SILICONE RUBBER
USP<88> class VI Study
Test Report

Client	**WYNCA TINYO SILICONE CO., LTD**
Testing Institution	**Biocompatibility Lab. of Leon Biotech. Co. Ltd.**
Report No.	**R-USP88-KL20160501**

Note:
1. The content of this test plan is invalid if it is not presented as the entire test plan.
2. Any unauthorized alteration, forgery or falsification of the content or appearance of this test plan is unlawful and offenders may be prosecuted to the fullest extent of the law.
3. The results shown in this test plan refer to the test article(s) tested only.

Contents

Schedule

Study	USP<88> class VI Study
Test article	SILICONE RUBBER
Service No.	KL20160501
Study Initiation date	2016.05.24
Experimental starting date	2016.05.27
Experimental completion date	2016.06.29
Study completion date	See Study Director's signature date in the report

Study Director

Name	Yu Jung Pan
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Study Personnel

Participants	Yu Jung Pan, Hsuan-Wen Wu, Ai Jie Han

Test Institution

Name	Biocompatibility Lab. of LEON Biotech. Co., Ltd.
Address	4F.-2, No.288-8, Xinya Rd., Qianzhen Dist., Kaohsiung City 806, Taiwan
Contact	Ming-Yang Tsao (07) 841-9003 ming_yang@seed.net.tw

Client

Name	WYNCA TINYO SILICONE CO., LTD
Address	No.36, Jingling Road, Qingyuan High-tech Zone, Qingyuan , Guangdong , China.
Contact	Phone: 0763-3608635 FAX: 0763-3608669

Test Article Information

Name	SILICONE RUBBER
Manufacture Date	2016.04.12
Expiry Date	N/A
Lot No.	N/A
Model	TYE771
Storage Condition	Room Temperature
Sterilization Condition	EO
Package	Plastic bag
Physical Description	Polysiloxane, Silica, Siloxane Oligomer
Appearance Description	Colorless-transparent, sheet
Category	Medical Device
Pre-treatment	N/A
✦ **Sponsor, who provided test facility with the test article information, will take full responsibility for all the facts of it.**	
Received date	**2016.05.03**
Test article no.	**KL20160501-a**

Report No. R-USP88-KL20160501

Statement of GLP Compliance

Study activities performed by Biocompatibility Lab. of LEON Biotech. Co., Ltd. are carried out in compliance with current OECD Principles of Good Laboratory Practice (Organization for Economic Cooperation and Development, Paris, ENV/MC/CHEM (98) 17) and U.S. Food and Drug Administration Good Laboratory Practice Regulations, 21 CFR Part 58. The study was conducted in accordance with the test plan and standard operating procedures and monitored in conformity with the test plan. All laboratory data are accurately recorded and verified. Biocompatibility Lab. of LEON Biotech. Co., Ltd. makes no GLP compliance claim for characterization and verification (6.2.2 and 6.2.3 in OECD principle on Good Laboratory Practice) of the test article identity and properties, which are the responsibility of the sponsor.

Study Director

Yu Jung Pan — 2016.07.26

Yu Jung Pan / LEON Biotech. Co. Ltd | **Date Completed**

Facility Manager

M.Y. Tsao — 2016.07.26

Ming-Yang Tsao/ LEON Biotech. Co. Ltd | **Date Completed**

Report No. R-USP88-KL20160501

Quality Assurance Statement

SILICONE RUBBER
USP<88> class VI Study

This study was inspected by Quality Assurance unit of LEON Biotech. Co. Ltd. Inspection activities included review of draft test plan, audit test procedure, and review of raw data and draft test report.

Study-base audit

Study Phase	Inspection Date	Submitted date to Study Director and Facility Manager
Test plan draft	2016/05/25	2016/05/25
Test Article extraction—Intracutaneous Test	2016/05/27	2016/05/27
Dose Administration—Systemic Injection Test	2016/06/20	2016/06/20
Dose Administration—Implant Test	2016/06/21	2016/06/21
Review of raw data	2016/07/26	2016/07/26
Test report draft	2016/07/26	2016/07/26

The final report has been found to reflect the raw data obtained.

Quality Assurance Manager

Wei Ti Wang

Wei Ti Wang/ LEON Biotech. Co. Ltd

2016.07.26

Date Completed

Archiving

All the study-related raw data, records, protocol and the final report will be kept in GLP cabinet of archives room of Leon Biotech. for 5 years. All of the records and test articles are handled according to GLP guideline.

Archiving List	
Test Plan	Test plan Test plan amendment (if necessary)
Final Report	Final report copy Final report amendment (if necessary)
Raw Data	All test data sheet
Records	Application form Test article information Test article control form and other supplementary record

Objective

The purpose of the study is to determine the biological response of animals to direct and indirect contact with the test article or injection of the test article extract. This study was conducted following USP<88>.

Test System

1. For Systemic Injection Test

Species/ Strain	ICR Mice
Resource	LASCO Co. Ltd. (base on SOP-Q02)
Reason	According to USP<88>
Body weights	17~23 g
Sex	Female, female should be nulliparous and not pregnant.
Numbers	40
Quarantine/ acclimation	Once animals are introduced in-house, they are subjected to quarantine and acclimatize before treatment. Animals are selected based on health status by qualified staff. (according to SOP-A02)
Animal restraint	The restraint of animals is according to internal document of standard operating procedure SOP-T00.
Identification	
Individual identification	Animals are identified by tail-marking.
Cage identification	Cages are properly labeled for identification including species/strain, sex, in-housing date, IACUC number, animal I.D. number.
Housing condition (according to SOP-A01)	
Environment temperature	22±3℃
Humidity	30~70%
Cage and animal number	5 animals/cage
Fodder/ Supply	Lab Diet; *ad libitum*
Drinking water/ Supply	Tap water; *ad libitum*

2. For Intracutaneous Injection Test

Species/ Strain	New Zealand White Rabbit (NZW)
Resource	Livestock Research Institute, Council of Agriculture, Executive Yuan (TLRI) (base on SOP-Q02)
Reason	According to USP<88>
Body weights	>2 kg
Sex	Female, female should be nulliparous and not pregnant.
Numbers	4
Quarantine/ acclimation	Once animals are introduced in-house, they are subjected to quarantine and acclimatize before treatment. Animals are selected based on health status by qualified staff. (according to SOP-A02)
Animal restraint	The restraint of animals is according to internal document of standard operating procedure SOP-T00.
Identification	
Individual identification	Animals are identified by ear-marking.
Cage identification	Cages are properly labeled for identification including species/ strain, sex, in-housing date, IACUC number, animal I.D. number.
Housing condition (according to SOP-A01)	
Environment temperature	23±3℃
Humidity	30~70%
Cage and animal number	1 animals/cage
Fodder/ Supply	Lab Diet; *ad libitum*
Drinking water/ Supply	Tap water; *ad libitum*

3. For Implant Test

Species/Strain	Rat/SD
Resource	LASCO Co. Ltd. (base on SOP-Q02)
Reason	According to USP<88>
Body weights	225~350 g
Sex	Female, female should be nulliparous and not pregnant.
Numbers	5
Quarantine/ acclimation	Once animals are introduced in-house, they are subjected to quarantine and acclimatize before treatment. Animals are selected based on health status by qualified staff. (according to SOP-A02)
Animal restraint	The restraint of animals is according to internal document of standard operating procedure SOP-T00.
Identification	
Individual identification	Animals are identified by tail-marking and ear-marking
Cage identification	Cages are properly labeled for identification including species/strain, sex, in-housing date, IACUC number, animal I.D. number.
Housing condition (according to SOP-A01)	
Environment temperature	22±3℃
Humidity	30~70%
Cage and animal number	2~5 animals/cage
Fodder/ Supply	Lab Diet; *ad libitum*
Drinking water/ Supply	Tap water; *ad libitum*

Material and Method

Reagent

1. 0.9% normal saline (Tai Yu Pharmaceutical Co., Ltd. Lot. No.QL3003)
2. Cottonseed oil (Sigma, C7767. Lot. No.MKBS9702V)
3. 100% EtOH (Ferak Berlin GmbH, Lot. No.574105)
4. PEG 400 (Fluka, 81172 Lot. No.BCBH2687V)
5. USP High Density Polyethylene RS (Lot. No.I0K217)

Preparation

Systemic and Intracutaneous Testing Preparation:

Prior to extraction, the test articles were washed two times with 70ml of distilled water. The test article samples prepared for extraction with cottonseed oil were dried at 50^{o}C for 1±0.1 hours.

The test article was combined with vehicle at a ratio of 3cm^{2} per 1 mL per USP guidelines (Thickness: 0.5~1mm). The test article was separately extracted in 0.9% Saline (NaCl), Cottonseed oil (CSO), 1:20 EtOH/0.9% saline, and PEG 400 at 50 ℃ for 72±2 hours. Properly prepared test articles were placed in separate extraction bottles, and to each bottle the appropriate medium was added. The extraction medium completely covered the test article. Each extracting medium (control article) was prepared for parallel treatments and comparisons. Each control article was prepared in the same manner as the test article. After extraction, cool to about room temperature for test. Do not use extract for test after 24 hours.

Subcutaneous Implant Testing Preparation:

The test articles and control articles (USP High Density Polyethylene RS) were cut into approximately 1 mm × 10 mm. The control article was sterilized by dipping in 75% ethanol prior to implantation.

Grouping

Tests	**Systemic injection**								**Intracutaneous Injection**				**Subcutaneous Implantation**
Test system	Mice								Rabbits				Rats
Extractant	NaCl		CSO		1:20 EtOH/ NaCl		PEG 400		NaCl	CSO	1:20 EtOH/ NaCl	PEG 400	
Group	T	C	T	C	T	C	T	C	T + C		T + C		2T + 2C
Animal numbers	5	5	5	5	5	5	5	5	2		2		5

- T─ Test group; C─ Control group; T+C—Test and control group will be conducted in different area in one animal.

The tests were conducted with different animal as recommended by the classification of plastic of USP guidelines for Class VI (see Table 1). The species and number of animals used in this study are recommended by the USP<88> guidelines.

Dose Administration

1 Systemic Injection Test

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

Extract	Route	Dose/kg
NaCl	Intravenous	50 mL
CSO	Intraperitoneal	50 mL
EtOH	Intravenous	50 mL
PEG	Intraperitoneal	10 g

2 Intracutaneous Injection Test

2.1 A volume of 0.2 mL of each test article extract was injected intracutaneously at five sites on one side of each of two rabbits.

2.2 Two test article extract was used per rabbit. At five sites on the other side of each rabbit, 0.2 mL of the corresponding control article was injected.

3 Subcutaneous Implant Test

3.1 2 samples of the test article (Approximately 1 mm × 10 mm) were implanted into the subcutaneous on one side of the spine of each of 5 rats. In a similar fashion, 2 USP High Density Polyethylene RS (Approximately 1 mm × 10 mm) were implanted in the

subcutaneous of each animal.

Procedure

1 Systemic Injection Test:

1.1 Administration

1.1.1 Acclimated animals were weighed prior to dosing.

1.1.2 For the Systemic Injection Test, the PEG test article extract and the corresponding control were diluted with NaCl to obtain PEG concentration of approximately 200 mg/mL (with 4.1 volumes of NaCl).

1.1.3 The animals were observed for clinical signs immediately after injection, 4 hours after injection, and at 24, 48, and 72±2 hours after injection. Observations conducted included all clinical and toxicological signs. The animals were weighed at the end of the observation period.

1.2 Evaluation

1.2.1 If during the observation period, none of the animals treated with the extract of the test article shows a significantly greater biological reactivity than the animals treated with the control article, the test article meets the requirements of this test.

1.2.2 The test was considered negative if none of the animals injected with the test article show a significantly greater biological reaction than the animals treated with the control article. If two or more mice die, or show signs of toxicity such as convulsions or prostration, or if three or more mice lose more than 2 g of body weight, the test article does not meet the requirements of the test.

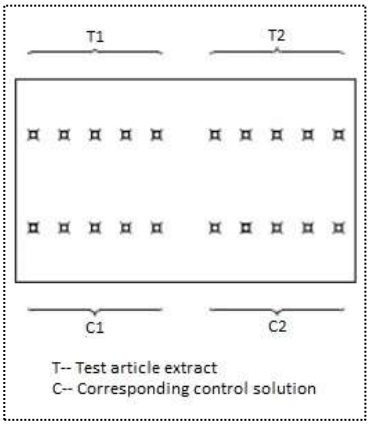
2 Intracutaneous Injection Test

2.1 Administration

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

2.1.2 For the Intracutaneous Test, the PEG test article extract and the corresponding control were diluted with NaCl to obtain PEG concentration of approximately 120 mg/mL (with 7.4 volumes of NaCl).

2.1.3 Two kinds of extract and its corresponding control solution will be injected in one rabbit (see figure upper right) and each kinds of extract will be conducted on



two rabbits.

2.1.4 The injection sites on each animal were observed for signs at 24, 48, and 72±2 hours after injection of the test article. Observations were scored according to the Table 2.

2.2 Evaluation

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

2.2.2 The requirements of the test were met if the difference between the test article and control article mean reaction scores (erythema/edema) was 1.0 or less.

3 Implant Test

3.1 Administration

3.1.1 On the day of the test, the animals were weighed and the skin on both sides of the spinal column was clipped free of fur. Clean the clipped area with 75% EtOH while animal was anesthetized.

3.1.2 Using aseptic technique, make 2 midline incision (approximately 1.0 cm long) through the skin at the cranial and caudal regions on the dorsal surface.

3.1.3 Using blunt dissection, separate the fascia connecting skin to muscle to form a pocket (base of pocket approximately 2.0 cm from the line of implant).

3.1.4 Insert a sterile sample into each pocket, and close the incision with wound clips or sutures.

3.1.5 Implant 2 test samples and 2 control samples in each rats and the implantation will be conducted with five rats.

3.1.6 The animals were maintained for a period of at least 7 days.

3.1.7 At the end of the observation period, the animals were weighed and sacrificed by CO_2.

3.2 Evaluation

3.2.1 Cut the skin (dorsal surface) longitudinally and lay back. Carefully examine macroscopically the area of the tissue surrounding the implant.

3.2.2 Observe the test article and control implant sites for hemorrhage, necrosis,

discolorations, and infections, and record the observations. Measure encapsulation, if present, by recording the width of the capsule (from the periphery of the space occupied by the implant control or test article to the periphery of the capsule) rounded to the nearest 0.1 mm. Score encapsulation according to table below.

3.2.3 Calculate the differences between average scores for the test article and control sites. The requirements of the test were met if the difference does not exceed 1.0.

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

Results

Systemic Injection Test

The results showed that there were no significant clinical signs and obvious weight loss in either the control or test group (Table below).

The test was considered negative because no animal was dead or abnormally in all test groups.

Group	Dose（ml/kg）	Sex	Animal No.	Body weight（g）		*Sign of Toxicity
				0hr	72hr	
Test (Test article NaCl extract)	50	female	M-160616-21	22.71	24.17	None
			M-160616-22	21.21	22.10	None
			M-160616-23	22.91	23.52	None
			M-160616-24	22.23	23.20	None
			M-160616-25	22.53	23.97	None
Control (NaCl)	50	female	M-160616-36	20.65	19.44	None
			M-160616-37	22.56	19.69	None
			M-160616-38	20.90	19.70	None
			M-160616-39	22.87	21.98	None
			M-160616-40	22.98	23.76	None

Group	Dose（ml/kg）	Sex	Animal No.	Body weight（g）		*Sign of Toxicity
				0hr	72hr	
Test (Test article CSO extract)	50	female	M-160616-16	22.06	24.41	None
			M-160616-17	22.66	23.33	None
			M-160616-18	22.01	23.94	None
			M-160616-19	22.74	26.60	None
			M-160616-20	22.80	23.21	None
Control (CSO)	50	female	M-160616-06	22.59	22.94	None
			M-160616-07	21.76	24.59	None
			M-160616-08	22.42	24.56	None
			M-160616-09	22.80	25.53	None
			M-160616-10	20.00	19.94	None

Group	Dose（ml/kg）	Sex	Animal No.	Body weight（g）		*Sign of Toxicity
				0hr	72hr	
Test (Test article EtOH extract)	50	female	M-160616-26	21.56	24.74	None
			M-160616-27	20.54	22.79	None
			M-160616-28	21.34	24.50	None
			M-160616-29	22.81	24.53	None
			M-160616-30	21.24	24.34	None
Control (EtOH)	50	female	M-160616-31	21.35	24.48	None
			M-160616-32	22.83	26.08	None
			M-160616-33	22.69	24.14	None
			M-160616-34	22.67	26.49	None
			M-160616-35	22.80	24.66	None

Group	Dose（g/kg）	Sex	Animal No.	Body weight（g）		*Sign of Toxicity
				0hr	72hr	
Test (Test article PEG extract)	10	female	M-160616-01	22.36	22.84	None
			M-160616-02	22.14	25.21	None
			M-160616-03	21.41	21.54	None
			M-160616-04	21.83	23.06	None
			M-160616-05	22.05	22.60	None
Control (PEG)	10	female	M-160616-11	22.98	24.07	None
			M-160616-12	22.16	22.29	None
			M-160616-13	21.77	22.13	None
			M-160616-14	22.26	24.15	None
			M-160616-15	21.84	22.23	None

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

Intracutaneous Injection Test

The results showed that there were no significant clinical signs and gross findings in either the control or test group, and there were no mortalities. Erythema and oedema were only recorded in cottonseed oil (CSO) group. The difference between the test article and control article mean reaction scores (erythema/edema) was less than 1.0 (NaCl group: 0/12-0/12=0; CSO group: 39/12-32/12=0.58; EtOH group: 0/12-0/12=0; PEG group: 5/12-3/12=0.17). The test article meets

the requirements of the Intracutaneous Test (Table below, five injection site grades).

Treated article	Sex	Animal No.	Items for Grading	Clinical Observation (time point/h)		
				24	48	72
Treatment group NaCl extract	F	RB-160303-01	Erythema formation	0	0	0
			Edema formation	0	0	0
	F	RB-160303-04	Erythema formation	0	0	0
			Edema formation	0	0	0
Control group "NaCl"	F	RB-160303-01	Erythema formation	0	0	0
			Edema formation	0	0	0
	F	RB-160303-04	Erythema formation	0	0	0
			Edema formation	0	0	0

Treated article	Sex	Animal No.	Items for Grading	Clinical Observation (time point/h)		
				24	48	72
Treatment group CSO extract	F	RB-160303-01	Erythema formation	5	2	2
			Edema formation	5	0	0
	F	RB-160303-04	Erythema formation	5	5	5
			Edema formation	5	5	0
Control group "CSO"	F	RB-160303-01	Erythema formation	5	3	2
			Edema formation	3	0	0
	F	RB-160303-04	Erythema formation	5	5	5
			Edema formation	3	1	0

Treated article	Sex	Animal No.	Items for Grading	Clinical Observation (time point/h)		
				24	48	72
Treatment group EtOH extract	F	RB-160114-05	Erythema formation	0	0	0
			Edema formation	0	0	0
	F	RB-160114-06	Erythema formation	0	0	0
			Edema formation	0	0	0
Control group "EtOH"	F	RB-160114-05	Erythema formation	0	0	0
			Edema formation	0	0	0
	F	RB-160114-06	Erythema formation	0	0	0
			Edema formation	0	0	0

Treated article	Sex	Animal No.	Items for Grading	Clinical Observation (time point/h)		
				24	48	72
Treatment group PEG extract	F	RB-160114-05	Erythema formation	3	0	0
			Edema formation	0	0	0
	F	RB-160114-06	Erythema formation	2	0	0
			Edema formation	0	0	0
Control group "PEG"	F	RB-160114-05	Erythema formation	0	0	0
			Edema formation	0	0	0
	F	RB-160114-06	Erythema formation	3	0	0
			Edema formation	0	0	0

F: Female

Implantation Test

There were no overt signs of toxicity noted in either animal. Macroscopic evaluation of the test and control article implant sites showed no significant infection, encapsulation, necrosis, or discoloration. The test was considered negative, since in each rat the difference between the average scores for encapsulation for the test article and control article implant sites did not exceed 1.0 (0-0=0). The test article meets the requirements of the Implantation Test (Table below).

Animal No.	R-160616-21		R-160616-22		R-160616-23		R-160616-24		R-160616-25	
Implant No.	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Infection	-	-	-	-	-	-	-	-	-	-
Hemorrhage	-	-	-	-	-	-	-	-	-	-
Necrosis	-	-	-	-	-	-	-	-	-	-
Discoloration	-	-	-	-	-	-	-	-	-	-
Encapsulation	0	0	0	0	0	0	0	0	0	0
Mean Score	0									

-: No symptom

Animal No.	R-160616-21		R-160616-22		R-160616-23		R-160616-24		R-160616-25	
Implant No.	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Infection	-	-	-	-	-	-	-	-	-	-
Hemorrhage	-	-	-	-	-	-	-	-	-	-
Necrosis	-	-	-	-	-	-	-	-	-	-
Discoloration	-	-	-	-	-	-	-	-	-	-
Encapsulation	0	0	0	0	0	0	0	0	0	0
Mean Score	0									

-: No symptom

Conclusion

The 0.9% Sodium Chloride for Injection (NaCl), Cottonseed Oil (CSO), 1 in 20 Ethanol in NaCl (EtOH), and Polyethylene Glycol 400 (PEG) extracts of the test article “SILICONE RUBBER”, did not produce a significant biological response following subcutaneous implantation in rats, intracutaneous injection test in rabbits and systemic injection in mice. Therefore, the test article meets the requirements of the USP guidelines, for Class VI Plastics.

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Table

1. Classification of Plastics

Plastic Classes [a]						Tests to be Conducted			
Ⅰ	Ⅱ	Ⅲ	Ⅳ	Ⅴ	Ⅵ	Test material	Animal	Dose	Procedures [b]
x	x	x	x	x	x	Extract of *Sample in Sodium Chloride Injection*	Mouse	50mL/kg	A (IV)
x	x	x	x	x	x		Rabbit or Guinea Pig	0.2mL/animal at each 10 or 6sites	B (IC)
	x	x	x	x	x	Extract of *Sample in 1 in20 Solution of Alcohol in Sodium Chloride Injection*	Mouse	50mL/kg	A (IP)
	x	x	x	x	x		Rabbit or Guinea Pig	0.2mL/animal at each 10 or 6sites	B (IC)
		x		x	x	Extract of *Sample in Polyethelene Glycol 400*	Mouse	10g/kg	A (IP)
				x	x		Rabbit or Guinea Pig	0.2mL/animal at each 10 or 6sites	B (IC)
		x	x	x	x	Extract of *Sample in Vegetable Oil*	Mouse	50mL/kg	A (IP)
			x	x	x		Rabbit or Guinea Pig	0.2mL/animal at each 10 or 6sites	B (IC)
			x		x	Implant strips of *Samples*	Rabbit	4 strips/ animal	C
			x		x	Implant *Sample*	Rat	2 Samples/ animal	C

a. Tests required for each class are indicate by "x" in appropriate columns.
b. Legend: A (IP)—Systemic Injection Test (Intraperitoneal); B—Intracutaneous Test (Intracutaneous); C—Implantation Test (Intramuscular or subcutaneous implantation)

2. Evaluation of Skin Reaction

Erythema and Eschar Formation	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema Formation *	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4

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

Test Plan Amendment

Detail of Amendment

Page 12: The ~~test and~~ control article are sterilized by dipping in 75% ethanol prior to implantation.

Reason of Amendment

The test article was already sterilized by EO, so dipping in 75% ethanol prior to implantation was not necessary.

This amendment does not affect the validity or interpretation of the data.
This amendment has been audited by the Quality Assurance Unit

Reference

1. Good Laboratory Practice for Nonclinical Laboratory Studies. Title 21 of the U.S. Code of Federal Regulations, Part 58. United States Food and Drug Administration.
2. Current OECD Principles of Good Laboratory Practice (Organization for Economic Cooperation and Development, Paris, ENV/MC/CHEM (98) 17).
3. United States Pharmacopeia 38. **<**88**>** Biological Reactivity Tests, *In Vivo*.
4. Biological evaluation of medical devices- Part 2: Animal welfare requirements. ISO 10993-2:2006.