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P.O. Box 140 • 1001 Proctor Drive • Elkhorn, WI 53121-0140
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GLOBAL HEALTH SOLUTIONS

CurX Antimicrobial Wound Dressing
Lot No.: 15F10E3

Primary Skin Irritation
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]
(Direct Contact)
(GLP)

March 15, 2016

JN16B0972

JN16B0972

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SECTION 1

TEST PROTOCOL

GLP0002* [redacted]

JN16B0972

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GLP PROTOCOL

Primary Skin Irritation Test
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]
(Direct Contact)

SPONSOR: Global Health Solutions P.O. No. CLS0005
P.O. Box 133/1360 Redmond Circle, NW
Rome, GA 30162

TEST ARTICLE: CurX Antimicrobial Wound Dressing

LOT/ID: 15F10E3

Signing of this protocol constitutes sponsor's approval of the procedure outlined on the following pages, and sponsor's confirmation that the conduct of this study does not unnecessarily duplicate previous work.

STUDY DIRECTOR: _____ STUDY INITIATION DATE: 02-16-2016
Sandy Ott
Study Director/Toxicology
Geneva Laboratories, Inc.

SPONSOR: Bradley Burnam DATE: 2/24/2016
Global Health Solutions

16-014

GENEVA LABORATORIES, INC.

PROTOCOL FOR PRIMARY SKIN IRRITATION TEST
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]
Title 21 CFR Part 58
Good Laboratory Practice for a Nonclinical Laboratory Study

§ 58.120 PROTOCOL

1). TITLE

Primary Skin Irritation Test
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]
Geneva Laboratories Proc. No.: CL1024*

2). PURPOSE

To assess the irritating potential of a test material or extract to produce dermal irritation.

3). IDENTIFICATION OF

	Name	CAS/Code (Lot No.)
Test Article:	CurX Antimicrobial Wound Dressing	15F10E3
Control Article:	Gauze 0.9% NaCl	Current Mfr. & Lot

4). SPONSOR NAME

Global Health Solutions
P.O. Box 133/1360 Redmond Circle, NW
Rome, GA 30162
ATTN: Mr. Brad Burnam

*Denotes Current Revision

5). TESTING FACILITY

Geneva Laboratories, Inc.
P.O. Box 140
Proctor Drive at McKenzie Lane
Elkhorn, WI 53121-0140

6). TEST SYSTEM

Number:	Three (3) test and three (3) positive control from historical data
Weight Range:	At least 2.0 kg
Sex:	Female, nulliparous and not pregnant
Source of Supply:	Bakkom Rabbitry
Species:	Oryctolagus cuniculus (Rabbit)
Strain:	New Zealand White, albino type
Age:	No particular age is prescribed for this test

7). TEST SYSTEM IDENTIFICATION

Rabbits are ear tagged before the start of the test with a permanent metal, individually numbered ear tag.

8). DESCRIPTION OF EXPERIMENTAL DESIGN TO INCLUDE METHODS FOR THE CONTROL OF BIAS

A. Positive Validation

Three (3) animals are used as the positive control referenced in historical data. Positive validation is required every six (6) months.

B. Preparation of Test Article

1. The test article is stored at room temperature until use.

2. Test article is prepared according to sponsor recommendations or according to ANSI/AAMI/ISO 10993-10:2010 Annex A, Section A.2 Materials for Direct-Contact Exposure.

C. Procedure

If irritation is anticipated, consideration shall be given to testing in one animal first. Unless a well-defined positive response [score greater than 2 for either erythema or edema (see Table I)] is observed, a minimum of two further animals shall be used. If no response is expected, initial testing may be conducted using three animals. If the response in the test using the minimum of three animals is equivocal, further testing shall be considered.

1. The day before test application, the backs are clipped free of hair, exposing two (2) test and two (2) control areas on each side of the spine.

2. Exposed skin may be wiped with alcohol and dried.

3. There are two (2) test sites, one on the left cranial section and one on the right caudal section of the dorsal region. There are two (2) control sites, one on the left caudal and one on the right cranial section of the dorsal region.

4. A 25 x 25 mm gauze patch saturated with 0.5 mL or 0.5g of the test article or its extract or a 25 x 25 mm piece of test article is applied to the clipped test sites.

5. A 25 x 25 mm gauze patch is used for the control and applied to the clipped control sites.

6. The patches are secured using hypoallergenic, waterproof, surgical tape over the test and control sites. The animal's trunk is securely wrapped, so as to maintain the position of the patches.

7. Patches are left applied for a minimum of four (4) hours.

D. Scoring

The test is observed at control and test sites for erythema and edema at one (1), twenty-four (24), forty-eight (48) and seventy-two (72) hours after application. Only the 24, 48 and 72 hour observations will be scored and used for calculations.

Table I
Scoring Criteria for Test Reactions

Reaction	Description	Score
Erythema (ER)	Erythema & Eschar	
	No erythema	0
	Very slight (barely perceptible)	1
	Well defined	2
	Moderate	3
	Severe (beet-redness) to eschar formation preventing grading of erythema	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 (edges raised ~1 mm)	3
	Severe (raised more than 1 mm and extending beyond exposure area)	4

E. Results

For each animal and each extract, when applicable, the scores for the test article for erythema and edema at each time are added. This total is divided by the total number of observations [six (6): two (2) at each time].

The same is done for control sites. The control result is subtracted from the test result to give the irritation index for each animal.

These scores for each animal are added and divided by the total number of animals to give the Primary Irritation Index.

Primary Irritation Index	Response Category
0 - 0.4	Negligible
0.5 - 1.9	Slight
2 - 4.9	Moderate
5 - 8	Severe

9). DESCRIPTION/IDENTIFICATION OF THE DIET TO INCLUDE ACCEPTABLE LEVELS OF CONTAMINANTS

Diet: Teklad Global Diet 2031C

A Certificate of Analysis and a mill date are retained on file at Geneva Laboratories, Inc.

10). DOSAGE OF TEST/CONTROL ARTICLES

A. Control -- 25 x 25 mm gauze patch prepared in the same manner as the test article

B. Test -- 25 x 25 mm patch of test article or 0.5 mL or 0.5g of the test article or its extract applied to a 25 x 25 mm gauze patch

11). METHOD AND FREQUENCY OF ADMINISTRATION

Two (2) 25 mm x 25 mm test article patches and 25 mm x 25 mm control gauze patches are applied. Patches of test and control articles are taped to the trunk of a rabbit for a minimum of four (4) hours and then removed.

12). TYPE AND FREQUENCY OF TEST MEASUREMENTS

The total erythema and edema scores are observed at twenty-four (24), forty-eight (48) and seventy-two (72) hours after application and calculated. An average is determined to arrive at the Primary Irritation Index.

Primary Irritation Index	Response Category
0 - 0.4	Negligible
0.5 - 1.9	Slight
2 - 4.9	Moderate
5 - 8	Severe

For any response, the Maximum Irritation Response, the time of onset of the response and the time of maximum response will be recorded.

13). RECORDS TO BE MAINTAINED

All raw data that are the result of original observations and activities of a study that are necessary for the reconstruction and evaluation of that study will be maintained in the Geneva Laboratories archives.

14). PROPOSED STATISTICAL METHODS

None.

15). REVISIONS TO APPROVED PROTOCOL

All changes and/or revisions of an approved protocol and the reasons for the changes will be documented, signed and dated by the Study Director and maintained with the protocol.

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GENEVA LABORATORIES, INC.
AMENDMENT TO GLP TEST REPORT

SPONSOR: Global Health Solutions
P.O. Box 133/1360 Redmond Circle, NW
Rome, GA 30162

TEST ARTICLE: CurX Antimicrobial Wound Dressing
Lot No.: 15F10E3

TEST PROCEDURE: Primary Skin Irritation Test (Direct Contact)
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]
Geneva Laboratories Proc. No.: CL1024 Rev. K

DATE AMENDED: 03-02-2016

REASON FOR AMENDMENT:

In the protocol. **8). DESCRIPTION OF EXPERIMENTAL DESIGN TO INCLUDE METHODS FOR THE CONTROL OF BIAS**, Section D. Scoring, has been amended to read:

> The test is observed at control and test sites for erythema and edema at one (1), twenty-four (24), forty-eight (48) and seventy-two (72) hours after patch removal.
>
> This was a typographical error and did not affect the conduct or outcome of the study.

SIGNED BY: _____ DATE: 03-02-2016

Sandy Ott
Study Director - Toxicology
Geneva Laboratories, Inc.

SECTION 2

TEST REPORT/STUDY PERSONNEL

JN16B0972
TP14778

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PRIM_ISO-A

REPORT TO: Mr. Brad Burnam
Global Health Solutions
P.O. Box 133 / 1360 Redmond Circle, NW
Rome, GA 30162

TEST ARTICLE: CurX Antimicrobial Wound Dressing
Lot No. 15F10E3

P.O. NO.: CLS0005

DATE RECEIVED: 02-12-2016

TEST INITIATION DATE: 03-08-2016 TEST COMPLETION DATE: 03-11-2016

TEST PROCEDURE: Primary Skin Irritation Test - Direct (GLP)
ANSI/AAMI/ISO 10993-10:2010/(R)2014
Ref. Geneva Laboratories Proc. No.: CL1024K

OBJECTIVE: To assess the potential of a test article to produce dermal irritation.

CONCLUSION: Under the conditions of this study:

Primary Irritation Index = 0

Test Article Response Category was Negligible

For a detailed description of test methods and findings, see pages 2-7.

ANALYST: Elizabeth Wettstein DATE: 03-14-2016

ACCEPTED BY: _____ DATE: 03-14-2016
Technical Reviewer

QA SIGNATURE: _____ DATE: 03-14-2016

STATISTICAL METHODS: None.

CONTROL ARTICLE: When applicable, a gauze patch with 0.5 mL of diluting media, prepared without the test article, is used for control.

_X_ 0.9% Sodium Chloride USP
Mfg.: Hospira
Lot No.: 51-039-JT
Exp. Date: 03-01-2017

N/A Cottonseed Oil
Mfg.:
Lot No.:
Exp. Date:

_X_ Gauze
Mfg.: Medline
Lot No.: 4505042314
Exp. Date: N/A

TEST SYSTEM:

Clinically healthy New Zealand white rabbits were received from Bakkom Rabbitry. Rabbits were identified with an individually numbered ear tag. Animals were acclimated a minimum of five (5) days.

Age at test initiation: No particular age was prescribed for this test.
Weight Range: Not less than 2 kg.
Sex: Female, nulliparous and not pregnant
Diet: _X_ Teklad Certified Rabbit No. 2031C (GLP studies)
N/A Teklad Rabbit No. 2031 (Non-GLP studies)
Water: Municipal source, ad libitum, monitored monthly for microbial count.
Number of animals used in this study:
Housing: Animals were housed one or two to an enclosure which was identified with a cage card stating the sex, arrival date, ID number and supplier.

All animals were observed daily during the study period and any health irregularities were recorded.

VALIDATION OF TEST METHOD:

A positive validation test is performed every six (6) months to confirm the sensitivity of the assay (see page 7 for results).

JUSTIFICATION OF TEST SYSTEM:

The New Zealand White rabbit has been utilized historically for dermal irritation studies.

STABILITY: The test article was stored at room temperature until use, unless otherwise specified by sponsor.

TEST METHODS:

A. Direct Application

The test article was prepared into 2.5 cm x 2.5 cm patches, not greater than 0.5 cm in thickness as recommended in the current ANSI/AAMI/ISO 10993-10 Annex A. For liquid test articles, 0.5 mL was applied directly onto a 2.5 cm x 2.5 cm gauze patch.

B. Test Procedure:

Within twenty-four (24) to four (4) hours before the test, the backs of the animals were clipped free of hair to expose approximately 15 cm x 15 cm.

Rabbits of acceptable skin quality were selected and used for the test.

The test sample employed was:

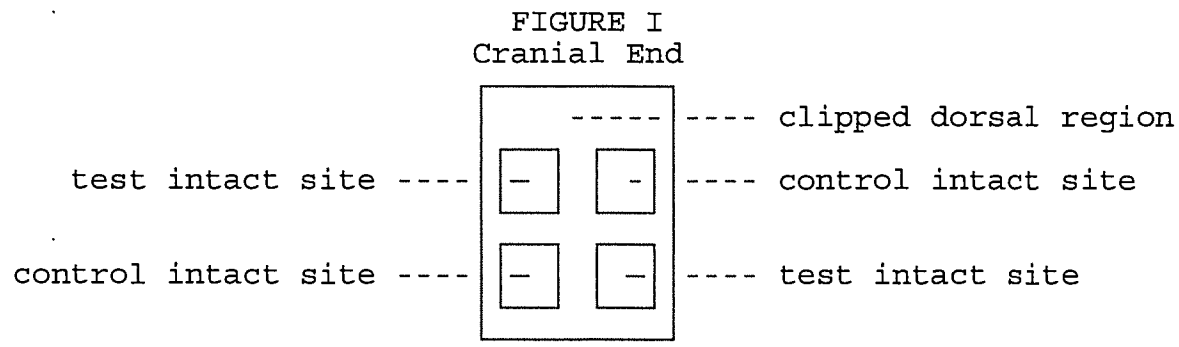
X A 2.5 cm x 2.5 cm gauze patch saturated with 0.5 mL of test article.

N/A A 2.5 cm x 2.5 cm gauze patch with 0.5 g of test article.

N/A A 2.5 cm x 2.5 cm piece of test article.

The test sample was placed over two (2) clipped test sites. The control is prepared in the same manner as test without the test article (see Figure I).

FIGURE I



The patches were secured in place using hypo-allergenic waterproof tape.

The rabbit's trunk was wrapped with an elastic self-adhering wrap. A stockinette was then placed over the wrap and secured with tape.

After a minimum of four (4) hours of exposure to the test and control substance, the tape and dressings were removed taking care not to cause any mechanical irritation. These steps were repeated as necessary for multiple exposure.

Using the criteria in Table I, the sites were scored for erythema and edema at intervals of one (1), twenty-four (24), forty-eight (48) and seventy-two (72) hours after patch removal.

TABLE I
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 grading of erythema	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

If no response was expected, testing was conducted using three (3) animals per test article. If irritation was anticipated, one (1) animal was tested initially. If the first animal received a score of 2 or less for either erythema or edema, two (2) additional rabbits were used to conclude the test.

DOSAGE OF TEST/CONTROL ARTICLES:

Two (2) test sites and two (2) control sites were used per rabbit.

-- If an intact test article was applied directly, a 2.5 cm x 2.5 cm piece was used.

-- If a liquid test article was used, 0.5 mL was applied to 2.5 cm x 2.5 cm piece of gauze.

-- If a powder was used, 0.5 g was applied to a 2.5 cm x 2.5 cm piece of gauze.

For control, a gauze patch saturated with 0.5 mL of the appropriate media is used when needed.

The test article and control were held in place on the animal for a minimum duration of four (4) hours.

DESCRIPTION OF CALCULATIONS PERFORMED ON DATA:

Only the twenty-four (24), forty-eight (48) and seventy-two (72) hour observations were used for calculations.

The total erythema and edema scores were added. The total erythema and edema scores for controls were subtracted from the total for test sites. The total score was then divided by six (6) to generate the average for each animal. The averages were totaled and divided by the number of animals used to give the Primary Irritation Index.

A compound producing a Primary Irritation Index of zero (0) to a 0.4 was classified as having negligible response, indexes of 0.5 to 1.9 were a slight irritant, indexes of 2.0 to 4.9 were moderately irritating and indexes of 5.0 or more were severe irritants.

COMMENTS: None

SKIN IRRITATION TOTALS

RESULTS: The skin reactions were not significant.

DIRECT APPLICATION OF TEST ARTICLE

	TEST			CONTROL		
Rabbit No. 14384	ER	ED	Total	ER	ED	Total
	0	0	0	0	0	0
	Test Total - Control Total = 0 Total Score Average = 0					
Rabbit No. 14387	ER	ED	Total	ER	ED	Total
	0	0	0	0	0	0
	Test Total - Control Total = 0 Total Score Average = 0					
Rabbit No. 14394	ER	ED	Total	ER	ED	Total
	0	0	0	0	0	0
	Test Total - Control Total = 0 Total Score Average = 0					

$$\frac{\text{Total Average (0)}}{\text{No. of Animals (3)}} = \underline{0} \text{ Primary Irritation Index}$$

POSITIVE VALIDATION:

A positive validation test is performed every six (6) months using 10% Sodium Dodecyl Sulfate (SDS) which is a known dermal irritant.

0.5 g of 10% SDS in petroleum jelly applied to a 2.5 cm x 2.5 cm gauze patch was utilized as the positive validator. 0.5 mL of 0.9% Sodium Chloride applied to a 2.5 cm x 2.5 cm gauze patch was the negative control.

A Primary Irritation Index in the moderate to severe range is considered a positive result.

The Test System and Test Methods utilized were the same as described in the Main Test.

Primary Skin Positive Validation Reference Date: 11-09-2015

RESULTS:

	TEST						CONTROL					
Rabbit No. 14279	ER	+	ED	=	Total		ER	+	ED	=	Total	
	18		14		32		0		0		0	
	Test Total - Control Total = 32 Total Score Average = 5.3											
Rabbit No. 14280	ER	+	ED	=	Total		ER	+	ED	=	Total	
	21		19		40		0		0		0	
	Test Total - Control Total = 40 Total Score Average = 6.6											
Rabbit No. 14281	ER	+	ED	=	Total		ER	+	ED	=	Total	
	23		21		44		0		0		0	
	Test Total - Control Total = 44 Total Score Average = 7.3											

$$\frac{\text{Total Average (19.3)}}{\text{No. of Animals (3)}} = 6.4 \text{ Primary Irritation Index}$$

GENEVA LABORATORIES, INC.

Toxicology Department Personnel

Dr. Colleen Stewart -- Director of Veterinary Medicine

Sandra Ott -- Toxicology Study Director

Scott Roberts -- Analyst

Elizabeth Wettstein -- Analyst

E. Jane Lewis -- QA Toxicology

Paul Norland -- QA Manager

SECTION 3

QUALITY ASSURANCE AUDIT REPORT & STATEMENT

JN16B0972

GLP0006*
Attachment 2-1/2

GENEVA LABORATORIES, INC.
GLP AUDIT SCHEDULE REPORT, TEST ID AND CERTIFICATION

SPONSOR: Global Health Solutions
P.O. Box 133/1360 Redmond Circle, NW
Rome, GA 30162

TEST ARTICLE: CurX Antimicrobial Wound Dressing
Lot No.: 15F10E3

NATURE OF STUDY: Primary Skin Irritation Test (Direct Contact)
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]

REFERENCE: Geneva Laboratories Procedure No.: CL1024 Rev. K

TEST SYSTEM: New Zealand White Rabbits

TEST STATUS: Study Initiated: 02-16-2016
Test Initiated: 03-08-2016
Test Completed: 03-11-2016
Study Completed: 03-15-2016

AUDIT DATES: See Table I

COMMENTS INCLUDING DEVIATIONS AND PROBLEMS: Under the conditions of this study, the test article response category was negligible.

My review of the study documents indicates that the facilities, equipment, personnel, methods, practices, records and controls are in conformance with the GLP Regulations. This final report accurately describes the methods and standard operating procedures used and the raw data generated during the course of the study.

The copies of the protocols and records of Quality Assurance inspections have been transferred to the Geneva Laboratories GLP archive and will be maintained as long as indicated in 21 CFR Part 58 §58.195 paragraph a) and b).

QA AUDITOR: E Jane Lewis DATE: 03-15-2016

QA MANAGEMENT: Paul Mc DATE: 03/15/2016

TABLE I

QUALITY ASSURANCE STATEMENT

INSPECTED BY INSPECTION DATE	STUDY SEGMENT INSPECTED	DATE FINDINGS WERE WRITTEN FOR MANAGEMENT AND STUDY DIRECTOR
E.J.L./03-08-2016	Direct Application	03-08-2016
E.J.L./03-08-2016	4 Hour Patches Removed and 1 Hour Scoring	03-08-2016
E.J.L./03-09-2016	24 Hour Scoring	03-09-2016
E.J.L./03-10-2016	48 Hour Scoring	03-10-2016
E.J.L./03-11-2016	72 Hour Scoring	03-11-2016
E.J.L./03-14-2016	Raw Data Review	03-14-2016
E.J.L./03-15-2016	Final Report Review	03-15-2016

*E.J.L. E. Jane Lewis

QA AUDITOR: E Jane Lewis DATE: 03-15-2016

QA MANAGEMENT: [signature] DATE: 03/15/2016

SECTION 4

COMPLIANCE/ARCHIVE STATEMENTS

GLP0001*

GENEVA LABORATORIES, INC.
STUDY DIRECTOR COMPLIANCE STATEMENT

SPONSOR: Global Health Solutions
P.O. Box 133/1360 Redmond Circle, NW
Rome, GA 30162

PROTOCOL: Primary Skin Irritation Test (Direct Contact)
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]

TEST ARTICLE: CurX Antimicrobial Wound Dressing
Lot No.: 15F10E3

STUDY INITIATION DATE: 02-16-2016 STUDY COMPLETION DATE: 03-15-2016

After a review of the pertinent raw data, I am led to conclude the test results were accurately recorded and verified, correctly analyzed, interpreted and all applicable GLP Regulations of 21 CFR Part 58 for Non-clinical Laboratory Studies were followed.

All raw data, documentation, protocols, specimens and final reports are retained for orderly storage and expedient retrieval as recommended in the 21 CFR Part 58 §58.190.00

STUDY DIRECTOR: _____ DATE: 03-15-2016
Toxicology

GENEVA LABORATORIES, INC.
GLP COORDINATOR ARCHIVE STATEMENT

SPONSOR: Global Health Solutions
P.O. Box 133/1360 Redmond Circle, NW
Rome, GA 30162

PROTOCOL: Primary Skin Irritation Test (Direct Contact)
[ANSI/AAMI/ISO 10993-10:2010/(R)2014]

TEST ARTICLE: CurX Antimicrobial Wound Dressing
Lot No.: 15F10E3

STUDY INITIATION DATE: 02-16-2016 STUDY COMPLETION DATE: 03-15-2016

For the purpose of information retrieval, we are informing you of our storage procedure of specimens and records.

Specimens and a copy of the final report are stored in the archives of Geneva Laboratories, Inc. Fragile specimens will be retained so long as the quality of the preparation affords evaluation.

Raw data for the above listed test compiled by Geneva Laboratories is stored at Geneva Laboratories, Inc. (or an alternate archive location) for not less than five (5) years.

GLP COORDINATOR: Rani Smith DATE: 03-15-2016