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CNAS L0637



TEST REPORT

Test Report No.: RZ22080041

Client: **BMF Nano material Technology Co., Ltd**

Name of Samples: **BIO**

Model / Type: **BIO/8g**

Test Type:
Certification ()

Commission ()

Others ()

Guangdong Medical Devices Quality Surveillance and Inspection Institute

Guangzhou Medical Instruments Quality Surveillance and Inspection

Center of State Food and Drug Administration



Statement

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7. The representativeness and authenticity of the entrusted testing samples shall be the responsibility of the client.

Contact us:

Testing Center: No.1, Guangpu West Road, Science City, Huangpu District, Guangzhou, Guangdong, 510663, China

Dongguan Laboratory: 7-8/F., R&D Building 7, Technology 2nd Road, Songshan Lake Park, Dongguan, Guangdong, 523808, China

Shenzhen Laboratory: No.9 Building, No.14 Jinhui Road, Pingshan District, Shenzhen, Guangdong, 518118, China

Sanshui Laboratory: No. 2, Southeast Road, Industrial Park of Leping, Sanshui District, Foshan, Guangdong, 528139, China

Zhanjiang Laboratory: No. 60, Shenchuan Avenue Middle, Xiashan District, Zhanjiang, Guangdong, 524000, China

Zhongshan Laboratory: No. 2, Building, No. 8-4, Buyun Road, Torch Development Zone, Zhongshan, Guangdong, 528437, China

Telephone: 020-66602388

Fax: 020-66602400

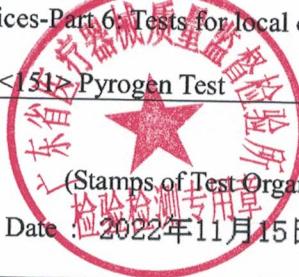
Website: gdmdt.gd.gov.cn

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Name of Samples	BIO		Samples' Serial №	RZ22080041
	Send-off (✓)	Spot check (/)		
Trademark	/		Model / Type	BIO/8g
Client	BMF Nano material Technology Co., Ltd		Test Type	Certification Test
Client's Address	5th Floor, East Entrance, Building No.8, GS Park, Wuhe Avenue, Longhua New District, Shenzhen, Guangdong Province, China		Products' № / Lot №	20211210B
Manufacturer	BMF Nano material Technology Co., Ltd		Sampling Bill №	—
Corporation being inspected	BMF Nano material Technology Co., Ltd		Manufacturing date	2021.12.10
Sampled by	—		Samples' Quantity	28 pcs+1bag Implanted samples
Sampling Place	—		Cardinal Number of Samples	—
Sampling Date	—		Test Place	DongGuan Laboratory
Receiving Date	2022.07.22		Test Date	2022.07.22~2022.11.11
Test Items	Skin sensitization test (Guinea pig maximization test), Animal Skin Irritation Test, Acute Systemic Toxicity, Haemolysis test, Test for local effects after implantation, Pyrogens Test			
Test According to	ISO 10993-10: 2010 Biological evaluation of medical devices-Part 10: Tests for irritation and skin sensitization ISO 10993-11:2017 Biological evaluation of medical devices-Part 11:Tests for systemic toxicity ISO 10993-4:2017 Biological evaluation of medical devices-Parts 4: Selection of tests for interactions with blood. ISO 10993-6:2016 Biological evaluation of medical devices-Part 6: Tests for local effects after implantation The Pharmacopoeia of the United States of American 41<151> Pyrogen Test			
Test Conclusion	For test results, see attachment.			
Remarks	1) In this test report, — means the item is not applicable, and / means the item is blank.			
Signature	Tested by: Mo Yifei 美柏飞 Huang Yanqian 黄燕倩 Reviewed by: Zheng Baoting 郑宝婷 Approved by(authorized signatory): 			



(Stamps of Test Organization)

Issued Date: 2022年11月15日

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Nº	Test Items	Test Results	Monomial Conclusion	Remarks
1	Skin sensitization test (Guinea pig maximization test)	The test sample has no sensitization.	/	/
2	Animal Skin Irritation Test	Under the conditions of this study, the test article is considered a negligible irritant.	/	/
3	Acute Systemic Toxicity	No acute systemic toxic reactivity	/	/
4	Haemolysis test	Under the conditions of this test , the hemolysis rate of the sample hemolysis test is 0.6% (+)	/	/
5	Test for local effects after implantation	Under the conditions of this study, after 1 week implantation, the test sample was considered as non-irritant to the tissue as compared to the negative control sample	/	/
6	Pyrogens Test	Under the conditions of this study, the test sample passes the test.	/	/
	The end			



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Skin sensitization test (Guinea pig maximization test)

1. SUMMARY

Objective: This test was conducted to determine whether the test sample would cause animal skin sensitization following applying into skin of albino Guinea pig.

Methods: This method is based on ISO 10993-10: 2010 Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization, Guinea pig assays for the detection of skin sensitization. The 0.9% physiological saline (NS) and cottonseed oil (CSO) extracts of the test sample were evaluated possible contact hazards from chemicals released that cause skin sensitization.

Result: No erythema and oedema were observed in the test sample groups. The test groups did not show significantly greater biological reactions than the control groups.

Conclusion: Under the conditions of this study, the test sample is considered to be no skin sensitization.

Test period: 2022.07.26~2022.08.25

2. MATERIALS

2.1 Test sample:

Physical Properties: Solid, Non-absorbable

Storage conditions: Room temperature

2.2 Extraction vehicle:

Polar extraction vehicle: 0.9% physiological saline (Manufacturer: Guangdong Kelun Pharmaceutical Co., Ltd.; Lot No.: H22011007)

Non-Polar extraction vehicle: Cottonseed oil (Manufacturer: J&K; Lot No.: LOC0V104)

2.3 Freund's complete adjuvant (Manufacturer: SIGMA; Lot No.: SLCG8831)

2.4 SDS (Manufacturer: Aladdin; Lot No.: G2108997)

2.5 Negative control: The same batch of extraction vehicles without the test sample.

2.6 Positive control: 0.5% DNB (Manufacturer: Hebei Bailing wei Superfine Material Co., LTD; Batch No.: LSC0S73). According to ISO 10993-10, 0.5% DNB as a positive control was tested every six months. Test period: 2022.06.21-2022.07.21

2.7 Test sample preparation:

The test article extract liquid was prepared at the ratio of 0.1g/mL, under the condition of 37°C for 72h, and the extract medium was 0.9% physiological saline and cottonseed oil. The appearance of the extract liquids

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and extract vehicles had no difference and there were no particulates in the extract liquids. So the extract liquids didn't need to be processed by filtration, centrifugation or other methods to remove suspended particulates. Extract pH wasn't adjusted and the extract liquid was used instantly after the preparation.

3. TEST SYSTEM

3.1 Species & Strain: Albino Guinea pig

3.2 Source: Guangdong Medical Laboratory Animal Center.

3.3 Passed No.: SCXK (粤) 2019-0035 (44411600010511)

3.4 Grade: CV

3.5 Number of animals: 30

3.6 Body weight at Day 1: 347g to 390g

3.7 Sex: males (No particular sex is required)

3.8 Acclimation period: 7 days

3.9 Justification of Test System:

The guinea pig is specified an appropriate animal for evaluating potential allergic response by the current ISO standards. The guinea pig is widely used for this purpose. Intradermal injection and patching of the extract liquid of the test materials is employed on Guinea pig intact skin. Topical applications are related to the human exposure route. After challenge phases, reactions of the topical application site can directly be observed. Reactions of the topical application site can be discriminated potential sensitivity on contact skin of animals.

3.10 Animal Management:

3.10.1 Housing: Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory) is an accredited facility and registered with the State Food and Drug Administration of China. Certification No.: SYXK (粤) 2022-0169. Animal care and housing will be in accordance with "Laboratory animal-Requirements of environment and housing facilities"; "ISO 10993-2:2006: Biological evaluation of medical devices Part 2: Animal welfare requirements". Animals will be housed in an environmentally monitored, well-ventilated room maintained at a temperature of 18.0~26.0°C and a relative humidity of 40.0%~70.0%. Fluorescent lighting will provide illumination approximately 12 hours per day.

3.10.2 Feed: Certified feed (Guangdong Medical Laboratory Animal Center) will be provided ad libitum. Nutritional ingredient and chemical index in the diet of every batch will be conducted by special detection institute.

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The result will be reviewed by Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory), to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The feed meets the feed standards according to the State Standard of the People's Republic of China GB14925.3-2010 and GB14925.2-2001.

3.10.3 Water: Water was provided ad libitum through an automatic watering system. Samples of water from the animal facility will be analyzed for toxicological parameter annually. Results of water analyses will be retained in the facility records, and to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The water meets the drinking water standards according to the State Standard of the People's Republic of China GB5749-2006.

3.11 Personnel: Associates involved were appropriately qualified and trained.

3.12 Selection: Only healthy, previously unused animals were selected.

4. EQUIPMENT

Electronic balance C2017-10-37(D), Constant temperature shock incubator T2018-04-10(D), Biological safety cabinets Z2015-25-11(D), Carbon dioxide anaesthetic box T2017-50-01(D)

5. METHOD

5.1 Intradermal induction (in first stage): One day prior to the intradermal injection, the hair of the test animals (The neck-shoulder) was depilated with hair scissor. The following day, the skin was cleaned with 75% ethanol and a pair of 0.1mL intradermal injections into each animal was made, as illustrated in Fig.1. The animals were observed for 7 days.

Site A: 0.1mL Freund's complete adjuvant application liquor

Site B: 0.1mL The test article extract liquid/Negative control

/Positive control

Site C: 0.1mL emulsified in a 50:50[v:v] Freund's complete adjuvant application liquor and the Site B liquid

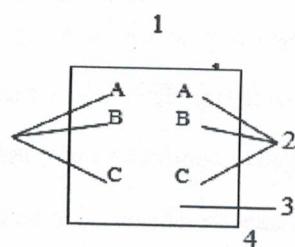


Fig.1 Intradermal injection sites

5.2 Topical induction (The second stage): 7 days after intradermal injection, if irritation symptom was not observed on the intradermal injection sites, the same area used during intradermal induction (in first stage) was clipped free of fur and treated with 10% sodium lauryl sulphate (SLS) suspension in petrolatum. The suspension

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was massaged into the skin over the injection site to provoke a mild acute inflammation. The area was left uncovered for 24h. Then 8 cm² section of medical gauze, saturated with the test article extract, was applied to the previously injected sites of the test animals. The control animal was similarly patched with the appropriate negative control. The trunk of each animal was wrapped with an elastic bandage. After 48h, the binders and patches were removed.

5.3 Challenge: 15 days following second induction stage, the hair of unused site on the right hind flank of each guinea pig was depilated with chemistry medicament. The next day, the skin was cleaned with 75% ethanol and a 25mm×25mm portion of the filter paper soaked with test article extract liquid were patched to the intact skin for the hair-off regions of each test animal. The filter paper was secured with non-irritative film and gauze. The flank of each animal was wrapped with an elastic bandage to hold the occluded test patch.

5.4 Observation: All wraps and patches were removed after 24 hours. The dermal reactions of the test article, negative control and positive control animals were observed at 24 and 48 hours after challenge patch removed. Observations for dermal reactions were conducted at 24h and 48h after challenge patch removal. Scores were recorded in accordance with the criteria below:

Magnusson and Kligman scale

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

Magnusson and Kligman grades of 1 or greater in the test group in the test group generally indicate sensitization, provided grades of less than 1 are seen in negative control animals. If grades of 1 or greater are noted in the negative control animals, then the reactions of test animals that exceed the most severe reaction in negative control animals are presumed to be due to sensitization.

6. RESULT

6.1 The scales of the test groups (NS) and control groups at 24h and 48h after challenging were presented in Table 1. No erythema and oedema were observed on the skin of guinea pigs of both the test article group and the negative control group. The grades of dermal erythema and oedema of the guinea pig were 0.0. The skin sensitization percentage was 0%. (Table 1)

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6.2 The scales of the test groups (CSO) and control groups at 24h and 48h after challenging were presented in Table 2. No erythema and oedema were observed on the skin of guinea pigs of both the test article group and the negative control group. The grades of dermal erythema and oedema of the guinea pig were 0.0. The skin sensitization percentage was 0%. (Table 2)

6.3 Obvious erythema and oedema were observed on the skin of the positive control group guinea pigs. (Table 3)

6.4 Results and conclusions apply only to the test articles tested. No further evaluation of these results is made by. Any extrapolation of these data to other samples is the responsibility of the sponsor.

7. CONCLUSION

Under the conditions of this study, the test sample is considered to be no skin sensitization.

8. ATTACHED TABLE

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TABLE 1 The result of skin sensitization test

	Animal Number	Body Weight (g)	Clinical observation	Hours Following Patch Removal	
				24h	48h
Test group (0.9% physiological saline)	1#	354	Appeared Normal	0	0
	2#	360	Appeared Normal	0	0
	3#	358	Appeared Normal	0	0
	4#	347	Appeared Normal	0	0
	5#	366	Appeared Normal	0	0
	6#	373	Appeared Normal	0	0
	7#	380	Appeared Normal	0	0
	8#	370	Appeared Normal	0	0
	9#	378	Appeared Normal	0	0
	10#	385	Appeared Normal	0	0
Negative control group (0.9% physiological saline)	1#	353	Appeared Normal	0	0
	2#	362	Appeared Normal	0	0
	3#	370	Appeared Normal	0	0
	4#	349	Appeared Normal	0	0
	5#	355	Appeared Normal	0	0

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TABLE 2 The result of skin sensitization test

Animal Number	Body Weight (g)	Clinical observation	Hours Following Patch Removal	
			24h	48h
Test group (cottonseed oil)	1#	359	Appeared Normal	0
	2#	367	Appeared Normal	0
	3#	374	Appeared Normal	0
	4#	382	Appeared Normal	0
	5#	390	Appeared Normal	0
	6#	376	Appeared Normal	0
	7#	384	Appeared Normal	0
	8#	365	Appeared Normal	0
	9#	378	Appeared Normal	0
	10#	389	Appeared Normal	0
Negative control group (cottonseed oil)	1#	372	Appeared Normal	0
	2#	368	Appeared Normal	0
	3#	381	Appeared Normal	0
	4#	357	Appeared Normal	0
	5#	373	Appeared Normal	0

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TABLE 3 The result of skin sensitization test (Positive control)

	Animal Number	Body Weight (g)	Hours Following Patch Removal Clinical observation	Patch Removal	
				24h	48h
Positive control group (Date: 2022.06.21~2022.07.21)	1#	363	Appeared Normal	2	3
	2#	371	Appeared Normal	1	2
	3#	380	Appeared Normal	1	2
	4#	357	Appeared Normal	3	3
	5#	368	Appeared Normal	1	1
	6#	375	Appeared Normal	2	3
	7#	384	Appeared Normal	3	2
	8#	377	Appeared Normal	2	3
	9#	388	Appeared Normal	1	1
	10#	390	Appeared Normal	2	3
Negative control group	1#	360	Appeared Normal	0	0
	2#	351	Appeared Normal	0	0
	3#	373	Appeared Normal	0	0
	4#	364	Appeared Normal	0	0
	5#	357	Appeared Normal	0	0

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Animal Skin Irritation Test

1. SUMMARY:

Objective: This test was conducted for assessing the biological response of animal skin irritation test to the test material.

Methods: This method is based on the requirements in ISO 10993-10:2010 Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization. The test article was evaluated for their potential to produce irritation after pasting the sample on New Zealand White Rabbits. The sites were observed for erythema and oedema at 1, 24, 48 and 72 hours after removal of the test sample and control sample.

Result: For Polar extraction vehicle group, the Primary Irritation Index of the New Zealand rabbits is 0; For non-polar extraction vehicle group, the Primary Irritation Index of the New Zealand rabbits is 0.

Conclusion: Under the conditions of this study, the test article is considered a negligible irritant.

Test period: 2022.07.22~2022.08.02

2. MATERIALS

2.1 Physical Properties: Solid, Non-absorbable

2.2 Storage conditions: Room temperature

2.3 Extraction vehicle:

Polar extraction vehicle :0.9% physiological saline (Manufacturer: Guangdong Kelun Pharmaceutical Co., Ltd.; Lot No.: H22011007)

Non - Polar extraction vehicle: Cottonseed oil (Manufacturer: J&K; Lot No.: LOC0V104)

2.4 Positive control: 20% Sodium dodecyl sulfate (SDS)(Manufacturer: Aladdin; Lot No.: H1909150) (In addition according ISO 10993 10 requirement, 20% SDS as a positive control was used previously for another study last six months.)

2.5 Negative control: The same batch of extraction vehicle without the test article.

2.6 Test article preparation: The test article extract liquid was prepared with extraction vehicle at the ratio of 0.1g/mL, under the condition of (37±1) °C for (72±2) h. The appearance of the extract liquid and extract vehicle had no difference and there were no particulates in the extract liquid. So the extract liquid didn't need to be processed by filtration, centrifugation or other methods to remove suspended particulates. Extract pH

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wasn't adjusted and the extract liquid was used instantly after the preparation.

3. TEST SYSTEM (Animals):

3.1 Species & Strain:: New Zealand White Rabbit

3.2 Source: Guangdong Medical Laboratory Animal Center. Passed No.: SCXK(YUE)

2019-0035(44411600010151)

3.3 Grade: CV

3.4 Number of animals: 6

3.5 Sex: Females (No particular sex is required)

3.6 Weight at day 1: 2.9~3.3kg

3.7 Acclimation period: 7 days

3.8 Justification of Test System: The New Zealand White Rabbit is specified as an appropriate animal for evaluating skin irritation by the current ISO 10993 standards. The New Zealand White Rabbit is widely used for this purpose and the skin irritation level can be evaluated by this method.

3.9 Animal Management:

Housing: Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory) is an accredited facility and registered with the State Food and Drug Administration of China. Certification No: SYXK (YUE) 2022-0169.

Animal care and housing will be in accordance with "Laboratory animal-Requirements of environment and housing facilities"; "ISO 10993-2:2006: Biological evaluation of medical devices Part 2: Animal welfare requirements".

Animals will be housed in an environmentally monitored, well-ventilated room maintained at a temperature of 18°C-26°C and a relative humidity of 40%-70%. Fluorescent lighting will provide illumination approximately 12 hours per day.

Feed: Certified rabbit feed (Guangdong Medical Laboratory Animal Center.) will be provided *ad libitum*. Nutritional ingredient and chemical index in the diet of every batch will be conducted by special detection institute. The result will be reviewed by Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory), to

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assure that no known contaminants are present that could interfere with or affect the outcome of studies. The feed meets the feed standards according to the State Standard of the People's Republic of China GB14925.3-2010 and GB14925.2-2001.

Water: Water was provided ad libitum through an automatic watering system. Samples of water from the animal facility will be analyzed for toxicological parameter annually. Results of water analyses will be retained in the facility records, and to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The water meets the drinking water standards according to the State Standard of the People's Republic of China GB5749-2006.

Personnel: Associates involved were appropriately qualified and trained.

Selection: Only healthy, previously unused animals were selected.

4. EQUIPMENT

Baby scales (Dial scale) C2019-11-02(D) Constant temperature oscillation incubator T2018-04-10(D)

Electronic balance C2017-10-36(D) Biological safety cabinets Z2015-25-11(D)

5. METHOD

5.1 Preparation

Clip the fur within 4h prior to treatment, testing parts on the backs of the animals have a sufficient distance on both sides of the spine for application and observation of all test sites (approximately 10cm×15cm).

5.2 Procedure

On the day of treatment, four sites, two on each side of the back that positioned cranial to caudal, were designated on each rabbit. The sites were free of blemishes that could interfere with the interpretation of results.

Apply generally 0.5mL appropriate extracts to the 25 mm×25 mm gauze patches to each site as shown in Fig.1. Similarly, apply the control patch of gauze moistened with the negative control to each rabbit. The patches were covered with a non-irritative bandage. Cover the application sites with a bandage for a minimum of 4 h. The trunk of each animal was wrapped with an elastic binder to maintain the test article and control patches in the position. After the 4-hour exposure, remove residual test material by washing with lukewarm water and careful drying.

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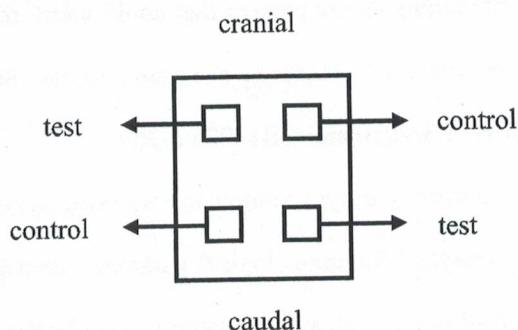


Fig.1. The test sites arrangement of primary skin irritation

5.3 Observations

Observe the appearance of the skin. The dermal responses for erythema and oedema were observed and recorded at 1, 24, 48 and 72 hours after removal of test article patches in accordance with the Scoring Criteria for Skin Reactions. The Primary Irritation Indexes of the test and solvent controls were calculated after test completed only the data of 24, 48 and 72 h.

Scoring Criteria for Skin Reactions

REACTION	DESCRIPTION	SCORE
Erythema (ER)	Erythema and Eschar	
	No erythema	0
	Very slight erythema (barely perceptible)	1
	Well-defined erythema	2
	Moderate	3
	Severe erythema (beet redness) to eschar formation preventing	4
Edema (ED)	Edema Formation	
	No edema	0
	Very slight (barely perceptible)	1
	Well-defined edema (edges of area well-defined by definite raising)	2
	Moderate edema (edges raised 1 mm)	3
	Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

The primary or cumulative irritation index is characterized by number (score) and description (response category) given below

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Primary or cumulative irritation index categories in a rabbit

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

6. RESULT

- 6.1 For Polar extraction vehicle group, the Primary Irritation Index of the New Zealand rabbits is 0; For non-polar extraction vehicle group, the Primary Irritation Index of the New Zealand rabbits is 0. (See Table 1, Table2)
- 6.2 A positive validation test data is given in table 3.
- 6.3 Results and conclusions apply only to the test articles tested. No further evaluation of these results is made by. Any extrapolation of these data to other samples is the responsibility of the sponsor.

7. CONCLUSION

According to the standard, the irritation response category of the sample is Negligible.

8. ATTACHED TABLE

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Table 1 The scores of the dermal reaction for erythema, eschar and oedema (Polar extraction vehicle)

Rabbit No.	weight (kg)	Test site	TEST						CONTROL						
			24h		48h		72h		24h		48h		72h		
			ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	
1#	2.9	1	0	0	0	0	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	0	0	0	0	
2#	2.9	1	0	0	0	0	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	0	0	0	0	
3#	3.2	1	0	0	0	0	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	0	0	0	0	
Total score of the 3 animals			0						0						
S=total score/18			0						0						
The Primary Irritation Indexes			0												
Response category			Negligible												

Table 2 The scores of the dermal reaction for erythema, eschar and oedema (non-polar extraction vehicle)

Rabbit No.	weight (kg)	Test site	TEST						CONTROL						
			24h		48h		72h		24h		48h		72h		
			ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	
1#	3.3	1	0	0	0	0	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	0	0	0	0	
2#	3.0	1	0	0	0	0	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	0	0	0	0	
3#	2.9	1	0	0	0	0	0	0	0	0	0	0	0	0	
		2	0	0	0	0	0	0	0	0	0	0	0	0	
Total score of the 3 animals			0						0						
S=total score/18			0						0						
The Primary Irritation Indexes			0												
Response category			Negligible												

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Table 3 The scores of the dermal reaction for erythema, eschar and oedema
 (Primary Skin Positive Validation Reference Date: 2022.03.07-2022.03.14)

Rabbit No.	weight (kg)	Test site	TEST						CONTROL						
			24h		48h		72h		24h		48h		72h		
			ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	
1#	2.2	1	3	3	4	4	4	3	0	0	0	0	0	0	
		2	3	3	4	4	4	3	0	0	0	0	0	0	
2#	2.2	1	4	4	4	4	3	4	0	0	0	0	0	0	
		2	3	4	4	4	3	4	0	0	0	0	0	0	
3#	2.3	1	3	3	4	4	4	4	0	0	0	0	0	0	
		2	3	3	4	4	4	4	0	0	0	0	0	0	
Total score of the 3 animals			131						0						
S=total score/18			7.3						0						
The Primary Irritation Indexes			7.3												
Response category			Severe												

Remark: ER for erythema and eschar and OE for oedema.

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Acute Systemic Toxicity Test

1. SUMMARY

Objective: This test was conducted to determine whether the test article would cause acute systemic toxicity following injection into mice. These extracts were evaluated for acute systemic toxicity.

Methods: This method is based on the requirements in ISO 10993-11:2017: Biological Evaluation of Medical Device, Part 11: Tests for Systemic Toxicity. Twenty KM mice were utilized. The test article was extracted in 0.9% sodium chloride injection (NS) and cotton seed oil (CSO) respectively. A single dose of the NS extract of the test article was injected by the intravenous route and the cotton seed oil extract of the test article was injected by intraperitoneal route respectively. Similarly, mice were dosed with corresponding reagent control. The animals were observed immediately and measured the body weights of all animals at 24, 48 and 72 hours after systemic injection to evaluate the acute systemic toxicity reaction.

Conclusion: Under the conditions of this study, there was no mortality or evidence of acute systemic toxicity from the extract of the test article.

Test period: 2022.07.29~2022.08.09

2. MATERIALS

2.1 Test Material

Physical Properties: Solid, Non-absorbable

Storage conditions: Room temperature

2.2 Extraction vehicle

Polar extraction vehicle: 0.9% physiological saline (Manufacturer: Guangdong Kelun Pharmaceutical Co., Ltd.; Lot No.: H22011007)

Non-Polar extraction vehicle: Cottonseed oil (Manufacturer: J&K; Lot No.: LMCOV23)

2.3 Negative control: The same batch of extraction vehicle without the test article.

2.4 Test article preparation: The test article extract liquid was prepared at the ratio of 0.1g/mL, under the condition of 37°C for 72h, and the extract medium was 0.9% physiological saline and cottonseed oil.

The appearance of the extract liquid and extract vehicle had no difference and there were no particulates in the extract liquid. So the extract liquid didn't need to be processed by filtration, centrifugation or other methods to remove suspended particulates. Extract pH wasn't adjusted and the extract liquid was used instantly after the

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preparation.

3. TEST SYSTEM (Animals)

3.1 Species & Strain: KM Mouse

3.2 Source: Guangdong Medical Laboratory Animal Center. Passed No.: SCXK(粤)2022-0002(44007200106353)

3.3 Grade: SPF

3.4 Number of animals: 20

3.5 Sex: Males, No particular sex is required

3.6 Weight at day 1: 17.2~21.0g

3.7 Acclimation period: 5 days

3.8 Justification of Test System

The KM Mouse is specified as an appropriate animal for evaluating acute systemic toxicity by the current ISO 10993 standards. The KM Mouse is widely used for this purpose and the acute systemic toxicity can be evaluated by this method.

3.9 Animal Management

3.9.1 Housing: Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory) is an accredited facility and registered with the State Food and Drug Administration of China. Certification No: SYXK (粤) 2022-0169. Animal care and housing will be in accordance with "Laboratory animal-Requirements of environment and housing facilities"; "ISO 10993-2:2006: Biological evaluation of medical devices Part 2: Animal welfare requirements". Animals will be housed in an environmentally monitored, well-ventilated room maintained at a temperature of 20.0-26.0°C and a relative humidity of 40.0-70.0%. Fluorescent lighting will provide illumination approximately 12 hours per day.

3.9.2 Feed: Certified rat feed (Guangdong Medical Laboratory Animal Center) will be provided ad libitum. Nutritional ingredient and chemical index in the diet of every batch will be conducted by special detection institute. The result will be reviewed by Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory), to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The feed meets the feed standards according to the State Standard of the People's Republic of China GB14925.3-2010 and GB14925.2-2001.

3.9.3 Water: Water was provided ad libitum through bottle type drinkers. Samples of water from the animal

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facility will be analyzed for toxicological parameter annually. Results of water analyses will be retained in the facility records, and to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The water meets the drinking water standards according to the State Standard of the People's Republic of China GB5749-2006.

3.10 Personnel: Associates involved were appropriately qualified and trained.

3.11 Selection: Only healthy, previously unused animals were selected.

4. EQUIPMENT

Electronic scales C2017-10-38(D), Electronic scales C2017-10-36(D), Biological safety cabinets Z2015-25-11(D), Constant temperature shock incubator T2018-04-10(D), Carbon dioxide anaesthetic box T2017-50-01(D)

5. METHOD

5.1 Preparation: Prior to dosing, each animal was identified and weighed. Twenty mice were divided into four groups, five in each.

5.2 Procedure: Two groups of five animals were injected respectively with the fresh extracts of cottonseed oil and the reagent control at a single dose of 50mL/kg by intraperitoneal injection. The other two groups of five animals were injected respectively with the fresh extracts of NS and the reagent control at a dose of 50mL/kg by intravenous injection.

5.3 Observations: Mice were observed for adverse reactions immediately after injection, again 4h after injection, and then 24, 48, and 72h respectively. Record the general state, symptom of toxicity, and the number of dead mice. Measure and record the body weights of all animals at 24, 48, and 72h post injection.

5.4 Evaluation of Results

If during the observation period none of the animals treated with the test sample shows a significantly greater biological reactivity than animals treated with the vehicle control, the extract of the test article is considered to have no acute systemic reactivity.

If two or more animals die or behaviour such as convulsions or prostration occurs out of five, or if body weight loss greater than 10% occurs in three or more animals, the extract of the test article is considered to have acute systemic reactivity.

If any animals treated with the sample show only slight signs of biological reactivity, and not more than one animal shows gross symptoms of biological reactivity or dies, repeat the testing using groups of ten animals.

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On repeat test, if all ten animals treated with the sample show no scientifically meaningful biological reactivity above the vehicle control animals during the observation period, the extract of the test article consider to have no acute systemic reactivity.

6. RESULT

There was no mortality during the study. Body weight data were acceptable. All animals appeared clinically normal throughout the study. Individual observations were presented in TABLE 1 and TABLE 2

Results and conclusions apply only to the test articles tested. No further evaluation of these results is made by. Any extrapolation of these data to other samples is the responsibility of the sponsor.

7. CONCLUSION

Under the conditions of this study, the 0.9% physiological saline and cottonseed oil test article extracts showed there was no mortality or evidence of acute systemic toxicity from the extract of the test article.

8. ATTACHED TABLE

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		Number of dead animals/Total animals	After injection	Daily observation			
Group				4h	24h	48h	72h
Control	0.9% physiological saline	0/5	Normal	Normal	Normal	Normal	Normal
	Cottonseed oil	0/5	Normal	Normal	Normal	Normal	Normal
Test	0.9% physiological saline	0/5	Normal	Normal	Normal	Normal	Normal
	Cottonseed oil	0/5	Normal	Normal	Normal	Normal	Normal

TABLE 2 Animal weight(g)

		Animal Number	Before injection	24h	48h	72h
Group						
Control	0.9% physiological saline	1	18.6	18.4	20.5	21.7
		2	20.1	21.6	23.4	24.7
		3	18.3	20.2	21.6	22.7
		4	20.6	21.7	22.7	24.1
		5	17.2	18.6	20.0	21.5
	Cottonseed oil	1	19.7	19.5	21.4	23.0
		2	18.2	18.7	20.3	21.8
		3	19.4	19.3	20.7	21.9
		4	18.6	18.3	20.1	21.7
		5	19.0	19.7	21.6	23.1
Test	0.9% physiological saline	1	19.2	21.1	22.1	24.0
		2	20.0	21.9	23.3	24.2
		3	19.6	20.7	22.5	23.4
		4	18.7	19.3	20.8	21.2
		5	19.9	21.0	23.4	24.5
	Cottonseed oil	1	21.0	22.9	24.6	26.0
		2	17.8	18.6	20.6	22.0
		3	19.4	19.8	22.1	23.8
		4	19.8	19.4	21.6	23.2
		5	17.6	17.9	20.0	21.5

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Haemolysis test

1. SUMMARY

Objective: This test was conducted to determine whether the test article would cause haemolysis.

Methods: This method is based on the requirements in ISO 10993-4:2017 Biological evaluation of medical devices-Parts 4: Selection of tests for interactions with blood. Put test tubes respectively with testing sample, negative control and blank control in 37°C water bath for 30 min. Add dilute anticoagulant fresh blood in each tube, continue keep in 37°C water bath for another 60 min. Pull out the liquid in tubes, centrifuge 800g, 5 min. Put the supernatant in cuvettes, analyze through ultraviolet spectrophotometer, test the absorbance on 545mm.

Result: The average absorbance of negative control group is 0.011,

the average absorbance of positive control group is 0.840,

the average absorbance of test material group is 0.016.

Conclusion: Under the conditions of this test , the hemolysis rate of the sample hemolysis test is 0.6%⁽⁺⁾.

Test period: 2022.08.08-2022.08.12

2. MATERIALS

2.1 Physical Properties: Solid, Non-absorbable

2.2 Package: Sterilization package

2.3 Storage conditions: Room temperature

2.4 Extraction vehicle: 0.9% physiological saline (Manufacturer: Guangdong Kelun Pharmaceutical Co., Ltd.; Lot No.: H22011007)

2.5 Negative control: The same batch of extraction vehicle without the test article.

2.6 Positive control: Distilled water.

2.7 Test article preparation: Base on ISO 10993-4:2017 Biological evaluation of medical devices-Parts 4: Selection of tests for interactions with blood. Tests shall use an appropriate model or system which simulates the geometry and conditions of contact of the device with blood during clinical applications. Base on 0.5g/mL ratio, take the test material 15g, according to the type and size of the test material, according to the standard cut into suitable test pieces (granular The test sample can be weighed directly.) The tubular and strip-shaped test materials are cut into small pieces of about 2.5cm, and the chip materials are cut into small pieces of about 0.5 cm x 2.5 cm. The

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prepared test material is then added to the three polypropylene test tubes on average to serve as a test material set and used as a spare .

2.8 Dilute anticoagulant fresh blood

2.8.1 Anticoagulant fresh blood: Take 10ml blood from New Zealand rabbit; add 0.5mL20g/L potassium oxalate, gently mix up.

2.8.2 Dilute anticoagulant fresh blood: Gently mix up 8ml anticoagulant fresh blood and 10ml 0.9% physiological saline.

3. TEST SYSTEM (Animals)

3.1 Species & Strain: New Zealand Rabbit

3.2 Source: Guangdong Medical Laboratory Animal Center.

3.3 Passed No.: SCXK(YUE) 2019-0035(44411600010152)

3.4 Grade: CV

3.5 Justification of Test System: The blood of New Zealand Rabbit is an appropriate animal blood for evaluating haemolysis by the current ISO 10993 standards. The blood of New Zealand Rabbit is widely used for this purpose and the haemolysis can be evaluated by this method.

3.6 Sex: Females (No particular sex is required)

3.7 Acclimation period: 7 days

3.8 Animal Management

3.8.1 Housing: Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory) is an accredited facility and registered with the State Food and Drug Administration of China. Certification No: SYXK (YUE) 2022-0169. Animal care and housing will be in accordance with "Laboratory animal-Requirements of environment and housing facilities"; "ISO 10993-2:2006: Biological evaluation of medical devices Part 2: Animal welfare requirements". Animals will be housed in an environmentally monitored, well-ventilated room maintained at a temperature of 18°C-26°C and a relative humidity of 40%-70%. Fluorescent lighting will provide illumination approximately 12 hours per day.

3.8.2 Feed: Certified feed (Guangdong Medical Laboratory Animal Center.) will be provided ad libitum. Nutritional ingredient and chemical index in the diet of every batch will be conducted by special detection institute. The result will be reviewed by Guangzhou medical instruments quality surveillance and inspection center of state food and drug

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administration (Dongguan laboratory), to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The feed meets the feed standards according to the State Standard of the People's Republic of China GB14925.3-2010 and GB14925.2-2001.

3.8.3 Water: Water was provided ad libitum through an automatic watering system. Samples of water from the animal facility will be analyzed for toxicological parameter annually. Results of water analyses will be retained in the facility records, and to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The water meets the drinking water standards according to the State Standard of the People's Republic of China GB5749-2006.

3.9 Personnel: Associates involved were appropriately qualified and trained.

3.10 Selection: Only healthy, previously unused animals were selected.

4. EQUIPMENT

Electronic balance(C2006-10-06(D)), Uv-vis spectrophotometer(Q2010-03-04(D)), Refrigerated centrifuge (X2010-08-05(D)), Water Baths Shaker(J2010-08-02(D)), Ultrapure Water System (X2015-13-27(D)).

5. METHOD

Put test tubes respectively with testing sample, negative control and blank control in 37°C water bath for 30 min. Add 0.2ml dilute anticoagulant fresh blood in each tube, gently mix up, keep in 37°C water bath for another 60 min. Pull out the liquid in tubes, centrifuge 800g, 5 min. Put the supernatant in cuvettes, analyze through ultraviolet spectrophotometer, test the absorbance on 545mm.

The absorbance of negative control should be less than 0.03, and the positive control should be 0.8 ± 0.3 then the test result is considered to be effective.

6. RESULT

The absorbance of negative control is 0.011, and the positive control is 0.840 and the test result is 0.016. The result see table 1

7. CONCLUSION

Under the conditions of this test , the hemolysis rate of the sample hemolysis test is 0.6% ⁽⁺⁾.

8. ATTACHED TABLE

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Table 1 The result of haemolysis rate

Group	Average Absorbance	Haemolysis rate
Test material	0.016	0.6% ⁽⁺⁾
Negative control	0.011	$\text{Haemolysis rate} = \frac{A - B}{C - B} \times 100\%$ Remark: A—Absorbance of test sample B—Absorbance of negative control C—Absorbance of positive control
Positive control	0.840	

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Test for local effects after implantation

1. SUMMARY

Objective: This test was conducted for assessing the biological response of subcutaneous tissue to the implanted material.

Methods: This method is based on the requirements in ISO 10993-6:2016 Biological Evaluation of Medical Devices, Part 6 Tests for local effects after implantation. Sterile implant samples and negative control were implanted into the subcutaneous tissue in rats. The animals were euthanatized respectively at 1 week after implantation. Tissues were excised and the implant sites were examined macroscopically. A microscopic evaluation of representative implant sites from each rat was conducted to further define any tissue response.

Conclusion: Under the conditions of this study, the microscopic reaction was not significant as compared to the negative control. Microscopically, the test article was classified as a non irritant as compared to the negative control article.

Test period: 2022.10.10~2022.10.27

2. MATERIALS

2.1 Test Material

Physical Properties: Solid, Non-absorbable

Storage conditions: Room temperature

2.2 Test article preparation: The test article was cut into 10mm in length, 1 mm in diameter.

2.3 Surface condition: Smooth

2.4 Control material:

Material: HDPE

Manufacturer: Hatano Research Institute, FDSC

Lot: E-211

Size: Long about 10mm, diameter about 1mm, smooth surface, short rod

3. TEST SYSTEM (Animals)

3.1 Species & Strain: SD Rat

3.2 Source: Guangdong Medical Laboratory Animal Center. Passed No.: SCXK(YUE) 2022-0002

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(44007200106902) ;

3.3 Grade: SPF

3.4 Number of animals: 5

3.5 Sex: Females

3.6 Weight at day 1: 292~306g

3.7 Acclimation period: 5 days

3.8 Justification of Test System

The rats is specified as an appropriate animal for evaluating biological response of subcutaneous tissue to the implanted material by the current ISO 10993 standards. The rats is widely used for this purpose and the biological response of subcutaneous tissue to the implanted material can be evaluated.

3.9 Animal Management:

3.9.1Housing: Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory) is an accredited facility and registered with the State Food and Drug Administration of China. Certification No: SYXK(YUE) 2022-0169. Animal care and housing will be in accordance with "Laboratory animal-Requirements of environment and housing facilities"; "ISO 10993-2: 2006: Biological evaluation of medical devices Part 2: Animal welfare requirements". Animals will be housed in an environmentally monitored, well-ventilated room maintained at a temperature of 20°C~26°C and a relative humidity of 40%~70%. Fluorescent lighting will provide illumination approximately 12 hours per day.

3.9.2Feed: Certified rat feed (Guangdong Medical Laboratory Animal Center) will be provided ad libitum. Nutritional ingredient and chemical index in the diet of every batch will be conducted by special detection institute. The result will be reviewed by Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory), to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The feed meets the feed standards according to the State Standard of the People's Republic of China GB14925.3-2010 and GB14925.2-2001.

3.9.3Water: Water was provided ad libitum through Drinking water bottles. Samples of water from the animal facility will be analyzed for toxicological parameter annually. Results of water analyses will be retained in the facility records, and to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The water meets the drinking water standards according to the State Standard of the People's Republic of

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China GB5749-2006.

3.10 Personnel: Associates involved were appropriately qualified and trained.

3.11 Selection: Only healthy, previously unused animals were selected.

4. EQUIPMENT

Electronic scales C2006-10-02(D)、Fully enclosed tissue dehydrator Q2019-44-02(D)、Sealed automatic dyeing machine (HMS740) Q2011-54-01(D)、Glass sealing machine (CTM6) Q2011-53-01(D)、Automatic slicer G2018-49-05(D)、Water Bath-Slide Drier Q2011-49-01(D)、Fluorescence Microscopy Digital Imaging System (DM2500) R2012-32-01(D)、Tissue Embedding Machine Q2011-45-01(D)、Biological safety cabinets Z2015-25-11(D)、Carbon dioxide anaesthetic box T2017-50-01(D)

5. METHOD

Prior to implantation, each animal was weighed and identified.

5.1 Preparation

The fur was clipped from the operation area. Then injected 60g/L Chloral Hydrate (5.0mL/kg, ip) to achieve whole anesthesia. Disinfected the skin with 2% iodine and 75% alcohol.

5.2 Procedure

Make an incision of the skin and make two subcutaneous pockets on the left back by blunt dissection. The base of the pocket shall be more than 10mm from the line of incision. Place one test specimen in each pocket. The implants shall not be able to touch one another. The control material were implanted on the contralateral back of each animal using the same method.

Rats were returned to the cages and observed daily for general health.

5.3 Observations

After 1 week implantation, the rats were euthanized and the tissue of implant sites from each animal were excised. The area of the tissue surrounding the implant strip was examined macroscopically.

5.4 Evaluation of Results

A sufficient area around the implant site was evaluated macroscopically as defined according to Histological evaluation system — Cell type/response and Histological evaluation system — Response.

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Histological evaluation system — Cell type/response

Cell type/response	Score				
	0	1	2	3	4
Polymorphonuclear cells	0	Rare, 1-5/phf	5-10/phf	Heavy infiltrate	Packed
Lymphocytes	0	Rare, 1-5/phf	5-10/phf	Heavy infiltrate	Packed
Plasma cells	0	Rare, 1-5/phf	5-10/phf	Heavy infiltrate	Packed
Macrophages	0	Rare, 1-5/phf	5-10/phf	Heavy infiltrate	Packed
Giant cells	0	Rare, 1-2/phf	3-5/phf	Heavy infiltrate	Sheets
Necrosis	0	Minimal	Mild	Moderate	Severe

phf = per high powered (400 ×) field

Histological evaluation system — Response

Response	Score				
	0	1	2	3	4
Neovascularisation	0	Minimal capillary proliferation, focal, 1-3 buds	Groups of 4-7 capillaries with supporting fibroblastic structures	Broad band of capillaries with supporting structures	Extensive band of capillaries with supporting fibroblastic structures
Fibrosis	0	Narrow band	Moderately thick band	Thick band	Extensive band
Fatty infiltrate	0	Minimal amount of fat associated with fibrosis	Several layers of fat and fibrosis	Elongated and broad accumulation of fat cells about the implant site	Extensive fat completely surrounding the implant

The histological scoring systems as described in TABLE 1 and TABLE 2 are converted to an implant evaluation system by calculating the average irritant score shown as below:

Total score of TABLE 1 × 2 + total score of TABLE 2

Average score = _____

Average irritant score = average score of test sample – average score of control sample.

Average irritant score is used to determine irritant ranking shown below:

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-
- non-irritant (0.0 up to 2.9)
 - slight irritant (3.0 up to 8.9)
 - moderate irritant (9.0 up to 15.0)
 - severe irritant (> 15)

6. RESULT

6.1 Clinical observation: All animals tolerated the surgical procedures well and appeared clinically normal throughout the duration of the study. During the experimental periods there was no evidence of infection or disturbed wound healing.

6.2 Macroscopic observation: There was no visible reaction at any test or control site. No signs of implant rejection, necrosis or infection were found. Gross examination of the retrieved specimens revealed that all the interfaces between the tissue and the sample were normal.

6.3 Biological response shall be evaluated in TABLE 1.

6.4 Results and conclusions apply only to the test articles tested. No further evaluation of these results is made by. Any extrapolation of these data to other samples is the responsibility of the sponsor.

7. CONCLUSION

Under the conditions of this study, after 1 week implantation, the test sample was considered as non-irritant to the tissue as compared to the negative control sample.

8. ATTACHED TABLE

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TABLE 1 Scoring system of biological response (1 week)

Animal number:	Test Sample					Control Sample				
	1	2	3	4	5	6	7	8	9	10
Animal number:	1	1	1	1	1	1	1	1	1	1
Polymorphonuclear	1	1	2	2	2	1	2	1	1	1
Lymphocytes	0	0	0	0	0	0	0	0	0	0
Plasma cells	1	1	1	1	1	1	1	1	1	1
Macrophages	0	0	0	0	0	0	0	0	0	0
Giant cells	0	0	0	0	0	0	0	0	0	0
SUB-TOTAL ($\times 2$)	6	6	8	8	8	6	8	6	8	6
Neovascularisation	0	0	1	1	1	0	0	0	0	0
Fibrosis	1	1	1	1	1	1	1	1	1	1
Fatty infiltrate	0	0	0	0	0	0	0	0	0	0
SUB-TOTAL	1	1	2	2	2	1	1	1	2	1
TOTAL	7	7	9	10	10	7	9	7	10	7
AVERAGE										
Number of implants examined	1	1	1	1	1	1	1	1	1	1
Foreign debris	None								None	
Traumatic necrosis	None								None	
A negative difference is recorded as zero										
										Blank below

TEST (-) CONTROL=8.7-7.5=1.2

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Pyrogens

1 SUMMARY

Objective: The pyrogen test is designed to limit to an acceptable level the risks of febrile reaction in the patient to the administration, by injection, of the product concerned. The test involves measuring the rise in temperature of rabbits following the intravenous injection of a test solution and is designed for products that can be tolerated by the test rabbit in a dose not to exceed 10 mL per kg injected intravenously within a period of not more than 10 minutes.

Methods: The test article, was evaluated for Pyrogens in accordance with the standard of the USP41 <151> Pyrogens Test. The test article was extracted in 0.9% physiological saline at $(37 \pm 1)^\circ\text{C}$ for (72 ± 1) h. A 10 mL/Kg dose of the appropriate extract was injected by the intravenous route into each rabbit. Record the normal temperature, maximum temperature and calculate the temperature variation of each three rabbit.

Result: No rabbit shows an individual rise in temperature of 0.5°C

Conclusion: The material under examination meets the requirements for the absence of pyrogens.

Test Date: 2022.08.14~2022.08.21

2 MATERIALS

2.1 Test article:

Physical Properties: Solid, Non-absorbable

Storage conditions: Room temperature

2.2 Extraction vehicle: polar extraction vehicle: 0.9% physiological saline (Manufacturer: Guangdong Kelun Pharmaceutical Co., Ltd.; Lot No.: H22011007)

2.3 Extract preparation: The test article extract liquid was prepared with extraction vehicle at the ratio of 0.1g/mL, under the condition of $(37 \pm 1)^\circ\text{C}$ for (72 ± 2) h.

2.4 Condition of Extracts: All the extracts of the test and controls were clear and without any special treatments.

3 TEST SYSTEM (Animal)

3.1 Species & Strain: New Zealand White Rabbit

3.2 Source: Guangdong Medical Laboratory Animal Center. Passed No.: SCXK(粤) 2019-0035 (44411600010446)

3.3 Grade: CV

3.4 Number of animals: 3

3.5 Sex: Females (No particular sex is required)

3.6 Weight at day 1: 2.2kg to 2.3kg

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3.7 Acclimation period: 7 day

3.8 Justification of Test System: The rabbit is specified as an appropriate animal for evaluating biological response of skin to the test material by the current USP41 <151> Pyrogen Test standards. The rabbit is widely used for this purpose.

3.9 Animal Management:

3.9.1 Housing: Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory) is an accredited facility and registered with the State Food and Drug Administration of China. Certification No: SYXK (YUE) 2022-0169. Animal care and housing will be in accordance with "Laboratory animal-Requirements of environment and housing facilities"; "ISO 10993-2:2006: Biological evaluation of medical devices Part 2: Animal welfare requirements". Animals will be housed in an environmentally monitored, well-ventilated room maintained at a temperature of 18~26°C and a relative humidity of 40%-70%. Fluorescent lighting will provide illumination approximately 12 hours per day.

3.9.2 Feed: Certified rat feed (Guangdong Medical Laboratory Animal Center.) will be provided ad libitum. Nutritional ingredient and chemical index in the diet of every batch will be conducted by special detection institute. The result will be reviewed by Guangzhou medical instruments quality surveillance and inspection center of state food and drug administration (Dongguan laboratory), to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The feed meets the feed standards according to the State Standard of the People's Republic of China GB14925.3-2010 and GB14925.2-2001.

3.9.3 Water: Water was provided ad libitum through an automatic watering system. Samples of water from the animal facility will be analyzed for toxicological parameter annually. Results of water analyses will be retained in the facility records, and to assure that no known contaminants are present that could interfere with or affect the outcome of studies. The water meets the drinking water standards according to the State Standard of the People's Republic of China GB5749-2006.

3.10 Personnel: Associates involved were appropriately qualified and trained.

3.11 Selection: Only healthy, previously unused animals were selected.

4 EQUIPMENT

Constant temperature shock incubator T2018-04-10(D); Electro-Thermostatic Water Bath T2018-14-29(D)

Intelligent pyrogen tester T2016-24-04(D); Baby scale C2019-11-02(D); Biological safety cabinets Z2015-25-11(D); Electronic balance C2017-10-36(D)

5 Experimental Procedure

Perform the test in a separate area designated solely for pyrogen testing and under environmental conditions similar to those under which the animals are housed and free from disturbances likely to excite them. Withhold all food from the rabbits used during the period of the test. Access to water is allowed at all times, but may be

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restricted during the test. If rectal temperature-measuring probes remain inserted throughout the testing period, restrain the rabbits with light-fitting neck stocks that allow the rabbits to assume a natural resting posture. Not more than 30 minutes prior to the injection of the test dose, determine the "control temperature" of each rabbit: this is the base for the determination of any temperature increase resulting from the injection of a test solution. In any one group of test rabbits, use only those rabbits whose control temperatures do not vary by more than 1°C from each other, and do not use any rabbit having a temperature exceeding 39.8 °C.

Unless otherwise specified in the individual monograph, inject into an ear vein of each of three rabbits 10 mL of the test solution per kg of body weight, completing each injection within 10 minutes after start of administration. The test solution is either the product, constituted if necessary as directed in the labeling, or the material under test treated as directed in the individual monograph and injected in the dose specified therein. Assured that all test solutions are protected from contamination. Perform the injection after warming the test solution to a temperature of $37 \pm 2^{\circ}\text{C}$. Record the temperature at 30-minute intervals between 1 and 3 hours subsequent to the injection.

6 RESULTS

Test result see ATTACHED TABLE 1.

7 CONCLUSION

Consider any temperature decreases as zero rise. No rabbit shows an individual rise in temperature of 0.5°C . The material under examination meets the requirements for the absence of pyrogens.

8 RECORD STORAGE

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

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TABLE 1 The result of Pyrogens

NO.	Weight (kg)	injected dose (mL)	normal temperature (°C)	Test1	Test2	Test3	Test4	Test5	Test6	temperature variation (°C)
34	2.30	23.00	38.75	38.50	38.44	38.75	38.81	38.56	38.44	0.06
14	2.30	23.00	38.72	38.69	38.75	38.75	38.69	38.69	38.82	0.10
19	2.20	22.00	38.72	38.69	38.82	38.88	39.00	38.88	38.94	0.28

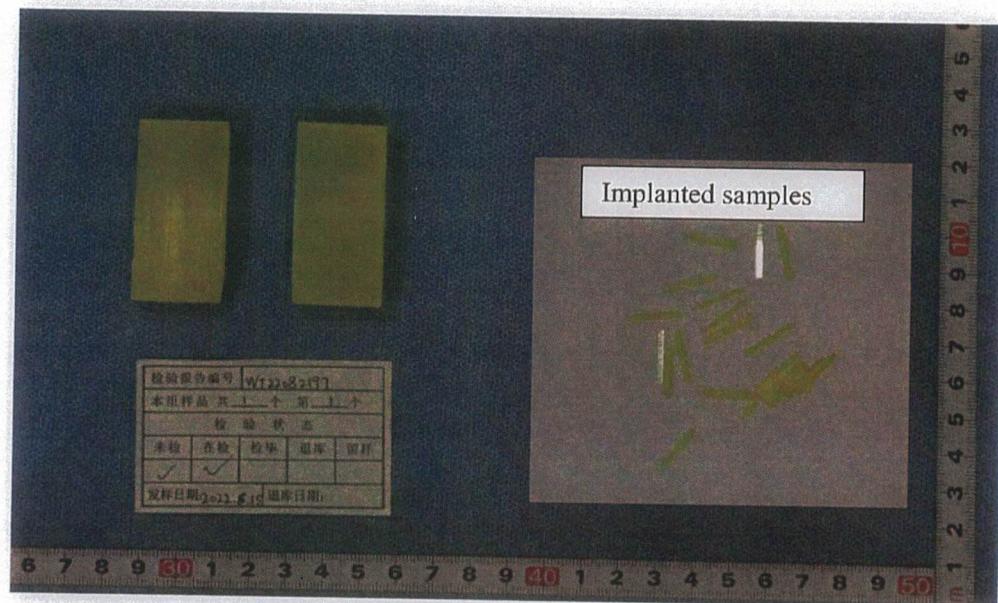
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Photos and Explanations



Samples' Descriptions

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Types and Specifications or Other Explanations

Model /Type: BIO/8g
Products' № /Lot №: 20211210B
Producing date: 2021.12.10

