Capsule Width	Score
None	0
Up to 0.5 mm	1
0.6 to 1.0 mm	2
1.1 to 2.0 mm	3
Greater than 2.0 mm	4

The differences between the average scores for the test article and control article implant sites were calculated.

8.0 EVALUATION CRITERIA

8.1 Systemic Injection Test:

The test is considered negative if none of the animals injected with the test article show a significantly greater biological reaction than the animals treated with the control article.

If two or more mice die, or show signs of toxicity such as convulsions or prostration, or if three or more mice lose more than 2 g of body weight, the test article does not meet the requirements of the test. If any animal treated with a test article shows only slight signs of biological reaction, and not more than one animal shows gross signs of biological reaction or dies, a repeat test is conducted using groups of 10 mice. On the repeat test, all 10 animals must not show a significantly greater biological reaction than the animals treated with the control article.

8.2 Intracutaneous Injection Test:

All average erythema and edema scores for the test and control sites at 24, 48, and 72 hours are totaled separately and divided by 12 (2 animals × 3 scoring periods × 2 scoring categories) to determine the overall mean score for the test article versus the corresponding control article. The requirements of the test are met if the difference between the test article and control article mean reaction scores (erythema/edema) is 1.0 or less.

If at any observation point, the average reaction to the test article sites is questionably greater than the corresponding control article sites, a repeat for the particular test article extract/solution is conducted using an additional 3 rabbits. On the repeat test, the requirements of the test is met if the difference between the test article and control article mean reaction scores (erythema/edema) is 1.0 or less.

8.3 Implant Test:

The test is considered negative if, in each rabbit, the difference between the average scores for each category of biological reaction for the test article and control article implant sites does not exceed 1.0; or if the difference between the mean scores for all categories of biological reaction for each test article and the average score for all categories for all the control implant sites does not exceed 1.0, for not more than one of four test article strips.

8.4 Class VI Requirements:

The test article satisfies the requirements of the USP Class VI test if the requirements described above are met.

8.5 Control of Bias Statement:

The study and its design employed methodology to minimize uncertainty of measurement and control of bias for data collection and analysis, which includes but is not limited to concurrent control data, system suitability assessment, blanks, and replicates.

9.0 RESULTS

9.1 Systemic Injection Test:

9.1.1 Animal Weights (Table 1):

Twelve test animals and eight control animals lost an insignificant amount of weight (less than 2g). All of the other test and control animals maintained or increased in weight.

9.1.2 Clinical Observations (Table 1):

None of the test or control animals exhibited overt signs of toxicity at any of the observation points.

9.1.3 The test is considered negative because none of the animals injected with extracts of the test article showed a significantly greater biological reaction than the animals treated with the control articles.

9.2 Intracutaneous Injection Test:

9.2.1 Animal Weights (Table 2):

All of the animals increased in weight.

9.2.2 Clinical Observations (Table 2):

None of the animals exhibited overt signs of toxicity at any of the observation points.

9.2.3 The difference between the test article and control article mean reaction scores (erythema/edema) was less than 1.0. The test article meets the requirements of the Intracutaneous Test (Table 3).

9.3 Implant Test:

9.3.1 Animal Weights (Table 2):

Animal #50877 lost an insignificant amount of weight (less than 1%). Animal #50879 increased in weight.

9.3.2 Clinical Observations (Tables 2 and 4):

None of the animals exhibited overt signs of toxicity at any of the observation points. Macroscopic evaluation of the test and control article implant sites showed no significant infection, encapsulation, hemorrhage, necrosis, or discoloration.

9.3.3 The test is considered negative, since in each rabbit the difference between the average scores for all of the categories of biological reaction for the test article and control article implant sites did not exceed 1.0, and the difference between the mean scores for all categories of biological reaction for all of the test article implant sites and the average score for all categories for all the control implant sites did not exceed 1.0. The test article meets the requirements of the Implantation Test (Table 4).

10.0 CONCLUSION

The USP 0.9% Sodium Chloride for Injection (NaCl), Cottonseed Oil (CSO), 1 in 20 Ethanol in NaCl (EtOH), and Polyethylene Glycol 400 (PEG) extracts of the test article, following Intracutaneous Injection in rabbits and Systemic Injection in mice, and the test article, following implantation in rabbits, did not produce a biological response.

Based on the criteria of the protocol and the USP guidelines for Class VI Plastics – 70 °C, the test article, THERMOLAST ® M TM9LFT, meets the requirements of the test.

11.0 RECORDS

11.1 Original raw data will be archived by Toxikon Corporation.

11.2 A copy of the final report and any report amendments will be archived by Toxikon Corporation.

11.3 The original final report and a copy of any protocol amendments or deviations will be forwarded to the Sponsor.

11.4 The test article shall be disposed by Toxikon.

11.5 Test article retention upon study completion is the responsibility of the Sponsor.

12.0 CONFIDENTIALITY AGREEMENT

Per corporate policy, confidentiality shall be maintained in general, and in specific accordance with any relevant agreement specifically executed between Toxikon and the Sponsor.

13.0 ANIMAL WELFARE STATEMENT

The Sponsor assured that, to the best of their knowledge, this study did not unnecessarily duplicate previous testing and that there were no non–animal alternatives acceptable for the evaluation of this test article as defined by the protocol.

No evidence of pain and distress was reported to the Veterinarian and/or Study Director.

Toxikon strictly adhered to the following standards in maintaining the animal care and use program:

United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service, 9 CFR Ch. 1 (November 2013 edition), Subchapter A–Animal Welfare.

"Guide for the Care and Use of Laboratory Animals," National Research Council, 2011. (NIH).

Office for Laboratory Animal Welfare (OLAW), "Public Health Service Policy on Humane Care and Use of Laboratory Animals," Health Research Extension Act of 1985 (Public Law 99–158 November 20, 1985), Reprinted 2015.

ISO 10993–2, 2006, Biological Evaluation of Medical Devices – Part 2: Animal Welfare Requirements.

Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.

14.0 UNFORESEEN CIRCUMSTANCES

Any unforeseen circumstances were documented in the raw data. However, no unforeseen circumstances that affected the integrity of the study were noted.

15.0 PROTOCOL AMENDMENTS/DEVIATIONS

There were no protocol amendments or deviations. No changes to the protocol were required.

TABLE 1:
Systemic Injection Test: Animal Weights and Clinical Observations

Group	Animal #	Sex	Dose (mL)	Body Weight (g)			Signs of Toxicity*
				Day 0 11/20/15	Day 3 11/23/15	Weight Change	
	1	Female	1.0	19.1	18.3	-0.8	None
NaCl Test	2	Female	1.0	19.2	19.3	0.1	None
IV	3	Female	1.1	22.7	21.3	-1.4	None
50 mL/kg	4	Female	0.9	18.8	19.2	0.4	None
	5	Female	1.1	22.4	22.1	-0.3	None
	6	Female	1.1	22.9	22.6	-0.3	None
NaCl Control	7	Female	1.0	20.6	21.2	0.6	None
IV	8	Female	1.0	19.8	20.1	0.3	None
50 mL/kg	9	Female	1.1	21.2	21.0	-0.2	None
	10	Female	1.1	21.4	21.0	-0.4	None
	11	Female	1.1	21.2	21.3	0.1	None
CSO Test	12	Female	1.0	19.1	18.4	-0.7	None
IP	13	Female	1.1	22.2	22.3	0.1	None
50 mL/kg	14	Female	1.1	22.3	21.9	-0.4	None
	15	Female	1.2	23.0	24.3	1.3	None
	16	Female	1.1	22.4	22.6	0.2	None
CSO Control	17	Female	1.1	22.8	22.9	0.1	None
IP	18	Female	1.0	20.0	20.1	0.1	None
50 mL/kg	19	Female	1.0	20.5	20.3	-0.2	None
	20	Female	1.0	19.9	19.9	0.0	None
	21	Female	1.1	22.8	21.4	-1.4	None
EtOH Test	22	Female	1.1	21.5	20.7	-0.8	None
IV	23	Female	1.0	20.3	20.6	0.3	None
50 mL/kg	24	Female	1.0	20.6	19.1	-1.5	None
	25	Female	1.1	21.8	21.6	-0.2	None
	26	Female	1.0	20.9	20.7	-0.2	None
EtOH Control	27	Female	1.0	19.5	19.8	0.3	None
IV	28	Female	1.1	22.8	22.8	0.0	None
50 mL/kg	29	Female	1.1	21.3	21.0	-0.3	None
	30	Female	1.1	21.5	21.4	-0.1	None
	31	Female	1.1	21.6	21.2	-0.4	None
PEG Test	32	Female	1.0	19.7	18.8	-0.9	None
IP	33	Female	0.9	18.2	18.5	0.3	None
10 g/kg	34	Female	1.1	21.3	20.9	-0.4	None
	35	Female	1.0	20.7	21.4	0.7	None
	36	Female	1.1	22.4	22.6	0.2	None
PEG Control	37	Female	1.1	21.2	21.8	0.6	None
IP	38	Female	0.9	18.0	18.6	0.6	None
10 g/kg	39	Female	1.0	19.6	19.6	0.0	None
	40	Female	1.1	22.9	22.8	-0.1	None

* Summary of clinical observations - Immediately, 4, 24, 48, and 72 hours after injection.

IV = Intravenous IP = Intraperitoneal

TABLE 2:
Intracutaneous Injection and Implant Tests:
Animal Weights and Clinical Observations

Group	Animal #	Sex	Body Weight (kg)			Signs of Toxicity*
			Day 0 11/20/15	Day 3 11/23/15	Weight Change	
NaCl & CSO	50983	Male	3.37	3.46	0.09	None
	50984	Female	3.15	3.21	0.06	None
EtOH & PEG	50985	Male	2.75	2.78	0.03	None
	50986	Female	3.38	3.41	0.03	None
Group	**Animal #**	**Sex**	**Body Weight (kg)**			**Signs of Toxicity***
			Day 0 11/19/15	**Day 6 11/25/15**	**Weight Change**	
USP Implant (6 Days)	50879	Male	3.56	3.60	0.04	None
	50877	Male	3.28	3.25	-0.03	None

* Summary of Clinical Observations, Day 0 through Day 3, excluding skin reactions for the Intracutaneous Injection Test, Day 0 through Day 6 for the Implant Test.

TABLE 3:
Intracutaneous Test Skin Reaction Scores

NaCl Extract

Animal #	Vehicle	Time	Site Numbers Scoring (ER/ED)									
			T–1	T–2	T–3	T–4	T–5	C–1	C–2	C–3	C–4	C–5
50983	NaCl	24 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		48 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		72 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
50984	NaCl	24 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		48 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		72 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Total/5 (sites)			0.0					0.0				

Overall Mean Score* for Test Article = 0.0/12 = 0.0
Overall Mean Score* for Control Article = 0.0/12 = 0.0
Difference between Test Article and Control Article Overall Mean Score = 0.0–0.0 = 0.0

CSO Extract

Animal #	Vehicle	Time	Site Numbers Scoring (ER/ED)									
			T–1	T–2	T–3	T–4	T–5	C–1	C–2	C–3	C–4	C–5
50983	CSO	24 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		48 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		72 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
50984	CSO	24 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		48 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		72 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Total/5 (sites)			0.0					0.0				

Overall Mean Score* for Test Article = 0.0/12 = 0.0
Overall Mean Score* for Control Article = 0.0/12 = 0.0
Difference between Test Article and Control Article Overall Mean Score = 0.0–0.0 = 0.0

ER = Erythema; ED = Edema; T = Test Sites; C = Control Sites
* Overall Mean Score = Total erythema plus edema scores divided by 12
(2 animals × 3 scoring periods × 2 scoring categories)

TABLE 3
Intracutaneous Test Skin Reaction Scores (Cont.)

EtOH Extract

Animal #	Vehicle	Time	Site Numbers Scoring (ER/ED)									
			T–1	T–2	T–3	T–4	T–5	C–1	C–2	C–3	C–4	C–5
50985	EtOH	24 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		48 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		72 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
50986	EtOH	24 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		48 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		72 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Total/5 (sites)			0.0					0.0				

Overall Mean Score* for Test Article = 0.0/12 = 0.0
Overall Mean Score* for Control Article = 0.0/12 = 0.0
Difference between Test Article and Control Article Overall Mean Score = 0.0–0.0 = 0.0

PEG Extract

Animal #	Vehicle	Time	Site Numbers Scoring (ER/ED)									
			T–1	T–2	T–3	T–4	T–5	C–1	C–2	C–3	C–4	C–5
50985	PEG	24 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		48 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		72 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
50986	PEG	24 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		48 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
		72 hours	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Total/5 (sites)			0.0					0.0				

Overall Mean Score* for Test Article = 0.0/12 = 0.0
Overall Mean Score* for Control Article = 0.0/12 = 0.0
Difference between Test Article and Control Article Overall Mean Score = 0.0–0.0 = 0.0

ER = Erythema; ED = Edema; T = Test Sites; C = Control Sites
* Overall Mean Score = Total erythema plus edema scores divided by 12
(2 animals × 3 scoring periods × 2 scoring categories)

TABLE 4:
Implant Test Macroscopic Observations

Animal #: 50879

Tissue Site	T1	T2	T3	T4	Test Average	C1	C2	Control Average
Infection	0	0	0	0	0	0	0	0
Encapsulation	0	0	0	0	0	0	0	0
Hemorrhage	0	0	0	0	0	0	0	0
Necrosis	0	0	0	0	0	0	0	0
Discoloration	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0
Mean Score (total/5)	0	0	0	0		0	0	

Animal #: 50877

Tissue Site	T1	T2	T3	T4	Test Average	C1	C2	Control Average
Infection	0	0	0	0	0	0	0	0
Encapsulation	0	0	0	0	0	0	0	0
Hemorrhage	0	0	0	0	0	0	0	0
Necrosis	0	0	0	0	0	0	0	0
Discoloration	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0
Mean Score (total/5)	0	0	0	0		0	0	

T = Test
C = Control

APPENDIX I:
Evaluation of Skin Reactions

Erythema and Eschar Formation	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well–defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Total possible erythema score = 4

Edema Formation*	Score
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well–defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

Total possible edema score = 4

* Excludes non–inflammatory (mechanical) edema from the blank or extract fluid.

APPENDIX II:
Software Systems

Software	Use	Publisher/Vendor	Location
Adobe Acrobat 8, 9 and 10 Professional	Document preparation	Adobe Systems, Inc.	San José, CA
Lotus Domino Rel. 5	Client–server application for Sponsor, sample, test codes, and quotation management application databases	IBM Corporation	Armonk, NY
Matrix Gemini 5.3.5	Laboratory Information Management System	Autoscribe Limited	Reading, UK
MS Office 2010 Small Business Suite and MS Office 2013 Professional Suite	Business software (suite includes Word, Excel, PowerPoint, Outlook, Publisher, Office tools)	Microsoft Corporation	Redmond, WA
Rees CentronSQL System 2.0	Environmental monitoring and metrology system	Rees Scientific	Trenton, NJ
TMS Web 7	Document management for SOPs and training records management software system	Quality Systems Integrators	Eagle, PA
Toxikon Protocol Manager 1.0	Protocol requisition application	Custom developed	Toxikon Corporation, Bedford, MA