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Final Report

Report Number: SDWH-M201904568-2(E)

Skin Sensitization Test of Impression material

According to ISO 10993-10:2010
Guinea Pig Maximization Test
0.9% Sodium Chloride Injection Extract

Sponsor: Zhengzhou Huaer Electro-Optics Technology Co., Ltd

Address: Floor 11, B of Building 18,the National University Science Park of Henan Province

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Content

Supplementary Explanation

(1) Please apply for rechecking within 15 days of receiving the report if there are any objections.

(2) Any erasure or without special inspection and testing seal renders the report null and void.

(3) The report is only valid when signed by the persons who edited, checked and approved it.

(4) The results relate only to the articles tested.

(5) The report shall not be reproduced except in full without the written approval of the institute.

Quality Assurance Statement

The Quality Assurance Unit inspected/audited this study in compliance with the following GLP regulations:

Good Laboratory Practice (GLP) Regulation 21 CFR Part 58, U.S. Food and Drug Administration (FDA). The laboratory is exempt from the following provisions: 21 CFR Part 58.105 Test and Control Article Characterization, and Part 58.113 Mixtures of Articles with Carriers.

The Quality Assurance Unit conducted inspections on the following dates. The findings were reported to the Study Director and to the Testing Facility Management.

The final report was reviewed by the Quality Assurance Unit. The final report accurately describes the test methods in accordance with standard operating procedures, and the results are consistent with raw data of non-clinical studies conducted according to the study protocol.

Inspections	Date of Inspection	Date Reported to Study Director	Date Reported to Testing Facility Management.
Study Protocol	2019-11-13	2019-11-13	2019-12-20
Study Procedure	2019-12-06 2019-12-09	2019-12-06 2019-12-09	2019-12-20
Raw Data	2019-12-20	2019-12-20	2019-12-20
Final Report	2019-12-20	2019-12-20	2019-12-20

Quality Assurance Unit: Zhang Yan, 2019-12-20

Quality Assurance Date

GLP Compliance Statement

This study was fully in accordance with the technical requirements of the study protocol. This study was conducted in compliance with Good Laboratory Practice (GLP) Regulation 21 CFR Part 58, U.S. Food and Drug Administration (FDA).

The laboratory is exempt from the following provisions: 21 CFR Part 58.105 Test and Control Article Characterization, and Part 58.113 Mixtures of Articles with Carriers.

Verification Dates

Test Article Receipt	2019-10-25
Protocol Effective Date	2019-11-13
Technical Initiation Date	2019-11-13
Technical Completion Date	2019-12-12
Final Report Completion Date	2019-12-20

Edited by: Wang Dehong 2019.12.20
Date

Reviewed by: Zhang Yan 2019-12-20
Study Director Date

Approved by: 2019.12.20
Authorized Signatory Date

Sanitation & Environment Technology Institute, Soochow University

Summary

1 Test Article

Test Article Name	Impression material
Manufacturer	Zhengzhou Huaer Electro-Optics Technology Co., Ltd
Address	Floor 11, B of Building 18,the National University Science Park of Henan Province
Model	Not supplied by sponsor (N/S)
Lot/Batch	N/S

2 Main Reference

ISO 10993-10:2010 Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization

3 Test Method

Potential skin sensitization of test article was evaluated using guinea pig maximization test in accordance with ISO 10993-10:2010 Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization.
Study protocol number: SDWH-PROTOCOL-GLP-M201904568-2.

4 Conclusion

Under the conditions of this study, the test article Impression material extract showed no significant evidence of causing skin sensitization in the guinea pig. The positive rate of sensitization was 0%. No evidence of skin sensitization in guinea pigs was found.

Test Report

1 Purpose

The test was designed to evaluate the potential of a test article to cause skin sensitization. The test is used as a procedure for screening of contact allergens in guinea pigs and extrapolating the results to humans, but it does not establish the actual risk of sensitization.

2 Reference

ISO 10993-10:2010 Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization
ISO 10993-12:2012 Biological evaluation of medical devices — Part 12: Sample preparation and reference materials
ISO 10993-2:2006 Biological evaluation of medical devices — Part 2: Animal welfare requirements

3 Compliance

Good Laboratory Practice Regulations, 21 CFR, Part 58.
ISO/IEC 17025:2005 General requirements for the competence of testing and calibration laboratories (CNAS—CL01 Accreditation criteria for the competence of testing and calibration laboratories) China National Accreditation Service for Conformity Assessment LABORATORY ACCREDITATION CERTIFICATE Registration No. CNAS L2954.
RB/T 214—2017 Competence assessment for inspection body and laboratory mandatory approval—General requirements for inspection body and laboratory Certification and Accreditation Administration of the People's Republic of China INSPECTION BODY AND LABORATORY MANDATORY APPROVAL Certificate No. CMA 180015144061.

4 Identification of Test and Control Articles

4.1 Test Article

Test Article Name	Impression material
Manufacturer	Zhengzhou Huaer Electro-Optics Technology Co., Ltd
Address	Floor 11, B of Building 18,the National University Science Park of Henan Province
Test Article Initial State	Sterilized , UV sterilization
CAS Code	N/S
Model	N/S
Size	N/S
Lot/Batch	N/S
Test Article Material	vinyl polysiloxane
Packaging Material	Food grace PP
Physical State	Solid
Color	blue,white
Density	1.6
Stability	24h<0.3%.336h<0.3%
Solubility	0
Storage Condition	Room Temperature
Intended Clinical Use	Used for all crown and bridge, edentulous, orthodontic and implant impression techniques.

The information about the test article was supplied by the sponsor wherever applicable.

The Sponsor is responsible for all test article characterization data as specified in the GLP regulations.

4.2 Control Article

4.2.1 Negative Control

Article Name: 0.9% Sodium Chloride Injection (SC)
Manufacturer: Guangxi Yuyuan Pharmaceutical Co., Ltd.
Size: 500mL
Lot/ Batch#: H19082605
Physical State: Liquid
Color: Colorless
Storage Condition: Room Temperature

4.2.2 Positive Control

Article Name: 2, 4-Dinitrochlorobenzene (DNCB)
Manufacturer: Chengdu Aikeda Chemical Reagent Co., Ltd.
Size: 100g
Lot/ Batch#: 201904101
Induction Concentration: 0.5%
Challenge Concentration: 0.1%
Solvent: 0.9% Sodium Chloride Injection
Date prepared: 2019-09-03
Physical State: Liquid
Color: Light Yellow
Storage Condition: Room Temperature

5 Equipment and Reagents

5.1 Equipment

Equipment Name	Equipment Number	Calibration Expire
Constant temperature vibrator	SDWH217	2020-05-04
Vertical pressure steam sterilizer	SDWH2097	2020-04-16
Electronic balance	SDWH2601	2020-06-19
Electronic scale	SDWH442	2020-05-04

5.2 Reagents

Reagent Name	Manufacturer	LOT
Freund's adjuvant, complete liquid	SIGMA	SLBX3240
Sodium dodecyl sulfate (SDS)	Sinopharm Chemical Reagent Co., Ltd	20181210

6 Identification of Test System

Species: Hartley guinea pig (Cavia Porcellus)
Number: 15 (10 test +5 negative control)
Sex: No particular gender is prescribed
Initial body weight: 300 ~ 500 g
Health status: healthy, not previously used in other experimental procedures
Housing: animals were housed in groups in cages identified by a card indicating the lab number, test code and first treatment date, etc.
Animal identification: Stain with dyeing liquid

Cages: plastic cage
Acclimation period: 7 days under the same conditions as for the actual test

7 Animal Care and Maintenance

Animal source: Shanghai Jia Gan Biotechnology Co., Ltd. <Permit Code: SCXK (HU) 2015-0005>
Bedding: corncob, Suzhou Shuangshi Laboratory Animal Feed Science Co., Ltd.
Feed: guinea pig diet, Suzhou Experimental Animal Sci-Tech Co., Ltd.
Water: drinking water met the Standards for Drinking Water Quality GB 5749–2006
Animal room temperature: 18 ~ 26°C
Animal room relative humidity: 30% ~ 70%
Lights: 12 h light/dark cycle, full-spectrum lighting
Personnel: associates involved were appropriately qualified and trained
Selection: only healthy, previously unused animals were selected
There were no known contaminants present in the feed, water, or bedding expected to interfere with the test data.

8 Justification of Test System and Route of Administration

The 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 guinea pig to a known sensitizing agent, 2,4-dinitrochlorobenzene (DNCB) has been substantiated at SDWH (listed in **Table 1** and **Table 2**).
The test article was extracted and administered in vivo through a medium compatible with the test system. Dermal application corresponds to the likely route of human exposure.

9 Experimental Design

9.1 Preparation of Extracts

9.1.1 Pretreatment

No pretreatment required.

9.1.2 Extraction

Under aseptic conditions, samples were taken according to the sampling method (Mix the two samples at the ratio of 1:1 by equal weight and extract together, see the image in Annex 2), and extracted in closed inert containers according to the extraction ratio of 0.2 g : 1 mL (sample: extraction vehicle). The extraction vehicle was 0.9% Sodium Chloride Injection (SC).

Test Period	Actual Sampling	Extract Procedure			Final Extract
		Extract Ratio	SC	Condition	
Intradermal Induction Phase I	2.0 g	0.2 g : 1 mL	10.0 mL	50°C, 72 h	Clear
Topical Induction Phase II	4.0 g	0.2 g : 1 mL	20.0 mL	50°C, 72 h	Clear
Challenge Phase	4.0 g	0.2 g : 1 mL	20.0 mL	50°C, 72 h	Clear

The state of the extract did not change after extraction. The extract was stored at 4°C, and tested within 24 h, without the process of adjusting its pH value, filtering, centrifuging, diluting, etc.

9.2 Experimental Procedure

9.2.1 Animal Preparation and Grouping

On the first day of treatment, 15 guinea pigs were weighed and identified. The fur from the dorsoscapular area of the animals was removed with an electric clipper. Grouping as follow:

Group Name	Group Size	Gender
Test	10 animals	No particular gender is prescribed.
Negative Control	5 animals	No particular gender is prescribed.

9.2.2 Intradermal Induction Phase I

A pair of 0.1 mL intradermal injections was made for each of the following, into each animal, at the injection sites (A, B and C) as shown in Figure 1 in the clipped intrascapular region.
Site A: a 50:50 (*V/V*) stable emulsion of Freund's complete adjuvant mixed with the chosen solvent.
Site B: the test sample (undiluted extract); the control animals were injected with the solvent alone.
Site C: the test sample at the concentration used at site B, emulsified in a 50:50 (*V/V*) stable emulsion of Freund's complete adjuvant and the solvent (50%); the control animals were injected with an emulsion of the blank liquid with adjuvant.

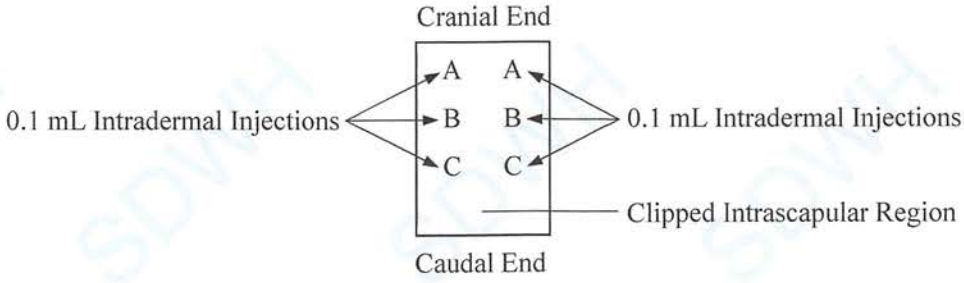


Figure 1 Locations of intradermal injection sites

9.2.3 Topical Induction Phase II

The maximum concentration that can be achieved in Intradermal induction phase I did not produce irritation. Animals are pretreated with 10% sodium dodecyl sulfate (Solvent: Distilled water, Date prepared: 2019-09-30) (24 ± 2) h before the topical induction application.
At 7 d after completion of the intradermal induction phase, administer 0.5 mL test article extract by topical application to the intrascapular region of each animal, using a patch of area approximately 8 cm^2 (absorbent gauze), so as to cover the intradermal injection sites. Secure the patches with an occlusive dressing. Remove the dressings and patches after (48 ± 2) h.
Treat the control animals similarly, using the blank liquid alone.

9.2.4 Challenge Phase

At 14 ± 1 d after completion of the topical induction phase, challenge all test and control animals with the test sample. Absorbent gauzes (2.5 cm × 2.5 cm) were soaked respectively with 0.5 mL test article and 0.5 mL control article. Apply the test article extract and control article topically to two sites that were not treated during the induction stage. Secure with an occlusive dressing. Remove the dressings and patches after (24 ± 2) h.

9.3 Observation of Animals

Observe the appearance of the challenge skin sites of the test and control animals (24 ± 2) h and (48 ± 2) h after removal of the dressings. Full-spectrum lighting was used to visualize the skin reactions. Describe and grade the skin reactions for erythema and oedema according to the Magnusson and Kligman grading given in the following table for each challenge site and at each time interval.

Patch Test Reaction	Grading Scale
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and/or swelling	3

9.4 Evaluation of Results

Magnusson and Kligman grades of 1 or greater in the test group generally indicate sensitization, provided grades of less than 1 are seen in control animals.
If grades of 1 or greater are noted in control animals, then the reactions of test animals which exceed the most severe reaction in control animals are presumed to be due to sensitization.
If the response is equivocal, rechallenge is recommended to confirm the results from the first challenge.
The outcome of the test is presented as the frequency of positive challenge results in test and control animals.

10 Results

The results of skin reaction after challenge were listed in **Table 3**. No skin sensitization reaction was found in the skin of guinea pigs using extracts of the test article, and the positive rate of sensitization was 0%.
The positive rate of sensitization in the positive control group was 100%, listed in **Table 1**.
Clinical observations and weight changes of guinea pigs were listed in **Table 4.**

11 Conclusion

Under the conditions of this study, the test article Impression material extract showed no significant evidence of causing skin sensitization in the guinea pig.

12 Record Storage

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

13 Confidentiality Agreement

Statements of confidentiality were as agreed upon prior to study initiation.

14 Deviation Statement

There were no deviations from the approved study protocol which were judged to have any impact on the validity of the data.

Annex 1 Test Data

Table 1 Guinea pig sensitization dermal reactions of positive control

Group	Animal Number	(24 ± 2) h Before Phase II Patch Application		(24 ± 2) h Following Challenge Phase		(48 ± 2) h Following Challenge Phase		Positive Rate after Challenge Phase
		Left	Right	Test Sites	Control Sites	Test Sites	Control Sites	
Positive Control	1	2	3	2	0	2	0	100%
	2	2	2	2	0	2	0	
	3	2	2	3	0	3	0	
	4	2	3	2	0	2	0	
	5	1	3	1	0	2	0	
Negative Control	6	0	0	0	0	0	0	-
	7	0	0	0	0	0	0	
	8	0	0	0	0	0	0	
	9	0	0	0	0	0	0	
	10	0	0	0	0	0	0	

Note: the data of positive control come from SDWH- M201903676-1 (Completed Date: 2019-09-30)

Table 2 Weigh change and clinical observation of positive control

Group	Animal Number	Weight (g)		Clinical Observation Except Dermal Reactions
		Before Injection	After Experiment	
Positive Control	1	307	370	Normal
	2	310	375	Normal
	3	306	369	Normal
	4	347	430	Normal
	5	308	372	Normal
Negative Control	6	326	399	Normal
	7	328	402	Normal
	8	353	439	Normal
	9	327	401	Normal
	10	311	376	Normal

Note: the data of positive control come from SDWH- M201903676-1 (Completed Date: 2019-09-30)

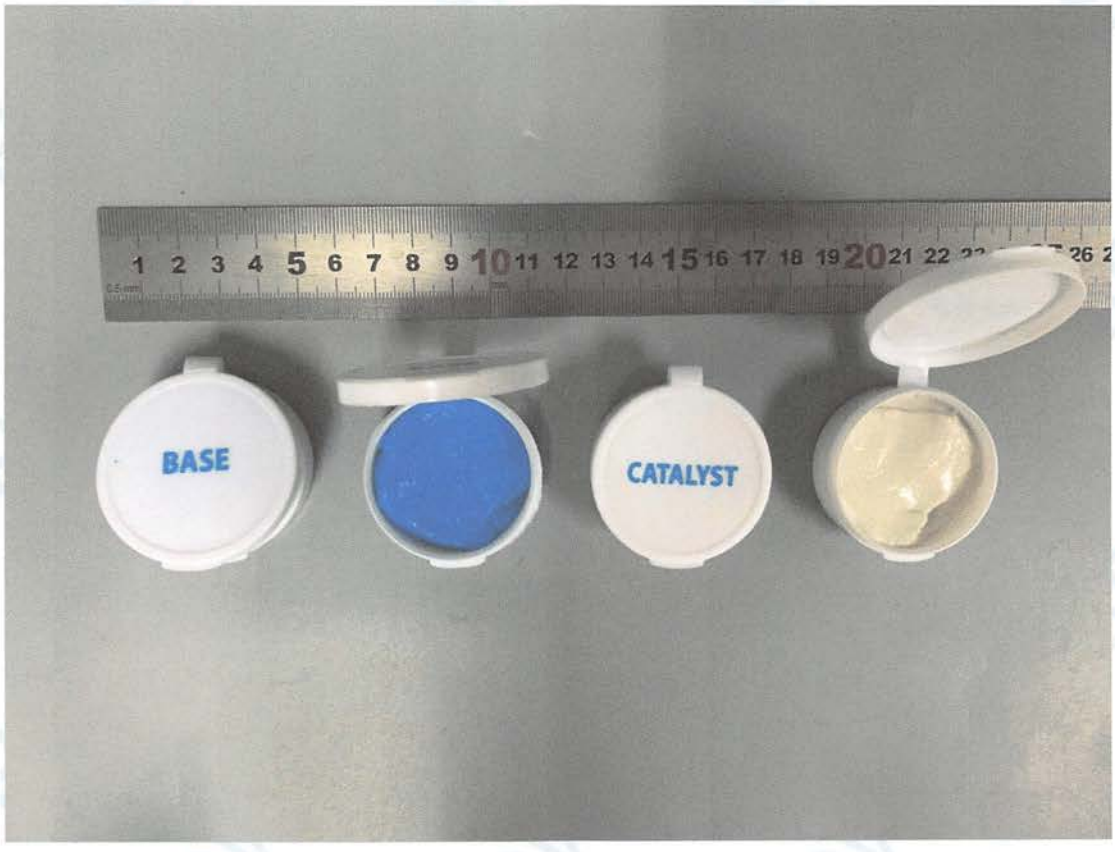
Table 3 Guinea pig sensitization dermal reactions

Group	Animal Number	(24 ± 2) h Before Phase II Patch Application		(24 ± 2) h Following Challenge Phase		(48 ± 2) h Following Challenge Phase		Positive Rate after Challenge Phase
		Left	Right	Test Sites	Control Sites	Test Sites	Control Sites	
Test	1	0	0	0	0	0	0	0%
	2	0	0	0	0	0	0	
	3	0	0	0	0	0	0	
	4	0	0	0	0	0	0	
	5	0	0	0	0	0	0	
	6	0	0	0	0	0	0	
	7	0	0	0	0	0	0	
	8	0	0	0	0	0	0	
	9	0	0	0	0	0	0	
	10	0	0	0	0	0	0	
Negative Control	11	0	0	0	0	0	0	-
	12	0	0	0	0	0	0	
	13	0	0	0	0	0	0	
	14	0	0	0	0	0	0	
	15	0	0	0	0	0	0	

Table 4 Weigh change and clinical observation

Group	Animal Number	Weight (g)		Clinical Observation Except Dermal Reactions
		Before Injection	After Experiment	
Test	1	357	442	Normal
	2	343	428	Normal
	3	339	422	Normal
	4	322	397	Normal
	5	320	390	Normal
	6	340	414	Normal
	7	332	409	Normal
	8	324	393	Normal
	9	308	376	Normal
	10	345	433	Normal
Negative Control	11	329	408	Normal
	12	317	387	Normal
	13	318	385	Normal
	14	349	437	Normal
	15	323	392	Normal

Annex 2 Photograph of Test Article



Annex 3 Information Provided by Sponsor

1 Production Process

Not supplied by sponsor.

2 Other Information

Not supplied by sponsor.

End of Report