REPORT

TEST FACILITY

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CONFIDENTIAL

STUDY TITLE

ISO Skin Irritation Study in Rabbits

TEST ARTICLE NAME

M106 Pressure Sensitive Adhesive

TEST ARTICLE IDENTIFICATION

M106 Pressure Sensitive Adhesive 11-16-15

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Summary

The test article, M106 Pressure Sensitive Adhesive, was evaluated for primary skin irritation in rabbits. This study was conducted in accordance with the guidelines of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. Two 25 mm x 25 mm sections of the test article and control article were topically applied to the skin of each of three rabbits and left in place for a minimum of 23 hours and a maximum of 24 hours. The sites were graded for erythema and edema at 1, 24, 48 and 72 hours after removal of the single sample application.

There was no to very slight erythema and no edema observed on the skin of the animals treated with the test article. The Primary Irritation Index for the test article was calculated to be 0.3. The response of the test article was categorized as negligible.

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Arizona E. Carter, BS, ALAT
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Date

1. Introduction

1.1 Purpose

The purpose of this study was to evaluate the test article for the potential to cause skin irritation in the rabbit.

1.2 Testing Guidelines

This study was conducted based on the International Organization for Standardization 10993-10, Biological evaluation of medical devices, Part 10: Tests for irritation and skin sensitization.

1.3 Dates

Test Article Received:	November 17, 2015
Treatment Started:	November 30, 2015
Observations Concluded:	December 4, 2015

2. Identification of Test and Control Articles

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

Table 1: Test Article

Name:	M106 Pressure Sensitive Adhesive
Identification:	M106 Pressure Sensitive Adhesive 11-16-15
Physical Description of the Test Article:	M106 adhesive on supporting substrate. Remove both white paper release liners before the test.
Storage Conditions:	Ambient Temperature

Table 2: Control Article

Name:	Four-ply gauze, supplied by the test facility, was cut into 25 mm x 25 mm sections.
Strength, Purity, Composition or Other Characteristics:	Purity: FDA Quality System Requirements (QSR) as stipulated in 21 CFR Part 820; Composition: 20% rayon, 80% polyester blend

3. Test System

3.1 Test System

Species:	Rabbit (*Oryctolagus cuniculus*)
Breed:	New Zealand White
Source:	Robinson Services, Inc.
Sex:	Male
Body Weight Range:	2.4 kg to 2.6 kg at selection
Age:	Young adult
Acclimation Period:	Minimum 5 days
Number of Animals:	Three
Identification Method:	Ear tag

3.2 Justification of Test System

The rabbit (animal) is specified as an appropriate animal model for evaluating potential skin irritants by the current ISO testing standards. The rabbit is widely used for this purpose and relative ranking of irritant scores can be determined.

4. Animal Management

4.1 Husbandry, Housing and Environment

Conditions conformed to NAMSA Standard Operating Procedures that are based on the "*Guide for the Care and Use of Laboratory Animals*." Animals were individually housed in stainless steel or plastic suspended cages identified by a card indicating the lab number, animal number, test code, sex, and date dosed.

The animal housing room temperature and relative humidity were monitored daily. The temperature for the room was set to 61-72°F and the relative humidity was set to 30-70%. 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).

4.2 Food, Water and Contaminants

A commercially available rabbit feed, Laboratory Rabbit Diet – 5326, was provided daily. Potable water was provided *ad libitum* through species appropriate water containers or delivered through an automatic watering system.

No contaminants present in the feed and water impacted the results of this study.

4.3 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.

4.4 Personnel

Associates involved were appropriately qualified and trained.

4.5 Veterinary Care

Standard veterinary medical care was provided in this study.

4.6 IACUC

This procedure has been approved by the NAMSA Institutional Animal Care and Use Committee (IACUC), and is reviewed at least annually by the same committee.

4.7 Selection

Only healthy, previously unused, animals free from irritation or other dermatological lesions that could interfere with the test were selected.

5. Method

5.1 Test Article Preparation

The test article was a pressure sensitive adhesive. One release liner was removed prior to preparation. The second release liner was removed prior to testing. Two 25 mm x 25 mm sections of the test article were prepared. The test article was backed with 4-ply gauze and the adhesive was tested against the skin of the rabbit.

5.2 Test Procedure

The animals were weighed and the fur on the back of each animal was clipped with an electric clipper 4 to 24 hours prior to treatment. On the day of treatment, four sites, two on each side of the back and positioned cranially and caudally, were designated on each animal. The sites were free of blemishes that could interfere with the interpretation of results.

The test article was applied to one cranial site and one caudal site (two sites per animal) by introduction under a 4 ply gauze layer to an area of skin approximately 25 mm x 25 mm square. The patches were covered with a nonreactive tape. The control was similarly applied to the opposite cranial and caudal sites. The trunk of each animal was wrapped with an elastic binder to maintain the test patches in position. Animals were returned to their cages after treatment.

After a minimum of 23 hours and a maximum of 24 hours exposure, the binders, tape, and patches were removed. The perimeter of each site was marked with nontoxic ink. The sites were gently wiped with a gauze sponge dampened with deionized water in an attempt to remove any remaining residue.

5.2.1 Laboratory Observations

1. Animals were observed daily for general health.
2. Body weights were recorded for each animal at pretreatment.
3. Dermal observations for erythema and edema were recorded at 1, 24, 48 and 72 hours after patch removal in accordance with the criteria in Appendix 1.

All times and temperatures reported herein are approximate and are within ranges established by the external standards described in the References section of this report and/or NAMSA standard operating procedures.

6. Evaluation and Statistical Analysis

The Primary Irritation Index of the test was calculated following test completion for each animal. The erythema and edema scores obtained at the 24, 48 and 72 hour intervals were added together and divided by the total number of observations. The 1 hour score was not included in the calculation. This calculation was conducted separately for the test and control article for each animal. The score for the control was subtracted from the score for the test article to obtain the Primary Irritation Score. The Primary Irritation Score for each animal was added together to determine the Combined Primary Irritation Score. The Combined Primary Irritation Score was divided by the number of animals to obtain the Primary Irritation Index. The Primary Irritation Index was characterized based on the definitions outlined in Appendix 1.

7. Results

7.1 Clinical Observations

At the 24 hour observation, animal 8495 had reduced feces. At the 48 hour observation, animal 8495 had no feces. Per veterinarian assessment, animal was bright, alert and responsive and well hydrated. Abdomen was mildly distended. Food supplements were provided as needed for the duration of this study. A general necropsy was conducted on animal 8495 at the conclusion of this study. All other animals were clinically normal throughout the study.

7.2 Necropsy

The stomach was liquid filled. The small and large intestines were gas and liquid filled. Otherwise, the animal was macroscopically normal.

7.3 Dermal Results

Individual results of dermal scoring are presented in Appendix 2. No to slight erythema and no edema reactions resulted in an overall evaluation of slight irritation to the skin of the animals treated with the test article. The time of onset of the Maximum Irritation Response was at 1 hour and the time to Maximum response was 1 hour. The Primary Irritation Index of the test article was calculated to be 0.7. The irritation calculations are shown below:

Table 3: Irritation Calculations

Animal Number	Test Score Average	-	Control Score Average	Individual Primary Irritation Score	Combined Primary Irritation Score (CPIS)	Primary Irritation Index (CPIS ÷ 3)	Response Category
8493	0.0	-	0.0	0.0	0.9	0.3	Negligible
8495	0.7	-	0.0	0.7			
8597	0.2	-	0.0	0.2			

8. Conclusion

There was no to very slight erythema and no edema observed on the skin of the animals treated with the test article. The Primary Irritation Index for the test article was calculated to be 0.3. The response of the test article was categorized as negligible.

Results and conclusions apply only to the test article tested. Any extrapolation of these data to other articles is the sponsor's responsibility.

9. Records

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

10. ISO Compliance

All procedures were certified to ISO 13485 and accredited to ISO 17025.

11. References

Code of Federal Regulations (CFR), Title 9, Parts 1-4, Animal Welfare Act.

Code of Federal Regulations (CFR), Title 16, Part 1500, Federal Hazardous Substances Act (FHSA) Regulations (2008).

International Organization for Standardization (ISO) 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (2009/Technical Corrigendum 1 2010).

International Organization for Standardization (ISO) 10993-2, Biological evaluation of medical devices - Part 2: Animal welfare requirements (2006).

International Organization for Standardization (ISO) 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization (2010).

International Organization for Standardization (ISO) 10993-12, Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (2012).

International Organization for Standardization (ISO) 13485, Medical devices - Quality management systems - Requirements for regulatory purposes (2003/Technical Corrigendum 1 2009).

International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 17025, General requirements for the competence of testing and calibration laboratories (2005/Technical Corrigendum 1 2006).

National Research Council, *Guide for the Care and Use of Laboratory Animals*, Washington, DC: National Academy Press, 2011.

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

Appendix 1 - Classification System For Skin Reaction

Reaction	Numerical Grading
Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Well-defined 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 exposure area)	4
Total possible score for irritation	8

NOTE: Other adverse changes at the skin sites shall be recorded and reported

Irritation Response Categories in the Rabbit

Response Category	Mean Score
Negligible	0.0 to 0.4
Slight	0.5 to 1.9
Moderate	2.0 to 4.9
Severe	5.0 to 8.0

Appendix 2 - Dermal Observations

Animal Number/ Sex	Weight (kg)	Group	Observation	Interval (hours)							
				1		24		48		72	
				Left	Right	Left	Right	Left	Right	Left	Right
8493 Male	2.6	Test	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0
8495 Male	2.4	Test	Erythema	0	1	1	1	1	0	1	0
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0
8497 Male	2.5	Test	Erythema	0	1	0	1	0	0	0	0
			Edema	0	0	0	0	0	0	0	0
		Control	Erythema	0	0	0	0	0	0	0	0
			Edema	0	0	0	0	0	0	0	0