GLP Final Report

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STUDY TITLE
Skin irritation Study

TEST ARTICLE
Vinyl Examination gloves
Model: clear, powder, L

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Summary

The test article, Vinyl Examination gloves, clear, powder, L, was evaluated for the potential to cause skin irritation following application on the skin of rabbits.

The test article was extracted in polar extraction vehicle (0.9% sodium chloride solution (SC)) and non-polar extraction vehicle (Sesame Oil (SO)), then 0.5ml of polar extract and blank control (polar extract without test article) was applied on a patch (2.5 cm×2.5 cm), respectively, the patches were further applied on test sites and control sites the rabbit skin, for 4 hours. The application sites were observed immediately and recorded in 1 hour, 24 hour, 48 hour and 72 hour respectively after removal of the patches. Repeat the above method with non-polar extract group.

According to what was observed, the skin reaction on test sites did not exceed that on the control sites. The primary irritation indexes for polar and non-polar extracts of the test article were calculated to be 0 (polar extract group) and 0 (non-polar extract group), respectively.

Under the conditions of this study, the irritation response category of the test article is classified as Negligible for polar extract and Negligible for non-polar extract.

Approved by: 傅立 2021、04、27

Lee Fu, Authorized Signatory / Study Director — Date

GLP STATEMENT

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

There was no deviation to the protocol or provisions of GLP Regulation noted during the course of the study.

Approved by: _____ 2021、04、27

Lee Fu, Authorized Signatory
Study Director

Date

1. Generals

1.1 Purpose

The purpose of this study was to evaluate the potential dermal irritation of a test article extract following applied on the skin of rabbits.

1.2 Guidelines

1) ISO 10993-10:2010 Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization.

1.3 Dates

Test Article Received:	01/27/2021
Initiated:	03/12/2021
Completed:	03/18/2021

2. Materials

Test Article	Vinyl Examination gloves
Model	clear, powder, L
Manufacturer	Same as sponsor
Manufacturer Address	Same as sponsor
Identification Number	20210120
Status	Non-sterile
Physical Description	Solid
Composition	Vinyl
Stability	Stability was determined by and on file with the sponsor.
Expiration Date (or Shelf Life)	Stable during the study.
Strength	Not applicable, no active ingredient
Purity	Not applicable, no active ingredient
Storage Condition	Room Temperature
Note	Information regarding the test article was provided by sponsor in the Sample Submission Form.

Extraction Vehicle (Control)	0.9% sodium chloride
Polar	
Manufacturer	China Otsuka Pharmaceutical Co.,Ltd.
Lot Number	20E3502
Physical Description	Clear, Colourless, Liquid
Composition	NaCl
Strength	250ml/bottle
Purity	Conforms to China Pharmacopoeia
Stability	Marketed product, stability is characterized by its labelling
Storage Condition	Room Temperature

Extraction Vehicle (Control)	Sesame Oil

Non-Polar

Manufacturer	Société Industrielle des Oléagineux
Lot Number	19C0302
Physical Description	Clear, Yellow to Green, Liquid
Composition	Sesame Oil
Strength	56.5 Kg/barrel
Purity	Pure
Stability	Marketed product, stability is characterized by its labelling
Storage Condition	Room Temperature

Sample Preparation Prior to the extraction, test article was removed from the package and covered in the extraction vehicle.

Extraction Procedure The test article and the control blank (extraction vehicle without the test article) were subjected to the extraction conditions as described below. The extracts were continuously agitated during extraction.

Group	**Polar (SC)**		**Non-Polar (SO)**	
	Test	**Control**	**Test**	**Control**
Extraction Ratio	6 cm^2:1ml	N.A	6 cm^2:1ml	N.A
Sample Amount	400 cm^2	N.A.	400 cm^2	N.A.
Extraction Vehicle Volume	66.6 ml	20.0 ml	66.6 ml	20.0 ml
Extraction Condition	50℃ 72 hours			
Condition of Extracts	Clear	Clear	Clear	Clear
	No Particulate	No Particulate	No Particulate	No Particulate

Note: All extracts were not centrifuged, filtered or otherwise altered prior to dosing. It was dosed immediately after extraction.

3. Test Systems and Justification

Species:	Rabbit
Breed:	Japanese White
Source:	Tianjin Yuda Laboratory Animal Breeding Co., Ltd.
Sex:	Male
Body Weight Range:	2.00 kg above
Age:	Young adults
Acclimation Period:	Minimum 5 days
Number of Animals:	Six (6), among them, three (3) for polar extract group and three (3) for non-polar extract group
Identification Method:	Ear tag
Justification:	The irritation test on rabbits is specified in the current ISO testing standards and has been used historically to evaluate biomaterial extracts. The sensitivity of the Rabbit (Japanese White) to a known irritant, 20% sodium dodecyl sulfate (SDS) has been substantiated at Mid-Link with this method. Detail information in provided in

Attachment: Positive Control Record.

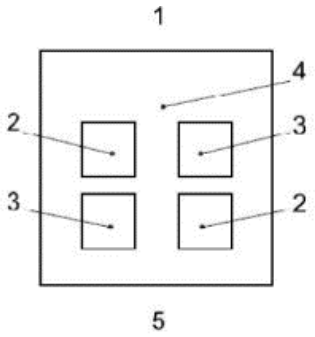
4. Animal Management

Husbandry, Housing and Environment	Conditions conform to MID-LINK Standard Operating Procedures. Animals were individually housed in a cage with an identification card indicating the animal number, test code.
Food, Water and Contaminants	A commercially available rabbit feed was provided daily. Potable water was provided ad libitum through species appropriate water containers. No contaminant present in the feed and water was expected to impact the results of this study.
Personnel	Associates involved in this study were appropriately qualified and trained.
Veterinary Care	Standard veterinary medical care was provided during the study, if applicable.
Selection	Only healthy, previously unused animals with healthy intact skin, were selected.

5. Methods

Fur will be clipped within 24 hours to 4 hours prior to testing on the backs of the animals, there shall be a sufficient distance on both sides of the spine for application and observation of all test sites (approximately 10 cm×15 cm). Apply 0.5 mL appropriate extract to a 2.5 cm×2.5 cm absorbent gauze patches. One patch will be applied on each side of the animal as shown in Figure 1. At the same time, a control patch of gauze moistened with the extract vehicle will be applied as shown in Figure 1. The application sites are covered with a bandage for a minimum of 4 hours. At the end of the contact time, the dressings are removed and the positions of the sites were marked with permanent ink. Remove the residual test material by washing with lukewarm water.

Fig 1 Location of skin application sites



1- cranial end;
2- test site;
3- control site;
4- clipped dorsal region;
5- caudal end.

Record the appearance of each application site at (1±0.1) h, (24±2) h, (48±2) h and (72±2) following removal of the patches. Use of natural or full-spectrum lighting is highly recommended to visualize the skin reactions. Describe and score the skin reactions for erythema and oedema according to the scoring system given in Table 2, for each application site at each time interval, and record the results for the test report. Other adverse changes at the skin sites shall be recorded and reported.

Table 1 Scoring System of Skin Reaction

Score	Erythema and Eschar Formation (ER)	Oedema Formation (OE)
0	No erythema	No oedema
1	Very slight erythema (barely perceptible)	Very slight oedema (barely perceptible)
2	Well-defined erythema	Well-defined oedema (edges of area well-defined

Score	Erythema and Eschar Formation (ER)	Oedema Formation (OE)
		by definite raising)
3	Moderate erythema	Moderate oedema (raised approximately 1 mm)
4	Severe erythema (beet redness) to eschar formation preventing grading of erythema	Severe oedema (raised more than 1 mm, and extending beyond exposure area)

6. Evaluation

The primary irritation index (PII) is determined as follows. Only (24±2) h, (48±2) h and (72±2) h observations are used for calculations. After the 72 h grading, all erythema grades plus oedema grades (24±2) h, (48±2) h and (72±2) h are totaled separately for each test sample and blank for each animal. The primary irritation score for an animal is calculated by dividing the sum of all the scores by 6. To obtain the primary irritation index for the test sample, all the primary irritation scores of the individual animals are added and divided by the number of animals. When blank or negative control is used, the primary irritation score is obtained by subtracting the primary irritation score of the controls. The cumulative irritation index is compared with the categories of irritation response given in.

Table 2 Mean score Response category

Mean score	Response category
0 to 0.4	Negligible
0.5 to 1.9	Slight
2 to 4.9	Moderate
5 to 8	Severe

7. Results

All animals appeared normal throughout the study. Results of scores for individual animals are provided in Attachment: Observations. The overall mean difference for the extracts is summarized below:

Table 3 Results

Extract	Overall Test Group Mean	Overall Control Group Mean	Overall Mean Difference
SC	0	0	0
SO	0	0	0

8. Conclusion

Under the conditions of this study, the irritation response category of the test article is classified as Negligible for polar extract and Negligible for non-polar extract.

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

9. Deviation

There was no deviation during the study.

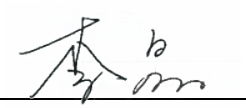
10. Records

All raw data pertaining to this study and a copy of final report are retained in designated Mid-Link's archive files in accordance with Mid-Link SOP.

STATEMENT OF QUALITY ASSURANCE ACTIVITIES

Phase Inspected	Date Inspected
Extraction	03/12/2021
Study Data Review	03/18/2021
Final Report Review	03/25/2021

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). Results are included in the Periodic Status Report to Management and Study Director.

QA Representative 

Authorized Signature

2021、04、27

Date

Attachment 1: Observations

Animal Number	Sex	Body Weight (kg)	Group	Scoring Interval											
				24 Hours				48 Hours				72 Hours			
				Test		Control		Test		Control		Test		Control	
				ER	OE	ER	OE	ER	OE	ER	OE	ER	OE	ER	OE
B3754	Male	2.36	SC	0	0	0	0	0	0	0	0	0	0	0	0
				0	0	0	0	0	0	0	0	0	0	0	0
B3751	Male	2.46	SC	0	0	0	0	0	0	0	0	0	0	0	0
				0	0	0	0	0	0	0	0	0	0	0	0
B3755	Male	2.38	SC	0	0	0	0	0	0	0	0	0	0	0	0
				0	0	0	0	0	0	0	0	0	0	0	0
B3759	Male	2.46	SO	0	0	0	0	0	0	0	0	0	0	0	0
				0	0	0	0	0	0	0	0	0	0	0	0
B3767	Male	2.36	SO	0	0	0	0	0	0	0	0	0	0	0	0
				0	0	0	0	0	0	0	0	0	0	0	0
B3784	Male	2.42	SO	0	0	0	0	0	0	0	0	0	0	0	0
				0	0	0	0	0	0	0	0	0	0	0	0

Attachment 2: Illustration of Test Article

Attachment 3: Periodic Positive Control Record

What was tested 20% sodium dodecyl sulfate (SDS)

Dates Application: 11/01/2020 Observations Concluded: 11/05/2020

Purpose A periodic positive control study was conducted for the Skin Irritation Test to meet the following objectives: 1) confirm the methodology in ISO 10993-10, Biological Evaluation of Medical Devices - Part 10: Tests for Irritation and Skin Sensitization and 2) substantiate the sensitivity of Rabbit (Japanese White) to skin irritation.

Methods Fur was clipped within 24 hours to 4 hours prior to testing on the backs of the animals, there shall be a sufficient distance on both sides of the spine for application and observation of all test sites (approximately 10 cm×15 cm). Apply 0.5 mL 20% SDS to a 2.5 cm×2.5 cm absorbent gauze patches. One patch was applied on each side of the animal as shown in Figure 1. At the same time, a control patch of gauze moistened with (0.9%SC without SDS) was applied as shown in Figure 1. The application sites were covered with a bandage for a minimum of 4 hours. At the end of the contact time, the dressings were removed and the positions of the sites were marked with permanent ink. Remove the residual test material by washing with lukewarm water. All erythema grades and edema grades (24, 48 and 72 hours) separately for each test and control for each individual animal were calculated according to Table 1. The mean score of test article or control on each individual animal was calculated by dividing each of the totals by 3(3 scoring time points ×2 sites). The overall mean for each test and control were calculated by adding the scores for the 3 animals and divide by 3. The difference between the overall mean score of the test article extracts and corresponding control extracts was calculated by subtracting the overall mean score for the control from the overall mean score for the test article extract. If the overall mean score of the test article extracts was less than the overall mean score of the corresponding control extracts, 0.0 was reported, and determine the irritation response (Table 2)

Result:

Table A1 Observations

Animal Number	Sex	Body Weight (kg)	Scoring Interval											
			24 Hours				48 Hours				72 Hours			
			Test		Control		Test		Control		Test		Control	
			ER	OE	ER	OE	ER	OE	ER	OE	ER	OE	ER	OE
#1	Female	2.72	3	2	0	0	3	3	0	0	3	3	0	0
B2101			3	2	0	0	3	2	0	0	3	3	0	0
#2	Female	2.42	2	3	0	0	3	3	0	0	3	3	0	0
B2120			3	2	0	0	3	3	0	0	4	3	0	0
#3	Female	2.59	2	2	0	0	3	2	0	0	3	3	0	0
B2124			3	2	0	0	3	2	0	0	3	2	0	0

Table A2 Irritation Response

Overall Test Group Mean	Overall Control Group Mean	Overall Mean Difference	Category
5.44	0.00	5.44	Severe (5~8.0)

Conclusion

Under the conditions of this study, the irritation response category of the 20% SDS is classified as Severe which demonstrated that 20% SDS can cause skin irritation on Rabbit (Japanese White).